TRB CHEMEDICA

Clinical evaluation report

for

OSTENIL PLUS solution for injection

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Relation to Overall Risk Management

This clinical evaluation report (CER) is part of the overall risk evaluation process of OSTENIL® PLUS.

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LIST OF ABBREVIATIONS

AAOS	American Academy of Orthopaedic Surgeons
ACR	American College of Rheumatology
ADME	absorption, distribution, metabolism, and excretion
AE	Adverse event
BSE	bovine spongiform encephalopathy
CEv	clinical evaluation
CER	clinical evaluation report
CGI	clinical global impression
CI	confidence interval
COX	cyclooxygenase
Da	Daltons
DIMDI	Deutsche Institut für Medizinische Dokumentation und Information
DNA	Deoxyribonucleic acid
ECM	Extracellular matrix
e.g.	*exempli gratia*, for example
EP	European pharmacopoeia
ESCEO	European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis
EULAR	European League Against Rheumatism
FDA	Food and Drug Administration
FU	Follow-up
g	grams
GAG	glycosaminoglycans
HA	hyaluronic acid, hyaluronan
HIV	human immunodeficiency virus
HMW	high molecular weight
i.a.	intraarticular
IFU	instruction for use
IL	interleukin
iv.	intravenous
ITT	intension to treat
kDa	Kilo Daltons
l	liter
Lequesne	Lequesne index/score
LMW	low molecular weight
LOCF	Last observation carried forward
LoE	Level of evidence
MDD	Medical device directive (Council Directive 93/42/EEC)
mg	miligrams
min	minute
ml	mililiters
MRI	Magnetic resonance imaging
MRT	magnetic resonance tomography
MW	molecular weight
N or n	Number
n.a.	Not applicable
NASHA	non-animal stabilised hyaluronic acid
ng	nanograms
NICE	National Institute for Health and Care Excellence
NSAID	non steroidal anti inflammatory drugs
OA	osteoarthritis
OARSI	Osteoarthritis Research Society International
ODQ	Oswestry Disability Questionnaire
OMERACT	Outcome Measures in Rheumatoid Arthritis Clinical Trials
PET	Positron emission tomography
PGA	patient global assessment
PLA_2	phospholipase A2
PMCF	Post-market clinical follow-up
PMS	Post-market surveillance
QoL	Quality of Life

RA	Rheumatoid arthritis
RCT	randomized controlled trial
RH	Relative humidity
ROS	Radical oxygen species
RR	relative risk
SAIR	severe acute inflammatory reaction
SF	Synovial fluid
SH	sodium hyaluronate
TA	triamcinolone acetonide
TH	triamcinolone hexacetonide
TNF	Tumor necrosis factor
TRP	transient receptor potential
VAS	visual analogue scale
vs.	versus
WOMAC	Western Ontario and McMaster Universities Arthritis Index
µg	micrograms

As sodium hyaluronate (SH) is the physiologically present form of hyaluronic acid (HA), both abbreviations will be used synonymously in this Clinical Evaluation Report (CER).

1. SUMMARY

This updated clinical report describes the medical device OSTENIL® PLUS, which has been developed for the intra-articular (i.a.) treatment of complaints due to degenerative and traumatic changes of the synovial joint. The applicable guidelines considered in the preparation of this report were Medical Device Directive (MDD) 93/42/EEC, MEDDEV 2.7.1, MEDDEV 2.12.2, NB-MED/2.7/Rec3 and NB-MED/2.7/Rec1. An own report exists for the biocompatibility of the OSTENIL® range of products to which reference is made.

OSTENIL® PLUS is a certified medical device with intra articular hyaluronan whose marketing began in 2009. I.a. hyaluronic acid (sodium hyaluronate, SH; hyaluronan, HA) from TRB Chemedica is on sale in numerous countries within and outside the European Union. The favourable benefit-risk profile of the OSTENIL® range of products is well known from biocompatibility studies, carried out according to the guidelines, from clinical studies on the safety and effectiveness and from the medical device vigilance system.

The mechanism of action of OSTENIL® PLUS is the viscosupplementation (improvement) of the synovial fluid, which is qualitatively and quantitatively reduced in osteoarthritis, with i.a. HA. OSTENIL® PLUS serves a therapeutic need for the treatment of synovial joints with an adequate fill volume of viscoelastic solution.

HA is a largely inert high molecular weight polysaccharide that occurs in tissues and body fluids of vertebrates where it carries out important structural and functional tasks. HA consists of repeating sequences of N-acetylglucosamine and glucuronic acid, which form linear, long chain molecules with a molecular weight of up to 10 million Daltons. Endogenous HA is found in higher concentrations in the tear fluid, the aqueous chamber and in the lens of the eye, in the joint cartilage and synovial fluid, and in the ground substance of the skin.

HA plays a special role in the joint fluid of the synovial joint where it acts as a lubricant, shock absorber, space filler and as a molecular sieve, which hinders the free passage of inflammatory cells and molecules into the joint space. A decrease in its quantity and quality due to degenerative processes or trauma in the joint or its washing out during arthroscopy or open surgery of the joint, causes pain and joint dysfunction. The improvement of the synovial fluid or its temporary substitution with the use of exogenous HA, in an animal model of experimentally-induced degeneration or partial degeneration of joint structures, results in the protection of these tissues. In clinical studies, a persistent effect on pain and joint mobility in the medium term (i.e. a carry-over effect) has been proven beyond doubt.

At first, the large-scale technical production of HA as an active agent for different medical devices was made by extraction from rooster combs; a more modern procedure is through fermentation of bacteria, whose mucin capsule is rich in HA. After this procedure, the highly purified HA is “made to measure” to suit the molecular weight range for the medical devices produced by TRB

Chemedica AG. Structurally, the exogenous HA obtained in this way is structurally identical to endogenous HA. Comparative studies in appropriate animal models demonstrate that viscosupplementation with medium molecular weight HA exercises greater protective effects on the synovial membrane, synovial fluid and cartilage surface. This “ideal molecular weight” apparently lies between one and two million Daltons. The average molecular weight of the active ingredient in OSTENIL® PLUS is within this range with 1.6 million Daltons (Da).

TRB Chemedica AG has extensive experience in the development, manufacture and use of HA products for viscosupplementation. Clinical studies and feedback from the market confirm that the product has a reliable effect. The low number of technical and medical complaints as well as the lack of notifiable incidents since its first launch underlines its safety. The efficacy and safety of OSTENIL® PLUS is described in this clinical evaluation report.

This clinical evaluation report on OSTENIL® PLUS looks at data from clinical studies with i.a. HA in osteoarthritis of synovial joints and broadly covers the benefits of this treatment. The data to support this notion go back on good designed clinical studies with OSTENIL® PLUS with high level of evidence and case series with high number of participants. Authoritative Cochrane Reviews on i.a. HA in osteoarthritis of the knee joint support this assessment and illustrate that HA is effective in this indication and other methods and products are not superior to treatment with HA products. Moreover, the number of adverse effects related to this class of products can be considered as low. Most adverse effects are of mild to moderate nature and limited in duration. While it is understood that i.a. injections carry some inherent risks, the extent to which adverse events are associated with the HA compound itself, as opposed to the injection procedure, is unclear. According to reviewing literature, trial data suggest that severe adverse events are not common. Potential adverse events and the referring information for the use of OSTENIL® PLUS are given in the package leaflet and are addressed in sections 2.3 and 3.1 of the CER. Another advantage of only a few injections of i.a. HA is the favourable long carry-over effect on the osteoarthritis symptoms.

The possible risks of the i.a. administration of OSTENIL® PLUS are presented in the product labelling. They are low in the comparison to the risks of a few effective alternative drugs (i.a. corticosteroids, systemic analgesics as well as nonsteroidal anti-inflammatory drugs) and are outweighed by the benefits of the treatment.

Overall, clinical studies with OSTENIL® PLUS demonstrate, in a consistent manner, an improvement in pain symptoms and a resultant improvement in functional impairment as well as an improvement in the quality of life of the patients concerned.

Evaluation of publications from clinical studies peformed with OSTENIL® PLUS found by literature search or performed by TRB Chemedica as sponsor together with the risk analysis show that conformity of OSTENIL® PLUS with essential requirements can be demonstrated. Based on these results it can be concluded that OSTENIL® PLUS performs as indicated by the instructions for use and that no additional extensive clinical investigation is needed.

To further follow up the clinical performance, safety and usability of OSTENIL® PLUS and to collect a broader market experience during use in pain and restricted mobility in degenerative and traumatic changes of synovial joints TRB Chemedica performs post market surveillance.

The body of clinical data identified in the literature together with results from clinical trials performed by TRB Chemedica and reported in this document is rather substantial and fully sufficient to allow a sound clinical evaluation of the product at hand.

Essential Requirements with regard to clinical evaluation (according Medical Device Directive 93/42/EEC) are fulfilled.

2. INTRODUCTION

2.1 Hyaluronan

The images in this chapter are from the websites from www.glycoforum.gr.jp/science/hyaluronan/hyaluronanE.html (2016).

2.1.1 History

In 1934 Meyer and Palmer[222] succeeded in extracting a new polysaccharide from the lens of bovine eyes which was named HA due to its content of uronic acid and its origin in the lens (hyaloid = glass). Under physiological conditions, HA exists as a polyelectrolyte with associated cations, frequently as a sodium salt; therefore, the name sodium hyaluronate. The name was later amended to ‘‘hyaluronate’’ in reference to its salt form or ‘‘hyaluronan,’’ a term used to encompass all forms of the molecule.[24] In the 1950‘s it was already observed that there was a defect of HA in osteoarthritis (OA), rheumatoid arthritis and in certain skin diseases. Ten years later HA was proposed as an active principle for the treatment of such diseases and the first studies on the therapeutic benefits of the substance appeared in the 1970‘s. At first HA was used to treat joint diseases in racehorses “with excellent results”. Later this was extended to other veterinary indications such as hip joint dysplasia in dogs. Hence many publications on HA during this period came from veterinary medical research. In the early eighties, HA was finally registered for use in man as Healon®, a viscoelastic that would be used during ocular surgery to maintain space and protect the sensitive corneal endothelium. Since then HA is used in several other indications in which such products, because of their physical mechanism of action, are almost exclusively registered as medical devices in accordance with the MDD.

2.1.2 Occurrence

HA is found in practically all living organisms (except plants) and is an essential component of the extracellular matrix. It is a linear polysaccharide (‘many sugars’) that belongs to a select group of substances that have an identical chemical structure in all living things, whether in simple bacteria

(about six strains have the ability to synthesise HA) or in human beings. HA is widely distributed but mainly localized in the extracellular matrix and body fluid. Higher concentrations of HA are found in the skin, in the lens of the eye, in the joint cartilage, the synovial flui (SF), in blood vessels and the umbilical cord.

2.1.3 Structure and Properties

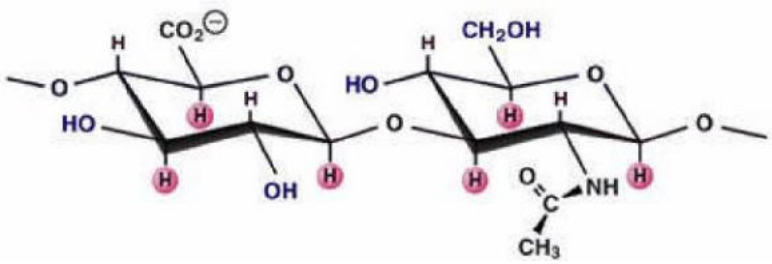
2.1.3.1 Molecular weight

HA is a glycosaminoglycan that is made up of repeating sequences of N-acetylglucosamine and D-glucuronic acid. These sugars are linked by a ß-glycosidic bond to form the basic disaccharide unit found in HA. Each disaccharide unit is twisted through 180 degrees (inverted) compared with those ahead and behind it in the chain. The structure of HA can be represented as a very stable, unbranched linear chain. Contrary to other glycosaminoglycans it contains no sulphate groups.[7] HA is a polyanion, which exerts specific characteristics, especially when dissolved in water or physiological fluids. There are on average about 2500 repeating disaccharide units in endogenous HA and the average molecular weight (MW) is approximately 1 x 10^6 Da (each disaccharide is approximately 400 Da). However, the number of repeating disaccharides in an HA molecule can reach 10,000 or more, with a MW of about 4 million Da.

2.1.3.2 Structure in solution

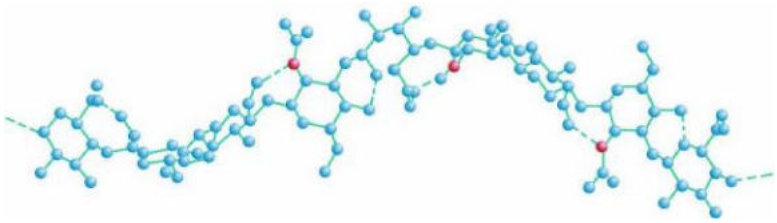
In a physiological solution, the backbone of an HA molecule is stiffened by a combination of the chemical structure of the disaccharide, internal hydrogen bonds and interactions with the solvent (the medium in which the HA is dissolved). The axial hydrogen atoms (shown in the figure below) form a non-polar, relatively hydrophobic face while the equatorial side chains form a more polar, hydrophilic face. The arrangement of these hydrogen atoms, combined with the alternately inverted disaccharide units, creates a twisting ribbon structure that is stabilised by water.

Figure 1 Glucuronic acid and N-acetylglucosamine basic unit



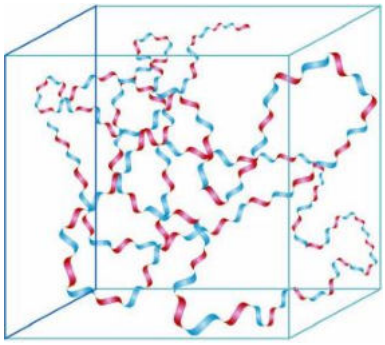
Glucuronic acid and N-acetylglucosamine form disaccharide hyalobiuronic acid, the basic unit of the long chain HA molecules (Figure 1). The three dimensional molecular configuration (helical structure) of a linear HA molecule is displayed in Figure 2.

Figure 2 Helical structure of a linear HA molecule



As a result, a molecule of hyaluronan assumes an expanded random coil structure in physiological solutions and occupies a very large three-dimensional space or domain.

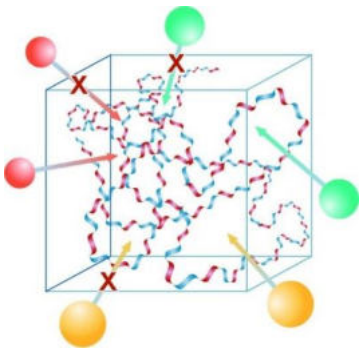
Figure 3 Random coil configuration of a HA molecule in water



As a 0.1% (1 mg/ml) solution, these random coils already pervade the entire volume of the solution. At higher concentrations, the hyaluronan coils intervene and entangle, forming a flexible molecular network.

The domain structure of HA has important consequences. Small molecules such as water, electrolytes and nutrients can freely diffuse through the solution. However, large molecules such as proteins will be partially excluded from the domain because of their volume in solution. As shown in the figure below, the HA network in the domain allows less and less space for other molecules as it becomes more and more concentrated. This leads both to slower diffusion of macromolecules through the network and to their lower concentration in the network compared to the surrounding hyaluronan-free compartments. The HA chains are constantly moving in the solution and the effective 'pores' in the network continuously change in size. This means that in principle, all molecules can pass through a HA network, but with different degrees of retardation depending on their volume (size) in solution.

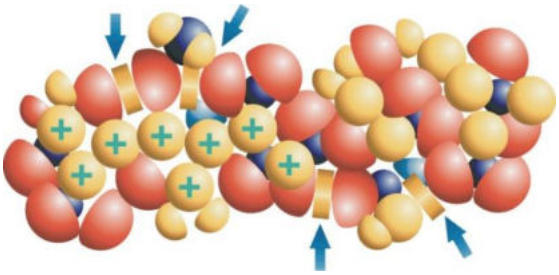
Figure 4 Sieve effect of a HA molecule in water



The HA molecule is mainly hydrophilic (i.e. it has a strong affinity for water). However, it has been shown that HA also has extensive hydrophobic patches (which have little affinity for water). Thus,

HA has the property of a highly hydrophilic material simultaneous with hydrophobic patches characteristic of lipids (i.e. it is an amphiphilic molecule). Hydrophobic patches have far-reaching implications for molecules in a watery environment. Hydrophobic molecules can clump together in water, thus reducing their interface with the solvent. This mechanism drives the formation of membranes and contributes to the stability of, for example, the double helix in DNA. It is called hydrophobic bonding, although no actual chemical bond is formed.

Figure 5 The hydrophobic patches in hyaluronan



The arrows point to the hydrophobic bonds of hyaluronan. The hydrogen atoms marked with a cross are part of a hydrophobic patch, consisting of 8 CH groups.

2.1.4 Viscoelasticity

A particularly useful property of HA solutions or gels is their viscoelastic behaviour, which is partly based on the water-binding capacity of the substance. The term viscoelasticity is applied to a liquid that exhibits both viscous and elastic properties resulting in properties of solids and liquids. This allows the joint to optimally adapt to different externally applied forces. The knee experiences low shear loads during simple range of motion. Under these conditions, viscous properties predominate and the HA molecules line up and act as a lubricant. Under high shear loads, HA molecules behave as an elastic substance and absorb energy that is transmitted across the joint.

Analyzing the rheological properties at a microscopic scale showed that HA forms a dynamic network in synovial fluid.[160] HA, in a concentration which corresponds to that in the SF, forms a network of molecular balls woven into each other. This network acts, among others, as sieve which hinders the passage of cells and substances into the joint space.

Figure 6 Hyaluronan network

In a normal joint, there are close functional and metabolic interdependences between the SF, articular cartilage and subchondral bone and the matrix proteoglycans and matrix collagens. HA plays a crucial role in maintaining these functional and metabolic interdependences and

homeostasis of joint environment. – All of these activities depend on the high viscoelasticity of HA present in the SF of the normal joint.

2.1.4.1 Elasticity

Solids that can compress or stretch under load and then return to their original form when the load is removed are said to be elastic. The elasticity of the joint cartilage, for example, prevents it from being damaged on loading through jumping or on falling.

The elasticity of HA solutions consists of two typical reaction patterns: if it is compressed very fast, it then returns just as rapidly to its original form; if it is deformed slowly, then it returns gradually to its original form once the load is removed. This behaviour is based on two different mechanisms. One mechanism is based on the random coil structure of the molecule that gives it the qualities of a spring, as it were. The molecule can therefore be compressed quickly and returns just as rapidly into its original configuration if the load is removed. However loads that have a slower effect cause the gradual release of water molecules that are bound to the HA and the volume of the molecule itself decreases. Through this ‘water-loss’, the osmotic pressure in the molecule itself increases. When the load is removed, HA absorbs water again and thus returns to its original volume. Elasticity is an important property of biopolymers such as HA since they frequently function as ‘packing materials’ for sensitive tissues. In the vitreous humour of the eye, HA protects the sensitive retina cells from possible damage, for example due to compression of the eyeball. Therefore exogenous HA is routinely used to support the cornea during operations in the eye. The HA gel imitates the function of the vitreous body and in this way protects the very sensitive structures of the eye during the operation. In similar way, HA acts as an absorber of load in the synovial joint during movement or gives healthy skin a smooth profile and softness.

2.1.4.2 Viscosity

Unlike solids, liquids are not compressible and respond to loads by flowing. The specific resistance of a liquid to flow is expressed by its viscosity. Plastic materials and some biopolymers possess both properties (viscosity and elasticity): some can be deformed under pressure and can flow like liquids. These materials have viscoelastic properties. Aqueous solutions of HA are viscoelastic.

Due to its non-Newtonian properties, the viscosity of a HA solution has a special importance in joint function. This means that, unlike water - which is a Newtonian fluid, a body with higher speed can move more easily through the solution. So-called drip solid thixotropic wall paints are a good example of the behaviour of Non-Newtonian solutions: they are viscous when taken with the roller; however, when applied onto the wall with the roller they become thinner under the influence of shear forces and hence can be spread easily. HA solutions behave quite similar. If a joint is not moved, the SF containing HA is viscous and has more solid elastic properties while, on movement, it becomes less viscous and its resistance decreases. This is based on a change in the alignment of HA molecules: the molecules initially behave like a network of random coils interwoven into each

other whereas on load they line up parallel to the load and can move against each other more easily.

2.1.5 Sources of Exogenous HA

2.1.5.1 The extractive presentation

Exogenous HA can be extracted from animal tissue that, in principle, has a higher content of HA. The first HA was extracted from the umbilical cord, while rooster combs often serve as the starting material today. For this purpose, the tissue is ground resulting in a mixture of blood with cellular and extracellular components. The extraction procedure is technically difficult and, because of the relatively low yields of HA, very expensive, especially if certain molecular weight fractions are to be produced. Due to the starting material, extractive HA can contain impurities such as animal proteins, chondroitin sulphate or beta D-glucans. In addition extractive HA, even though it also corresponds to the requirements of the European Pharmacopoeia, can apparently result in a higher incidence of allergic reactions. There is also a theoretical risk of transferring viral diseases.

2.1.5.2 The fermentative presentation

The more modern fermentative process has a series of obvious advantages. Bacteria, which possess an HA-rich mucin capsule, can through their selection and using carefully controlled culture conditions (e.g. type of nutrient medium, temperature, oxygen supply or duration of fermentation) produce ‘custom-made’ HA with a high degree of purity. HA is formed by hyaluronan synthetase in the cell membrane and is then extruded in the extracellular space (Figure 7). The yield from bacterial fermentation is higher than that with the extraction procedure and hence HA is obtained more economical. The availability of HA from fermentation has promoted the sustained development of HA-containing medical devices.

Figure 7 Hyaluronan synthesis

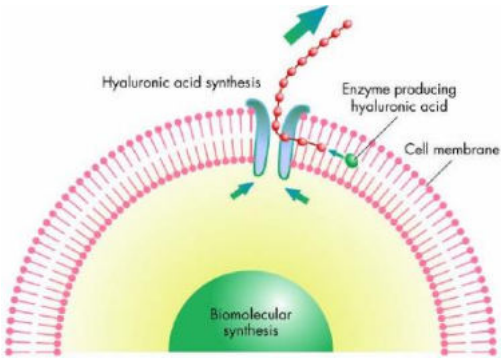
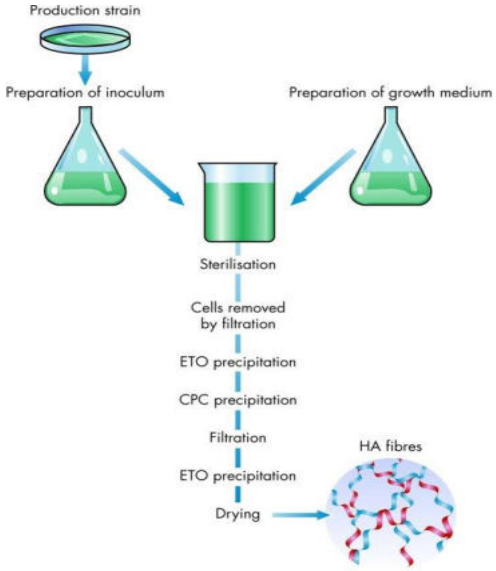


Figure 8 Scheme of hyaluronan production by fermentation



2.1.6 Effects of HA

Despite its simple chemical composition, HA fulfills several distinct molecular functions that contribute not only to the structural and physiological characteristics of tissues, but also to the mediation of cell behaviors during morphogenesis, tissue remodeling, inflammation and diseases. Owing to its unique biophysical properties, HA contributes directly to the maintenance of tissue homeostasis and biomechanics. Through its interactions with proteoglycans and link proteins, HA organizes and maintains the structural integrity of extracellular and pericellular matrices. As a signaling molecule, HA interacts with a variety of cell surface receptors and HA-binding proteins to activate intracellular events to mediate cell functions.[7] The biological roles of HA are widespread and widely appreciated; for comprehensive reviews see the work of Toole, Laurent, and others.[308,303,316,182,138,56] HA is a crucial element in embryonic development,[272] tissue organization,[158,305] wound healing,[21,246,95] angiogenesis,[321] tumorigenesis,[300] and possibly even in the biomechanical properties of tissues.

The synovial lining cells of a healthy joint secrete HA. Endogenous HA serves numerous functions, including lubrication during slow movement of the joint, facilitating motion; decreased friction between joint surfaces during rapid movement of the joint facilitating control of joint movement; exclusion of large molecules (such as proteins and cells) from the joint cavity, carrying nutrition from the synovium to the cartilage and waste products from the cartilage to the synovium; acting as a ‘sink’ for inflammatory products; acting through the synovial cells to stimulate production of normal HA; and acting on synovial lining nerves to reduce the transmission of pain signals. HA in the joint space forms a molecular sieve which prevents the free passage of inflammatory cells and molecules, while allowing the flow of catabolic compounds from the synovial membrane to the non-vascularised joint cartilage.

2.1.6.1.1. Anti-inflammatory effects

HA has been shown to alter many of the actions of inflammatory cells and their effect on leukocyte function, which appears to be dependent on molecular weight.[295]

HAs have also been shown to be effective at inhibiting metalloproteinases that are responsible for cartilage degradation in OA.[124] Additionally, HAs have been shown to significantly decrease synovial levels of tumor necrosis factor (TNF)-α and interleukin (IL)-1α, which are proinflammatory cytokines involved in cartilage destruction.[68,292] Other studies have shown that inflammatory intermediaries such as arachidonic acid, prostaglandins, leukotrienes, cyclic adenosine monophosphate, and nitric oxide are all decreased in the arthritic knee after i.a. injection of HA.[285]

Little clinical data corroborate the anti-inflammatory effect of HA. In a double-blind study, 110 patients with OA of the knee were randomly assigned to receive either four weekly injections of HA or four weekly injections of saline.[77] At 8 weeks after the first injection, patients who had received HA injections reported significantly fewer effusions compared with patients who had received saline. Joint effusion was used as the clinical marker for inflammation associated with OA of the knee, leading the authors to suggest that the benefit of HA was at least in part ascribable to its anti-inflammatory effect.

2.1.6.1.2. Anabolic effect

Viscosupplementation with i.a. injections of HA has been shown to stimulate synovial fibroblasts and synoviocytes to secrete natural HA.[280,310] In a positive feedback mechanism, exogenous HA thus has an anabolic effect on synovial cells that is most likely sustained even after the exogenous HA is cleared from the joint. This effect is dependent on molecular size, with MWs greater than 5×10^5 Da being the most effective.[280]

2.1.6.1.3. Anti-nociceptive effects

The comprehensive 2006 Cochrane meta-analysis from Bellamy and colleagues[36] reviewed single- and double-blinded randomized controlled trials (RCTs) that evaluated the effect of 12 HA products on OA of the knee. Studies compared HA products with placebo, i.a. steroids, non steroidal anti inflammatory drugs (NSAIDs), physical therapy, exercise, and each other. Efficacy data for different products couldn't be combined because the studies measured different sets of outcomes at different time points. Overall, the authors concluded that HA injections effectively reduced pain scores, with the largest benefit occurring within 5 to 13 weeks.

Theoretically, the perceived anti-inflammatory effects of HA injections likely play a role in reducing pain in the osteoarthritic joint. In addition, some studies have suggested that HA injections achieve their effect via independent anti-nociceptive mechanisms[119,27] and indirectly through decreasing the synthesis of or binding to bradikinin, substance P, and other hyperalgesic compounds.[224,112,120,121] Intra-articular injection of HA alleviates pain in osteoarthritic patients[19,41,63] and decreases the augmented movement-induced nerve impulse activity in sensitized joint nociceptor fibres.[119,118]

Polymodal transient receptor potential vanilloid subtype 1 (TRPV1) channel is a non-selective cationic channel preferentially expressed by primary nociceptive neurons that has been implicated in arthritic pain.[60,108,291,150] Accordingly, the pharmacological modulation of TRPV1 has been shown

to produce anti-nociception in arthritis animal models.[149,258] It was found that HA inhibits TRPV1 channel activity and reduces action potential firing in nociceptive neurons and shows a previously unknown molecular mechanism that explains the attenuation by HA of peripheral nociceptor activity and pain.[55] However, the molecular mechanisms underlying HA anti-nociceptive activity remain poorly understood.[55]

2.1.6.1.4. Lubricating and gliding effects

Mammalian synovial joints are extremely efficient lubrication systems reaching very low friction coefficient (μ) at high pressures and shear rates; however, despite much previous work, the exact mechanism responsible for this behavior is still unknown.[274]

HA is abundant in cartilage and SF and high molecular weight (HMW) HA has been shown to function effectively as a cartilage boundary lubricant, decreasing friction at a cartilage-cartilage interface.[271] Similarly, HMW of HA is thought to provide the viscoelastic component to SF,[89] which may affect the cartilage lubricating ability of normal SF in a fluid film mode of lubrication.

HA provide excellent wear protection for surfaces shearing at high pressures (200 atmospheres), even though high friction coefficients ($\mu = 0.15 - 0.3$) were measured. These results imply that friction and wear are not necessarily correlated and that a layer of strongly immobilized HA could protect a cartilage surface from wear (damage) if not necessarily contributing to low friction.[125]

2.1.6.1.5. Chondroprotective potential

Some authors have suggested that i.a. HA has a disease-modifying chondroprotective potential. Several studies have focused on clinical outcomes consistent with disease modification following i.a. HA. Outcome parameters include imaging studies and direct inspection via arthroscopy or histology. Listrat et al. (1997)[206] found less deterioration of joint space in HA-treated patients than did controls as seen during arthroscopy 1 year following three cycles of i.a. HA. Frizziero et al. (1998)[105] found reconstitution of the superficial amorphous cartilaginous layer, improvement in chondrocyte density, and reduction in synovial inflammation on arthroscopy after i.a. HA. Using weight-bearing radiographs, Jubb et al. (2003)[166] found a significant reduction in joint space narrowing at 1 year following i.a. HA. This reduction in joint space narrowing was only seen in patients with less severe OA. Bagga and colleagues (2006)[20] observed that at 3 months after 3 weekly injection of HMW HA, the mean HA concentration in the SF of 27 patients had increased by 13% ($p < 0.0008$). By the 6-month follow-up, the HA concentration of approximately half of the patients was still above baseline values. This suggests that HA injections may have stimulated production of endogenous HA and thus altered disease progression.

Despite these data suggesting the possibility of chondroprotection and disease-modifying potential of i.a. HA, current data do not support such claims. Larger studies with standardized outcome parameters are required.

2.1.6.1.6. Wound healing

The tissue injury and repair process is characterized by the turnover of the matrix components, and HA plays important and multifaceted roles in this dynamic process.[61] After a lesion, a number of processes are activated to promote tissue repair and synthesis of HA is indeed one of the most important ones. Exogenous HA has been used for decades and is now widely recognized by clinicians and patients as an important agent for tissue repair. Its biological properties supporting the clinical application in wound repair have been the subject of several reviews[61,48,162,7,253,161] and it is now considered as proven that its addition

1) increases the migration and proliferation of fibroblasts and the formation of granulation tissue;
2) promotes the organized deposition of collagen fibers by the fibroblasts;
3) promotes the formation of new blood vessels (neoangiogenesis), and
4) favours re-epithelialisation.

2.1.6.1.7. Cell behavior

HA is a primary constituent of the cell coat (also known as the pericellular matrix or glycocalyx) of fibroblasts, myofibroblasts, smooth muscle cells and other cell types, and participate in the regulation of cell behavior such as adhesion, proliferation, differentiation, and migration.[86,87,299,221,139] This may occur through the physiochemical properties of HA or via direct interaction with cells.[281,18] When HA is synthesized and released to the extracellular environment, its physiochemical characteristics of viscosity and elasticity contribute to local tissue hydration. Observations revealed that HA accumulation coincides with periods of cellular migration.[301,249,302] The expansion of the extracellular space from HA (by binding salt and water) creates a highly hydrated extracellular matrix (ECM). This results in weakening of cell anchorage to the extracellular matrix, allowing temporal detachment to facilitate cell migration and division.[299,72] Beyond the physiochemical interactions with HA, cells may be able to mediate, direct, and control their migration and locomotor mechanism through specific interactions via cell surface HA receptors.[61] The formation and repair of mature hard tissue require cell proliferation. Cell proliferation is activated by HA, which increases volume and surface area for cell migration and cellular activities, stimulates receptor-mediated events.[281] HA levels have been shown to have a direct influence on cell cycle and proliferation.[61,46,331]

Chondrocytes reside and directly interact with their surrounding ECM, which comprises many different molecules that contribute to articular cartilage's unique structure and composition to perform its function as a lubricating and load-bearing surface in joints. In a recent experimental study human chondrocytes were shown that human chondrocytes in ECMs close to the native in vivo environments (HA hydrogels) supported better performances with regard to proliferation, differentiation, and migration.[241] Further, HA was shown to suppressed apoptosis in human chondrocyte in a dose-dependent manner in an interleukin (IL)-1beta-induced osteoarthritis model and following oxidative stress.[127,330]

2.1.6.1.8. Radical scavenging

Reactive oxygen species, such as hydrogen peroxide (H_2O_2), hypochlorite ion (OCl^-), hydroxyl radical ($^{\bullet}OH$) and superoxide anion (O^{2-}), are derived from oxygen and involve in both normal intracellular signal transduction and degenerative cellular processes.[140,141]

Many findings have evidenced antioxidant properties of HA, both *in vitro* and *in vivo*, by means of which it can scavenge free radicals and exert its effect on pathologies. HA acts as an antioxidant since it is a substrate of radical oxygen species (ROS) and reduces the production of ROS by chelating metal ions. HA is susceptible of ROS attack which leads to changes in structure and its degradation modulating oxidative damage.[262] Recent literature reveals a relation between HA depolymerisation by ROS and its capacity to scavenge this species and therefore to exert its antioxidant ability.[30,227,306] Among ROS, $^{\bullet}OH$ is the most effective species in HA degradation, which is in agreement with studies that show this ROS is responsible for HA depolymerisation in inflammation.[283,131,185,226,298] Elevated production of ROS and/or depletion of antioxidants has been observed in a variety of pathological conditions, including inflammatory joint diseases.[141,2,130] Specifically, studies have shown that chondrocyte apoptosis and articular cartilage degradation can be caused by elevated ROS production, contributing to the aging of cartilage and the pathogenesis of OA.[2,140,141,16,293,260] Miki et al.[223] demonstrated that HA treatment could attenuate mechanical stress-enhanced ROS synthesis and reverse proteoglycan synthesis inhibited by mechanical stress in bovine cartilage, supporting the antioxidant activity of HA. Recently it was shown that the levels of H_2O_2 and O^{2-} in the SF of OA patients were significantly reduced following i.a. therapy, and that external HA treatment of human OA chondrocytes suppressed H_2O_2-induced cell death in vitro.[325] The ability of HA to achieve antioxidative properties has been shown to be MW- and concentration-dependent, as high MW HA forms a more effective protection than low MW HA.[227,225,250,179,69] During antioxidant activity HA is known to lose viscosity and undergo modification and chain depolymerisation.[227] However, we do not yet fully understand the molecular mechanisms through which HA offers its chondroprotective effects under oxidative stress.[325]

2.1.7 HA-Characteristics and Performance

2.1.7.1 Molecular weight and performance

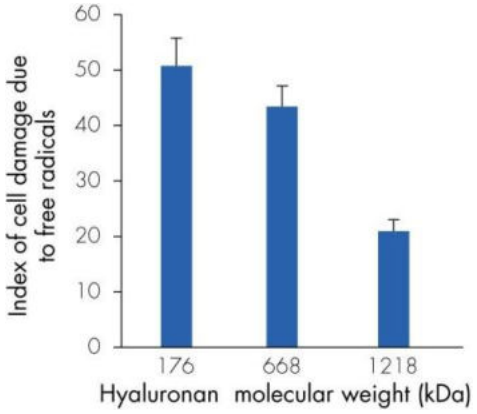
The presence of small size HA molecules in the synovial fluid not only alters its rheological properties but also facilitates the production of pro-inflammatory cytokines,[267] thereby contributing to sensitize nociceptive terminals and enhancing spontaneous and movement-evoked joint pain.[232]

In vitro and *in vivo* studies have also shown that the MW of HA has an impact on its effects.

- HA in the MW range of 0.5–1.0 x 10^6 Da partially restores SF rheological properties and fibroblast-like synoviocytes metabolism in animal models.[110]
- High MW HA inhibits phospholipase A2 (PLA_2) activity and thus protects phospholipid integrity.[234]

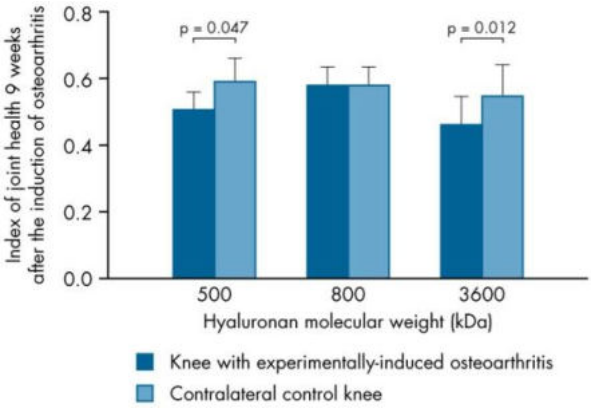
- In rabbit models i.a. administration of the higher MW HA (1,900 kilo Daltons (kDa)) was more effective than the lower MW HA (800 kDa) in inhibiting cartilage degeneration in early osteoarthritis,[169]
- 920 kDa HA is superior to 170 kDa at inhibiting lymphocyte proliferation,[243]
- HA is effective only between MW of 500 kDa and 4,000 kDa (promotion of the synthesis of endogenous HA),[115]
- Increasing HA MW (6.4, 51, 780, 4000 kDa) result in decreasing friction,[13]
- 250 kDa and 800 kDa are superior to 60 kDa at blocking proteoglycan depletion,[266]
- 1,100 kDa is superior to 160 kDa at protecting against oxygen-derived free radicals,[179] and
- 1,218 kDa is superior to 176 kDa and 668 kDa at protecting against hydroxyl free radicals.[250]

Figure 9 Molecular weight and performance of HA (Presti and Scott 1994)



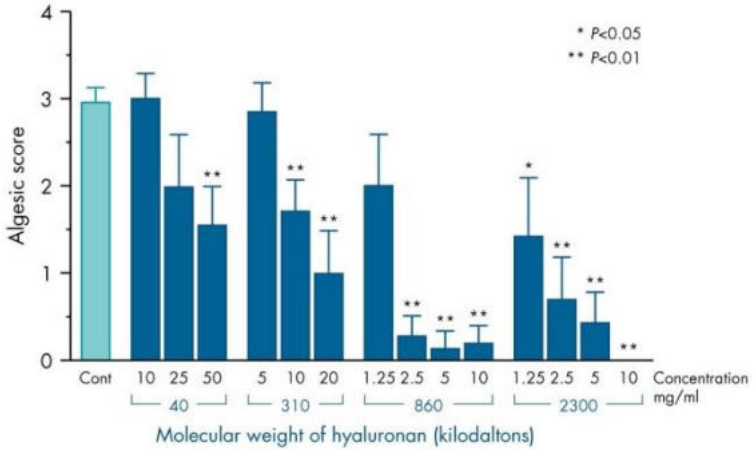
- In rats, the analgesic effect of 860 kDa has been found to be greater than that of 6.8 kDa, 40 kDa or 310 kDa and similar to that of 2,300 kDa.[121]
- The effect of HA on the inflammatory response appears to be related to its molecular size, i.e. larger HA has anti-inflammatory activity while smaller HA has proinflammatory activity.[282,57,324] HMW HA has an inhibitory effect on cytokine expression and a therapeutic effect in osteoarthritis and bacterial peritonitis.[17,247,45] Therefore, the effects of HA at inflamed sites have been suggested to be molecular weight dependent. In rats, 800 kDa has been demonstrated to have a greater protective effect against osteoarthritis than 500 kDa or 3,600 kDa.[276] In addition, 1,900 kDa has been shown to be more protective than 800 kDa.

Figure 10 Molecular weight of HA and inflammation (Shimizu et al. 1998)



- It has been shown in rats that HA with a molecular weight of greater than 40 kDa produces analgesic effect. In addition, HA of 860 and 2300 kDa produces high and long-lasting analgesia.[121]

Figure 11 Effects of different molecular weight hyaluronan (Gotoh et al 1993)



There have been several reviews[11,211,167,84] and meta-analyses[313,207] on the clinical efficacy of i.a. HA in the treatment of pain associated with osteoarthritis – including, most recently, publication by the Cochrane Collaboration of the most comprehensive meta-analysis of this class.[36] However, there have been no reports of any well-controlled, randomized clinical studies directly comparing HAs across a wide range of MWs. Several clinical studies have compared 2 or more HAs of differing MWs.

2.1.7.2 Molecular weight, cross-linking and safety

As a class, the HAs have a well-documented tolerability profile, with no known systemic effects and few contraindications or drug interactions.[132] The most common side effect noted in most clinical studies has been injection pain. Although any i.a. injection can elicit an inflammatory response, a clinically distinct reaction known as pseudosepsis (or severe acute inflammatory reaction, SAIR) has emerged after HA injections. Although it is not clear whether pseudoseptic reaction can occur with any HA, all published reports to date have been linked to the high MW cross-linked product hylan G-F 20 (Synvisc®). Whereas the manufacturing practice for HA products has similar quantitative specifications for the amount of allowable proteins within the products (generally <0.1%), qualitatively the protein contaminants in hylan G-F 20 that have been linked to potential cross-linking by formaldehyde and vinylsulfone have been shown to be immunologically distinct.[132,52] Indeed, cross-linking is known to enhance or modify the immunogenicity of antigens, and rabbit studies have demonstrated an inflammatory reaction to hylan but not to HA preparations after injection into the joint space.[270]

Interestingly there have been several case reports of patients having a SAIR to hylan G-F 20 and subsequently being treated with HA with good clinical results and without further sequelae,[114] adding further support for hylan G-F 20 specific reactions.

Antibodies to hylan have been noted in the sera of some patients.[114] In addition, the immunologic response may progress to more serious conditions such as granulomatous reactions. Cases of hylan G-F 20 related granulomatous reactions have been reported in patients who had knee OA treated with i.a. injections of this agent.[114] The reactions take the form of a chronic inflammation of the perisynovial area and surrounding tissues and are shown by histologic evaluation to include histiocytic and foreign body giant cells: A recent report also characterized this response as a pseudosarcoma.[164] A recent animal study comparing the biocompatibility of linear 0.9 x 10^6 Da HA (Supartz®, Seikagaku Japan) and saline with cross-linked hylan G-F 20 has confirmed these clinical observations.[268] After intradermal injection in guinea pigs and intramuscular injections in rabbits, hylan G-F 20 induced definitive macroscopic changes in guinea pigs by day 14 and in rabbits by day 28. Severe granulomatous inflammation in guinea pigs and acute inflammation with minimal infiltration of macrophages and foreign body giant cells in rabbits were seen on histologic assessment. Furthermore, specific antibodies against hylan G-F 20 were demonstrated in guinea pigs by passive cutaneous anaphylaxis, and substancial deposits of immunoglobulin G on hylan G-F 20 were evident by immunohistochemistry.[268]

In its native state HA is a linear polymer usually with a MW in the excess of 10^6 Da. Under inflammatory conditions, HA has been shown to be more polydisperse, with a preponderance of lower MW forms.[263] The generation of low MW HA fragments signals a disruption of the normal homoeostatic environment and alerts the immune system that significant tissue damage has occurred at the site of inflammation.[15] If unabated, the generation of low MW HA fragments may contribute to the pathophysiology of chronic tissue inflammation. The lower MW fragments have biological activity to promote inflammation.[162] Low MW HA has been reported to induce pro-inflammatory cytokine gene expression in mast cells, monocytes and macrophages, and could potentially exacerbate inflammation in patients with inflammatory disorder.[235,220,145]

2.1.7.3 HA-concentration and performance

HA concentration in SF of human knee joint ranges from ~2–4 mg/ml.[28,74,213] which grossly corresponds to a total amount of 4-8 mg HA in healthy subjects where the volume of SF is assumed to range from 0.5-4 ml.[74,23,178]

HA injections are frequently used as a treatment for joint osteoarthritis.[111] The ideal dose and injection frequency has not been determined yet in randomized controlled clinical trials. Another point to take into consideration is the fact that different HAs could give different results, since they have a different composition.

First results from a dose-finding study in horses with surgically-induced arthropathy showed that the 20 mg / 2 ml dose of HA restored normal joint function within one week after treatment, while the 5 mg / 2 ml (0.25%) and 10 mg / 2 ml (0.5%) doses did not cause any significant changes.[113]

The justification for using the higher concentration of 40 mg / 2 ml used in OSTENIL® PLUS was to reduce number of injections necessary to obtain improvement in osteoarthritic joints complaints.

2.1.7.4 Summary

Taken together, the data available suggest that in order to maximise the beneficial effects and the safety of treatment with exogenous HA, the structure and the molecular weight used should be similar to that chosen for OSTENIL® PLUS (1.6 kDa, linear unbranched chains).

2.2 Absorption, distribution, metabolism and excretion of exogenous hyaluronan in humans

HA is found ubiquitously in the ECM of all vertebrate tissues, although its concentration and binding partners vary. It is synthesized in the most tissues and present in connective tissue, such as skin, vitreous humor, cartilage, and umbilical cord. The largest amount is found in the intracellular matrix of skin and musculoskeletal tissues,[103] but the largest single reservoir is the SF of the diarthrodal joints, where concentrations of 0.5 – 4 mg/ml are achieved, with an estimated total concentration of 4-8 mg/knee[23], being slightly higher in younger adults than in older adults.[26,29,74,99,182,228] HA is also a major component of the vitreous body of the eye, but at a lower concentration of approximately 200 µg/ml, in the phakic human eye vitreous,[189] and in the aqueous humor being only about 1 µg/ml.[239] The concentration of HA in the human body varies greatly from about 4 g/kg in umbilical cord, 0.2 g/kg in dermis[203], and about 0.1-18 µg/ml in the lymph fluid.[296] Distribution of HA in the connective tissue gives the extracellular matrix much of its characteristics. The HA content of human articular cartilage is about 500–2500 µg/g.[147] Human skin contains approximately 400–500 µg HA/g tissue, mostly in the dermis.[294] Fetal skin and young skin have higher HA contents than older skin. Other organs have much less HA. Laurent and Tengblad reported HA contents of approximately 1–100 µg HA/g wet tissue weight for most organs.[188] The total body content of HA in a 70 kg human is approximately 15 g.[284] In the blood serum of healthy human adults, the concentration of HA is usually between 10 and 100 ng/ml, mostly 20–40 ng/ml, and averaging about 30 ng/ml.[82,102,188,296] Normal human urine also contains a low level of HA, around 100–300 ng/ml,[188] and human milk similarly contains HA at about 200–800 ng/ml.[143]

Measurement of HA content is of continuing high interest, because there are multiple studies correlating changes in HA content with tissue remodeling and pathological processes. While the normal HA concentration in human serum is usually <40 ng/ml, it is elevated (>46.5 ng/ml) in hepatic cirrhosis,[71] in rheumatoid arthritis[126,269] (highly variable; reports up to nearly 200 µg/ml, but more generally between 0.07 and 6.4 µg/ml[70]), in ankylosing spondylitis[126] (7–13 µg/ml), and in osteoarthritis[126,175] (0.04–2.3 µg/ml).

The metabolism of HA is very dynamic. It has been estimated that almost one-third of the total hyaluronan in the human body is metabolically removed and replaced during an average day.[137] The half-life of a HA molecule in the blood is very short, only a few minutes.[137] Some cells, such as chondrocytes in cartilages, actively synthesize and catabolize HA throughout the lifetime of the tissue. Synthesis is usually balanced by catabolism, thereby maintaining a constant concentration in the tissue. Metabolic studies have shown that the half-life of a HA molecule in cartilage is normally 2-3 weeks.[137] Keratinocytes in epidermis are another example of cells that actively synthesize and catabolize HA. In this case, the half life of a HA molecule is surprisingly short, less than a day (~12 hours). The cells in the dermis actively synthesize more HA than they catabolize,

much of which escapes only to be rapidly captured by receptors on reticuloendothelial cells in lymph nodes and liver, which internalize them for subsequent catabolism in lysosomes. Injected HA and its derivatives undergo local degradation.[148] The metabolites are then further catabolized by the liver into carbon dioxide and water. Reactive oxygen species produced by keratinocytes are probably involved in the catabolism of epidermal HA.[4]

2.2.1 HA excretion

The turnover of HA is tissue dependent.[99] Extravascular HA concentration far exceeds that in the bloodstream because of rapid degradation by hepatic and other endothelium after lymphatic discharge.[83,185,255,256,296] Thus, the intravascular HA pool is being constantly removed, whereas the extravascular pool serves its physiological tissue functions.[103,198] In dense structures, HA is more likely to be degraded in situ rather than drained by the lymphatic system, since there are no lymph vessels.[288] In the normal body, depending on its location, most of the HA is catabolised within days. Besides direct enzymatic degradation in the extracellular space by hyaluronidases and non-enzymatic depolymerisation (e.g. by exposure to radicals), there are two pathways in the body that are engaged in HA catabolism: local turnover (internalization and degradation within tissues),[171] and secondly, release from the matrix, drainage into the vasculature and clearance in lymph nodes, the liver and the kidneys.[317]

Large amounts of HA are transported by the lymphatic vessels to the bloodstream,[186,187,296] where it is degraded to low-molecular products.[83] HA in lymph is polydisperse but contains a large fraction of high-molecular weight (MW > 10^6).[296] When entering the bloodstream, 85–90% of HA is mostly taken up by the liver where catabolism takes place in the endothelial cells and HA breaks down into acetate and lactate and is eliminated.[279] Circulating HA is mainly internalized by specific receptors on the endothelial cells in the liver sinusoids,[99,100,96,102,183,279] and HA is degraded intracellularly in the lysosomes.[183,279] At high serum level of HA, Kupffer cells of the liver also probably take part in the clearance of the polysaccharide.[8] A small fraction, about 1-2%, and constituting the smallest molecules, is excreted by the kidneys.[186,187] Same circulating HA is also taken up by the spleen and other lymphoid organs.[97,100,296] The liver endothelial cells preferentially bind and process the large polymers,[183,296] and the remaining circulating HA is therefore of relatively low molecular weight (weight-average 10^5 - 2 x 10^5 kDa).[296] HA is normally found at low concentrations in the circulation, because it is rapidly cleared from the bloodstream.[83] Low molecular fractions are excreted in the urine.[102,186] Investigation of urinary excretion in healthy subjects was 330 µg / 24 h and correlation with body weight.[186] The MW of the main fraction of urinary HA was in the range of 4000 to 12,000 in accordance with the hypothesis that it originates from blood and arises by glomerular filtration.[186] A small fraction was of higher molecular weight and could have been produced in the urinary tract. HA in male and female urine displayed the same molecular weight distributions.[186]

The endogenous input from tissues via the lymphatics to the circulation is estimated to be 10–100 mg HA per day.[82] In healthy humans the circulating plasma pool of HA is fairly constant with a concentration of 10–100 µg/l in adults[82] but there is a significant increase with old age.[82,202] HA is rapidly cleared from the circulation: The plasma half-life is 2–5 min in healthy man and the turnover

corresponds to the calculated endogenous input.[102] The maximal elimination rate (V_{max}) in healthy humans has been estimated to be about 180 µg/min, which is 10 times as high as the normal endogenous production rate.[82]

Elevated plasma concentrations of HA have been observed in several disease states. At normal serum concentrations HA has a very short half-life of 2-6 min in rabbits, sheep and humans.[100,102,191] Analysis of serum and plasma from adult animals (rat, rabbit, dog, pig, goat, sheep, cow and horse) gave HA concentrations of the same order or higher than in human serum.[82]

2.2.2 Transsynovial flow

Synovium is the main barrier to the transport of molecules in SF and plasma, such as lubricant molecules and plasma proteins, into and out of the synovial joint. Synovium is a vascularized, thin sheet of connective tissue with fibroblast-like (type B) cells and macrophage-like (type A) cells within an ECM composed primarily of HA, collagen, and proteoglycans. The blood-joint barrier has been modeled as a double barrier, in series, consisting of synovial interstitial space that limits diffusion of small molecules, and microvascular endothelium that limits transport of proteins.[197,277]

Fluid flow through normal rabbit synovium occurs through interstitial spaces that range from 0.1 - 11.8 µm and average ~2 µm,[194] which has a hydraulic conductivity of ~10^{-11} $cm^4s^{-1}dyne^{-1}$ [193] The synovium matrix hydraulic conductivity, a measure of ease of fluid flow that depends on matrix content, is generally low, but increases with inflammation and increased pressure. At elevated i.a. pressure, the matrix stretches, increasing surface area and reducing fluid path-length.[194] The concentration of matrix constituents, including collagens and glycosaminoglycans (GAGs), are altered due to the joint capsule stretch at elevated i.a. pressures, effectively diluting their concentration, explaining some of the increased conductivity of synovium.[251,252] Diffusive and convective passive transport of molecules occurs by size-selective molecular sieving through synovial ECM, and can be modeled as transport through pores with a calculated pore radius of ~20 – 90 nm.[122,264,273] HMW lubricant molecules are selectively retained in the joint, as the reflection coefficient of synovium to HMW HA is ~57 – 75%.[265] Injecting exogenous HA confirms the importance of matrix molecules in determining synovium hydraulic conductivity.[64]

Levick and co-workers[196,217,264] have made a series of studies of the role of fluid flux through the synovium and its effect on the synthesis of HA. They show that besides providing lubrication, HA greatly attenuates transsynovial fluid loss, a phenomenon called ‘outflow buffering’, by a reduction of the driving force via a concentration polarized layer at the surfaces of the joint capsule.[65,218,264,322] This prevents draining of the SF rapidly out of the joint cavity when pressure is raised, as it is during joint flexion and in arthritic joints.[66] This ability to retain fluid in the joint by HA depends on the amount of HA present and declines if the HA molecular weight is reduced.[65] This finding is consistent with previous studies performed in vivo with fluoresceinated HA showing a minimal penetration of HMW HA in the synovial lining following i.a. injection.[17] Changes in the synovial joint that occur in OA and injury, including decreased HA content and joint tissue degeneration, are likely to alter the formation of this layer.

Molecular transport through synovium is markedly altered in diseased synovium. In arthritis, the size of SF HA is reduced, with an increased rate of HA loss from SF.[264] Although synovial membrane inflammation is also recognized as a key factor in OA pathophysiology, the transport characteristics of synovium in OA are less affected than in rheumatoid arthritis (RA), with apparent permeabilities to proteins over a range of sizes (molecular radii ~3 – 9 nm) over threefold higher in RA compared to OA.[242]

2.2.3 Intravenous administration

The pharmacodynamics and elimination kinetics of escalating doses (1.5-12 mg/kg) of HA infusions were studied in healthy human volunteers by **Hamilton et al. (2009)**.[135] The primary objective of this single-dose, dose escalation, and pharmacokinetic study was to evaluate the pharmacokinetic profile of HA after 120 min iv. infusion of a sterile 1% HA solution at escalating doses of 1.5 mg/kg, 3.0 mg/kg, 6.0 mg/kg and 12 mg/kg. Each dose subsequent to the 1.5 mg/kg dose was administered following a 7-day washout period. In each case a total volume of 250 ml of stock solution of HA, diluted appropriately with 0.9% sodium chloride, was administered over a period of 120 min. The average MW of HA used in this study was 276.6 (hereafter referred to as 280) kDa after heat sterilization (which fragments HA slightly), and 519.7 kDa prior to heat exposure. Blood was sampled from all volunteers at 2, 1.5, 1, and 0.5 h before administration and at 2, 4, 6, 10, 14, 18, 22, 32, 38, 50 and 74 h after administration of the HA solution. Blood samples were collected and serum HA levels were measured. Blood collected from a subset of 6 subjects (3 females and 3 males) at 0, 1, 4, 12, 24 and 72 h post-infusion of each HA dose were analyzed to determine the molecular weight profile of serum HA and to assess HA binding by T cells, B cells and blood monocytes. Measurement of these parameters was the first step in assessing pharmacodynamic disposition of HA and as described below. Samples were not segregated according to gender. In summary, the present study describes dose-dependent (Michaelis-Menten) elimination kinetics of escalating doses of HA in healthy volunteers. Regardless of the mechanisms by which HA is eliminated, this study demonstrates that healthy human subjects tolerate escalating injected doses of HA and sustained serum HA levels with no treatment-related side effects, providing a favorable safety profile for use of HA in drug delivery/enhancement, white cell trafficking, or other uses. Processes that increase HA binding to cells including disease states or as noted in the present study, exposure to HA, is associated with altered elimination kinetics and it will be interesting to determine whether or not detection of changes in elimination kinetics can be used to monitor HA-mediated disease processes.

A HA-loading test has been developed for assessment of HA kinetics and applied in patients with liver and joint diseases by **Lindqvist and colleagues in 2000**.[205] This test describes the metabolic process of HA but cannot define the specific contribution of different organs. A method for labelling of HA with the short-lived positron-emitting radionuclide [^{11}C] has been published and in this study applied in healthy subjects and liver diseases. Positron emission tomography (PET) was used for the regional assessment and quantification of [^{11}C]-HA uptake in 3 healthy subjects, 4 patients with alcoholic liver cirrhosis, 1 with alcoholic hepatitis and 1 with liver steatosis. After intravenous (iv.) administration of 60 MBq of [^{11}C]-HA, a 55-min PET scan was performed over the liver and plasma

radioactivity was analysed. Rate constants describing the transport of the [^{11}C]-HA tracer from plasma to the liver were calculated. High uptake was observed in the liver combined with a rapid elimination of tracer from plasma. The liver uptake rate (k1) was significantly lower in patients (0.018 min-1) than in healthy subjects (0.043 min-1, p = 0.002). The rate constants seem to be related to the severity of the disease as defined by the Child-Pugh score. The study suggests that PET with [^{11}C]-HA could be an accurate method by which to assess liver dysfunction, in conditions where endothelial cell function is impaired. The possibility of quantification over extended portions of the body also opens up possibilities to explore regional differences in liver function and to assess other elimination routes of HA.

Torsteinsdottir et al. (1999)[304] evaluated the benefit of determining the maximal elimination rate (V_{max}) and the endogenous production of HA in relation to the basal HA concentration (C_0) in RA patients; and to evaluate the compatibility of a new model for HA kinetics, taking renal elimination into separate account in the overall clearance of HA from the blood. The calculations of production and elimination of HA were based on the HA loading test, which was performed in 21 patients with RA and 15 healthy controls. A blood sample was drawn before the loading test, followed by an iv. injection of HA as a single bolus dose of 7.5 mg. Blood samples were taken regularly during the next 60 minutes. A theoretical model with computational analysis of the data collected was used for calculating HA production and elimination. Patients with RA had significantly higher C_0 than healthy controls, although in 10 of 21 patients C_0 was within the normal range. The RA patients also had higher V_{max} than healthy controls, but the difference was not significant. The calculated production of HA was increased in RA patients ($p = 0.001$) and correlated with C_0 ($p < 0.0001$). The new model for HA kinetics, in which the renal elimination was taken separately into account, proved to be more compatible than the previous model. It was concluded that the HA loading test can help determine whether the increased serum level of HA in RA patients is due to a high production or reduced elimination of HA or both.

The purpose of a study performed by **Lindqvist et al. (1997)**[204] with various models of HA kinetics has been to find the most appropriate model for estimation of parameters which characterize liver endothelial cell function. Five theoretical models for serum HA distribution and elimination were evaluated by computer analysis of serial measurements of the mass concentration of HA in serum following an iv. bolus dose. Three of the models were based on one-compartment distribution of iv.ly injected HA. Model 1A, with assumed first-order elimination, was found to be compatible with measured data and had identifiable parameters. Model 1B, with assumed non-linear Michaelis-Menten kinetics, was also found to be compatible but the Michaelis-Menten constant (K_m) was not well determined. In model 1C, with non-linear Michaelis-Menten elimination kinetics, K_m was set to a fixed value of 340 µg/l, and the remaining parameters were well determined and the model was found to be compatible. Two models with an assumed two-compartment distribution of iv. injected HA, were not acceptable due to unidentified parameters not discriminating between patients and healthy persons. In conclusion, model 1C, with one-compartment distribution and non-linear Michaelis-Menten kinetics, best fulfilled the criteria of validity and was accepted for further evaluation of clinical materials.

Based on results from a study in sheep **Lebel et al (1994)**[192] evaluated the elimination of iv. injected HA from the blood in 12 healthy volunteers to investigate whether iv. injected HA was eliminated by Michaelis-Menton type kinetics in human, too. Three consecutive 30 min infusions of HA were given, separated by 90 minutes washout periods. Blood samples were taken before, during and after each infusion and the plasma HA concentration was determined. The deposition of HA was modelled according to a Michaelis-Menten kinetic model which included natural synthesis of HA. Michaelis-Menten constant K_m and maximum metabolic rate was estimated to 0.34 ± 0.13 µg ml^{-1} and 3.48 ± 0.97 µg min^{-1} kg^{-1} body weight, respectively. The endogenous input was calculated to be 24 ± 11 µg min^{-1} and was found to correlate to the age of the subjects ($p < 0.05$). As the baseline HA concentration was 0.031 ± 0.21 µg ml^{-1}, the rate of elimination was linear in the normal concentration range. The calculated volume of distribution was about 75% higher than a weight-estimated plasma volume. The total amount of HA excreted by the kidneys during the study period was 394 ± 77 µg, which corresponded to approximately 1.7% of the total input of HA into the circulation during the experiment.

Single compartment models either with linear elimination of HA or with Michaelis-Menten elimination kinetics fitted serum data of iv.ly injected HA and could be used to describe the kinetics of circulating HA.[102,191,192,200] A clinical study in liver and connective tissue diseases has been performed for quantitative characterization of residual functional capacity of the liver was performed by **Lindqvist et al. in 1992**.[201] The serum HA disappearance data, after an iv. bolus injection of HA, were evaluated in terms of model-based parameters. The loading test was performed in 10 healthy persons (basal serum hyaluronan concentration, C_0, 24.9 ± 8.9 µg/l [mean ± S.D.]), 6 patients with joint disease (62.3 ± 41.1 µg/l) and 19 patients with liver disease (206 ± 214 µg/l). The highest maximum Michaelis-Menten elimination rate (V_{max} = 287 ± 86 µg/min) was found in patients with joint disease, significantly higher than in healthy persons (V_{max} = 179 ± 16, $p = 0.0015$) and in patients with liver disease (V_{max} = 149 ± 59, $p = 0.0002$).

The kinetics of labelled HA (tritiated on the acetyl moiety) after a single iv. administration to 4 healthy volunteers has been described by **Fraser et al (1984)**.[102] No febrile or other types of reactions were observed in the treated subjects. There was a rapid fall in radioactivity with over 90% decline within the first 10 min. The elimination half-life in plasma was calculated to be between 2.5 and 5.5 min. in the 4 subjects (estimated plasma volume: 2560-3430 ml). After the first 10 min. there was a slowing down in the loss of radioactivity, which disappeared after longer periods of time. Elimination was mainly renal for fractions with a molecular weight of less than 25,000 Da. Circulating HA was rapidly concentrated in the liver (88% of the injected dose found in the liver 20 min. after the injection) where it was rapidly degraded. An estimation of tritium-labelled H_2O in urine suggested a very rapid onset of the oxidative catabolism of hyaluronan. Accordingly, approximately 55% of the acetyl residues of the injected HA were completely oxidized after 3 hours and 85% after 1 day. The daily turnover of HA was calculated to be about 150-700 mg. The mechanisms for the removal of HA from the circulation are extremely efficient and mean that at the doses used for i.a. injection in man, it is practically impossible that the drug would accumulate in organs and tissues other than those of the articular cavity. In addition, even if there was a wrong injection of 5-20 mg HA directly into the circulation, this would cause only a slight and transitory increase in the levels of circulating HA.

aised concentrations of HA in serum have been observed in patients with inflammatory joint disease,[80,79,81,199] where increased production and/or increased degradation of connective tissue is likely to be the mechanism for the observed elevation of serum HA.[184] Turnover studies in rheumatoid arthritis have shown that the biological half-life (2 – 3 min) of intravenously injected [^{3}H]-hyaluronan is unchanged compared with healthy individuals but that the total turnover is increased.[101]

2.2.4 Intra-articular administration

For a drug with a direct mode of action, local administration offers several advantages over systemic delivery, including increased bioavailability, reduced systemic exposure, fewer off-target effects and adverse events, and lower total drug cost.[88] Being discrete cavities, most diarthrodial joints are well suited to local drug delivery via i.a. injection. Most common disorders of diarthrodial joints - with RA the exception - are not accompanied by clinically significant extra-articular manifestations, which make the prospect of local therapy particularly appealing.

Systemically delivered, soluble substances enter the joint space via the capillary network of the sub-synovium, which is highly vascularised. For certain indications, it is necessary to deliver therapeutics to cartilage. Because cartilage is avascular, it is inefficiently targeted by systemic delivery of drugs, which must first reach the SF and then diffuse through the cartilagenous ECM. I.a. therapy improves delivery to cartilage and can thus increase therapeutic efficacy. To enter the joint space from the synovial circulation, solutes need to pass through two layers of resistance in series: the capillary wall and the ECM of the synovial intima.[277] The endothelial lining of the subsynovial capillaries is fenestrated, with the fenestrations orientated towards the joint space; this orientation facilitates the directed exit of solutes from these capillaries. Because the synovium has no basement membrane to impede molecular transit,[170] small molecules pass freely through the vascular endothelium, and the major determinant of their entry into the joint space is their rate of diffusion through the synovial interstitium. With this entry route being dependent on the small pores of the capillary endothelium and the tight spaces of the interstitial matrix, unimpeded transport through passive diffusion occurs only for small molecular weight compounds, typically <10 kDa. For larger molecules, the endothelial lining imposes a size-dependent sieving effect on the rate of passage.

Molecules entering or leaving the joint space must traverse both the capillary endothelium and the interstitial space between the synoviocytes.[197] The joint-space ‘dwell time’ of a therapeutic agent is influenced by the rate at which the molecule reaches and is cleared from the SF. The former parameter depends on the size and route of administration of the drug, whereas the rate of efflux of a soluble agent is largely independent of these properties. Although entry of macromolecules into joints is constrained, their removal from joints occurs via the lymphatic system in a fashion that, unlike their entry, is independent of size.[88] Because lymphatic drainage is highly efficient, the i.a. dwell time in joints is typically a few hours or less. This timescale presents obvious problems when attempting to treat chronic joint disorders with large molecules. Although i.a. injection can circumvent the entry restrictions imposed by synovial sieving, it cannot avoid rapid lymphatic clearance of a therapeutic agent. Concentration–time profiles were described by a triexponential

expression and the terminal part of the curve represented systemic absorption rather than elimination (termed 'flip-flop case'). Interestingly, high molecular weight drugs (HA and a glycoprotein, ulinastatin) administered into joints also demonstrated slow elimination from the joint or 'flip-flop' kinetics.[204,236] Intra-joint half-lives illustrate the challenges facing i.a. therapy, especially for chronic conditions.

Traditionally, i.a. injections have been performed using anatomical landmarks to identify the correct trajectory for needle placement. However, different anatomical-guided injection techniques have yielded inconsistent i.a. needle positioning due, in large part, to the fact that the physician cannot directly visualize the area of interest, and variations in anatomy are common.[40] Incorrect needle placement has been partially attributed to variable clinical outcomes.[85,159,163,177,219] Accuracy of injection is an issue, even for large, accessible joints such as the knee where as many as 50% of intended i.a. injections by experienced physicians can end up in extra-articular locations.[159,163] The results of a recent analysis demonstrate that use of imaging guidance improves the accuracy of i.a. injection in large joints including the knee.[40] Overall, the use of imaging guidance, in particular ultrasound, improves the accuracy of correct needle placement, including the knee. These findings confirm and extend similar conclusions reached by **Daley et al.**[75] in their systematic review of injection accuracy. Relative to corticosteroids that act to quell the inflammatory reaction in i.a. and peri-articular structures, injection accuracy may be particularly important for HA because this therapeutic agent directly confers a number of protective properties to joint fluid.[40]

While numerous disease-modifying drugs have been developed, the widely used route of systemic administration may not achieve therapeutic effects in the joint space because of relatively slow and nonspecific transport of molecules to the joint tissues.[6] As OA is a disease often localized to a single joint, local delivery of a therapeutic may be preferred.[53,109,181] I.a. injection is widely used for delivery of corticosteroids and HA,[45,53,109] although their disease modifying actions are nonexistent, not well understood, or not widely accepted. There is increasing interest in the delivery of disease-modifying agents directly to the joint space for the treatment of OA, to achieve maximal drug activity and residence time in the joint tissues.[181]

2.2.4.1 Humans

In human knee joint SF, the $t_{1/2}$ of HA is 13.5 h[103] which is similar to the value (13.2 h) obtained in healthy rabbits.[49] It can therefore be assumed that the pharmacokinetic studies carried out in animals are sufficiently predictive of the metabolic fate of HA in man to justify, from the ethical point of view, not carrying out i.a. studies with labelled HA in humans. As the product is injected directly into the joint cavity, the problem of absorption by the target organ does not arise; all the injected HA is distributed into the SF and follows the same metabolic fate as endogenous HA. The amount of HA injected to humans in the clinical trials is 20–40 mg and this is well within the range for HA quantity physiologically present in the joint cavity. Even though exogenous HA does not remain in the joint for very long, this may be sufficient to stimulate the de-novo synthesis of good quality high molecular weight HA by human synoviocytes which may explain the long term clinical benefits.[2]

The short half-life of i.a. administered drugs can be explained by the synovial ultra-structure which offers little barrier to the diffusion of molecules in and out of the joint.[128] The synovial cavity is incompletely lined by a thin layer of synoviocytes. Type A synoviocytes function as macrophages, clearing debris generated within the joint by phagocytosis.[238] Type B synoviocytes (70%) closely resemble fibroblasts and synthesise HA, the primary lubricant within SF.[12] Knight and Levick (1984)[170] showed that the synovial surface consists of a discontinuous layer of synoviocytes (covering 80% of the synovial lining) with wide intercellular gaps measuring 0.1–5.5 µm and no basement membrane. Effectively there is direct continuity between the joint cavity and intercellular spaces of the synovium.[34] Underlying capillaries, a mix of fenestrated and non-fenestrated, are very superficial with a modal depth of 5 µm below the synovial surface.[170] As a consequence of the synovial ultrastructure there is free trans-synovial flux of water and solutes such that the volume of fluid in a joint cavity is completely replaced many times over in 24 h.[109] Small molecules (MW < 10,000 Da) such as lactate, cytokines and most drugs, including local anaesthetics, steroids and NSAIDs, diffuse easily through the interstitium and across capillary walls and are therefore in equilibrium between SF and plasma.[109,237] Albumin also diffuses easily through the interstitium; the reflection of albumin by the synovium is negligible for practical purposes.[195] SF is therefore a dialysate of plasma plus HA secreted by type B synoviocytes. With synovitis there is often increased blood vessel permeability and subsequent leakage of serum proteins which promotes synovial oedema, increased SF volume and the accumulation of fibrin on the intimal surface.[104,318]

Lindqvist and co-workers (2002)[204] investigated the elimination of stabilized HA following i.a. injection into the knee joint in 6 healthy male human volunteers. Subjects received a single i.a. injection (3 ml; 20 mg/ml) of [^{131}I]-labeled non-animal stabilized hyaluronic acid (NASHA). Radioactivity in the knee, blood, urine and over the liver was measured with gamma counters for 3 weeks post-injection; magnetic resonance and gamma camera imaging of the knee were also performed at 24 hours post-injection. Radioactivity uptake data were tested for conformity of fit to different mathematical models. Elimination of [^{131}I]-labelled NASHA from the knee was characterized by a fast initial phase and a slow late phase, and conformed to a three-exponential-function model with elimination half-lives of 1.5 hours, 1.5 days and 4 weeks. Radioactivity distribution within the knee joint was homogenous, and no local leakage was observed. Hepatic radioactivity uptake was low, but significantly above background levels, for the first 2 days post-injection, before declining to background levels. Visual imaging indicated an increase in i.a. fluid volume at 24 hours post-injection. The elimination kinetics of [^{131}I]-labelled NASHA from the human knee joint was described by three distinct phases, with half-times of 1.5 hours, 1.5 days and 4 weeks. Most likely, the last value reflects the true half-life of NASHA following i.a. injection since the labeling method used causes minimal modification of HA.

2.2.4.2 Animal models

The ADME (absorption, distribution, metabolism, and excretion) pattern of HA following i.a. administration of the labelled substance in rabbits was investigated in a study by **Komatsu**

(1999)[174]. The animals were given an i.a. injection of 1 mg/kg BW of a C^{14} -glucose labelled HA with a molecular weight of approximately 2 Mio Da. The passage of this HA into the circulation was studied by measuring the concentration in blood and in the joint space. The kinetics of entry and elimination from the blood of i.a. hyaluronic followed a first-order model. Samples of SF, synovial membrane and joint cartilage were removed 24 and 72 hours after the i.a. injection of HA, in order to follow the appearance of different molecular weight fractions into these tissues. The molecular weight was determined in each case by means of gel filtration chromatography, with a column calibrated with HA of a known molecular weight of 2 million, as well as 300 and 500 kDa. The distribution of radioactivity in the SF showed a peak for the 2 MioDa equivalent 24 and 72 hours after the injection, whereas in the synovial membrane there was a peak of 300 kDa after 24 hours and of 50 kDa after 72 hours. The distribution of radioactivity in the joint cartilage showed peaks for the 2 million and 300 kDa equivalents after 24 hours, whereas a 50 kDa equivalent peak appeared 72 hours after the injection. Information about the re-synthesis of endogenous substances from HA metabolites was obtained by measuring the radioactivity in acid-soluble lipid and protein fractions from plasma, blood cells and the liver 72 hours after the injection. Results showed that HA was metabolised to C1-units, which were then incorporated into the synthesis of endogenous molecules.

Further studies with labelled HA with an MW greater than 6×10^6 was shown in rabbit knee joints to have a mean $t_{1/2}$, of 13.2 h and hourly turnover rate of 5%. Corresponding figures for HA of 0.09×10^6 MW were significantly different (10.2 h and 7%) though clearly not changed in proportion to the 60-fold difference in MW.[49] Studies with HA of high MW in sheep hock joints showed a mean $t_{1/2}$ of 21 h and hourly turnover of 3.4%.[98]

2.3 Clinical Background

2.3.1 Osteoarthrosis

With worldwide estimates that over 10% of the population above 60 years is affected by OA, the impact of this health problem is still underestimated.[153] Even if OA can involve single and/or multiple peripheral joints, including the knee, hip, and hand[42], the knee is the most common joint localization of symptomatic OA[244]. OA is characterized by focal areas of damage to the cartilage surfaces of synovial joints and is associated with remodeling of the underlying bone. OA is usually age-dependent and the prevalence increases with age. Genetic as well as acquired factors, which include joint trauma and life-style-associated risk factors (such as obesity and excessive joint use in occupational or leisurely activities) can contribute to the onset and progression of the disease.[42,152] The socioeconomic impact of OA is high and, because aging and obesity are increasing in the population, costs for OA management will also likely increase in the future.[190,153]

Osteoarthrosis has been defined as “a progressive disease of synovial joints that represents failed repair of joint damage that results from stresses that may be initiated by an abnormality in any of the synovial joint tissues, including articular cartilage, subchondral bone, ligaments, menisci (when present), periarticular muscles, peripheral nerves, or synovium”.[180] OA is now regarded as a

disease of the whole joint, and this must be taken into consideration when evaluating new and old treatments.[91,208] Although many researchers support the idea that OA is a disease of articular cartilage, there is an ongoing debate about the function of subchondral bone in OA[212,289,93,59,116] and increasing support for the theory that subchondral bone should be a priority target of OA treatment.[59]

A classical view considers OA primarily as a disease of the articular cartilage.[297] Fibrillations and ulcerations, loss of extracellular matrix and cell death occur in this tissue. Damage in the articular cartilage is typically characterized by fissures in its superficial layer that gradually extend into the deeper layers and finally lead to severe loss of cartilage structure and volume. This will then result in secondary changes to the underlying (subchondral) bone and to other tissues of the joint. However, recent observations suggest that OA should be approached as a failure of the entire joint organ and that early disease-related changes can be detected both in the cartilage and in the subchondral bone.[44,209]

OA is classically defined as a progressive degenerative rather than an inflammatory articular disease with considerable implications for the affected patients: severe pain limits joint function and thus also the patient's range of movement and quality of life. Degenerative processes lead to atrophy of the hyaline articular cartilage and to the formation of osteophytes and bone cysts at the terminal bone. Cartilaginous detritus and inflammatory factors irritate the inner surface of the joint and cause particularly painful episodes of the disease. HA, a biopolymer that gives the SF its typical viscosity, is reduced qualitatively (through depolymerisation) and quantitatively (in the diluted serous SF). This degradation of the HA upsets the synovial balance of the joint and results in the harmful pathophysiological effects.

The existence and relevance of inflammatory changes in OA can be described with the expression 'activated osteoarthritis'. In this phase of osteoarthritis free radicals, especially so called ROS, can cause depolymerisation of HA in the SF of the joint,[30] resulting in an earlier elimination of HA from the joint space. In vitro studies show that several agents can reduce this depolymerisation process.[30]

While diagnosis of OA is mainly based on clinical and radiological features,[9] pain represents the first and prevailing symptom that leads patients to seek medical advice. Stiffness is generally linked to physical inactivity, while loss of movement and function can limit the patient's daily activities. Symptomatic OA is often associated with depression and disturbed sleep, greatly reducing patients' quality of life.[42]

2.3.2 Current treatments

To date, there is no known cure for OA nor is there a disease-modifying agent. The best treatment for OA to reduce pain and improve tolerance for functional activity is not yet clear, and an early diagnosis still plays a key role in the management of this condition. Current treatment options for OA are limited. In addition to physiotherapy, regular exercise and weight loss, pharmacological interventions are restricted to symptomatic relief with local (i.a.) injections of corticosteroids and/or systemic administration of analgesics and non-steroidal antiinflammatory drugs (NSAIDs).[42]

The current treatment of OA is based on symptom management, primarily pain control, and relies on the combination of non-pharmacological and pharmacological approaches that are generally tailored to the patient's needs and risk factors. Joint replacement surgery or a joint salvage procedure may be considered for selected patients with severe symptomatic OA who have not obtained adequate pain relief and functional improvement from medical therapy.

Current therapies are based on a critical appraisal of existing guidelines, a systematic review of research evidence, and the consensus opinions of an international, multidisciplinary group of experts.[214]

NICE guideline[231] point out

- that very little data exist on the use of pharmacological and non-pharmacological treatments for osteoarthritis in very old people where treatment recommendation should be seen in relation to risks associated with comorbidities;
- that data from clinical studies for treatment recommendations should take into account combinations of several treatments because most people with OA have symptoms for many years and over the time they will receive several treatments;
- that most clinical trials are of short duration but most patients with OA have symptoms for many years;
- that benefits of treatments (if in combination or not) should be seen in relation to particular anatomic site;
- that current research evidence focus on treatment of knee joint OA , and to a lesser extent hip or hand osteoarthritis, but there are very few trials that examine other prevalent sites of osteoarthritis such as the first metatarsophalangeal (bunion) joint, the mid-foot joints, the ankle or the shoulder;
- that evaluations of clinical data normally take not into consideration
    - the common but poorly researched problem that patients with OA have pain in more than one joint;
    - that mechanism that causes pain may differ in people with single joint complaints compared to several affected joints;
    - that bilateral or symptoms from additional joints may influence evaluation of 'index' (most painful) joint;
    - whether systemic treatments work less well if a person has more than one painful site, and whether local treatment of one joint can lead to benefits at other sites

and influence on treatment recommendations remains unknown.

In order to enhance the specificity of the treatment recommendations for individuals with varying health profiles and OA burden, the guideline from the OA Research Society International (OARSI) defined four clinical subphenotypes demanded from National Institute for Health and Care Excellence (NICE): single vs multiple joint affection and moderate vs. high comorbidities risk.

The OARSI 2013[214] guidelines for the management of knee OA represent an update to the previous OARSI publications in 2010 and 2008. Incorporation of evidence from recent and best-available previously published research publications was leading to the decision from the OARSI to

examine knee OA separately due to disparities in available evidence between hip OA and knee OA and differences in best treatment practices between these conditions. This guidelines diverge from the previous OARSI guidelines in 2010 and 2008 as well as from recent American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) guidelines by focusing specifically on treatment of OA of the knee.[214] Thus, recommendations for individuals with multiple-joint OA may not take into account all evidence regarding other joint sites.

The ACR updated their recommendations for hip and knee OA in 2012 develop new recommendations for hand OA.[144] The American Academy of Orthopaedic Surgeons (AAOS) treatment recommendations are focusing on treatment of OA of the knee.[1] The EULAR separately developed recommendations for the treatment of OA of the knee, the hip and hand.[326,327,165]

While several international professional societies have published evidence-based guidelines for OA management,[51,92,144,165,214,328,329] no complete agreement on the different treatment modalities exists, highlighting the need for a debate to try to understand the differences and to develop a general consensus for disease management. A symposium devoted to the recent therapeutic recommendations for OA management was held on June 12, 2014, in the framework of the 2014 Annual European Congress of Rheumatology to review, compare, and discuss the most important guidelines and recommendations for the treatment of knee OA published by the EULAR, the OARSI, the ACR, and the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO). An article by Cutolo et al. (2015)[73] summarizes the comparisons of the guidelines for knee OA treatment regarding four specific topics, inter alia i.a. HAs.

2.3.2.1 Nonpharmacologic Therapy

Nonpharmacologic modalities for OA are quite diverse but broadly divide into educational approaches and physical activities. Educational approaches are based on the premise that patients can be encouraged to change their lifestyle patterns — including diet and exercise — both for musculoskeletal strengthening and weight loss (where appropriate) to reduce the load on affected joints.[214] Physical exercises for hip and knee OA patients include aerobic activity, muscle strengthening, and range-of-motion exercises.[214] Consultation with a physical therapist to guide patient exercise regimens and, if necessary, advise symptomatic patients on the use of walking aids, is also recommended. Advice regarding proper footwear for patients with hip and knee OA, as well as the use of local heat for symptom relief, is further recommended. With regard to non-pharmaceutical treatments, recommendations from societies are largely similar, consistently recommending exercise programs for individuals with knee OA as well as weight loss programs for overweight individuals. Several guidelines (EULAR, OARSI, AAOS, NICE, ACR) recommend biomechanical interventions, exercise (land-based and water-based), self-management and education, strength training, and weight management as appropriate treatment modalities for all individuals with OA.[327,214,1,231,144] Use of local heat and, when necessary, splints, are also recommended. Identification and appropriate treatment of depression is also essential; if it is not addressed, some nonpharmacologic therapies will not be effective.

2.3.2.2 Pharmacologic Therapy

General agreement exists among all of these guidelines that patient education is the cornerstone of any treatment plan; non pharmacologic strategies, such as exercise, should also always be part of the plan; and treatments should be introduced in a stepwise approach, with less invasive, mild analgesic drugs first, followed by nonselective NSAIDs.

Pharmacologic treatments for OA of all kinds include, but are not limited to, analgesics (eg, paracetamol [otherwise known as acetaminophen], opioids, and capsaicin) and anti-inflammatory agents with analgesic properties (eg, nonselective nonsteroidal anti-inflammatory drugs [NSAIDs], cyclooxygenase [COX]-2 inhibitors, topical NSAIDs, and i.a. corticosteroids). Slower-acting pharmacologic options include i.a. HA, as well as glucosamine sulfate and chondroitin sulfate.

Nonselective NSAIDs, while moderately effective, carry potentially unacceptable gastrointestinal, cardiovascular and renal risks.[278] COX-2-selective inhibitors, although with potencially fewer gastrointestinal effects, are not more effective than non-selective NSAIDs and still carry cardiovascular and renal risks. The factors involved in the exchange of drugs and small solutes between plasma and synovial effusions are complex and are related to synovial pathophysiology, transsynovial absorption rates and the properties of the drug.[312] For most low molecular weight drugs, the barrier for transsynovial exchange between SF and plasma is the synovial tissue interstitium.[312] There are several factors related to the nature of the solute or drug molecules that are known to influence the transport of drugs into and out of the SF, including drug dissociation constant, molecular radius, serum half-life, protein binding and drug solubility.[312]

I.a. corticosteroids have been observed to have an earlier onset of pain relief that is relatively short-lived, whereas i.a. hyaluronan takes effect more slowly, but this effect persists in some cases for 1 year or longer.[233,173]

2.3.2.2.1. NSAIDs

Oral NSAIDs are common treatment modalities for patients with early OA. They are designed to reduce the inflammatory markers associated with OA. NSAIDs relieve pain and increase mobility for approximately 60%of patients with OA, acting by inhibiting activity of the cyclooxygenase (COX) enzymes.[307] NSAIDs have long been a mainstay of treatment for mild to moderate OA but are associated with significant side effects and are not well tolerated by all patients. Recent concerns related to cardiovascular risk with both nonselective and cyclooxygenase-2-selective NSAIDs have forced at least one drug off the market and have prompted further investigation.[142],[94] Nonselective NSAIDs also are strongly associated with gastrointestinal adverse effects. Some analyses estimate that the risk of developing significant ulcer disease while taking even a short course (6 days to 2 weeks) of NSAIDs is 16% to 22%.[146,117] As many as 44% of patients can develop significant dyspepsia, requiring additional medical treatment.[146] A systematic review of the use of NSAIDs for knee OA failed to show any difference in the types or dosages of NSAIDs, so the author of the review recommended that the selection of NSAIDs be physician dependent and based on safety and cost.[314]

2.3.2.2.2. Corticosteroids

Corticosteroid injections have also been a useful tool in the treatment of OA. The main indication and beneficial effect for i.a. corticosteroid injection is pain relief.[129] The major preparations in terms of popularity are methylprednisolone acetate, triamcinolone hexacetonide, triamcinolone acetonide, betamethasone acetate/betamethasone sodium phosphate and betamethasone dipropionate/betamethasone sodium phosphate. These preparations are ester compounds that dissolve slowly in order to achieve a prolonged effect. The duration of response had been found to vary and depends on underlying disease, type of disease, amount of structural damage, type and dose of steroid, presence of joint effusion, level of inflammatory mediators, emptiness of joint effusion, availability of imaging, and others.[129] The comprehensive 2006 Cochrane meta-analysis from Bellamy and colleagues[35] evaluated the efficacy and safety of i.a. corticosteroids in treatment of OA of the knee. 28 trials (1973 participants) comparing i.a. corticosteroid against placebo, against i.a. hyaluronan/hylan (HA products), against joint lavage, and against other i.a. corticosteroids, were included. The authors concluded that the short-term benefit of i.a. corticosteroids in treatment of knee OA is well established, longer term benefits have not been confirmed based on this analysis. i.a. corticosteroids are usually well tolerated, but must be limited to 3 to 4 injections per year owing to the risk of advancing articular cartilage degradation with more frequent use.[229,107] Potential side effects include post-injection flares of pain, crystal synovitis, haemarthrosis, joint sepsis and steroid articular cartilage atrophy, as well as systemic corticosteroid effects such as fluid retention or aggravation of hypertension or diabetes mellitus. There is conflicting evidence regarding a negative effect of corticosteroids on articular cartilage.[134]

2.3.2.2.3. Local anesthetics

Local anesthetic agents are often used for the treatment of acute osteoarthritic pain, but with only short-term relief. Administration of local anesthetics directly into the knee joint can promote adequate pain control without causing the side effects observed for anti-inflammatory agents administered through a systemic route.

2.3.2.3 Hyaluronan (Viscosupplemenatation)

Based on knowledge of the important physiological function of endogenous HA in the joint, the concept of viscosupplementation of the SF using exogenous HA was developed. As HA is rapidly metabolised after systemic administration, thus becoming ineffective, the only feasible treatment form of arthrosis with HA is direct administration into the affected joint. I.a. HA has firmly established itself in the treatment of degenerative joint disease: in many cases, it offers the chance to avoid joint replacement or allows the procedure to be performed at a later date.

Clinical studies of i.a. HA injection in the nonoperative management of knee OA has shown positive results; however, the reported benefits have been variable.[47,315] The largest and most comprehensive systematic review is the Cochrane review **(Bellamy et al. 2006a[36])**. In a very

sophisticated meta-analysis on the benefits of i.a. HA in knee OA, only randomised, controlled studies were reviewed and weighted using four main criteria (from OARSI and OMERACT) and furthermore the authors used the stringent criteria of the Cochrane Systematic Review. Bellamy and colleagues examined a total of 76 randomized controlled clinical trials with an average evidence score of 3 (range 1 to 5). The follow-up period in these studies varied between day of last injection and up to 18 months after treatment. 40 trials included comparisons of hyaluronan/hylan and placebo, 10 trials included comparisons of intra-articular corticosteroids, and 6 trials included comparisons of non-steroidal anti-inflammatory drugs (NSAIDs), 3 trials included comparisons of physical therapy, 2 trials included comparisons of exercise, 2 trials included comparisons of arthroscopy, 2 trials included comparisons of conventional treatment, 15 trials included comparisons of other hyaluronans/hylan and found that i.a. HA injection was an effective treatment for knee OA.[36] The pooled analyses of the effects of viscosupplements against 'placebo' controls generally supported the efficacy of this class of intervention. The authors concluded that i.a. HA supplementation represents an effective principle for the treatment of OA of the knee joint, with favourable results regarding the parameters pain, joint function and global judgment by the patient, that persist for different durations but more particularly for 5 to 13 weeks after treatment. Finally, it overall supports the use of viscosupplementation for the treatment of knee OA.

In a recent meta-analysis of clinical trials with low risk of bias **Richette and colleagues (2015)**[259] analyzed data from trials with i.a. HA versus saline solution. Randomised controlled trials (RCTs) with adequate randomisation and concealment and double-blind design were eligible. The primary efficacy measure was pain intensity and secondary outcome function at 3 months. The treatment effect was summarised with the standardised mean difference (SMD) calculated from differences in means of pain and function measures between treatment and control groups at 3 months. Trials were pooled by a random-effects model with DerSimonian and Laird weights. Statistical heterogeneity was explored by a visual exploration of forest plots and the I2 statistic. A total of eight RCTs (2199 randomised patients) met our inclusion criteria. I.a. HA significantly reduced the pain intensity (SMD=-0.21, 95% CI (95% CI) -0.32 to -0.10) and improved function (SMD= -0.12, 95% CI -0.22 to -0.02). Trials showed no heterogeneity. This meta-analysis of high-quality trials of i.a. HA versus saline conformed that i.a. HA provides a moderate but real benefit for patients with knee OA.

HA, when taken orally, is degraded in the digestive system. When injected in the systemic circulation, the half-life of the product is few minutes. Consequently the only way giving no previous metabolisation is by i.a. administration. Relative to corticosteroids that act to quell the inflammatory reaction in i.a. and peri-articular structures, injection accuracy may be particularly important for HA because this therapeutic agent directly confers a number of protective properties to joint fluid, including shock absorption, traumatic energy dissipation, protective coating of the articular surface, and lubrication. The precise mechanism of action of exogen HA is unknown. However, proposed mechanisms of HA activity occurs in 2 stages: a mechanical / physical stage, and a physiologic stage. Under the mechanical / physiologic stage OA SF is replaced by higher concentrations of HA, thereby improving viscosity.[110] This also restores the shock-absorbing and lubricating abilities of depleted SF[22] and maintains a boundary layer around nociceptors, reducing pain induction.[120,248] The friction-reducing properties of HA at the cartilage-cartilage interface depend on the

concentration and molecular weight of HA.[13,74] High-MW HA has distinct cartilage lubricating abilities, and in vitro supplementation with high-MW HA is believed to partially restore the cartilage boundary lubricating function of SF.[13] The physiologic stage induces the biosynthesis of HA and extracellular matrix components,[280] which reduces proteoglycan loss in cartilage[22,110] and apoptosis of chondrocytes.[76] It also reduces inflammatory cell activities to reduce HA degradation[110] and acts by reducing induction of pain mediators.[110,120,248]

Among the available HA products for i.a. application a range of products can be found on the market. The HA preparations differ, either in their derivation, production method, molecular weight, biologic properties, injection protocol, or some combination thereof.

Sources for hyaluronic acid

Most of the HA used in industry is harvested either from rooster combs or produced by bacteria.[309,275] Although the purification of HA has been approved by the Food and Drug Administration (FDA), HA isolated from tissues often contains residual proteins that may easily lead to immune reactions if used for medical purposes. Therefore, it has to be additionally purified. Similarly, a residual content of desoxiribonucleic acid (DNA) may lead to the induction of proinflammatory cytokines. Few patients may develop allergic reactions if they are sensitive to the residual avian proteins that may exist in these products. Therefore, obtaining very pure HA from these animal tissue sources is rather difficult and, thus, the use of animal sources for sampling HA is in continuous decline.[309,275]

Much of the required HA is obtained from the HA capsule of bacterial strains - often termed ‘Non-Animal-Source-Hyaluronan’ or ‘fermentative HA’ - in a special fermentation process. *Staphylococcus equi* is today most often used for the production of HA.[172] This HA is identical to the HA fraction obtained from vertebrate tissues but free from harmful substances such as hepatitis, HIV- or bovine spongiform encephalopathy (BSE)-pathogens. Nevertheless, a risk of mutation of the bacterial strains, possible coproduction of various toxins, pyrogens or immunogens cannot be ruled out.[172] In any case a high level of diligence is required in order to assure an appropriate quality standard in accordance with the European Pharmacopeia.

The bacterial strain for the industrial production of sodium hyaluronate in OSTENIL® PLUS comes from a natural, freely occurring strain that has been identified as belonging to the species ***Streptococcus equi*** subsp. ***equi*** (Group C of the *Lancefield Classification*). The assumed proportion of mutated bacteria created during a sodium hyaluronate production is about 0.00002% to 0.0002% of the total bacterial count. This proportion always remains the same, since the subcultures are always produced under the same conditions from the same working cell bank and master cell bank.

It can therefore be shown that the bacterial strains used for the manufacture of SH create no toxins under the given conditions.

At the end of the fermentation process, the bacteria are destroyed by a validated technique and with them, any exotoxins that may have been produced. Due to the

numerous purification steps during HA production, the occurrence of allergens in the HA produced by fermentation is also considered extremely small.

The HA used for the production of OSTENIL® PLUS fulfils the specifications of the European Pharmacopoeia in all respects.

Chemically modified hyaluronic acid

Chemical modification allows tailoring the physicochemical properties of the glycosaminoglycan according to the desired applications and can have a significant impact on the turnover and clearance of the HA derivate. [172,31]. Cross-linking the HAs stabilises them, so that they can survive rapid degradation and provide an extended residence time. The HA polysaccharide chain contains three types of functional groups which can be used for derivitization, namely, hydroxyl-, carboxy-, and acetamido groups. There is an enormous number of derivates which may be obtained through chemical reactions of these functionalities with various reagents. The first cross-linked HA derivates are of the 'hylan' type, modified only through hydroxyl groups.[25]

Variety of hyaluronic acid products

To produce novel biomaterials with desirable physicochemical, mechanical and biocompatible properties, HA has been combined with other materials. This includes blends with polyvinyl alcohol for ophthalmic use, with carboxymethylcellulose (cross-linked with carbodiimide) to produce a bioabsorbable film for the prevention of postsurgical adhesions, and for woundhealing applications with collagen.[319] Other compounds added to HA fillers are lidocaine, reducing the pain of injection and providing some anti-inflammatory capacity and mannitol as a radical scavenger for hydroxyl radicals.

I.a. injection of HA has been accepted as an effective therapy for OA and several trials have attempted to evaluate the benefits of i.a. HA for knee OA (e.g., improvements in painful knee movements and general pain relief).[23,216,261,230,176,320,151,157,290] HA has a very short half-life (12 to 17 h) once injected into the joint, but its clinical effects can last six to 12 months.[176,182] Thus, HA appears to provide its clinical benefits by providing viscous fluid replacement and triggering multifunctional biological responses.

2.4 Legal Background: Applicable Regulations, Standards and Guidelines

Within the scope of the conformity assessment procedures leading to CE marking, the legal manufacturer is required to provide a CEv of his products to demonstrate compliance of these products with the essential requirements of the MDD and to reflect knowledge of current medical practice and 'state of the art' technologies in the field of the medical device under evaluation.

In the presentation of the relevant data for this report, the following regulatory guidelines and recommendations were considered:

- Medical Device Directive (Council Directive 93/42/EEC; Annex I and X)
- EN ISO 14155:2012 Clinical investigation of medical devices for human subjects – Good Clinical Practice.

- EN ISO 10993-1:2010 Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process.
- EN ISO 14971:2012 “Medical devices - Application of risk management to medical devices”.
- MEDDEV 2.7.1 rev.3, December 2009: Evaluation of Clinical Data: A Guide for Manufacturers and Notified Bodies
- MEDDEV 2.12-2 rev.2, 2012 Guideline on Post-market Clinical Follow-Up
- NB-MED/2.7/Rec3 Evaluation of Clinical Data, Chapter 2.7. Clinical Investigations, Clinical Evaluation
- NB-MED/2.7/Rec1 Guidance on Clinical trials, Chapter 2.7. Guidance on when a clinical investigation is needed for CE marking

The MDD appendix X defines the requirements for clinical evaluations. The Guideline ‘Evaluation of clinical data: a guide for manufacturers and Notified Bodies’ (MEDDEV 2.7.1 Rev 3) published in December 2009 defines in detail the possible ways of providing the required evidence. Taking into account that the MEDDEV 2.7.1 Rev.3 guideline is based on the GHTF Guideline SG5/N2R8:2007 Clinical Evaluation of June 2007, as stated in the guideline itself, the clinical evaluation at hand conforms to both guidelines. In the CER at hand the above mentioned guidelines will be referred to as CEv Guidelines.

This clinical report follows the appropriate MEDDEV recommendation in the combined description of the results from relevant scientific literature (the ‘literature route’) and from clinical studies with own reference products (the ‘clinical investigation route’).

2.5 Objective(s) and Scope of the Clinical Evaluation

This report is a critical analysis and summary of literature reviewed for the medical device OSTENIL® PLUS, in accordance with MDD 93/42/EEC as amended by Directive 2007/47/EC Annex X, Literature review route requirements and compiled according to TRB Chemedica specifications.

This analysis is based on relevant scientific literature currently available relating to the medical device OSTENIL® PLUS in the aspects of safety, performance, design characteristics, and intended purpose. The literature reviewed is based on the devices under evaluation itself and a demonstration of equivalence of the device to the device(s) placed on the market. Only products evaluated as equivalent to OSTENIL® PLUS will be taken into consideration.

The objective of this CEv is to demonstrate that the device under evaluation complies with the relevant essential requirements covering safety and performance.

CEv Guidelines advocate literature searching in order to identify published clinical data that are not in the possession of the manufacturer and which assist to document acceptable performance and safety of the medical device in question. By the CER at hand such data sets were taken into account as far as they accorded to the objective of the literature review and the general criteria of the literature search (see appendix A1). Irrespective of the indications and the design of the product under review, the approach to the CER at hand involves three consecutive stages in

regard to identification, appraisal and analysis of the clinical data relating to the safety and performance of the medical device under review. Following the appraisal of the individual data sets (from the literature search, clinical experience and clinical investigation) according to their suitability and contribution to address the questions about the product under review, the collective analysis of the available data sets is performed in order to make conclusions about the performance and safety of the assessed product in relation to its indication. However, if the analysed clinical data are not sufficient to declare conformity of the product with the relevant essential requirements, the described approach of the data assessment, appraisal and analysis may be repeated after the inclusion of new data.

This CEv is performed in order to:

- Identify and discuss any literature data on HA products aimed for a similar indication and based on similar formulations as OSTENIL® PLUS, which support the safety and performance claims of OSTENIL® PLUS.
- Identify and discuss any literature data on any other products based on similar formulations as OSTENIL® PLUS or based on similar principles of action; and if such products are found, discuss if these data can be extrapolated with regards to the clinical safety and performance claims of OSTENIL® PLUS.
- Evaluate the results of *in vitro* performance test data supporting the clinical effectivness of OSTENIL® PLUS.
- Evaluate results of clinical (case) studies and Post Market Surveillance data supporting the safety and performance of OSTENIL® PLUS.
- Achieve essential information for assessing clinical benefits and foreseeable risks of OSTENIL® PLUS. In case risks are identified, an assessment is made if risks are acceptable when weighted against the clinical benefit and a verification is made if sufficient control measures have been taken including information provided in the Instructions for Use.
- Justify the need for a Clinical Investigation or Post Market Clinical Follow Up.
- Assess if OSTENIL® PLUS is safe when used as intended and applied in its indication and complies with the safety requirements of the MDD.
- Assess if OSTENIL® PLUS performs as claimed when used as indicated and complies with the performance requirements of the MDD.

2.6 Structure of the Clinical Evaluation

The format of the CER at hand is adjusted to suit previously described clinical evaluation approach with regard to identification of data, appraisal, analysis and conclusions and is adopted by the sections as advocated by the Appendix E of the CEv Guideline. The compilation of the clinical evaluation document in the standardized format should enable efficient review via Notified Bodies and Conformity Assessment Bodies and reflects a structured presentation of the clinical evaluation process.

Moreover, the literature search protocol and the literature search report are generated as recommended by Appendix A and Appendix B of the CEv Guideline, respectively. Both are integrated into Appendix A1 and Appendix A2 of the clinical evaluation report and should enable fast access to the methodology employed for the literature search. Appendix A4 of the clinical

evaluation includes information on authors' professional background. These appendices appear within the clinical evaluation at hand as listed below.

Table 1 Structure of the CER

Appendices
Appendix A1: The literature search protocol
Appendix A2: The literature search report
Appendix A3 Tables Literature Evaluation
Appendix A4: Qualification - The authors' professional background

3. DEVICE DESCRIPTION AND INTENDED APPLICATION

OSTENIL® PLUS (viscoelastic solution for i.a. injection) pre-filled syringes contains a highly purified specific fraction of HA derived by fermentation from bacteria. It is present in the solution as sodium hyaluronate in a 2.0% concentration. OSTENIL® PLUS is a class III medical device indicated for the symptomatic treatment of pain and restricted mobility in degenerative and traumatic changes of big and small synovial joints.

3.1 Manufacturer

The manufacturer is TRB Chemedica AG, Richard-Reitzner Allee 1, 85540 Haar, Germany.

3.2 Proprietary name of device and company code name

The proprietary name of the device is OSTENIL® PLUS.

3.3 Classification of the medical device in accordance with Annex X of Council Directive 93/42/EEC, UMDNS and GMDN coding

From the performance characteristics of OSTENIL® PLUS, as well as the relevant definitions, regulations for use, and rules of classification of the MDD, Annex IX, Parts I, II and III, and the underlying requirements of the directive (Annex I, Section 8), OSTENIL® PLUS is to be classified as follows:

In accordance with the definitions given in Article 1, Paragraph 2a of the MDD, OSTENIL® PLUS **is a medical device.** It meets the description given in the following passages of Paragraph 2a:

"Medical device:
Any … material …., whether used alone or in combination, intended by its manufacturer to be used for human beings for the purpose of:

- diagnosis, prevention, monitoring, treatment or alleviation of disease …
- investigation, replacement or modification of the anatomy or of a physiological process, …

and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means."

Relevant passage in Annex IX, MDD		Classification
I.	Definitions	
1.	Definitions for the classification rules	
1.1.	Duration Short-term Normally intended for continuous use for not more than 30 days.	applicable
1.2.	Surgically invasive device An invasive device which penetrates inside the body, through the surface of the body, as part of a surgical operation. For the purposes of this Directive, devices ..... which produce penetration other than through an established body orifice, shall be treated as surgically invasive devices.	applicable
III.	Classification	
2.	Invasive devices	
2.3.	Rule 7, fourth indent All surgically invasive devices intended for short-term use are in Class IIa unless they are intended..... - to have a biological effect or to be wholly or mainly absorbed, in which case they are in Class III.	applicable

As further aids to classification, reference is also made to the following:

MEDDEV. 2.4/1, Rev. 9, June 2010, Classification of Medical Devices.

MEDDEV. 2.1/3, Rev. 3 – December 2009, Borderline products, drug-delivery products and medical devices incorporating, as integral part, an ancillary medicinal substance or an ancillary human blood derivative.

Following in-depth examination of all relevant regulatory specifications, the following has been determined:

In accordance with Rule 7, fourth indent, of Annex IX of the COUNCIL DIRECTIVE 93/42/EEC concerning medical devices (MDD), OSTENIL® PLUS is to be classified as a Class III medical device.

The procedure in accordance with Annex II.3 and Annex II.4 of the MDD is suitable for the conformity assessment procedure.

UMDNS code: 18-569 Viscoelastic Solutions, intra-articular

GMDN code: 44757 Synovial Fluid Supplementation Substance

3.4 Product Description

3.4.1 Hyaluronan

OSTENIL® PLUS has marketing approval since years and several clinical trials show very good efficacy and safety in the treatment of osteoarthritis. The product contains 2% HA (40 mg / 2 ml) with a MW of 1.6 x 10^6 Da plus 10 mg mannitol / 2 ml. Independently from the recommended number of injections (1-3) safety and efficacy could be clearly demonstrated in clinical trials and are supported by pharmacovigilance system.

3.4.2 Product description

OSTENIL® PLUS is a HA containing medical device for i.a. application to achieve viscosupplementation of SF.

3.4.2.1 Technical product description

- The product is a ready-to-use sterile gel for i.a. injection.
- The product is filled in 2 ml portions into Becton-Dickinson glass syringes and sealed in a sterile blister in which it is sterilized by moist heat.
- The assembled, pre-filled syringe consists of a glass barrel with a Luer-Lok connection for a cannula, a tip cap, a finger grip and a stopper with a plunger rod screwed in.
- The product is stored between 2 °C and 25 °C.
- The content and the outer surface of the OSTENIL® PLUS pre-filled syringe are sterile as long as the sterile pack is intact. The pre-filled syringe has to be taken out of the sterile pack, the Luer lock cap has to be unscrewed from the syringe, a suitable needle (for example 18-25 G) attached and secured by turning it slightly. Air bubbles, if present, should be removed before injection.
- The pre-filled syringe is packed into a deep moulded tray which is sealed with moist heat diffusible paper and is then sterilised by moist heat in a validated procedure.
- The sterilisation process is carried out in accordance with European Norms EN ISO 17665 and EN ISO 556, using steam. As a result, both the contents and the outer surface of the pre-filled syringe are sterile.
- The sterile syringe in the blister is packed into a foldable carton box together with a multilingual package insert.

3.4.2.2 Biological product description

OSTENIL® PLUS is a viscoelastic solution containing 2% SH in isotonic sodium chloride solution, buffered with disodium phosphate and sodium dihydrogen phosphate at a pH between 6.8 and 7.5.

The SH in OSTENIL® PLUS is produced by bacterial fermentation (*Streptococcus zooepidermicus*) and is highly purified. Neither the fermentation nor the purification process involves animal proteins, so the allergic potential of OSTENIL® PLUS is negligible. All ingredients apply the quality standards of the European Pharmacopoeia.

3.5 Intended therapeutic and/or diagnostic indications and claims; listed side effects

3.5.1 Intended use

Viscoelastic solution for injection into the joint cavity.

3.5.2 Indications and contraindications for use of the medical device

3.5.2.1 Indication of the medical device

Pain and restricted mobility in degenerative and traumatic changes of the knee joint and other synovial joints.

3.5.2.2 Contraindications and precautions

Contraindications and precautions for the product to be assessed are:

- The products should not be used in patients with ascertained hypersensitivity to one of its constituents.Caution should be exercised in patients with known hypersensitivity to drugs.
- The general precautions for i.a. injections should be observed, including measures to avoid joint infections.
- The product should be injected accurately into the joint cavity, if necessary under imaging control.
- Injections into blood vessels or surrounding tissues should be avoided.
- As no clinical evidence is available on the use of HA in children, pregnant and lactating women or in inflammatory joint diseases such as rheumatoid arthritis or Bechterew disease, treatment with OSTENIL® PLUS is not recommended in these cases.
- Any solution not used immediately after opening must be discarded. Otherwise the sterility is no longer guaranteed.
- Damaged pre-filled syringes or sterile packs shall not be used.
- The product must not be used after the expiry date indicated on the box.
- The product is to be used by a physician only.

3.5.3 Claims made for the medical device

Claims stated in the IFU are:

As a rule this results in a decrease in pain and an improvement in joint mobility which may last for several months after a treatment cycle.

Supported by

Frobenius K. A new high-dose treatment with intraarticular hyaluronic acid facilitates the management of osteoarthritis Orthopädische Praxis. 2009;46(5):252-256.

Borrás-Verdera A, Calcedo-Bernal V, Ojeda-Levenfeld J, Clavel-Sainz C. [Efficacy and safety of a single intra-articular injection of 2% hyaluronic acid plus mannitol in knee osteoarthritis over a 6-month period]. Rev Esp Cir Ortop Traumatol. 2012;56(4):274-80.

Guler O, Mutlu S, Isyar M, Seker A, Kayaalp ME, Mahirogullari M. Comparison of short-term results of intraarticular platelet-rich plasma (PRP) and hyaluronic acid treatments in early-stage gonarthrosis patients. Eur J Orthop Surg Traumatol. 2015;25:509-13.

Lertwanich P, Lamsam C. Efficacy of a Single Intra-Articular Injection of 2% Sodium Hyaluronate Plus 0.5% Mannitol in Patients with Symptomatic Osteoarthritis of the Knee: A Preliminary Report. J Med Assoc Thai. 2016;99(10):1094-101.

As shown above, the claims made can be supported with adequate scientific evidence from the device under evaluation.

3.5.4 Description of use / principles of operation

Normal SF, which contains ~0.5% HA is the protective medium of all synovial joints. It is essential for joint homeostasis and ensures normal, painless movement. The combination of molecular weight and concentration of HA provides the characteristic viscoelasticity to the SF. In traumatic and degenerative diseases of synovial joints, the homeostasis of the affected joint is disrupted. The SF is more abundant, less viscous and has a lower concentration of HA. This is probably due to many different factors including increased water content and the presence of free radicals, which would cause the long chain hyaluronan molecules in the SF to break down into smaller fragments. Depolymerisation of high molecular weight HA molecules is an essential step in the physiological catabolism of this biopolymer. A resulting reduction in the viscoelasticity of the SF is the consequence and a decrease in its protective, lubricating, shock absorbing and barrier function, is eventually leading to cartilage breakdown accompanied by pain and restricted mobility in the affected joint.

The rationale for the chondroprotective use of OSTENIL® PLUS in its indication is based on the principle of viscosupplementation.

Dosage and administration:

- The product shall be administered into the affected joint. If required, OSTENIL® PLUS may be administered into the affected joint once a week for a total of 1-3 injections.
- Several joints may be treated at the same time. Repeat treatment cycles may be administered as required.

- In case of joint effusion it is advisable to reduce the effusion by aspiration, rest, and application of an ice pack and / or i.a. corticosteroid injection. Treatment with OSTENIL® PLUS can be started two to three days later.
- Remove any air bubble, if present, before injection.

3.5.5 Concomitant events and side effects

Side effects for the product to be assessed as listed in the instructions for use (IFU) are:

- Local secondary phenomena such as pain, feeling of heat, redness and swelling/joint effusion may occur in the joint treated with OSTENIL® PLUS. Application of an ice pack onto the treated joint for five to ten minutes will reduce the incidence of these events.

3.5.6 Characteristics and mode of action

SF, which is viscoelastic due to the presence of HA, is found in all synovial joints where it ensures normal, painless movement due to its lubricating and shock-absorbing properties. It is also responsible for the nutrition of the cartilage. In degenerative joint disorders such as osteoarthritis, the viscoelasticity of the SF is markedly reduced thereby decreasing its lubricating and shock-absorbing functions. This increases mechanical loading of the joint and cartilage destruction which ultimately results in pain and restricted mobility of the affected joint. Supplementing this SF with i.a. injections of highly purified HA can ameliorate the viscoelastic properties of SF. This improves its lubricating and shock-absorbing functions and reduces mechanical overload of the joint. As a rule this results in a decrease in pain and an improvement in joint mobility which may last for several months after a treatment cycle.

4. METHODS USED FOR EVALUATION AND CHOICE OF CLINICAL DATA TYPES

This clinical report follows the recommendation of MEDDEV 2.7/1 and combine the evaluation of the results from relevant scientific literature (literature route) and from own clinical studies with TRB Chemedica reference products. Clinical data from OSTENIL® PLUS and from essential similar comparators in sufficient quality and quantity are available and will be used for this CER.

4.1 Issues related to the Evaluation of Benefit-Risk Ratio

The risk management file is available from the manufacturer. The risk management file was checked concerning risks which require assessment by clinical data. The residual risks which might occur with the application of OSTENIL® PLUS were stated in section 3.5.5 and also mentioned in the IFU.

4.2 Methodology of Systemic Data Search and Presentation

The literature search protocol (see appendix A1) describes the basic criteria which are applied during identification and appraisal of the clinical data. The publications identified by the literature search are classified as relevant literature and non-relevant literature according to the scheme given within the literature search protocol (see appendix A1) and further described in section 4.4. Some review publications which were classified as non-relevant were used as background information. This background information as well as literature found by manual search contribute to the clinical background and current knowledge/state-of-the-art evaluation.

The literature search report is generated after the public database search was performed according to above defined objective of the literature review (see section 2.5). It is presented in the appendix A2 of the clinical evaluation at hand.

To support the performance and biocompatibility of i.a. HA published data as well as unpublished data from own studies with TRB Chemedica products were consulted.

Following are data from publications found in the context of bibliographic databases, clinical trials registry platforms and from a systematic checking of the literature for overviews and original studies on the relevant topics. Additional literature search in relevant journal(s) not indexed for MEDLINE, and in CENTRAL (Cochrane database) and DIMDI (Deutsche Institut für Medizinische Dokumentation und Information) was performed.

Publications found in literature search had to fulfil following criteria to be judged as relevant for a more extensive specification of HA product used:

- in the indication: osteoarthritis
- with the intervention(s): intra-articular HA injection
- with the use of: linear (not crosslinked) HA ≥1.5%

47 publications were found and further investigated with regard to equivalence of HA containing competitior used.

4.3 Identification and Appraisal of Equivalence and Competitors

The general criteria for the equivalence are described in the Appendix A1 of the clinical evaluation at hand.

Clinical equivalence

Products are considered to be equivalent when they are used

a) for the treatment of degenerated and traumatic changes of the knee and other synovial joints;
b) i.a.ly in synovial joints;
c) to relieve pain, improve mobility and promote joint recovery.

Products which are claimed for single administration were excluded from evaluation.

Biological equivalence

Products containing HA or one of its salts, either in native or modified form as active ingredient, are considered to be equivalent to the product under review.

Such products are considered highly equivalent to the products under review when they contain linear native HA from fermentative origin at a molecular weight of about 1.6 – 2.0 x 10^6 Da, a HA concentration of 2.0% (20mg/1ml) and 0.5-1% mannitol.

Products containing different molecular weight or concentration of linear HA or modified HA are considered to be moderately to not equivalent, depending on the chemical structure or added compound. Products which are crosslinked were excluded from evaluation.

Technical equivalence

Technical equivalence is given for liquids and gel like products which are injected by pre-filled syringes. Products rated with higher equivalence are from fermentative production, their content is sterilized by moist heat and content plus surface of the syringe are sterilized by moist heat.

Equivalence of products mentioned in relevant literature articles:

Table 2 Definitions product equivalence

Categories		Assessment of the single categories		Total assessment	
C	Clinical	3	high (very similar)	8-9	high
T	Technical	2	probable (similar)	6-7	probable
B	Biological	1	doubtful (in some aspects similar)	3-5	doubtful
		0	not substantiated (no equivalence)	0-2	not substantiated

4.4 Relevance of Selected Literature

A careful examination and evaluation of data from pre-clinical testing in accordance with EN ISO 10993-1 on safety/biocompatibility of OSTENIL® PLUS as test items was performed.

In a next step, identification and assessment of relevant published and unpublished data from clinical studies with medical devices from TRB Chemedica, of relevant published data with regard to safety and efficacy of HA retained in the archives of TRB Chemedica, and of relevant clinical studies retrieved by literature search (see appendix A1 and A2) was performed.

Only publications relevant for the same indication, with equivalent products with comparable characteristics, or relevant to evaluate biocompatibility of OSTENIL® PLUS were considered for this clinical evaluation.

Appraisal criteria for suitability were:

- appropriate device (actual device or essential similar comparator)
- appropriate device application (same intended use; e.g. methods of deployment, application, etc.)
- appropriate patient group (representative of intended treatment population)
- appropriate indication
- appropriate risk potential
- appropriate report/data collation (publication contained sufficient extent and scientific quality of information)

Relevance of the publication for clinical evaluation is also influenced by the impact on the interpretation with regard to:

- appropriate study design
- outcome measures (appropriate for evaluation of effects)
- follow-up period (long enough to assess duration of treatment effects and identify complications)
- statistical analysis (provided and appropriate)
- clinical significance (magnitude of treatment effects significant)

Beside identification of the level of evidence (LoE) of the study, the number of patients (N) and the trend of the clinical data (T) assessed during literature appraisal, the extraction of number of patient groups, the number of products tested, the inclusion of placebo group and the conduction of statistical analysis is considered as advantageous for subsequent analysis of clinical effectiveness and safety data sets.

In order to avoid bias, literature with both positive and negative outcomes, in terms of supporting the claim for OSTENIL® PLUS, was sought. Data were required to be the most comprehensive and up-to date available, and that they should be preferably come from recognized, scientific, peer-reviewed journals in the field.

All relevant publications will be presented independently from study findings.

5. RESULTS AND EVALUATION

5.1 Identification of Essential Similar Comparators

Only products with high essential similarity were judged as equivalent to OSTENIL® PLUS and thus able to show conformity of OTENIL® PLUS with essential requirements.

Assessment of product equivalence on the basis of clinical, biological and technical equivalence showed that no competitor identified in publications from literature search was judged to be highly equivalent to OSTENIL® PLUS. Most products show not sufficient similarity with regard to biological equivalence: not 2% in HA concentration, molecular weight too high or too low and no additional radical scavenger mannitol. Two products contain 4% sorbitol as radical scavenging agent (Go-on matrix and Synolis V-A), but this is judged as not equivalent to 0.5% mannitol.

Publications with competitors rated as not equivalent to OTENIL® PLUS were excluded from demonstration of adequate clinical performance of OTENIL® PLUS but taken into account of their suitability in the evaluation of clinical safety and risks.

Clinical data from OSTENIL® PLUS are available in sufficient quality and quantity to demonstrate compliance of OSTENIL® PLUS with the relevant essential requirements.

Table 3 shows products (listed in alphabetic order) found in relevant publications by literature search.

Table 3 Evaluation product equivalence

Product name/ Manufacturer	Indication	Features	Product characteristics	Equivalence C	T	B	Total
Coxarthrum	• Therapeutic indications are all forms of painful coxarthrosis.	• Sterilisation technique: water steam autoclaving • a single intraarticular injection that may be repeated once two or three months after the first injection if pain has returned to its initial level	• 2.4 x10^6 Da • 75mg/3ml (2,5%) • fermentation	2	3	1	6
Fermathron Plus	• To the relief of pain and improvement of joint mobility of knee joint and other joints in patients with degenerative and/or traumatic changes of synovial joints.	• 3 injections recommended • Content of syringe is sterilized by filtration, syringe surface sterilized by ethylene oxide	• 2 x10^6 Da • 30mg/2ml (1.5%) • fermentation	3	1	2	6
Go-On Matrix (Rottapharm-Madaus)	• For pain relief and improvement of joint mobility in osteoarthritis of knee and other synovial joints.	• Content and surface of syringe is sterile by moist heat • 3-5 injections recommended • Injection into joint space	• 2.2 x10^6 Da • 40mg/2ml (2.0%) • + 80mg (4%) sorbitol • fermentation	3	3	1	7
HyalOne	• Temporary synovial fluid replacement for patients affected by degenerative or mechanical arthropathy of the hip and knee that causes an alteration of the functional performances of the synovial liquid, without active synovitis.	• Sterilized by moist heat.	• > 1.500 kDa • 60mg/4ml (1.5%) • fermentation	3	3	1	7
Hyalubrix Fidia (Italy)	• HYALUBRIX is a temporary replacement for the synovial fluid in patients with degenerative joint disease or mechanical, causing a disturbance in the functioning of the synovial fluid, without active synovitis.	• Content of the syringe is sterile by moist heat, syringe surface low germ • 3 or more injections recommended • Injection into joint space	• 1.5-1.9 x10^6 Da • 30mg/2ml (1.5%) • fermentation	3	3	1	7
Orthovisc Ortho Biotech Anika (USA)	• Treatment of knee pain due to osteoarthritis	• Content of the syringe is sterile by filtration, syringe surface low germ • 3 injections recommended • Injection into joint space	• 1.5 x10^6 Da • 30mg/2ml (1.5%) • fermentation	3	1	1	5
OSTENIL Plus (OSTEONIL Plus) TRB Chemedica	• Pain and restricted mobility in degenerative and traumatic changes of the knee joint and	• Content and surface of syringe is sterile by moist heat • 1-3 injection recommended	• 1.6 x10^6 Da • 40mg/2ml (2%) + 10mg mannitol	3	3	3	9

Product name/ Manufacturer	Indication	Features	Product characteristics	Equivalence C	T	B	Total
	other synovial joints.	• Injection into joint space	• fermentation				
Sinovial One IBSA	• Pain and restricted mobility in degenerative and traumatic diseases or changes of joints.	• Content and surface of the syringe is sterile by moist heat • 3-5 injections recommended • Injection into joint space	• 0,8-1,2 x 10^6 Da • 50mg/2,5 ml (2%) • fermentation	3	3	1	7
Synolis V-A	• Synolis V-A reduces the local pain and discomfort caused by osteoarthritis and it improves mobility of the synovial joints.	• Injection into joint space. • 3 injections in weekly interval recommended • Sterilized by moist heat.	• 2 x 10^6 Da • 20mg/1ml (2%) • + 4% sorbitol • fermentation	3	3	1	7

5.2 Suitability of literature data

For demonstration of essential requirements relevant literature must include coverage of adequate information for equivalence of safety, performance, design characteristics as well as intended purpose without exception.

According to suitability of appraisal criteria (see section 4.4) and from product equivalence evaluation (section 5.1) transferability of data from literature search on clinical performance of OSTENIL® PLUS will be regarded as suitable when:

- OSTENIL® PLUS are used (appropriate device),
- devices are used to treat pain and restricted mobility in degenerative and traumatic changes of the knee joint and other synovial joints,
- study patients show no contraindication for intended treatment population for OSTENIL® PLUS (appropriate patient group),
- devices are used for viscosupplementation of SF (appropriate indication),
- risk potential is comparable with regard to materials and application,
- publication contain sufficient extent and scientific quality of information (appropriate report/data collection), e.g:
    - appropriate study design
    - outcome measures
    - follow-up period
    - statistical analysis
    - clinical significance

Evaluation is performed critically, showing the advantages as well as disadvantages of the device.

5.3 Performance Relevant Results and Evaluation

730 publications were found according to literature search (Appendices A1 and A2). After appraisal for relevance 537 publications were evaluated as ‘non-relevant’, 36 as relevant for further evaluation and 157 were classified as doublings. Appraisals are given as summary in Table 4 and Table 5.

Table 4 Classification of publications for relevance

N°	Classification for relevance
537	Non-relevant for appraisal
157	Doublings
36	Relevant for appraisal
Σ 730	

Table 5 Non-relevant publications

N°	Reasons for non-relevance
56	Reviews
4	Editorials, comments, letters, etc.
5	Pre-clinical/in vitro studies

88	Not related to the subject
324	Not comparable technique
60	Missing scientific information
Σ 537	

The major part of non-relevant publications (324 / 537) was classified with 'not comparable technique' meaning that device use was not classified to be 'equivalent' to the product to be assessed in this CER or procedure performed was not comparable. 88 / 537 citations were excluded due to wrong diagnosis or indication ('not related to the subject'). Some of the excluded review articles were used as background information, i.e., articles giving an overview on the medical device or an equivalent product, the technique used, or its field of use, were used for this CER. Exclusion of publications due to 'missing scientific information' means that necessary information concerning the device (e.g. concentration or MW of HA is not mentioned, abstract or poster) or procedure performed are not mentioned, making evaluation of equivalence or similarity of device or procedure impossible.

Evaluation of publications from literature search including update citations resulted in 36 / 730 publications for further appraisal focusing on equivalence of competitor. As equivalence could not be shown for competitors only publications with OSTENIL® PLUS (Table 6) were appraised as they were strictly focused on the topic of this clinical evaluation.

Table 6 Publications with OSTENIL® PLUS

	Source	N° in scource	Citation	Product	Level of Evidence
1	MeSH Medline	63	Colen S, van den Bekerom MP, Bellemans J, Mulier M. Comparison of intra-articular injections of hyaluronic acid and corticosteroid in the treatment of osteoarthritis of the hip in comparison with intra-articular injections of bupivacaine. Design of a prospective, randomized, controlled study with blinding of the patients and outcome assessors. BMC Musculoskelet Disord. 2010 Nov 16;11:264. doi: 10.1186/1471-2474-11-264. PubMed PMID: 21080920; PubMed Central PMCID: PMC2998460.	Ostenil Plus	Ib
2	Clinicaltrials.gov	Study: 42	Title: Study of Evaluating the Duration of Efficacy of One Intra Articular Injection of Sodium Hyaluronate 2.0% in Patients With Painful Osteoarthritis of the Knee Recruitment: Completed Study Results: No Results Available Conditions: Osteoarthritis Patient Interventions: Drug: Ostenil plus URL: https://ClinicalTrials.gov/show/NCT01288001 Abstract available.	Ostenil Plus	abstract
3	Manual search	1a	Dreiser RL, Avouac B, Bardin T. Efficacy of One Intra-Articular Injection of 2% Natural Sodium Hyaluronate Is Non-Inferior To Chemically Crosslinked Hylan G-F 20 In The Treatment Of Painful Tibiofemoral Osteoarthritis. Abstract publication: Osteoporos Int 2015;26(Suppl 1): P308 Ann Rheum Dis 2015;74(Suppl 2):376.	Ostenil Plus	abstract
4	Manual search	1b	Maheu E, Dreiser RL, Avouac B, Bardin T. Comparison of Therapeutic Response Rates, Using Various Response Definitions in a Prospective Randomized Non-Inferiority Trial Comparing Two Intra-Articular Hyaluronic Acid	Ostenil Plus	abstract

	Source	N° in scource	Citation	Product	Level of Evidence
			Preparations (1-Shot IAHA) in symptomatic Knee Osteoarthritis (OA), and Predictive Factors of a Better Response. SAT0443 EULAR congress 2016 London, UK. Abstract		
5	Manual search	2	Guler O, Mutlu S, Isyar M, Seker A, Kayaalp ME, Mahirogullari M. Comparison of short-term results of intraarticular platelet-rich plasma (PRP) and hyaluronic acid treatments in early-stage gonarthrosis patients. Eur J Orthop Surg Traumatol. 2015;25:509-13.	Osteonil Plus (Ostenil plus)	III
6	Manual search	3	Borrás-Verdera A, Calcedo-Bernal V, Ojeda-Levenfeld J, Clavel-Sainz C. Efficacy and safety of a single intra-articular injection of 2% hyaluronic acid plus mannitol in knee osteoarthritis over a 6-month period. Rev Esp Cir Ortop Traumatol. 2011;56:274-80.	Ostenil Plus	IV
7	Manual search	4	Frobenius K. A new high-dose treatment with intraarticular hyaluronic acid facilitates the management of osteoarthritis. Orthopädische Praxis. 2009;46(5):252-7	Ostenil Plus	IV

Study evaluation and assessment of the risk of bias is facilitated through the use of an appraisal instrument (tabular evaluation) addressing the specific features of the study design. Tables are listed in Appendix 3.

5.3.1 Clinical data generated and held by TRB Chemedica

Clinical studies are in descending order of year of publication.

5.3.1.1 Dreiser RL 2015 and Maheu E 2016

A clinical trial was performed under sponsorship of TRB Chemedica SA (Switzerland; Study N° OSTP-EUR-10-01) with the title “A comparative study evaluating the efficacy and safety of two intra-articular preparations of sodium hyaluronate 2% in patients with painful knee osteoarthritis. A prospective, randomised, double-blind, controlled study.” The clinical investigation plan and report are available and results were published as:

Dreiser RL, Avouac B, Bardin T. Efficacy of one intra-articular injection of 2% natural sodium hyaluronate is non-inferior to chemically crosslinked hylan G F 20 in the treatment of painful tibiofemoral osteoarthritis. Osteoporos Int. 2015 Mar;26(Suppl 1): Abstract No. P308.

Dreiser RL, Avouac B, Bardin T. A 6-month trial evaluating efficacy of one intraarticular injection of 2 per cent sodium hyaluronate versus hylan G F 20 in the treatment of painful tibiofemoral osteoarthritis. Ann Rheum Dis. 2015;74(Suppl 2):376. Abstract No. THU0488.

Maheu E, Dreiser RL, Avouac B, Bardin T. Comparison of therapeutic response rates, using various response definitions in a prospective randomised non-inferiority trial comparing two intra-articular hyaluronic acid preparations (1-shot IAHA) in symptomatic knee osteoarthritis (OA) and predictive factors of a better response. Ann Rheum Dis. 2016;75(Suppl 2):831-2. Abstract no. SAT0443.

This prospective, randomized, double blind, controlled, parallel group, non-inferiority study was conducted from June 2011 through November 2012 at 50 sites in France. Patients were included if they were aged 40–85 years, with tibiofemoral OA (Kellgren-Lawrence grade Ib to III) according to the ACR criteria and WOMAC A pain of at least 40 mm. After an NSAID washout period, eligible patients were randomized to receive one intra articular injection of either 40 mg/2.0 ml natural HA (OSTENIL® PLUS) or 48 mg/6.0 ml chemically crosslinked hylan G-F 20 (hylan) (Synvisc One). Efficacy parameters were evaluated by a blinded assessor on Days 0, 30, 90 and 180. The primary endpoint was the change from baseline in WOMAC A at Day 180. The lower margin of non-inferiority was pre specified at 8 mm. The per protocol (PP) set was used for the main analysis. A total of 292 patients were randomized into the study (HA=144, hylan=148): 142 received one injection of HA, 146 received one injection of hylan; 266 patients (91.1 %) completed the study. The efficacy analysis performed on the PP set (HA=113, hylan=112) showed that both preparations reduced pain and improved functional activity over 6 months. The mean WOMAC A change from baseline at Day 180 was 34.3±19.0 mm and 36.2±22.0 mm for HA and hylan, respectively (p=0.4895). The mean observed difference between groups was 1.9±20.5 mm with a 95% CI of [7.3;3.5] mm. Therefore, the lower margin of the 95%CI of the difference in mean WOMAC A was higher than the pre-specified bound for non-inferiority. The OMERACT OARSI responder rates at day 180 were 83.0 and 85.7% in the HA and hylan groups, respectively (p=0.5809). Results were similar in the full analysis set (HA=139, hylan=141). Local reactions to the injection occurred in 8.4% of patients in the HA group vs. 13.0% in the hylan group. No serious reaction related to the injection was reported.

Maheu E et al (2016) used data from the clinical trial performed by Dreiser et al. (2015) and compared responder's rates using various definitions of response in a knee OA trial of i.a. HA, and to identify factors associated with a better response. As non-inferiority of the non-crosslinked HA was demonstrated over 6 months, data of both treatment groups were pooled (280 patients in the full analysis set, 266 completers). Uni- and multivariate stepwise regression analyses were performed to compare response criteria and identify potential factors associated with the best clinical response. OMERACT-OARSI responder criteria were compared to the Patient Acceptable Symptom State (≤40 mm) and minimum clinical important improvement (MCII, ≥15 mm improvement) responder criteria calculated for the following outcomes: pain using WOMAC A1 0–100 mm VAS format, physical function using WOMAC C (VAS format) and the 0–100 normalized Lequesne index, and patient global assessment (PGA) on a 0–100 mmVAS.

Results showed that the three most sensitive response instruments were the MCII (relative) for pain, followed by the OMERACT-OARSI responder criteria and the MCII (absolute) for pain with around 80% responders (Fig1). Factors associated with a better response were: a higher pain at baseline (OR [95%CI]: 1.05 [1.02; 1.08]), a shorter delay since diagnosis of knee OA (0.93 [0.88; 0.99]), bilateral knee OA (2.51 [1.11; 5.68], and a better PGA (i.e. a lower score; 0.95 [0.92; 0.98]).

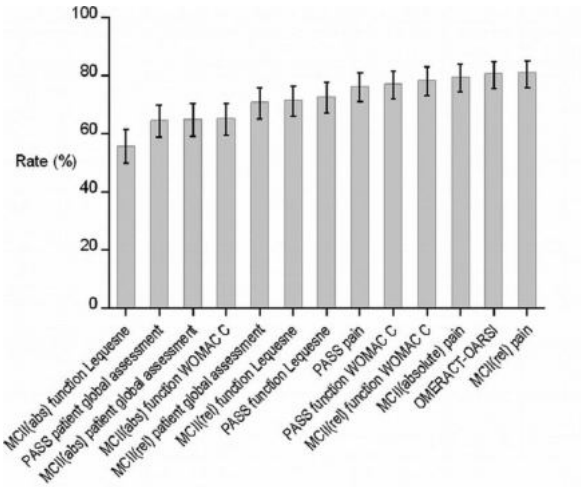


Fig. 1 Responder rates at 6 months using various response criteria (full analysis set, 280 patients)

In this analysis, comparing for the first time several definitions of therapeutic response in a clinical trial of IAHA in knee OA, it was concluded that MCII for pain and OMERACT-OARSI criteria seemed to be the most responsive outcome criteria. Response rates were higher in patients presenting with more pain at baseline, a shorter duration since diagnosis, bilateral knee OA and a better PGA.

In Summary:

- *Data were generated with **actual device**.*
- *Device was used within the **approved indications.***
- *Patients **are representative** of the intended treatment population and clinical condition.*
- *Outcome measures **reflect** the intended performance of the device.*
- *Duration of follow-up **is** long enough to assess whether duration of treatment effects and identify complications.*
- *Magnitude of the within-group treatment effect observed **is** clinically significant.*

Study results were presented by Dreiser at the World Congress on Osteoporosis, Osteoarthritis and Musculoskeletal Diseases WCO-IOF-ESCEO 2015 and with abstract and poster presentation and Maheu at the Annual European Congress of RHEUMATOLOGY EULAR 2016. Data were appraised critically and rated as clinically relevant. Results are suitable to show safety and efficacy of OSTENIL® PLUS in its indication and conformity with essential requirements.

5.3.1.2 Lertwanich P 2014

Clinicaltrials.gov Study 42 (NCT01288001) was performed by TRB Chemedica SA (Switzerland; Study N° OSTP-THA-10-01) in the Mahidol University, Faculty of Medicine Siriraj Hospital Bangkoknoi, Bangkok, Thailand.

First results were published by Chanin Lamsam in abstract format:

This clinical trial was performed to assess efficacy and safety of single dose i.a. injection of 2% HA in patients with osteoarthritis of the knee. 20 patients between 40-70 years old with OA of the knee (Kellgren-Lawrence grade II or III) were included in the study. After a 2-week NSAIDs washout period, 10 patients in the intervention group received one i.a. injection of 2 ml OSTENIL® PLUS and 10 patients in the control group received no injection. No other OA and pain-killer medication was allowed during the study except diclofenac as rescue pain medication. For efficacy WOMAC index and consumption of diclofenac and for safety evaluation all adverse events were recorded.

Results show that patients who received i.a. injection of 2% HA had a significant improvement from baseline on all WOMAC subscales over 24 weeks ($p < 0.001$), and had significant lower pain, stiffness and function subscale than control group from baseline until week 20, 12 and 16, respectively ($p<0.05$). The intervention group also required significant lower diclofenac consumption ($p<0.05$). No serious adverse events were reported. This study demonstrated efficacy and safety of single dose intra-articular injection of 2% HA for treatment of knee osteoarthritis over a 24-week period.

In Summary:

- *Data were generated with **actual device**.*
- *Device was used within the **approved indications**.*
- *Patients are **representative** of the intended treatment population and clinical condition.*
- *Outcome measures **reflect** the intended performance of the device.*
- *Duration of follow-up is **long enough** to assess safety and efficacy.*

As a clinical investigation report or publication are in preparation but not available yet, the published abstract was appraised critically and rated as clinically relevant. Results are suitable to show safety and efficacy of OSTENIL® PLUS in its indication and conformity with essential requirements.

5.3.1.3 Frobenius K 2009

Frobenius et al. (2009) reported for the first time, data on a new 'high dose treatment' in 25 patients with radiologically ascertained symptomatic osteoarthritis of the hip or knee joint. Within the scope of an open, prospective study patients received either one (in hip osteoarthritis) or three (in knee osteoarthritis) intra-articular injections of OSTENIL® PLUS, a new medical device for viscosupplementation, that contains 40 mg fermentative hyaluronic acid and 10 mg mannitol in one terminally sterilised pre-filled syringe with a 2 ml fill volume. In this formulation mannitol functions as a free-radical scavenger which will protect the exogenous HA from rapid depolymerisation, especially in the activated stage of osteoarthritis. When the test product was administered repeatedly, an interval of two weeks between injections was respected. In this study OSTENIL® PLUS proved to be safe and, in a high percentage of the patients, reliably effective. Of the 24 patients that were included in the analysis at the end of the study, 12 were free from pain on movement while 10 reported mild pain and 2 reported moderate pain. Regarding the global treatment satisfaction, both the investigator and patients assessed treatment as satisfactory in 87.5% of the cases. The tolerability of OSTENIL® PLUS was assessed as very good in 94.7% of the cases and good in 5.3%.

In Summary:

- *Data were generated with **actual device**.*
- *Device was used within the **approved indications.***
- *Patients are **representative** of the intended treatment population and clinical condition.*
- *Information in publication is of **high quality** to be able to undertake a rational and objective assessment.*
- *Design of the study **is** appropriate.*
- *Outcome measures **reflect** the intended performance of the device.*
- *Duration of follow-up **is** long enough to assess safety and efficacy.*
- *Statistical analysis of the data provided **is** appropriate.*

- *Magnitude of the treatment effect observed **is** clinically significant.*

This publication was appraised critically and rated as clinically relevant. Common types of bias are evaluated (Appendix 3), results are regarded as internal valid and generalizable, thus suitable to show safety and efficacy of OSTENIL® PLUS in its indication and conformity with essential requirements.

5.3.2 Clinical data from literature

5.3.2.1 Guler O 2015

This study aimed to compare short-term clinical outcomes between i.a. platelet-rich plasma (PRP) and HA treatments in early-stage gonarthrosis patients. Data of gonarthrosis patients, who were stage 1 or stage 2 according to Kellgren-Lawrence classification and underwent i.a. PRP or HA treatment, were obtained retrospectively. The patients received treatment for three times at one-week intervals (i.a. PRP or HA). They were evaluated using the Knee Society's Knee Scoring System (KSS) and the visual analog scale (VAS) scoring system before treatment and at the second and sixth months of treatment. The study included 132 patients (mean age, 55.06±8.41 years). 63 patients (86 knees) were in the HA group and 69 patients (89 knees) were in the PRP group. Changes in KSS and VAS scores over time and the differences between the treatment groups in terms of changes in KSS and VAS scores over time were significant.

In Summary:

- *Data were generated with **actual device**.*
- *Device was used for the **same use.***
- *Patients are **representative** of the intended treatment population and clinical condition.*
- *Information in publication **has minor deficiencies** to be able to undertake a rational and objective assessment.*
- *Design of the study **is not** appropriate.*
- *Outcome measures **reflect** the intended performance of the device.*
- *Duration of follow-up **is** long enough to assess whether treatment effects and to identify complications.*
- *Statistical analysis of the data provided **is** it appropriate.*
- *Magnitude of the treatment effect observed **is** clinically significant.*

This publication was appraised critically and rated as clinically relevant. Common types of bias are evaluated (Appendix 3), results are regarded as suitable to show safety and efficacy of OSTENIL® PLUS in its indication and conformity with essential requirements.

5.3.2.2 Borrás-Verdera A 2013

A pilot, multicenter, open, non-comparative study was performed by Borrás-Verdera and colleagues[43] and results were first presented as a poster and abstract (abstract no. 28398) at

conference of Société Internationale de Chirugie Othopédique et de traumatology (SICOT) in Prague September 2011.

Safety and efficacy of a single intraarticular injection of 2% HA + 0.5% mannitol was evaluated in 80 patients with painful knee osteoarthritis. They received one injection of 2 ml of 2% HA + 0.5% mannitol (Day 0) and were followed-up for 6 months, with assessments on Days 0, 15, 30, 60, 90, 120, 150 and 180. Clinical evaluation of pain and joint function was performed using a visual analogical scale (VAS) and WOMAC index. The opinion of both the investigator and the patient on efficacy and safety was recorded. Rescue medication was also quantified. A significant reduction in joint pain, stiffness and functional disability compared with baseline was observed at every follow-up visit ($p<0.001$), starting on Day 15. Joint pain improved by 40.7% (VAS) and 38.7% (WOMAC) on Day 30, reaching 46.5% and 47.5% on Day 180, respectively. Habitual rescue medication intake decreased from 58.2% at baseline to 2.5% on Day 90 and increased at the last visits. Efficacy and safety evaluations by investigators and patients were considered excellent throughout the study. No serious adverse events were observed. Mild side effects were reported on Day 15 in 4 patients (local pain and swelling in the area of infiltration). Results showed that one single intra-articular injection of 2% HA + mannitol is effective in reducing pain and improving joint function in patients with knee osteoarthritis over a period of at least 6 months.

In Summary:

- *Data were generated with **actual device**.*
- *Device was used for the **same use.***
- *Patients are **representative** of the intended treatment population and clinical condition.*
- *Information in publication is of **high quality** to be able to undertake a rational and objective assessment.*
- *Design of the study **is** appropriate.*
- *Outcome measures **reflect** the intended performance of the device.*
- *Duration of follow-up **is** long enough to assess whether treatment effects and to identify complications.*
- *Statistical analysis of the data provided **is** appropriate.*
- *Magnitude of the treatment effect observed **is** clinically significant.*

This publication was appraised critically and rated as clinically relevant. Common types of bias are evaluated (Appendix 3), results are regarded as suitable to show safety and efficacy of OSTENIL® PLUS in its indication and conformity with essential requirements.

5.3.2.3 Colen S 2010

A randomized, controlled trial with a three-armed, parallel-group design was planned by Colen and co-workers (2010). 315 patients complying with inclusion and exclusion criteria were randomized into one of the following treatment groups: infiltration of the hip joint with hyaluronic acid, with a corticosteroid or with 0.125% bupivacaine. The following outcome measure instruments were assessed at baseline, before the intra-articular injection of one of the study products, and then again at six weeks, 3 and 6 months after the initial injection: Pain (100 mm VAS), Harris Hip Score and HOOS, patient assessment of their clinical status (worse, stable or better then at the time of enrollment) and intake of pain rescue medication (number per week). In addition patients were

asked if they have complications/adverse events. A six-month follow-up period for all patients was planned.

In Summary:

- *Data were generated with **actual device**.*
- *Device was used for the **same use.***
- *Patients are **representative** of the intended treatment population and clinical condition.*
- *Information in publication **has minor deficiencies** to be able to undertake a rational and objective assessment.*
- *Design of the study **is** appropriate.*
- *Outcome measures **reflect** the intended performance of the device.*
- *Duration of follow-up **is** long enough to assess whether treatment effects and to identify complications.*
- *Statistical analysis of the data provided **is** appropriate.*
- *Magnitude of the treatment effect observed **is** clinically significant.*

Study protocol and data from biostatistical report were appraised critically and rated as clinically relevant. Common types of bias are evaluated (Appendix 3) and results are regarded as suitable to show safety and efficacy of OSTENIL® PLUS in its indication and conformity with essential requirements.

5.3.3 Overall Conclusion on Clinical Efficacy

The publication of an article in a peer-reviewed journal is an essential building block in the development of a coherent and respected network of knowledge. It is a direct reflection of the quality of work of the authors and the institutions that support them. Peer-reviewed articles support and embody the scientific method.

Case-series is a descriptive study design and in terms of generating evidence regarding various aspects of the disease process, a case-series is generally assumed a weak study design. The main advantage of this method is that it minimizes confounding due to its within-person design, where the patients act as their own control. The within person design controls implicitly for fixed known and unknown confounders that do not vary over time. If patients feel better (or return to work) after a procedure or other treatment, how do we know whether this is the result of the efficacy of the procedure or the natural history of the disease under study?

Limitations of case series often result from small sample sizes. On the one hand, a larger sample size provides more data so that estimates of performance have less sampling variability and hence become more precise. On the other hand, larger sample size can also result in an analysis for a clinically insignificant outcome that demonstrates it is statistically significant. Studies should be designed to show both clinical and statistical significance. It is also important to note that increased sample size will not necessarily address issues of bias, inappropriate outcomes assessment, a marginal improvement in outcomes that fails to show clinical relevance, or other study design problems.[90]

With this background and in compliance with characteristics of good case series (that are but are not limited to: clearly defined question, well-described study population, well-described intervention, use of validated outcome measures, appropriate statistical analyses, well-described results, discussion/conclusions supported by data, and funding source acknowledged) the

appraised publications from literature search and from clinical studies performed by TRB Chemedica as sponsor) are regarded as sufficient and suitable to show conformity of OSTENIL® PLUS with the essential requirements.

The available clinical data show that the intra-articular injection of OSTENIL® PLUS in patients with degenerative and traumatic joint problems results in a rapid onset of efficacy and a long-lasting beneficial effect on pain and reduced function after treatment.

5.4 Safety Relevant Data

5.4.1 Literature Evaluation

Intra-articular HA is well tolerated and is associated with a low prevalence of local adverse events. The prevalence of AEs from clinical studies was approximately 2% to 5% of injections, and 5% to 10% of patients, comparable to the rate observed with i.a. saline placebo. Because HA products are locally delivered, most adverse events are local in nature. The large majority of reactions consist of local pain, warmth, and minimal swelling that last 24 to 48 hours **(Benke et al., 2009**[39]**)**. These are self-limited in that they resolve without treatment, they do not necessarily recur with subsequent injection, and discontinuation of treatment is unnecessary **(Goldberg et al., 2004**[114]**)**. There are no known crossreactions with other medications **(Benke et al., 2009**[39]**)**.

However, products on the market with the source from rooster combs may induce systemic hypersensitivity reactions in patients allergic to avian proteins. In a recent comparison of avian and non-avian origin HA in the treatment of knee OA during a long-term follow-up **Petrella et al. (2010)**[245] enrolled 4,412 patients on a consecutive basis from all referrals received from 1997 to 2007. There was a significantly greater number of adverse events (4.8% versus 1.7%; $p < 0.01$) in the avian- compared to non-avian originated HA treated patients.

Reviewers from meta-analyses examining adverse events have concluded that HA for knee OA seems well tolerated and safe **(Espallargues et al. 2003**[84]**)**, is associated with few AEs **(Wang et al. 2004**[313]**)**, generates minor side effects **(Aggarwal et al. 2004**[3]**)**, leads to more AEs than controls **(Arrich et al. 2005**[14]**)**, is safe with repeated treatments **(Pagnano et al. 2005**[240]**)**, and seems safe **(Bellamy et al. 2006a**[36]**)**. Reviewers described small relative increased risk. **Wang et al. (2004)**[313] reported a pooled relative risk for minor events of 1.2 (95% CI: 1.01 to 1.41) and **Arrich et al. (2005)**[14] 1.08 (95% CI; 1.01 to 1.15). **Bellamy et al. (2006a)**[36] estimated a pooled relative risk for local reactions accompanying hylan G-F 20 (5 RCTs) of 1.9 (95% CI: 0.51 to 7.3, five RCTs) and other hyaluronans (5 RCTs) of 1.6 (95% CI: 0.54 to 5.6).

Rare but serious AEs, including severe acute inflammatory reaction, infection, allergic reaction, and anaphylaxis, have been reported with HA and hylan G-F 20 **(Hamburger et al. 2003**[133]**)**. A Canadian post-marketing surveillance study of 1,537 hylan G-F 20 injections given to 336 patients with knee OA reported 28 local AEs **(Hammesfahr et al. 2003**[136]**)**. A study of 4,253 patients receiving 12,699 i.a. injections of hylan G-F 20 for knee OA from 840 physicians in Germany reported 365 AEs, including one serious AE **(Kemper et al. 2005**[168]**)**.

The most frequent AEs were local effusion (2.4%), swelling (1.3%), arthralgia (1.2%), warmth (0.6%), and erythema (0.3%). Over 60% were mild to moderate. No major safety issues were detected, apart from some local adverse events such as transient pain and swelling at the injection site (RR = 1.49, 95% CI 1.21, 1.83) **(Bellamy et al. 2006a[36])**.

Furthermore in the Cochrane Review mentioned above **(Bellamy et al, 2006a[36]),** the authors conclude that intra-articular hyaluronan does not statistically significant differ from placebo for the following parameters:

- total withdrawals overall (1 to 4 weeks, 5 to 13 weeks, 14 to 26 weeks, 45 to 52 weeks postinjection),
- patients with local adverse reaction and study drug discontinued,
- number of patients with local adverse reaction but study drug continued,
- number of patients discontinued due to adverse events,
- withdrawals due to lack of efficacy,
- number of adverse events due to local skin reaction,
- number of patients with gastro-intestinal complaints,
- number of patients with treatment related adverse events,
- number of patients with possible study medication related events,
- number of serious adverse events,
- number of adverse events probably/possibly related to treatment,
- number of patients reporting adverse events.

A statistically significant event favouring placebo was noted in the number of adverse events for injection site pain (RR 1.70; 95%CI 1.19 to 2.44, p value 0.004).

Altogether only few adverse events were found by the reviewers in the analysed clinical studies with hyaluronan/hylan, these involved few systemic and more local reactions.

The results from safety evaluation in literature regarded as relevant for this CER indicate that i.a. treatment with linear HA ≥1.5% is well tolerated (see Appendix 3 for tabular presentation of safety results.

5.4.2 Common complications

The practice of chronic pain management has grown steadily in recent years. Consequently, prevention of complications should be one of the most important aspects of interventional pain management. This requires an adequate appreciation of the risks and complications associated with the procedures. It is difficult, however, to know the true incidence of complications.[62] This is mainly due to the facts that such complications are usually under reported, that there is limited statistical analysis of such incidences, and that only a small fraction of such complications ends up in litigation.[62] A differentiation between complication due to injection procedure itself and/or administered substance is important. In case of HA injections it further has to be differentiated

between fermentative and extractive as well as between the naturally found linear and chemically cross-linked (hylans) products.

Despite extensive evidence to the contrary,[14,32,33,67,207,257,313] the safety of viscosupplementation for knee OA has recently been called into question.[261] In a review and meta-analysis performed by **Strand and co-workers (2015)**[287] the safety of US-approved viscosupplements for symptomatic knee OA was determined. MedLine and EMBase were searched for randomized, sham-controlled trials evaluating patients with symptomatic knee OA. Knee pain severity and knee joint function were assessed at 4 to 13 weeks and 14 to 26 weeks. Safety outcomes included serious adverse events, treatment-related serious adverse events, patient withdrawal, and adverse event-related patient withdrawal occurring at any time during follow-up. There were no statistically significant differences between viscosupplementation and controls for any safety outcome, with absolute risk differences of 0.7% (95% confidence interval [CI]: -0.2 to 1.5%) for serious adverse events, 0% (95% CI: -0.4 to 0.4%) for treatment-related serious adverse events, 0% (95% CI: -1.6 to 1.6%) for patient withdrawal, and 0.2% (95% CI: -0.4 to 0.8%) for adverse event-related patient withdrawal.

No significant systemic side effects with HAs/hylans have been reported in patients, including gastrointestinal, cardiovascular, and renal events.[115,50,311] Overall, HAs/hylans are well tolerated with few AEs in patients, which are mostly local; however, the way AEs are reported differs among, randomized, placebo-controlled trials.[254] Local AEs are typically mild to moderate, transient, usually occur within the first 2 days of injection and resolve spontaneously.[311] Minor side effects include pain at the injection site, local joint pain and swelling, and local skin reactions.[78] However, the overall incidence of these local events in patients is low, ranging from 0% to 14% for HAs.[10,58,123,154,210,286] The local AE incidences with HAs/hylans are similar to those reported with intra-articular saline[323] or steroid injections.[106,54] More serious side effects can occur. Pseudoseptic reactions (occurring in 1 to 3% of patients), which are characterized by inflammation and swelling of the joint that are not caused by infection, can be severe and may require further medical treatment. These reactions usually occur after sensitization with the second or third injection of a series or with a repeat treatment course. True joint infections also have been reported, but these appear to be rare.[5]

Some forms of HA may cause these adverse effects more frequently than others. A meta-analysis of AEs showed that the frequency of flares of pain and swelling was higher after i.a. injections of high molecular mass hylan (a modified form of HA) than after injections of the standard form of i.a. HA (relative risk, 2.04; 95% confidence interval [CI], 1.18 to 3.53).[257] There is increasing evidence that the cross-linked hylans (eg, G-F 20) are associated with a higher incidence of pseudosepsis, also known as severe acute inflammatory reaction, which is more severe and is distinct from the milder forms of inflammatory reactions seen. Pseudosepsis is defined as a severe reaction that occurs within 24-72 hours after the injection, which may occur as a result of a reaction to the formaldehyde and vinyl sulfone associated with the chemical cross-linking of high molecular weight hylans.[114]

Avian derived proteins have been shown to be the cause of injection site flare up, as antibodies to chicken serum protein were present in patients who demonstrated injection site adverse reaction after being treated with avian derived extractive HA.[114]

A recent review by Rutjes et al.[261] raised concerns about an increased risk of serious adverse events (relative risk, 1.41; 95% CI, 1.02 to 1.97), including gastrointestinal and cardiovascular adverse events and cancer. It is difficult to interpret these data[215] because of limitations of transparency in the study reporting and the biologic implausibility of some of the adverse events (especially with regard to cancer[286]) relative to the timing of treatment administration.

In general, the incidence of local side effects with HA is comparable with that of intra-articular steroid therapy[54,106] or saline injections. [10,45,286]

5.4.3 Results from studies with OSTENIL® PLUS

Information concerning adverse events from publications and from Clinical Investigation Reports (if available) are listed in Table 7. Events in studies with OSTENIL® PLUS are assumed to be related in very few cases with the application of HA itself. The most common adverse reaction to these medications is an inflammatory response at the injection site, characterized by local swelling and associated pain and comply with common complications found by literature search and published in public journals. Although the correlation with the reaction to a foreign body is evident, the molecular mechanisms behind the pathogenesis are still unknown.

Table 7 Safety information

Publication	Site	Information from publication
Guler O 2015	knee	….none of the patients developed major complication. *HA as control group.*
Borrás-Verdera A 2013	knee	Regarding safety, no severe adverse effects were observed during the study. Mild adverse effects were reported in the second follow-up visit by 5.06% of patients (n = 4). These adverse effects consisted of mild pain and swelling in the area of infiltration in all cases, and disappeared during subsequent visits. The excellent safety profile of the treatment resulted in a positive benefit/risk ratio for patients.
Frobenius K 2009	knee, hip	The tolerability of Ostenil® Plus was assessed as very good in 94.7% of the cases and good in 5.3%. No adverse events that could be attributed to the test product were observed.
Dreiser RL 2015	knee	Local reactions to the injection occurred only in 8.4% of patients in the SH group versus 13.0% in the hylan group. No serious reaction related to the injection was reported.
Maheu E 2016	knee	*Safety results not mentioned, but identical to Dreiser RL 2015.*

5.4.4 Summary and conclusion

The highly pure fermentative hyaluronan in OSTENIL® PLUS corresponds to the quality standards of the European Pharmacopoeia for the i.a. application. Internal and published data on the biocompatibility of hyaluronan, which demonstrate the exceptionally good compatibility and the lack of antigenicity of this natural biopolymer, are available. Results of pre-clinical evaluation show an excellent safety profile for hyaluronan in OSTENIL® PLUS.

The biological evaluation of the finished medical device OSTENIL® PLUS was performed according to EN ISO 10993-1. The biocompatibility tests with the finished product VISIOL® which is identically equal to OSTENIL® PLUS besides the filling volume showed good tolerance. Neither in-vitro tests on cytotoxicity nor the in-vivo tests comprising implantation, systemic toxicity,

intracutaneous reactivity and sensitization showed signs of incompatibilities. A reverse mutation assay using bacteria and chromosome aberration tests in human lymphocytes showed no genotoxic potency.

OSTENIL® PLUS is presented in a pre-filled syringe, which is sealed in a sterile blister and then terminally sterilized by moist heat. The validation data proves that, with the procedures applied, both the solution in the pre-filled syringe as well as the outer surface of the syringe are sterilised.

No safety concerns are assumed for the device OSTENIL® PLUS.

After a careful review and evaluation of data from relevant studies on the safety and biocompatibility of fermentative SH, together with data on SH from the supplier HTL, biocompatibility data obtained using applicable standards of the EN ISO 10993 as well as from published clinical studies, the medical device OSTENIL® PLUS can be described as safe.

5.5 Tabular Presentation of Relevant Clinical Studies

Table 8 Tabular presentation of relevant clinical studies

Publication							Safety data / Complication rates			
Author	Year		Product	Level of Evidence	N [(b)]	Drop-outs	Immediate/ early	Late	Other	Remarks
Dreiser RL / Maheu E (France)	2015 / 2016	Congress abstracts and poster	Ostenil Plus vs. hylan G-F 20	Ib	142 vs. 146	8 vs. 14	Local reactions to the injections: 8.4% in Ostenil Plus group and 13.0% in hylan group	---	---	292 randomized / 266 completers. No SAE related to injections.
Lertwanich P (Thailand)	2014	Abstract	Ostenil Plus	IIb	20	No data available.	Study report in preparation.	Study report in preparation.	Study report in preparation.	10 patients in untreated control group, no SAE.
Fobenius (Germany)	2009	Publication	Ostenil Plus	IV	25	1 (AE)	No adverse reaction related to investigational product itself was reported in the patients or observed by the investigator.		---	Case series. No SAE related to injections.
Guler O (Turkey)	2015	Publication	Ostenil Plus	III	63 (86 knees)	NA	NA	NA	NA	69 (89 knees) in control group
Borrás-Verdera A (Spain)	2011 / 2013	Study report / Publication	Ostenil Plus	IV	80	No data available.	Mild side effects were reported during the second visit in 4 patients (local pain and swelling in the	none	---	Case series. No SAE.

Publication							Safety data / Complication rates			
							area of infiltration)			
Colen S (Belgium)	2010	Study protocol (Publication), Statistical report	Ostenil Plus	NA	105	No data available.	No data available.	No data available.	No data available.	2015 patients in control groups

5.6 Usability

The application of usability engineering to the medical device OSTENIL® PLUS according to DIN EN 62366 is addressed in the document “Usability Engineering File: Pre-filled syringes 1.25ml/3ml supplied by BD, filled with a viscoelastic solution, sealed in a sterile barrier system”.

The investigation concludes:
Developing pre-filled syringe designs and SBS that are ergonomic, usable, human-centered and robust requires consideration of many different factors and contexts. By maintaining a focus on the unique needs of the target user audience the TRB Chemedica AG medical devices equipped with BD syringes 1.25ml/3ml greatly increase healthcare professional and patient safety, performance and satisfaction. For the document, please refer to section B 2 of the Design Dossier.

The favourable usability is achieved by the successful mitigation of all foreseeable risks possibly caused by usability problems associated with the use of OSTENIL® PLUS within its indications.

After consideration of all accessible data it can be stated that all remaining risks associated with handling and application of the medical device are acceptable, confirming the positive benefit-risk-assessment for user and patient. The conclusion of the risk management plan, analysis and report on the medical device OSTENIL® PLUS that the benefit of treatment far outweighs the presumable risks due to specific hazards can be enforced.

5.7 Appropriateness of Product Related Documents from Manufacturer

OSTENIL® PLUS is produced under controlled conditions which guarantee that OSTENIL® PLUS can be reproduced consistently in the same quality. For the description of the manufacturing process and quality control steps reference is made to the Design Dossier and the underlying Quality Management System.

The applicable Essential Requirements of MDD and standards are identified in the Essential Requirements Checklist (section B1 of the Design Dossier).

Product and process risks are documented in the Risk Management Report.

At the early stage of development several literature evaluations and in vitro studies have been performed for selection of the component SH. These data provided the first insight into the biological safety and effectiveness aspects of SH as candidate for further development and resulted in the final product specification. OSTENIL® PLUS was developed based on the SH as important active component and the favourable clinical experience combined with the use of OSTENIL®.

Based on that specification the biological safety evaluation of OSTENIL® PLUS was performed. An own report exists for the biocompatibility of OSTENIL® PLUS to which reference is made.

In addition, a literature review was performed according to MEDDEV 2.7.1 and EN ISO 14155 focusing on equivalent products with regard to their clinical safety and effectiveness, in order to justify the need of a clinical investigation and to achieve essential information on the benefits and risks of OSTENIL® PLUS.

Agreement of the safety and performance characteristics claimed by the manufacturer of OSTENIL® PLUS with published data is evaluated and documented.

Clinical studies are in compliance with existing guidance and legal binding documents.

In summary, after an analysis of the available pre-clinical, clinical and technical data it is determined that product related documents are appropriate to show that the medical device OSTENIL® PLUS corresponds to the pre-determined performance characteristics.

5.8 Results and Evaluation from Post-market Surveillance

TRB Chemedica AG maintains a medical device surveillance system, which meets the regulatory requirements (MEDDEV and national legislations) for the documentation, evaluation and reporting of so-called medical complaints. Technical complaints are also included. Where necessary, CAPAs ('Corrective Actions Preventive Actions') are initiated. The co-distributors of the medical devices are committed to reporting complaints of any type to TRB Chemedica AG. Customer complaints generally reach TRB Chemedica AG from wholesalers, pharmacies, doctors, co-distributors and, in some cases, patients. In individual cases, TRB Chemedica AG receives reports from the responsible Competent Authority. Medical complaints are statistically analysed for information about the nature of the respective complaints and any obvious trends.

The following data were obtained from the first launch of the reference product OSTENIL® PLUS in 2009 up to the data lock point 31st March 2016 and includes the whole OSTENIL® PLUS range of products (OSTENIL® PLUS, HYA-JECT® PLUS, OST® PLUS, MAXIOSTENIL® PLUS).

5.8.1 Sales Data

Since February 2009 OSTENIL® PLUS is marketed with the indication "pain and restricted mobility in degenerative and traumatic changes of the knee joint and other synovial joints".

Table 9 Sales Data

Product (incl. variants)	Period	No of units sold (secondary sales)
OSTENIL® PLUS	From 2009-02 to 2016-03	944.335 syringes

5.8.2 Product history: Medical and technical complaints

Since launch to March 2016 26 medical complaints, consisting of 42 single symptoms, were reported to TRB Chemedica AG. The medical complaint rate was calculated to be 0.002 % for OSTENIL® PLUS or 1 complaint per 36 321 sold syringes (Table 10). Neither of the reports was

judged as serious adverse event. Therefore, no case report was submitted to competent authorities. Neither quality nor quantity of the reported medical complaints gave reasons for safety concerns of the products under review. The presumed benefit of the treatment outweighs the small risk of occurrence of adverse events by far.

Table 10 Medical complaints

Product	Reporting period	Number of medical complaints	Total medical complaint rate	Cases reported to CA
OSTENIL® PLUS and parallel products	2009-02 to 2016-03	26	0.002 %	5

In the period from launch to March 2016, 40 technical complaints were reported to TRB Chemedica AG. Since the switch back from Schott- to BD-syringes in 2011 32 technical complaints within a number of 753 190 sold syringes were issued to TRB Chemedica, see Table 11 below. No field safety corrective actions were necessary.

Table 11 Technical complaints

Product	Reporting period	No of technical complaints	Technical complaint rate [%]	Total technical complaint rate*
OSTENIL® PLUS and parallel products	2009-02 to 2016-03	40	0.004 %	1 Complaint per 23 608 units
OSTENIL® PLUS and parallel products	2012-02 to 2016-03	32	0.004 %	1 Complaint per 23 537 units

5.8.3 Summary from Post-market Surveillance OSTENIL® PLUS

The summary report for i.a. products of TRB Chemedica AG in the post-market phase collects safety related data from health agencies, scientific literature, and internal sources of TRB like complaint statistics, clinical evaluation reports, risk analyses, clinical studies, and user reflections. After review of all accessible data concerning safety and efficacy of i.a. products of TRB can be concluded:

- There is no knowledge of worsening long-term performance or decreasing reliability nor information about chronic complications after use of either medical device under review;
- There is no evidence for the existence of so far unknown risks related with the application of i.a. medical devices of TRB Chemedica AG or comparable devices of other manufacturers;
- There is no evidence for the existence of so far unknown risks related with the application of peritendinous/intrasheath medical devices of TRB Chemedica AG;
- There is no information about deliberate misuse of the devices;
- There is no evidence that i.a. viscoelastic supplementation is not longer regarded as state-of-the-art treatment option;

In conclusion the risk-benefit ratio, weighing the limited probability of mild adverse reactions against the expected benefit of reduced pain and improved mobility, remains positive in TRB AG i.a. medical devices.

6. RISK-BENEFIT- RATIO

The benefits of i.a. HA-treatment has been demonstrated by many years of successful therapeutic use reported in numerous publications. The treatment concept of viscosupplementation - “where the joint is supplied with what is missing” – guarantees the optimal availability of the active ingredient at the site where it will carry out its effects, with only a minimal involvement of the other organ systems, and with an uncomplicated metabolisation and excretion of the active ingredient. This treatment option is especially important for patients in whom other medications may be contraindicated. HA treatment has a rapid onset of effect on reducing pain and improving function and this persists for a moderate period time after treatment. Evaluation of efficacy and safety of OSTENIL® PLUS is given in this CER from scientific literature as well as from clinical studies. They clearly show that the i.a. injection of OSTENIL® PLUS in patients with degenerative and traumatic joint problems results in a rapid onset of efficacy and a long-lasting beneficial effect on pain and reduced function after treatment. Data are further supported by the comparable medical devices OSTENIL®/OSTENIL® MINI (TRB Chemedica AG) with identical composition but 1% HA concentration: very satisfactory effects have been reported with a low incidence of medical problems.

The highly pure fermentative SH in OSTENIL® PLUS corresponds to the quality standards of the European Pharmacopoeia for i.a. SH. Internal and published data on the biocompatibility of HA, which demonstrate the exceptionally good compatibility and the lack of antigenicity of this natural, physiologically in human present biopolymer, are available. The biocompatibility was shown in appropriate studies conforming to the EN ISO 10993 standards. Data from the clinical studies with OSTENIL® PLUS as well as data from the medical device vigilance system indicate that this medical device causes mostly locally limited, non-serious adverse events.

The possible risks for the patient arise mainly from the compatibility of the active ingredient and from the intervention, namely the i.a. injection. By correctly observing the pre-determined guidelines issued by the specialist societies, such risks are minimal as demonstrated by the data from the medical device surveillance system. The possible risks from the application of the active ingredient HA are apparently theoretical in nature: in toxicological studies, no LD_{50} values could be ascertained for this substance for technical reasons given that it is very similar to endogenous HA. When used at the therapeutic dose, which according to its pharmacokinetic characteristics, is clearly lower than the amounts of endogenous HA, it is metabolised every day and is subsequently also synthesised.

The potential misuse of each medical device of TRB Chemedica AG is discussed in the respective Risk-Management-Files. OSTENIL® PLUS is intended “to be used by a physician only”. This safety advice is printed on the outer carton box and leaflet. Therefore, the potential of misuse is minimal.

Nevertheless, in case of any conceivable misuse either by oral, epidermal, intradermal or ocular administration there will not be any adverse reaction. In the contrary TRB Chemedica AG markets certified medical devices with sodium hyaluronate for dermal, subcutaneous and ocular administration and food supplements for oral administration. Even with high doses no serious adverse events, if any, are expected, irrespective of the way of administration, as HA is a physiologically in humans present non-toxic and nonimmmunogenic substance (as detailed in the biological evaluation report).

Finally the benefits and risks of i.a. HA treatment must be seen in the context of the available therapeutic alternatives. Beside physical therapy, medications that offer the advantage of a quick onset of analgesic action are used for a short time (the patient therefore feels better faster), but these have considerable adverse effects. I.a. corticosteroids can be very helpful because of their reliable anti-inflammatory effect but their use is limited due to their negative influence on the immune system as well as on sugar and bone metabolism. Non-steroidal anti-rheumatic drugs (NSAR/NSAID), in different presentations, are another alternative; their effects are also quite reliable but the incidence of their adverse events, especially at the level of the gastrointestinal tract, is quite high (up to 25%) and on occasions are deleterious (stomach bleeding, perforating ulcers). Concerning their mechanism of action, both corticosteroids and NSAR lower the permeability of the cell membrane. This has been shown to unfavourably influence cartilage structure both in chondrocyte cultures and clinically.

Taking into account the low rate of medical complaints (0.002%), the most time local limitation of adverse events after i.a. administration, the lack of low-risk alternatives and the successful therapeutic use in osteoarthritis, the benefit-risk-assessment is clearly in favour of OSTENIL® PLUS. For detailed information please refer to the ‘Risk Management Plan Analysis and Report’ in the Design Dossier for OSTENIL® PLUS Section B1.

OSTENIL® PLUS can be characterised as a “low risk - high benefit – product”. OSTENIL® PLUS does not incorporate features which lay over the criteria for an acceptable risk as recorded by TRB Chemedica AG. The high benefit is well documented in this clinical report of the medical device.

Considering all the performance and safety data, it can be determined that the benefits of the use of OSTENIL® PLUS, within the pre-determined field of application, clearly outweigh the possible risks.

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8. TEXT OF THE PACKAGE INSERT

INSTRUCTIONS FOR USE

OSTENIL® Plus
Sodium hyaluronate from fermentation 2.0 %. Viscoelastic solution for injection into the joint cavity. Sterile by moist heat.

Composition:
1 ml isotonic solution (pH 7.3) contains 20.0 mg sodium hyaluronate from fermentation and sodium chloride, disodium phosphate, sodium dihydrogen phosphate, mannitol and water for injections.

Indications:
Pain and restricted mobility in degenerative and traumatic changes of the knee joint and other synovial joints.

Contra-indications:
OSTENIL® Plus should not be used in patients with ascertained hypersensitivity to one of the constituents.

Interactions:
No information on the incompatibility of OSTENIL® Plus with other solutions for intra-articular use is available to date. The concomitant use of an oral analgesic or anti-inflammatory drug during the first few days of treatment may be helpful for the patient.

Side effects:
Local secondary phenomena such as pain, sensation of heat, redness and swelling may occur in the joint treated with OSTENIL® Plus. Application of an ice pack for five to ten minutes onto the treated joint will reduce the incidence of these events.

Directions for use:
Inject OSTENIL® Plus into the affected joint once a week for a total of 1–3 injections. Several joints may be treated at the same time. Repeat treatment cycles may be administered as required. In case of joint effusion it is advisable to reduce the effusion by aspiration, rest, application of an ice pack and/or intra-articular corticosteroid injection. Treatment with OSTENIL® Plus can be started two to three days later.
The content and the outer surface of the OSTENIL® Plus pre-filled syringe are sterile as long as the sterile pack is intact. Take the pre-filled syringe out of the sterile pack, unscrew the Luer lock cap from the syringe, attach a suitable needle (for example 18 to 25 G) and secure it by turning slightly. Remove any air bubble, if present, before injection.

Precautions:
Caution should be exercised in patients with known hypersensitivity to drugs. The general precautions for intra-articular injections should be observed, including measures to avoid joint infections. OSTENIL® Plus should be injected accurately into the joint cavity, if necessary under imaging control. Avoid injections into blood vessels or surrounding tissues! As no clinical evidence is available on the use of hyaluronic acid in children, pregnant and lactating women or in inflammatory joint diseases such as rheumatoid arthritis or Bechterew disease, treatment with OSTENIL® Plus is not recommended in these cases. Do not use if the pre-filled syringe or sterile pack are damaged. Any solution not used immediately after opening must be discarded. Otherwise the sterility is no longer guaranteed. Store between 2 °C and 25 °C! Do not use after the expiry date indicated on the box.
Keep out of the reach of children!

Characteristics and mode of action:
Synovial fluid, which is viscoelastic due to the presence of hyaluronic acid, is found in all synovial joints, particularly the large weight bearing joints, where it ensures normal, painless movement due to its lubricating and shock-absorbing properties. It is also responsible for the nutrition of the cartilage. In degenerative joint disorders such as osteoarthritis, the viscoelasticity of the synovial fluid is markedly reduced thereby decreasing its lubricating and shock-absorbing functions. This increases mechanical loading of the joint and cartilage destruction which ultimately results in pain and restricted mobility of the affected joint. Supplementing this synovial fluid with intra-articular injections of highly purified hyaluronic acid can ameliorate the viscoelastic properties of synovial fluid. This improves its lubricating and shock-absorbing functions and reduces mechanical overload of the joint. As a rule this results in a decrease in pain and an improvement in joint mobility which may last for several months after a treatment cycle.
OSTENIL® Plus is a transparent solution of natural and highly purified sodium hyaluronate obtained by fermentation and is devoid of animal protein. OSTENIL® Plus also contains mannitol, a free radical scavenger, which helps to stabilise the chains of sodium hyaluronate. In biocompatibility studies, OSTENIL® Plus was found to be particularly safe.

Presentation:
One pre-filled syringe of 40 mg / 2.0 ml OSTENIL® Plus in a sterile pack.

OSTENIL® Plus is a medical device. To be used by a physician only.

Last revision date: December 2010

9. APPENDICES

Appendix A 1 The literature search protocol

Literature Search Protocol

Clinical Evaluation Report OSTENIL® PLUS 2016-06-28

According to Directive 93/42/EEC (2007), MEDDEV 2.7.1 Rev.3 (2009)
and GHTF SG5/N1/R8:2007

General criteria and strategy for the literature review are given in this document. The literature search process itself and the results of the literature search are presented within the Literature Search Report of the clinical evaluation (see Clinical Evaluation Report Appendix A2).

The objective of the literature review is to find clinical data supporting the performance and safety aspects of the product to be assessed, as well as of the equivalent competitor products. All relevant publications will be presented independently from study findings.

The studies and publications identified by the literature search will be selected according to their equivalence and impact on performance and safety. Citations that are not relevant to the topic will be excluded and not processed any further. The relevance to the topic is decided on the basis of the inclusion and exclusion criteria and on the equivalence to the product to be assessed. Potentially relevant citations (which are initially relevant to the topic) are reviewed in detail and if necessary excluded giving reasons or further processed to literature evaluation. A summary of this process is documented in the flow chart of Appendix A2.

1. Data sources used

1.1 Literature data base search

A number of databases were identified, which were thought to be most suitable for conducting this specific application, including PubMed (Medline), Google and references from literature.

Literature sources used to identify data include but are not restricted to:

- bibliographic databases: PubMed/MEDLINE/PMC, CENTRAL, DIMDI
- clinical trial registry platforms: WHO International Clinical Trials Registry Platform (http://www.who.int/ictrp/en/) and the US National Institutes of Health (https://clinicaltrials.gov/).
- professional journal(s) not referenced in Medline

- literature from own studies (published and unpublished) with TRB Chemedica products
- cross-referenced literature

MEDLINE is the National Library of Medicine (NLM) journal citation database. The MEDLINE database is directly searchable from NLM as a subset of the PubMed database (MEDLINE the largest subset of PubMed) as well as through other numerous search services that license the data. In addition to the comprehensive journal selection process, what sets MEDLINE apart from the rest of PubMed is the added value of using the NLM controlled vocabulary, Medical Subject Headings (MeSH), to index citations. MEDLINE data base was chosen for literature search because articles go through quality control and are indexed with MeSH or converted to out-of-scope status.

CENTRAL (Cochrane Central Register of Controlled Trials).

DIMDI (Deutsche Institut für Medizinische Dokumentation und Information) is used for search in about 40 databases which contain scientific literature references and facts from the field of medicine, drugs, toxicology, medical devices, biology and psychology. Search is restricted on publication titles, as this database is not free of charge.

PMC (PubMed Central) is a free archive for full-text biomedical and life sciences journal articles and is used for hand search.

Depending on the research question, and if available, disease specific journal web pages which are not indexed in MEDLINE (e.g. “Cartilage” in the orthopedic field) or from professional societies will be subjected to searched.

Identification of unpublished and ongoing trials: WHO International Clinical Trials Registry Platform (http://www.who.int/ictrp/en/ and the US National Institutes of Health https://clinicaltrials.gov/). Including a search for unpublished trials is useful to assess the presence and magnitude of publication bias.

1.2 Data from clinical experience

Data generated through clinical use outside the conduct of clinical trials may include:

- Manufacturer-generated post-market surveillance reports, registries or cohort studies,
- Adverse event data bases (manufacturer or regulatory authorities),
- Data generated from individual patients under compassionate usage prior to marketing of the device,
- Details of clinically relevant field corrective actions.

Data from clinical experience have to contain sufficient information to be able to undertake a rational and objective assessment of the information and make a conclusion about its significance with respect to the safety and performance of the device under evaluation.

1.3 Data from clinical investigations

Clinical investigations carried out by or on the behalf of the manufacturer especially for the purpose of conformity assessment in accordance with applicable regulations are included.

2. Criteria for literature appraisal

The Clinical Evaluation (CEv) Guidelines require an appraisal of the quality of the study; this can be done best by the criteria of evidence-based medicine (EbM). Evidence-based medicine aims to define the quality criteria for scientific knowledge and to make literature qualitatively comparable by grading evidence levels. Citations referred to are appraised with the aid of criteria described in the following subsections.

2.1 Clinical performance and safety data

It is necessary to appraise data in terms of their suitability for establishing the safety and performance of the medical device under review. Thus, the relevant literature is assessed for the contribution to demonstration of performance and/or safety of the product.

Performance	Clinical data that support the ability of a medical device to achieve its intended purpose as claimed by the manufacturer.
Safety	Clinical data that support the absence of unacceptable clinical risks, when using the device according to the manufacturers' instruction for use.

2.2 Relevance of data

The publications identified by the literature search are classified according to the following scheme.

Background information	Articles which give an overview about the field of use or the product class. In general, these are reviews. Publications considered as background information are not appraised.
Relevant literature	Publications in which experimental data about the field of use or the product class are published.
Non-relevant literature	Publications which are either not related to the subject or which are not included due to exclusion criteria (see section 0). Other reasons for the exclusion are specifically documented. Publications considered non-relevant are not appraised further.

2.2.1 Exclusion criteria

The following are generally considered exclusion criteria. If necessary, more specific exclusion criteria are introduced and documented within the flowchart of the literature search report (see Appendix A2):

- Full text publication not in English or German language;
- Review articles (no clinical trial);

- Editorials, comments, letters, etc;
- Preclinical study, e.g., in vitro or data from animal models;
- Isolated case reports, random experience, non-substantiated options;
- Not related to the subject (e.g. wrong indication or diagnosis);
- Not comparable technique (e.g. device not equivalent or essential similar);
- Missing scientific information for evaluation; publication contain not sufficient information to undertake a rational and objective assessment of the information and make a conclusion about its significance with respect to performance and/or safety impossible (e.g. concentration or MW of HA is not mentioned);
- Publication is an older version of a more current version;
- Doublication.

Exclusion criteria are not applicable in case of safety relevant information.

2.2.2 Equivalence of the products to be assessed (V)

The CEv Guidelines specify that in order to estimate the value of a publication, it is necessary to make a statement on the equivalence of the product(s) from the literature that can be used to evaluate the product to be assessed. This statement on equivalence is graded according to the following criteria:

Indication(s)	– used for the same clinical condition or purpose (related to severity and stage of disease) – used at the same site in the body – used in similar population (including age, anatomy, physiology) – have similar relevant critical performance according to expected clinical effect for specific indication(s)
Technical characteristics	– used under similar conditions of use – is similar related to the design, specifications and properties (e.g. tensile strength, viscosity, surface characteristics) – is similar to physiochemical requirements, critical performance requirements, principles of operation and conditions of use
Biological characteristics	– use same materials in contact with the same human tissues or body fluid

The products in the literature will be assessed according to the criteria (indication(s), technical and biological characteristics) and are rated into the following four levels of comparability or equivalence:

High	Very similar
Probable	Similar
Doubtful	In some aspects similar
Not substantiated	No equivalence

2.3 Quality of data

2.3.1 Level of evidence (LoE)

This clinical evaluation has been compiled on the basis of the 'level of evidence' model drawn up by the Agency for Health Care Policy and Research (today: Agency for Healthcare Research and Quality) and published in AHCPR Publication 1991, 92-0032:100-107 Circulation 2000-102. This classification of evidence levels is considered as one of the most important classification systems by the Cochrane Centre (http://www.cochrane.de/de/gradesys.html) as well as the BQS (BQS Bundesgeschäftsstelle Qualitätssicherung GmbH - http://www.bqs-qualitaetsindikatoren.de). Furthermore, this classification is the basis of the classification according to SIGN (Scottish Intercollegiate Guidelines Network). (SIGN. Hypertension in Older People. Publication No. 49. January 2001)

There are a total of six levels that are graded as follows:

Grade	Evidence type
Ia	Evidence obtained from meta-analysis of randomized controlled trials (RCTs).
Ib	Evidence obtained from at least one randomized controlled trial (RCT).
IIa	Evidence obtained from meta-analysis of well-designed controlled study without randomization.
IIb	Evidence obtained from at least one well-designed controlled study without randomization.
III	Evidence obtained from non-experimental descriptive studies, such as comparative studies, correlation studies and case-control studies.
IV	Case series (a report of multiple patients with the same treatment, but no control group or comparison group)
V	Case report, expert committee reports or opinion, clinical experience from respected authorities (personal observation)

2.3.2 Statement trend (T)

The CEv Guidelines also require that not only publications that confirm the clinical suitability of the product to be assessed are to be included, but also those that cast doubt on this suitability. According to the guidelines, the publications should be identified as follows:

Favorable	Confirms clinical suitability
Unfavorable	Does not confirm clinical suitability
Indifferent*	No statement on the clinical suitability can be made

* An additionally introduced category

2.3.3 Number of patients in the study (N)

Since the number of patients plays a decisive role, especially in studies that do not achieve any of the highest LoEs, the number of patients in the study is always indicated. In controlled studies, the total number of patients in both the treatment group and the control group is stated. In meta-analyses and systematic reviews, the total number of patients as well as the number of studies included is given.

e.g. N = 256	Treatment group + control group
e.g. N(St) = 1023(5)	Total number of patients (N) and the number of studies included (St)

2.3.4 Quality of data source (S)

If not stated otherwise, the publications assessed were taken from scientific journals (i.e. peer reviewed). The sources can be as follows:

Peer-reviewed	Literature from peer review journals
Not peer-reviewed	Other literature from publically accessible journals
Proceedings	Abstracts from scientific meetings
Thesis	Theses and dissertations
Company	Company data
Unpublished	Unpublished literature

Appendix A 2 The literature search report

Literature Search Report

Clinical Evaluation Report OSTENIL® PLUS 2016-06-28

According to Directive 93/42/EEC (2007), MEDDEV 2.7.1 Rev.3 (2009)
and GHTF SG5/N1/R8:2007

1. Product name

Trade name: OSTENIL® PLUS.

2. Objectives of the literature search

The objective of the literature review is to find clinical data supporting the performance and safety aspects of the product to be assessed, in its intended purpose and application, as well as other claims made by the manufacturer and of the equivalent competitor products (see table in section 4.3 of the main document).

Literature search was performed

- in the indication: osteoarthritis
- with the intervention(s): intra-articular injection
- with the use of: hyaluronan + mannitol

3. Methods

(a) This literature search was conducted by Dr. Petra Dobner – TRB Chemedica AG

(b) Literature sources used to identify data:

- bibliographic databases: PubMed/MEDLINE/PMC, CENTRAL, DIMDI
- clinical trials registry platforms (clinicaltrials.gov and who.int/ictrp)
- professional journal(s) not referenced in Medline: *Cartilage*
- literature from own studies (published and unpublished) with TRB Chemedica products
- cross-referenced literature
- citations provided by the manufacturers of equivalent products to OSTENIL® PLUS will be added to the list of potentially relevant citations in order to complete the literature search

PubMed/MEDLINE/PMC will be used to generate clinical data through literature searching for this clinical evaluation (CEv). MEDLINE is the National Library of Medicine (NLM) journal citation database. This bibliographic database is the primary component of PubMed, a free resource developed and maintained by the National Center for Biotechnology Information (NCBI) at the National Library of Medicine's (NLM). The U.S. NLM premier database of citations and abstracts contains over 20 million references from approximately 5,600 biomedical journals published in the United States and worldwide. MEDLINE covers life sciences fields such as medicine, nursing, dentistry, veterinary medicine, health care systems, and preclinical sciences. The MEDLINE database is directly searchable from NLM as a subset of the PubMed database as well as through other numerous search services that license the data. In addition to the comprehensive journal selection process, what sets MEDLINE apart from the rest of PubMed is the added value of using the NLM controlled vocabulary, Medical Subject Headings (MeSH), to index citations. Search can use Medical Subject Headings (MeSH) terms, author names, title words, text words or phrases, journal names, or any combination of these. Additional search modes offer the ability to perform more complex searches by specifying data fields, age groups, gender, or human or animal studies. In addition, all available abstracts can be viewed for free, which is helpful to decide on inclusion and exclusion criteria. The result of a MEDLINE/PubMed search is a list of citations (including authors, title, source, and often an abstract) to journal articles and an indication of free electronic full-text availability. Searching is free of charge and does not require registration. Further the identified review articles and review articles were used to extend the search by cross-referencing and adding in order to substantiate background information and to include clinical studies not detected with the MEDLINE searches.

PMC (PubMed Central) launched in 2000 as a free archive for full-text biomedical and life sciences journal articles. PMC serves as a digital counterpart to the NLM extensive print journal collection; it is a repository for journal literature deposited by participating publishers, as well as for author manuscripts that have been submitted in compliance with the NIH Public Access Policy and similar policies of other research funding agencies. Some PMC journals are also MEDLINE journals. Journals must be in scope according to the NLM Collection Development Manual. Although free access is a requirement for PMC deposit, publishers and individual authors may continue to hold copyright on the material in PMC and publishers can delay the release of their material in PMC for a short period after publication. There are reciprocal links between the full text in PMC and corresponding citations in PubMed. PubMed citations are created for content not already in the MEDLINE database. Some PMC content, such as book reviews, is not cited in PubMed.

In conclusion, PubMed citations come from 1) MEDLINE indexed journals, 2) journals/manuscripts deposited in PMC, and 3) NCBI Bookshelf.

CENTRAL (Cochrane Central Register of Controlled Trials): Each month, CENTRAL is re-built, using records from the four sources, in the following order of precedence: (1) MEDLINE, (2) EMBASE, (3) handsearch results and (4) Specialised Registers.

DIMDI search was performed by search access without contract (access to all free and selected fee-based databases, without a contract): → Database Search → Search Access without

contract → Database Preselection Medical Literature (https://portal.dimdi.de/websearch/servlet/Gate?accessid=freeStdDbDe#__DEFANCHOR__).

Identification of unpublished and ongoing trials: WHO International Clinical Trials Registry Platform (http://www.who.int/ictrp/en/ and the US National Institutes of Health https://clinicaltrials.gov/). Including a search for unpublished trials is useful to assess the presence and magnitude of publication bias. Clinicaltrials.gov is a registry and results database of publicly and privately supported clinical studies of human participants conducted around the world.

Further the identified review articles and review articles were used to extend the search by cross-referencing and adding in order to substantiate background information and to include clinical studies not detected with the MEDLINE searches.

(c) General selection criteria applied to choose articles according to objective of the literature review are listed within the literature search protocol in appendix A1 of the clinical evaluation at hand.

4. Selection Criteria

The potentially relevant citations identified by the literature search will be reviewed and classified according to their relevance to OSTENIL® PLUS. The selected references of interest will be further examined and if necessary, excluded giving reasons (see section 0 below). Citations that are not relevant to the topic or excluded will not be processed any further. Citations identified as relevant to the topic and useable for this CEv will be reviewed in detail and appraised individually. The relevance to the topic and exclusion criteria are decided on the basis of the scope of the CEv defined in Section 4 of the Clinical Evaluation Report (CER). A summary of the selection process is documented in the flowchart of the Literature Search Report (see section 0).

Some reviews which were excluded from appraisal were used as background information (i.e., articles giving an overview on the medical device or an equivalent product, the technique used, or its field of use) and citet in this CER.

4.1 Relevance

Any data on very similar product to OSTENIL® PLUS used to treat osteoarthritis are considered as relevant to the topic and included in this CEv.

4.2 Exclusion criteria

Exclusion criteria are listed in Appendix 1 section 2.2.1 and coded according to section 0.
Terms were linked and filtered by ‚OR' to eliminate doublication.

Exclusion of publications due to 'missing scientific information' means that necessary information concerning the device (e.g. concentration or MW of HA is not mentioned) or procedure performed are not mentioned, making evaluation of equivalence or similarity of device or prodcedure impossible.

If necessary, more specific exclusion criteria were introduced and documented within the flowchart.

5. MEDLINE Search

5.1 General Medline search

Medline Search:
- cut off date 28.06.2016
- limited to literature in English or German
- on 'humans'
- limited to 'clinical trials'

User queries		**N° citations**
# 1	hyaluron* OR hyaluronan OR hyaluronic OR hylan OR hyaluronate	1452
# 2	osteoarthr* OR osteoarthritis OR arthritis OR arthrosis OR pain OR trauma OR degeneration	97740
# 3	synovial joint	660
# 4	intraarticular	439
# 5	mannitol	737
# 5	# 1 AND # 2 AND # 3 AND # 4 AND # 5	0
# 6	# 1 AND # 5	2
# 7	# 2 AND # 5	102
# 8	# 1 AND # 2 AND # 3 AND # 4 (hyaluron* OR hyaluronan OR hyaluronic OR hylan OR hyaluronate) AND (osteoarthr* OR osteoarthritis OR arthritis OR arthrosis OR pain OR trauma OR degeneration) AND (synovial joint OR intraarticular)	97

Mannitol is a well-known and safe substance for human use. The pharmacologically approved medical use of mannitol includes oral, intravenous, and pulmonal application as well as the use in solutions for heart-reperfusion after cardioplegia and for the conservation of grafts until transplantation. The addition of 0.5% mannitol in OSTENIL® PLUS only serves an excipient to delay the degradation of hyaluronate as a radical scavenger substance. In the literature searches with # 6 (2 citations) and # 7 (102 citations) no publication in the indication of osteoarthrosis was found. Publications dealing with the topic of pain reduction (which is an important point in the treatment of osteoarthritis) are focussed on patients with complex regional pain syndrome and thus allow no conclusion on intraarticular application of mannitol. Furthermore, mannitol was administered intravenously and concentration was substantially higher (e.g. 10-20%) which lays far beyond concentration in OSTENIL® PLUS. Thus, literature search for clinical evaluation of OSTENIL® PLUS will not be performed with 'mannitol' as search term.

User query #8	
Database	
	PubMed (cut off date 28.06.2016)
Results	
	97 citations
Translations	
hyaluronan	"hyaluronic acid"[MeSH Terms] OR ("hyaluronic"[All Fields] AND "acid"[All Fields]) OR "hyaluronic acid"[All Fields] OR "hyaluronan"[All Fields]
hylan	"hylan"[Supplementary Concept] OR "hylan"[All Fields]
osteoarthritis	"osteoarthritis"[MeSH Terms] OR "osteoarthritis"[All Fields]
arthritis	"arthritis"[MeSH Terms] OR "arthritis"[All Fields]
arthrosis	"joint diseases"[MeSH Terms] OR ("joint"[All Fields] AND "diseases"[All Fields]) OR "joint diseases"[All Fields] OR "arthrosis"[All Fields]
pain	"pain"[MeSH Terms] OR "pain"[All Fields]
trauma	"injuries"[Subheading] OR "injuries"[All Fields] OR "trauma"[All Fields] OR "wounds and injuries"[MeSH Terms] OR ("wounds"[All Fields] AND "injuries"[All Fields]) OR "wounds and injuries"[All Fields]
joint	"joints"[MeSH Terms] OR "joints"[All Fields] OR "joint"[All Fields]
Humans[Mesh]	"humans"[MeSH Terms]
User Query	
	(hyaluron* OR hyaluronan OR hyaluronic OR hylan OR hyaluronate) AND (osteoarthr* OR osteoarthritis OR arthritis OR arthrosis OR pain OR trauma OR degeneration) AND (synovial joint OR intraarticular) AND (Clinical Trial[ptyp] AND Humans[Mesh] AND (English[lang] OR German[lang]))
Query Translation	
	((hyaluron[All Fields] OR hyaluronacid[All Fields] OR hyaluronaciduria[All Fields] OR hyaluronaciduriaval[All Fields] OR hyaluronadase[All Fields] OR hyaluronal[All Fields] OR hyaluronam[All Fields] OR hyaluronan[All Fields] OR hyaluronan's[All Fields] OR hyaluronana[All Fields] OR hyaluronanase[All Fields] OR hyaluronane[All Fields] OR hyaluronanem[All Fields] OR hyaluronanic[All Fields] OR hyaluronanon[All Fields] OR hyaluronanosis[All Fields] OR hyaluronanreceptor[All Fields] OR hyaluronans[All Fields] OR hyaluronanu[All Fields] OR hyaluronase[All Fields] OR hyaluronasome[All Fields] OR hyaluronat[All Fields] OR hyaluronate[All Fields] OR hyaluronate's[All Fields] OR hyaluronated[All Fields] OR hyaluronatelyase[All Fields] OR hyaluronateprotein[All Fields] OR hyaluronates[All Fields] OR hyaluronatimplantat[All Fields] OR hyaluronatlyase[All Fields] OR hyaluronatlyases[All Fields] OR hyaluronatu[All Fields] OR hyaluronazidurie[All Fields] OR hyaluronc[All Fields] OR hyalurondase[All Fields] OR hyalurondasen[All Fields] OR hyalurondiase[All Fields] OR hyaluronectin[All Fields] OR hyaluronectine[All Fields] OR hyaluronection[All Fields] OR hyaluronen[All Fields] OR hyaluronfiller[All Fields] OR hyaluroni[All Fields] OR hyaluronian[All Fields] OR hyaluronians[All Fields] OR hyaluronic[All Fields] OR hyaluronica[All Fields] OR hyaluronicacid[All Fields] OR hyaluronicacids[All Fields] OR hyaluronicase[All Fields] OR hyaluronics[All Fields] OR hyaluronid[All Fields] OR hyaluronid'aze[All Fields] OR hyaluronid'azou[All Fields] OR hyaluronid'azy[All Fields] OR hyaluronida[All Fields] OR hyaluronidaasista[All Fields] OR hyaluronidas[All Fields] OR hyaluronidasa[All Fields] OR hyaluronidase[All Fields] OR hyaluronidase'[All Fields] OR hyaluronidase'in[All Fields] OR hyaluronidase'nin[All Fields] OR hyaluronidase's[All Fields] OR hyaluronidase1[All Fields] OR hyaluronidase2[All Fields] OR hyaluronidaseaktivitat[All Fields] OR hyaluronidaseantihyaluronidase[All Fields] OR hyaluronidaseartige[All Fields] OR hyaluronidasebildung[All Fields] OR hyaluronidasebildungsfahigkeit[All Fields] OR hyaluronidasebildungsvermogen[All Fields] OR hyaluronidaseferment[All Fields] OR hyaluronidaseforschung[All Fields] OR hyaluronidasefreisetzung[All Fields] OR hyaluronidasegabe[All Fields] OR hyaluronidasegatlas[All Fields] OR hyaluronidasegehalt[All Fields] OR hyaluronidasegehaltes[All Fields] OR hyaluronidasehemmenden[All Fields] OR hyaluronidasehemmung[All Fields] OR hyaluronidasehemoglobin[All Fields] OR hyaluronidasehyaluronic[All Fields] OR hyaluronidaseinduced[All Fields] OR hyaluronidaseinhibitor[All Fields] OR hyaluronidasen[All Fields] OR hyaluronidasens[All Fields] OR hyaluronidasensystem[All Fields] OR hyaluronidasepraparat[All Fields] OR hyaluronidasequaddel[All Fields] OR hyaluronidasereaktionens[All Fields] OR hyaluronidases[All Fields] OR hyaluronidases'[All Fields] OR hyaluronidasesystem[All Fields] OR hyaluronidasesystems[All Fields] OR hyaluronidasetherapie[All Fields] OR hyaluronidasetilsetting[All Fields] OR hyaluronidaseval[All Fields] OR hyaluronidasewirksamkeit[All Fields] OR hyaluronidasewirkung[All Fields] OR hyaluronidasezusatz[All Fields] OR hyaluronidasi[All Fields] OR hyaluronidasic[All Fields] OR hyaluronidasinhibitorer[All Fields] OR hyaluronidasinhibitorerna[All Fields] OR hyaluronidasique[All Fields] OR hyaluronidasobildung[All Fields] OR hyaluronidasou[All Fields] OR hyaluronidasu[All Fields] OR hyaluronidasum[All Fields] OR hyaluronidasy[All Fields] OR hyaluronidasze[All Fields] OR hyaluronidate[All Fields] OR hyaluronidaza[All Fields] OR hyaluronidaze[All Fields] OR hyaluronidazou[All Fields] OR hyaluronidazovy[All Fields] OR hyaluronidazy[All Fields] OR hyaluronide[All Fields] OR hyaluronidinase[All Fields] OR hyaluronihaposta[All Fields] OR hyaluronin[All Fields] OR hyaluronio[All Fields] OR hyaluronique[All Fields] OR hyaluronisaein[All Fields] OR hyaluronisase[All Fields] OR hyaluronization[All Fields] OR hyaluronlyticus[All Fields] OR hyalurono[All Fields] OR hyaluronodextrins[All Fields] OR hyaluronoglucosaminidase[All Fields] OR hyaluronoglucosaminidases[All Fields] OR hyaluronoglucosidase[All Fields] OR

	hyaluronoglucuronidase[All Fields] OR hyaluronolytic[All Fields] OR hyaluronon[All Fields] OR hyalurononglucosaminadase[All Fields] OR hyaluronosis[All Fields] OR hyaluronosulfuric[All Fields] OR hyaluronova[All Fields] OR hyaluronove[All Fields] OR hyaluronsaeure[All Fields] OR hyaluronsaure[All Fields] OR hyaluronsaurebasis[All Fields] OR hyaluronsaurebestimmung[All Fields] OR hyaluronsaureestermembranen[All Fields] OR hyaluronsaurefiller[All Fields] OR hyaluronsaurefillern[All Fields] OR hyaluronsauregehalt[All Fields] OR hyaluronsaurehaltige[All Fields] OR hyaluronsaureinjektionen[All Fields] OR hyaluronsaurekonformation[All Fields] OR hyaluronsaurelosung[All Fields] OR hyaluronsaurelosungen[All Fields] OR hyaluronsauren[All Fields] OR hyaluronsaurepraparat[All Fields] OR hyaluronsaurepraparaten[All Fields] OR hyaluronsaurepraparates[All Fields] OR hyaluronsaurespaltenden[All Fields] OR hyaluronsauresynthese[All Fields] OR hyaluronsauretherapie[All Fields] OR hyaluronsaureunterspritzung[All Fields] OR hyaluronsav[All Fields] OR hyaluronsavhyaluronidase[All Fields] OR hyaluronsavvizsgalatok[All Fields] OR hyaluronsure[All Fields] OR hyaluronsyra[All Fields] OR hyaluronsyran[All Fields] OR hyaluronsyre[All Fields] OR hyaluronsyrens[All Fields] OR hyaluronuria[All Fields] OR hyaluronydasewirkung[All Fields] OR hyaluronyl[All Fields] OR hyaluronzuur[All Fields]) OR ("hyaluronic acid"[MeSH Terms] OR ("hyaluronic"[All Fields] AND "acid"[All Fields]) OR "hyaluronic acid"[All Fields] OR "hyaluronan"[All Fields]) OR hyaluronic[All Fields] OR ("hylan"[Supplementary Concept] OR "hylan"[All Fields]) OR hyaluronate[All Fields]) AND ((osteoarthr[All Fields] OR osteoarthral[All Fields] OR osteoarthralgia[All Fields] OR osteoarthralgias[All Fields] OR osteoarthralgic[All Fields] OR osteoarthrealgia[All Fields] OR osteoarthrectomy[All Fields] OR osteoarthretic[All Fields] OR osteoarthri[All Fields] OR osteoarthric[All Fields] OR osteoarthricular[All Fields] OR osteoarthririts[All Fields] OR osteoarthris[All Fields] OR osteoarthrisis[All Fields] OR osteoarthrist[All Fields] OR osteoarthristis[All Fields] OR osteoarthritc[All Fields] OR osteoarthrite[All Fields] OR osteoarthrites[All Fields] OR osteoarthrithis[All Fields] OR osteoarthriti[All Fields] OR osteoarthritic[All Fields] OR osteoarthritic'[All Fields] OR osteoarthritics[All Fields] OR osteoarthritides[All Fields] OR osteoarthrities[All Fields] OR osteoarthritis[All Fields] OR osteoarthritis'[All Fields] OR osteoarthritisand[All Fields] OR osteoarthritisis[All Fields] OR osteoarthritisprogression[All Fields] OR osteoarthritiss[All Fields] OR osteoarthritistis[All Fields] OR osteoarthrititis[All Fields] OR osteoarthritits[All Fields] OR osteoarthrits[All Fields] OR osteoarthro[All Fields] OR osteoarthrocutaneous[All Fields] OR osteoarthrodesis[All Fields] OR osteoarthrodysplasia[All Fields] OR osteoarthrography[All Fields] OR osteoarthrologiai[All Fields] OR osteoarthrological[All Fields] OR osteoarthrology[All Fields] OR osteoarthromuscular[All Fields] OR osteoarthromusculovascular[All Fields] OR osteoarthromyalgias[All Fields] OR osteoarthromyopathies[All Fields] OR osteoarthroonychodysplasie[All Fields] OR osteoarthropathe[All Fields] OR osteoarthropathi[All Fields] OR osteoarthropathi'aja[All Fields] OR osteoarthropathia[All Fields] OR osteoarthropathiaja[All Fields] OR osteoarthropathic[All Fields] OR osteoarthropathie[All Fields] OR osteoarthropathien[All Fields] OR osteoarthropathies[All Fields] OR osteoarthropathique[All Fields] OR osteoarthropathy[All Fields] OR osteoarthropathy1[All Fields] OR osteoarthropatia[All Fields] OR osteoarthropatias[All Fields] OR osteoarthropatic[All Fields] OR osteoarthropatie[All Fields] OR osteoarthropaties[All Fields] OR osteoarthrophy[All Fields] OR osteoarthrophytes[All Fields] OR osteoarthroplasty[All Fields] OR osteoarthros[All Fields] OR osteoarthrose[All Fields] OR osteoarthrosed[All Fields] OR osteoarthroseentwicklung[All Fields] OR osteoarthrosen[All Fields] OR osteoarthroser[All Fields] OR osteoarthroses[All Fields] OR osteoarthrosic[All Fields] OR osteoarthrosique[All Fields] OR osteoarthrosis[All Fields] OR osteoarthrosis'[All Fields] OR osteoarthrosis,[All Fields] OR osteoarthrosisok[All Fields] OR osteoarthritis[All Fields] OR osteoarthrotendinous[All Fields] OR osteoarthrotenocutaneous[All Fields] OR osteoarthrotic[All Fields] OR osteoarthrotically[All Fields] OR osteoarthrotics[All Fields] OR osteoarthrotis[All Fields] OR osteoarthrotischen[All Fields] OR osteoarthrotischer[All Fields] OR osteoarthrotomy[All Fields] OR osteoarthrpathy[All Fields] OR osteoarthrtic[All Fields] OR osteoarthrtis[All Fields] OR osteoarthrtitis[All Fields]) OR ("osteoarthritis"[MeSH Terms] OR "osteoarthritis"[All Fields]) OR ("arthritis"[MeSH Terms] OR "arthritis"[All Fields]) OR ("joint diseases"[MeSH Terms] OR ("joint"[All Fields] AND "diseases"[All Fields]) OR "joint diseases"[All Fields] OR "arthrosis"[All Fields]) OR ("pain"[MeSH Terms] OR "pain"[All Fields]) OR ("injuries"[Subheading] OR "injuries"[All Fields] OR "trauma"[All Fields] OR "wounds and injuries"[MeSH Terms] OR ("wounds"[All Fields] AND "injuries"[All Fields]) OR "wounds and injuries"[All Fields]) OR degeneration[All Fields]) AND ((synovial[All Fields] AND ("joints"[MeSH Terms] OR "joints"[All Fields] OR "joint"[All Fields])) OR intraarticular[All Fields]) AND (Clinical Trial[ptyp] AND "humans"[MeSH Terms] AND (English[lang] OR German[lang]))

5.2 Medline search for product name(s)

As OSTENIL® PLUS is also available as OSTEONIL® PLUS, OST® PLUS, MAXIOSTENIL® PLUS and HYAJECT® PLUS on the market, an additional search (# 9) was performed with all names.

Medline Search: • cut off date 30.06.2016 • limited to literature in English or German		
User queries		
# 9	"Ostenil Plus" OR "Osteonil Plus" OR Ost Plus" OR "Maxiostenil Plus" OR "Hyaject Plus"	9

User query #9	
	(Ostenil[All Fields] AND Plus[All Fields]) OR (Osteonil[All Fields] AND Plus[All Fields]) OR (Ost[All Fields] AND Plus[All Fields]) AND "OR "[All Fields] AND Plus[All Fields] AND "OR "[All Fields] AND Plus[All Fields] AND (Clinical Trial[ptyp] AND "humans"[MeSH Terms] AND (English[lang] OR German[lang]))
Database	
	PubMed (cut off date 30.06.2016)
Results	
	9 citations
Phrase(s) Not Found:	
	Maxiostenil
	Hyaject
Quoted phrase not found:	
	"Ostenil Plus"
	"Osteonil Plus"
Translations	
Humans[Mesh]	"humans"[MeSH Terms]
User Query	
	"Ostenil Plus" OR "Osteonil Plus" OR Ost Plus" OR "Maxiostenil Plus" OR "Hyaject Plus" AND (Clinical Trial[ptyp] AND Humans[Mesh] AND (English[lang] OR German[lang]))
Query Translation	
	(Ostenil[All Fields] AND Plus[All Fields]) OR (Osteonil[All Fields] AND Plus[All Fields]) OR (Ost[All Fields] AND Plus[All Fields]) AND "OR "[All Fields] AND Plus[All Fields] AND "OR "[All Fields] AND Plus[All Fields] AND (Clinical Trial[ptyp] AND "humans"[MeSH Terms] AND (English[lang] OR German[lang]))

5.3 Medline [MeSH] search

MeSH search was performed to identify relevant search keys and to optimize user queries.

Medline [MeSH] Search: • cut off date 30.06.2016 • limited to literature in English or German • on 'humans' • limited to 'clinical trials'		
User queries		**N° citations**
# 10	("Osteoarthritis/drug therapy"[Mesh] OR "Osteoarthritis/therapy"[Mesh])	3878
# 11	("Hyaluronic Acid/therapeutic use"[Mesh] OR "Hyaluronic Acid/therapy"[Mesh])	851
# 12	"Injections, Intra-Articular/therapy"[Mesh]	0

# 13	# 10 AND # 11 AND # 12 ((("Osteoarthritis/drug therapy"[Mesh] OR "Osteoarthritis/therapy"[Mesh])) AND "Hyaluronic Acid"[Mesh]) AND ("Injections, Intra-Articular/therapeutic use"[Mesh] OR "Injections, Intra-Articular/therapy"[Mesh])	3
# 14	# 10 AND # 11 (("Osteoarthritis/drug therapy"[Mesh] OR "Osteoarthritis/therapy"[Mesh])) AND ("Hyaluronic Acid/therapeutic use"[Mesh] OR "Hyaluronic Acid/therapy"[Mesh])	219

User query # 14	
Database	
	MeSH PubMed (cut off date 30.06.2016)
Results	
	219 citations
Translations	
Humans[Mesh]	"humans"[MeSH Terms]
User Query	
	(("Osteoarthritis/drug therapy"[Mesh] OR "Osteoarthritis/therapy"[Mesh])) AND ("Hyaluronic Acid/therapeutic use"[Mesh] OR "Hyaluronic Acid/therapy"[Mesh]) AND (Clinical Trial[ptyp] AND Humans[Mesh] AND (English[lang] OR German[lang]))
Query Translation	
	("Osteoarthritis/drug therapy"[Mesh] OR "Osteoarthritis/therapy"[Mesh]) AND ("Hyaluronic Acid/therapeutic use"[Mesh] OR "Hyaluronic Acid/therapy"[Mesh]) AND (Clinical Trial[ptyp] AND "humans"[MeSH Terms] AND (English[lang] OR German[lang]))

6. Other Sources

6.1 PMC Search

Relevant articles identified by literature search (search keys):

PMC Search:

- cut off date 27.06.2016

User queries

# 1	hyaluron* AND osteoarthritis AND "synovial joint" AND intraarticular AND human AND "clinical trial"	32 citations

6.2 Cartilage

An additional literature search was performed in *Cartilage (http://car.sagepub.com/search)*, since this scientific journal is not indexed for MEDLINE and might be a relevant source of clinical data for this CEv.

Cartilage is the official journal of the International Cartilage Repair Society (ICRS; cartilage.org). It is published quarterly by SAGE on behalf of the ICRS beginning in January 2010. *Cartilage* aims to bridge a gap in the literature by focusing on both clinical and basic science perspectives of the diverse disciplines in cartilage research and repair. The journal is to serve as a focal point and a

forum for the exchange of ideas for the many kinds of researchers and practitioners related to articular cartilage.

The search was perfomed on 28th June 2016. Abstract review of all scientific papers published in *Cartilage* from January 1847 to December 2016 was performed. A combination of the same keywords than for the literature search in MEDLINE/PubMed were used (http://car.sagepub.com/content).

6.3 CENTRAL

http://www.cochranelibrary.com/about/central-landing-page.html

CENTRAL Search:

- cut off date 29.06.2016
- limited to literature in English or German

User queries

# 1	(hyaluronan OR hyaluronic) AND osteoarthritis AND intraarticular AND human AND "clinical trial"	88 citations

6.4 DIMDI

DIMDI (Deutsche Institut für Medizinische Dokumentation und Information) search was restricted on publications in English or german language.

DIMDI Search:

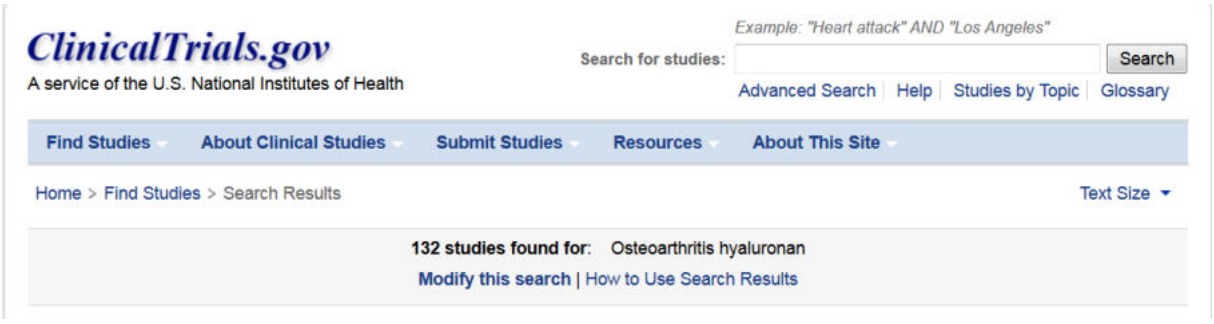
- cut off date 28.06.2016
- limited to literature in English or German

User queries

# 1	hyaluron* AND osteoarthritis AND "synovial joint" AND intraarticular AND human AND "clinical trial"	71 citations

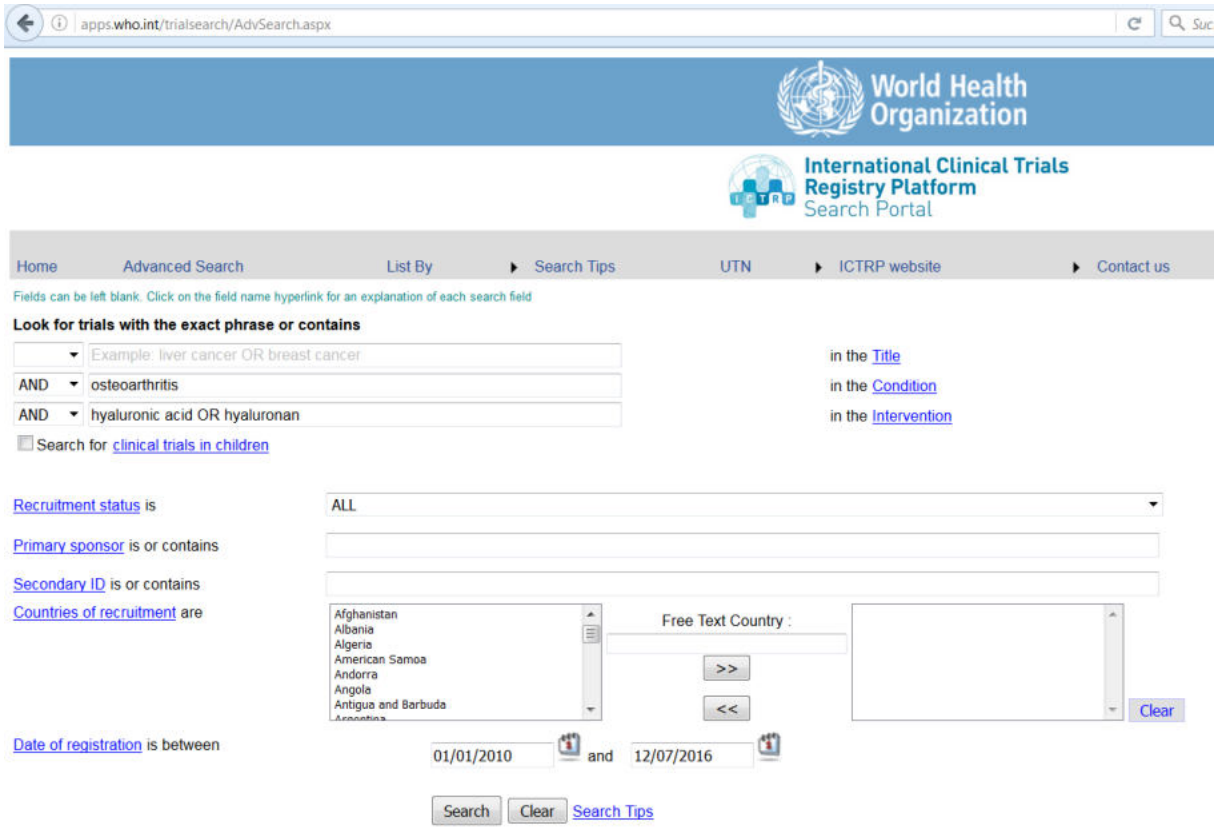
6.5 Clinicaltrials.gov

Search was performed on 29.06.2016.



6.6 International Clinical Trials Registry Platform (ICTRP) who.int/ictrp/en/

Search was performed on 12.07.2016.



6.7 Manual Searching

Literature from “hand search” is obtained by the following sources

(1) A regular systematic and documented monthly literature research for the product under evaluation (using product names) and for the clinical background / state-of-the-art treatment is performed monthly in Medline. Search strings include terms for the treatment principle / active substance and for the relevant indication(s). Search keys correspond to the search keys used for this CER.

Currently, the hand search is performed by using:
(hyaluron* OR hyaluronan OR hyaluronic OR hylan OR hyaluronate) AND (osteoarthr* OR osteoarthritis OR arthritis OR arthrosis OR pain OR trauma OR degeneration OR synovial) AND "last 1 months"[dp] AND English OR German

Relevant articles are fed into the Infotehna database, independent of favourable or unfavourable outcome (see below).

(2) Identified systematic review articles and meta-analyses were used to extend the search by cross-referencing and adding in order to substantiate background information and to include clinical studies not detected with the MEDLINE searches.

Relevant articles are fed into the Infotehna database, independent of favourable or unfavourable outcome (see below).

(3) Based on economic interests on the currently available data and innovative therapy concepts, as well as from suggestion from congresses, TRB Chemedica searches regularly databases and the internet for clinical relevant publications. Publications relevant with regard to indications and products/active substances are entered into the internal Infotehna literature database (Infotehna data management system; actually contains about 40.000 files) which also can be used as a data source for literature search, if required.

For this literature search Infotehna database is searched for ‘osteoarthritis’

Results from the hand search are listed in section 7.5.

7. Outputs

The data selection process is presented by the following flow chart, showing how all publications were assessed regarding suitability for inclusion in the clinical evaluation.

Citations were classified with the following criteria:

R	Relevant
NR	Not Relevant
BI	Background Information

If citation had not been selected, reason(s) were:

1	Review article
2	Editorials, comments, letters, etc.
3	Preclinical study (e.g. in vitro or data from animal models)
4	Not related to the subjects (e.g. wrong indication or diagnosis)
5	Not comparable technique (e.g. non-equivalence to product to be assessed)
6	Missing scientific information
7	Publication is an older version of a more current version
8	Duplicates
OR	
9	Appraisal

Identification of duplicates was performed in the following order:

(1) General Medline Search

(2) Medline search for product names

(3) Medline [MeSH] search

(4) PMC Search

(5) Cartilage

(6) CENTRAL

(7) DIMDI

(8) Clinicaltrials.gov

(9) ICTRP

7.1 MEDLINE

7.1.1 User query # 8

Results are ordered according their relevance (high to low).

User query # 8: (hyaluron* OR hyaluronan OR hyaluronic OR hylan OR hyaluronate) AND (osteoarthr* OR osteoarthritis OR arthritis OR arthrosis OR pain OR trauma OR degeneration) AND (synovial joint OR intraarticular)				
Citation		**Relevance NR=non-relevant R=relevant**	**Reason for non-relevance or Appraisal**	
1	Nelson FR, Zvirbulis RA, Zonca B, Li KW, Turner SM, Pasierb M, Wilton P, Martinez-Puig D, Wu W. The effects of an oral preparation containing hyaluronic acid (Oralvisc®) on obese knee osteoarthritis patients determined by pain, function, bradykinin, leptin, inflammatory cytokines, and heavy water analyses. Rheumatol Int. 2015 Jan;35(1):43-52.	NR	4	
2	Yang L, Zhang J, Wang G. The effect of sodium hyaluronate treating knee osteoarthritis on synovial fluid interleukin -1β and clinical treatment mechanism. Pak J Pharm Sci. 2015 Jan;28(1 Suppl):407-10. PubMed PMID: 25631505.	NR	6	
3	Chareancholvanich K, Pornrattanamaneewong C, Narkbunnam R. Increased cartilage volume after injection of hyaluronic acid in osteoarthritis knee patients who underwent high tibial osteotomy. Knee Surg Sports Traumatol Arthrosc. 2014 Jun;22(6):1415-23.	NR	5	Hyalgan
4	Yu CJ, Ko CJ, Hsieh CH, Chien CT, Huang LH, Lee CW, Jiang CC. Proteomic analysis of osteoarthritic chondrocyte reveals the hyaluronic acid-regulated proteins involved in chondroprotective effect under oxidative stress. J Proteomics. 2014 Mar 17;99:40-53.	NR	3	
5	Tang AC, Hong WH, Chen HC, Tang SF. Intra-articular intervention by hyaluronic acid for knee osteoarthritis can modify locomotor pattern of muscle activity. Clin Neurol Neurosurg. 2015 Feb;129 Suppl 1:S16-20.	NR	5	Artz
6	Ostałowska A, Nowak D, Święchowicz S, Birkner E, Brenk A, Kasperczyk S, Dobrakowski M, Machoń A. Assessment of knee function and biochemical parameters of articular fluid and peripheral blood in gonarthrosis patients following intra-articular administration of hyaluronic acid. Pol Orthop Traumatol. 2013 Aug 16;78:173-81.	NR	5	Euflexxa
7	Takahashi D, Majima T, Onodera T, Kasahara Y, Inoue M, Irie T, Kasemura T. Celecoxib does not affect the release of hyaluronic acid in end stage osteoarthritic joints. Mod Rheumatol. 2013 Sep;23(5):934-8.	NR	4	
8	Khanasuk Y, Dechmaneenin T, Tanavalee A. Prospective randomized trial comparing the efficacy of single 6-ml injection of hylan G-F 20 and hyaluronic acid for primary knee arthritis: a preliminary study. J Med Assoc Thai. 2012 Oct;95 Suppl 10:S92-7.	NR	5	Hyalgan, hylan G-F 20 (Synvisc)
9	Foti C, Cisari C, Carda S, Giordan N, Rocco A, Frizziero A, Della Bella G. A prospective observational study of the clinical efficacy and safety of intra-articular sodium hyaluronate in synovial joints with osteoarthritis. Eur J Phys Rehabil Med. 2011 Sep;47(3):407-15.	**R**	**9**	**Hyalubrix**
10	Schütz A, Dobner P. [Effect of wrist arthroscopy with intraarticular hyaluronan substitution therapy: a randomised, controlled, prospective, non-blinded, single-centre, comparative trial]. Handchir Mikrochir Plast Chir. 2013 Oct;45(5):277-84.	NR	4	Ostenil
11	Altman RD, Rosen JE, Bloch DA, Hatoum HT. Safety and efficacy of retreatment with a bioengineered hyaluronate for painful osteoarthritis of the knee: results of the open-label Extension Study of the FLEXX Trial. Osteoarthritis Cartilage. 2011 Oct;19(10):1169-75.	NR	5	Euflexxa

User query # 8: (hyaluron* OR hyaluronan OR hyaluronic OR hylan OR hyaluronate) AND (osteoarthr* OR osteoarthritis OR arthritis OR arthrosis OR pain OR trauma OR degeneration) AND (synovial joint OR intraarticular)				
Citation		**Relevance NR=non-relevant R=relevant**	**Reason for non-relevance or Appraisal**	
12	Baker JF, Solayar GN, Byrne DP, Moran R, Mulhall KJ. Analgesic control and functional outcome after knee arthroscopy: results of a randomized double-blinded trial comparing a hyaluronic acid supplement with bupivacaine. Clin J Sport Med. 2012 Mar;22(2):109-15.	NR	4	
13	Eyigör C, Pirim A, Eyigör S, Uyar M. Efficacy of intraarticular hyaluronic acid injection through a lateral approach under fluoroscopic control for advanced hip osteoarthritis. Agri. 2010 Oct;22(4):139-44.	NR	5	Adant
14	Thein R, Haviv B, Kidron A, Bronak S. Intra-articular injection of hyaluronic acid following arthroscopic partial meniscectomy of the knee. Orthopedics. 2010 Oct 11;33(10):724.	NR	4	Viscoseal
15	**Karatay S, Kiziltunc A, Yildirim K, Karanfil RC, Senel K. Effects of different hyaluronic acid products on synovial fluid NO levels in knee osteoarthritis. Clin Rheumatol. 2005 Sep;24(5):497-501.**	**R**	**9**	**Orthovisc**, hylan G-F 20 (Synvisc)
16	Tang YL, Zhu GQ, Hu L, Zheng M, Zhang JY, Shi ZD, Liang XH. Effects of intra-articular administration of sodium hyaluronate on plasminogen activator system in temporomandibular joints with osteoarthritis. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2010 Apr;109(4):541-7.	NR	5	Sofast
17	Evanich JD, Evanich CJ, Wright MB, Rydlewicz JA. Efficacy of intraarticular hyaluronic acid injections in knee osteoarthritis. Clin Orthop Relat Res. 2001 Sep;(390):173-81.	NR	5	hylan G-F 20
18	Miltner O, Schneider U, Siebert CH, Niedhart C, Niethard FU. Efficacy of intraarticular hyaluronic acid in patients with osteoarthritis--a prospective clinical trial. Osteoarthritis Cartilage. 2002 Sep;10(9):680-6.	NR	5	Hyalart
19	Karalezli N, Ogun TC, Kartal S, Saracgil SN, Yel M, Tuncay I. The pain associated with intraarticular hyaluronic acid injections for trapeziometacarpal osteoarthritis. Clin Rheumatol. 2007 Apr;26(4):569-71.	NR	4	Ostenil
20	Jüni P, Reichenbach S, Trelle S, Tschannen B, Wandel S, Jordi B, Züllig M, Guetg R, Häuselmann HJ, Schwarz H, Theiler R, Ziswiler HR, Dieppe PA, Villiger PM, Egger M; Swiss Viscosupplementation Trial Group. Efficacy and safety of intraarticular hylan or hyaluronic acids for osteoarthritis of the knee: a randomized controlled trial. Arthritis Rheum. 2007 Nov;56(11):3610-9.	NR	5	Ostenil
21	**Karatay S, Kiziltunc A, Yildirim K, Karanfil RC, Senel K. Effects of different hyaluronic acid products on synovial fluid levels of intercellular adhesion molecule-1 and vascular cell adhesion molecule-1 in knee osteoarthritis. Ann Clin Lab Sci. 2004 Summer;34(3):330-5.**	**R**	**9**	**Orthovisc**, hylan G-F 20 (Synvisc)
22	Grecomoro G, Piccione F, Letizia G. Therapeutic synergism between hyaluronic acid and dexamethasone in the intra-articular treatment of osteoarthritis of the knee: a preliminary open study. Curr Med Res Opin. 1992;13(1):49-55.	NR	4	Hyalgan
23	Grecomoro G, La Sala F, Francavilla G. Rheologic changes in the synovial fluid of patients with gonarthritis induced by intraarticular infiltration of hyaluronic acid. Int J Tissue React. 2001;23(2):67-71.	NR	5	Hyalart
24	Saw KY, Anz A, Merican S, Tay YG, Ragavanaidu K, Jee CS, McGuire DA. Articular cartilage regeneration with autologous peripheral blood progenitor cells and hyaluronic acid after arthroscopic subchondral drilling: a report of 5 cases with histology. Arthroscopy. 2011 Apr;27(4):493-506.	NR	4	
25	Petrella RJ, Petrella M. A prospective, randomized, double-blind, placebo controlled study to evaluate the efficacy of intraarticular hyaluronic acid for osteoarthritis of the knee. J Rheumatol. 2006 May;33(5):951-6.	NR	5	Suplasyn
26	Bagga H, Burkhardt D, Sambrook P, March L. Longterm effects of intraarticular hyaluronan on synovial fluid in osteoarthritis of the knee. J Rheumatol. 2006 May;33(5):946-50.	NR	5	hylan G-F 20
27	Adams ME. An analysis of clinical studies of the use of crosslinked hyaluronan, hylan, in the treatment of osteoarthritis. J Rheumatol Suppl. 1993 Aug;39:16-8. PubMed PMID: 8410879.	NR	5	hylan G-F 20
28	Petrella RJ. Hyaluronic acid for the treatment of knee osteoarthritis: long-term outcomes from a naturalistic primary care experience. Am J Phys Med Rehabil. 2005 Apr;84(4):278-83	NR	5	Suplasyn
29	**Kotevoglu N, Iyibozkurt PC, Hiz O, Toktas H, Kuran B. A prospective randomised controlled clinical trial comparing the efficacy of different**	**R**	**9**	hylan G-F 20 6 ml,

User query # 8: (hyaluron* OR hyaluronan OR hyaluronic OR hylan OR hyaluronate) AND (osteoarthr* OR osteoarthritis OR arthritis OR arthrosis OR pain OR trauma OR degeneration) AND (synovial joint OR intraarticular)				
Citation		**Relevance NR=non-relevant R=relevant**	**Reason for non-relevance or Appraisal**	
	molecular weight hyaluronan solutions in the treatment of knee osteoarthritis. Rheumatol Int. 2006 Feb;26(4):325-30.			**Orthovisc**
30	Ozgen M, Fırat S, Sarsan A, Topuz O, Ardıç F, Baydemir C. Short- and long-term results of clinical effectiveness of sodium hyaluronate injection in supraspinatus tendinitis. Rheumatol Int. 2012 Jan;32(1):137-44.	NR	4	hylan G-F 20 (Synvisc)
31	Shimizu M, Higuchi H, Takagishi K, Shinozaki T, Kobayashi T. Clinical and biochemical characteristics after intra-articular injection for the treatment of osteoarthritis of the knee: prospective randomized study of sodium hyaluronate and corticosteroid. J Orthop Sci. 2010 Jan;15(1):51-6.	NR	5	Artz dispo
32	**Stahl S, Karsh-Zafrir I, Ratzon N, Rosenberg N. Comparison of intraarticular injection of depot corticosteroid and hyaluronic acid for treatment of degenerative trapeziometacarpal joints. J Clin Rheumatol. 2005 Dec;11(6):299-302.**	**R**	**9**	**Orthovisc**
33	Hakshur K, Benhar I, Bar-Ziv Y, Halperin N, Segal D, Eliaz N. The effect of hyaluronan injections into human knees on the number of bone and cartilage wear particles captured by bio-ferrography. Acta Biomater. 2011 Feb;7(2):848-57.	NR	5	Euflexxa
34	Schneider U, Miltner O, Graf J, Thomsen M, Niethard FU. [Mechanism of action of hyaluronic acid in gonarthrosis of both knee joints in a right/left comparison. Study with dynamometry, oxygen partial pressure, temperature and Lequesne score]. Z Orthop Ihre Grenzgeb. 1997 Jul-Aug;135(4):341-7. German.	NR	5	Hyalart
35	Frizziero L, Govoni E, Bacchini P. Intra-articular hyaluronic acid in the treatment of osteoarthritis of the knee: clinical and morphological study. Clin Exp Rheumatol. 1998 Jul-Aug;16(4):441-9.	NR	5	Hyalgan
36	**Brandt KD, Block JA, Michalski JP, Moreland LW, Caldwell JR, Lavin PT. Efficacy and safety of intraarticular sodium hyaluronate in knee osteoarthritis. ORTHOVISC Study Group. Clin Orthop Relat Res. 2001 Apr;(385):130-43.**	**R**	**9**	**Orthovisc**
37	Altman RD, Moskowitz R. Intraarticular sodium hyaluronate (Hyalgan) in the treatment of patients with osteoarthritis of the knee: a randomized clinical trial. Hyalgan Study Group. J Rheumatol. 1998 Nov;25(11):2203-12. Erratum in: J Rheumatol 1999 May;26(5):1216.	NR	5	Hyalgan
38	Creamer P, Sharif M, George E, Meadows K, Cushnaghan J, Shinmei M, Dieppe P. Intra-articular hyaluronic acid in osteoarthritis of the knee: an investigation into mechanisms of action. Osteoarthritis Cartilage. 1994 Jun;2(2):133-40.	NR	5	Hyalgan
39	**Neustadt D, Caldwell J, Bell M, Wade J, Gimbel J. Clinical effects of intraarticular injection of high molecular weight hyaluronan (Orthovisc) in osteoarthritis of the knee: a randomized, controlled, multicenter trial. J Rheumatol. 2005 Oct;32(10):1928-36.**	**R**	**9**	**Orthovisc**
40	Jones AC, Pattrick M, Doherty S, Doherty M. Intra-articular hyaluronic acid compared to intra-articular triamcinolone hexacetonide in inflammatory knee osteoarthritis. Osteoarthritis Cartilage. 1995 Dec;3(4):269-73.	NR	5	Hyalgan
41	Goto M, Hanyu T, Yoshio T, Matsuno H, Shimizu M, Murata N, Shiozawa S, Matsubara T, Yamana S, Matsuda T. Intra-articular injection of hyaluronate (SI-6601D) improves joint pain and synovial fluid prostaglandin E2 levels in rheumatoid arthritis: a multicenter clinical trial. Clin Exp Rheumatol. 2001 Jul-Aug;19(4):377-83.	NR	4	
42	Pasquali Ronchetti I, Guerra D, Taparelli F, Boraldi F, Bergamini G, Mori G, Zizzi F, Frizziero L. Morphological analysis of knee synovial membrane biopsies from a randomized controlled clinical study comparing the effects of sodium hyaluronate (Hyalgan) and methylprednisolone acetate (Depomedrol) in osteoarthritis. Rheumatology (Oxford). 2001 Feb;40(2):158-69.	NR	5	Hyalgan
43	Wobig M, Dickhut A, Maier R, Vetter G. Viscosupplementation with hylan G-F 20: a 26-week controlled trial of efficacy and safety in the osteoarthritic knee. Clin Ther. 1998 May-Jun;20(3):410-23.	NR	5	hylan G-F 20
44	Hirota W. Intra-articular injection of hyaluronic acid reduces total amounts of leukotriene C4, 6-keto-prostaglandin F1alpha, prostaglandin F2alpha and interleukin-1beta in synovial fluid of patients with internal derangement in disorders of the temporomandibular joint. Br J Oral Maxillofac Surg. 1998 Feb;36(1):35-8.	NR	5	Artz

User query # 8: (hyaluron* OR hyaluronan OR hyaluronic OR hylan OR hyaluronate) AND (osteoarthr* OR osteoarthritis OR arthritis OR arthrosis OR pain OR trauma OR degeneration) AND (synovial joint OR intraarticular)				
Citation		**Relevance NR=non-relevant R=relevant**	**Reason for non-relevance or Appraisal**	
45	Anandacoomarasamy A, Bagga H, Ding C, Burkhardt D, Sambrook PN, March LM. Predictors of clinical response to intraarticular Hylan injections -- a prospective study using synovial fluid measures, clinical outcomes, and magnetic resonance imaging. J Rheumatol. 2008 Apr;35(4):685-90.	NR	5	hylan G-F 20
46	Richette P, Ravaud P, Conrozier T, Euller-Ziegler L, Mazières B, Maugars Y, Mulleman D, Clerson P, Chevalier X. Effect of hyaluronic acid in symptomatic hip osteoarthritis: a multicenter, randomized, placebo-controlled trial. Arthritis Rheum. 2009 Mar;60(3):824-30.	NR	5	Adant
47	Nunez SE, Draeger HT, Rivero DP, Kettwich LG, Sibbitt WL Jr, Bankhurst AD. Reduced pain of intraarticular hyaluronate injection with the reciprocating procedure device. J Clin Rheumatol. 2007 Feb;13(1):16-9.	NR	5	hylan G-F 20
48	Kawasaki T, Kurosawa H, Ikeda H, Takazawa Y, Ishijima M, Kubota M, Kajihara H, Maruyama Y, Kim SG, Kanazawa H, Doi T. Therapeutic home exercise versus intraarticular hyaluronate injection for osteoarthritis of the knee: 6-month prospective randomized open-labeled trial. J Orthop Sci. 2009 Mar;14(2):182-91.	NR	5	Artz
49	Skwara A, Ponelis R, Tibesku CO, Rosenbaum D, Fuchs-Winkelmann S. Gait patterns after intraarticular treatment of patients with osteoarthritis of the knee--hyaluronan versus triamcinolone: a prospective, randomized, doubleblind, monocentric study. Eur J Med Res. 2009 Apr 16;14(4):157-64.	NR	5	Ostenil
50	Wu JJ, Shih LY, Hsu HC, Chen TH. The double-blind test of sodium hyaluronate (ARTZ) on osteoarthritis knee. Zhonghua Yi Xue Za Zhi (Taipei). 1997 Feb;59(2):99-106.	NR	5	Artz
51	Cohen MM, Altman RD, Hollstrom R, Hollstrom C, Sun C, Gipson B. Safety and efficacy of intra-articular sodium hyaluronate (Hyalgan) in a randomized, double-blind study for osteoarthritis of the ankle. Foot Ankle Int. 2008 Jul;29(7):657-63.	NR	5	Hyalgan
52	Bunyaratavej N, Chan KM, Subramanian N. Treatment of painful osteoarthritis of the knee with hyaluronic acid. Results of a multicenter Asian study. J Med Assoc Thai. 2001 Oct;84 Suppl 2:S576-81.	NR	5	Hyalgan
53	Guidolin DD, Ronchetti IP, Lini E, Guerra D, Frizziero L. Morphological analysis of articular cartilage biopsies from a randomized, clinical study comparing the effects of 500-730 kDa sodium hyaluronate (Hyalgan) and methylprednisolone acetate on primary osteoarthritis of the knee. Osteoarthritis Cartilage. 2001 May;9(4):371-81.	NR	5	Hyalgan
54	Punzi L, Schiavon F, Cavasin F, Ramonda R, Gambari PF, Todesco S. The influence of intra-articular hyaluronic acid on PGE2 and cAMP of synovial fluid. Clin Exp Rheumatol. 1989 May-Jun;7(3):247-50.	NR	5	Hyalgan
55	Aydogan NH, Baydar ML, Atay T, Perktas I, Baykal BY, Ozmeric A. The effect of arthroscopic surgery and intraarticular drug injection to the antioxidation system and lipid peroxidation at osteoarthritis of knee. Saudi Med J. 2008 Mar;29(3):397-402.	NR	5	hylan G-F 20
56	**Ozturk C, Atamaz F, Hepguler S, Argin M, Arkun R. The safety and efficacy of intraarticular hyaluronan with/without corticosteroid in knee osteoarthritis: 1-year, single-blind, randomized study. Rheumatol Int. 2006 Feb;26(4):314-9.**	**R**	**9**	**Orthovisc**
57	Rennesson-Rey B, Rat AC, Chary-Valckenaere I, Bettembourg-Brault I, Juge N, Dintinger H, Pourel J, Loeuille D. Does joint effusion influence the clinical response to a single Hylan GF-20 injection for hip osteoarthritis? Joint Bone Spine. 2008 Mar;75(2):182-8.	NR	5	hylan G-F 20
58	Auerbach B, Melzer C. [Cross-linked hyaluronic acid in the treatment of osteoarthritis of the knee--results of a prospective randomized trial]. Zentralbl Chir. 2002 Oct;127(10):895-9.	NR	5	hylan G-F 20
59	Sugimoto H, Yamada H, Terada N, Kanaji A, Kato S, Date H, Ichinose H, Miyazaki K. Intraarticular injection of high molecular weight hyaluronan for osteoarthritis of the knee - prediction of effectiveness with biological markers. J Rheumatol. 2006 Dec;33(12):2527.	NR	5	Artz
60	Tang SF, Chen CP, Chen MJ, Hong WH, Yu TY, Tsai WC. Improvement of muscle strength in osteoarthritic knee patients after intraarticular knee injection of hyaluronan. Am J Phys Med Rehabil. 2005 Apr;84(4):274-7.	NR	6	1% HA solution, 2.5ml, 860 kd
61	Hempfling H. Intra-articular hyaluronic acid after knee arthroscopy: a two-year study. Knee Surg Sports Traumatol Arthrosc. 2007 May;15(5):537-46.	NR	5	Viscoseal

User query # 8: (hyaluron* OR hyaluronan OR hyaluronic OR hylan OR hyaluronate) AND (osteoarthr* OR osteoarthritis OR arthritis OR arthrosis OR pain OR trauma OR degeneration) AND (synovial joint OR intraarticular)				
Citation		**Relevance NR=non-relevant R=relevant**	**Reason for non-relevance or Appraisal**	
62	Fuchs S, Erbe T, Fischer HL, Tibesku CO. Intraarticular hyaluronic acid versus glucocorticoid injections for nonradicular pain in the lumbar spine. J Vasc Interv Radiol. 2005 Nov;16(11):1493-8.	NR	5	Ostenil
63	Henderson EB, Smith EC, Pegley F, Blake DR. Intra-articular injections of 750 kD hyaluronan in the treatment of osteoarthritis: a randomised single centre double-blind placebo-controlled trial of 91 patients demonstrating lack of efficacy. Ann Rheum Dis. 1994 Aug;53(8):529-34.	NR	5	Hyalgan
64	Miltner O, Schneider U, Siebert CH, Wirtz DC, Niethard FU. [Measuring isokinetic force in patients with gonarthrosis before and after hyaluronic acid therapy]. Z Orthop Ihre Grenzgeb. 2001 Jul-Aug;139(4):340-5.	NR	5	Hyalart
65	Bum Park Y, Ah Choi W, Kim YK, Chul Lee S, Hae Lee J. Accuracy of blind versus ultrasound-guided suprapatellar bursal injection. J Clin Ultrasound. 2012 Jan;40(1):20-5.	NR	4	
66	Itokazu M, Shinozaki M, Ohno T. Quantitative analysis of hyaluronan in the synovial tissues of patients with joint disorders. Clin Rheumatol. 1998;17(3):261-2.	NR	4	
67	Day R, Brooks P, Conaghan PG, Petersen M; Multicenter Trial Group. A double blind, randomized, multicenter, parallel group study of the effectiveness and tolerance of intraarticular hyaluronan in osteoarthritis of the knee. J Rheumatol. 2004 Apr;31(4):775-82.	NR	5	Artz
68	Brocq O, Tran G, Breuil V, Grisot C, Flory P, Euller-Ziegler L. Hip osteoarthritis: short-term efficacy and safety of viscosupplementation by hylan G-F 20. An open-label study in 22 patients. Joint Bone Spine. 2002 Jun;69(4):388-91.	NR	5	hylan G-F 20
69	Herrero-Beaumont G, Guerrero R, Sánchez-Pernaute O, Acebes C, Palacios I, Mas S, Rodriguez I, Egido J, Vivanco F. Cartilage and bone biological markers in the synovial fluid of osteoarthritic patients after hyaluronan injections in the knee. Clin Chim Acta. 2001 Jun;308(1-2):107-15.	NR	5	Adant
70	Skwara A, Peterlein CD, Tibesku CO, Rosenbaum D, Fuchs-Winkelmann S. Changes of gait patterns and muscle activity after intraarticular treatment of patients with osteoarthritis of the knee: a prospective, randomised, doubleblind study. Knee. 2009 Dec;16(6):466-72.	NR	5	Ostenil
71	Manicourt DH, Bevilacqua M, Righini V, Famaey JP, Devogelaer JP. Comparative effect of nimesulide and ibuprofen on the urinary levels of collagen type II C-telopeptide degradation products and on the serum levels of hyaluronan and matrix metalloproteinases-3 and -13 in patients with flare-up of osteoarthritis. Drugs R D. 2005;6(5):261-71.	NR	4	
72	Basterzi Y, Sari A, Demirkan F, Unal S, Arslan E. Intraarticular hyaluronic acid injection for the treatment of reducing and nonreducing disc displacement of the temporomandibular joint. Ann Plast Surg. 2009 Mar;62(3):265-7.	NR	4	Ostenil
73	Kraus VB, Birmingham J, Stabler TV, Feng S, Taylor DC, Moorman CT 3rd, Garrett WE, Toth AP. Effects of intraarticular IL1-Ra for acute anterior cruciate ligament knee injury: a randomized controlled pilot trial (NCT00332254). Osteoarthritis Cartilage. 2012 Apr;20(4):271-8.	NR	4	
74	Luciani D, Cadossi M, Tesei F, Chiarello E, Giannini S. Viscosupplementation for grade II osteoarthritis of the ankle: a prospective study at 18 months' follow-up. Chir Organi Mov. 2008 Dec;92(3):155-60.	NR	5	hylan G-F 20
75	**Sezgin M, Demirel AC, Karaca C, Ortancil O, Ulkar GB, Kanik A, Cakçi A. Does hyaluronan affect inflammatory cytokines in knee osteoarthritis? Rheumatol Int. 2005 May;25(4):264-9.**	**R**	**9**	**Orthovisc**
76	Liu ZM, Peng YJ, Long X, Li J, Ke J, Fang W. Mutual effect between neuropeptides and inflammatory cytokines in neurogenic SMSCs of human temporomandibular joint. J Huazhong Univ Sci Technolog Med Sci. 2014 Aug;34(4):602-7.	NR	4	
77	Rovetta G, Monteforte P. Intraarticular injection of sodium hyaluronate plus steroid versus steroid in adhesive capsulitis of the shoulder. Int J Tissue React. 1998;20(4):125-30.	NR	4	
78	Carpenter B, Motley T. The role of viscosupplementation in the ankle using hylan G-F 20. J Foot Ankle Surg. 2008 Sep-Oct;47(5):377-84.	NR	5	hylan G-F 20
79	Caborn D, Rush J, Lanzer W, Parenti D, Murray C; Synvisc 901 Study Group. A randomized, single-blind comparison of the efficacy and	NR	5	hylan G-F 20

User query # 8: (hyaluron* OR hyaluronan OR hyaluronic OR hylan OR hyaluronate) AND (osteoarthr* OR osteoarthritis OR arthritis OR arthrosis OR pain OR trauma OR degeneration) AND (synovial joint OR intraarticular)				
Citation		**Relevance NR=non-relevant R=relevant**	**Reason for non-relevance or Appraisal**	
	tolerability of hylan G-F 20 and triamcinolone hexacetonide in patients with osteoarthritis of the knee. J Rheumatol. 2004 Feb;31(2):333-43.			
80	Dahlberg L, Lohmander LS, Ryd L. Intraarticular injections of hyaluronan in patients with cartilage abnormalities and knee pain. A one-year double-blind, placebo-controlled study. Arthritis Rheum. 1994 Apr;37(4):521-8.	NR	5	Artz
81	Cleary M, Keating C, Poynton AR. Viscosupplementation in lumbar facet joint arthropathy: a pilot study. J Spinal Disord Tech. 2008 Feb;21(1):29-32.	NR	5	Suplasyn
82	Okroj M, Holmquist E, Sjölander J, Corrales L, Saxne T, Wisniewski HG, Blom AM. Heavy chains of inter alpha inhibitor (IαI) inhibit the human complement system at early stages of the cascade. J Biol Chem. 2012 Jun 8;287(24):20100-10.	NR	4	
83	Diracoglu D, Vural M, Baskent A, Dikici F, Aksoy C. The effect of viscosupplementation on neuromuscular control of the knee in patients with osteoarthritis. J Back Musculoskelet Rehabil. 2009;22(1):1-9.	NR	5	hylan G-F 20
84	Matsuno H, Yudoh K, Kondo M, Goto M, Kimura T. Biochemical effect of intra-articular injections of high molecular weight hyaluronate in rheumatoid arthritis patients. Inflamm Res. 1999 Mar;48(3):154-9.	NR	5	NRD101
85	Tanaka N, Sakahashi H, Sato E, Hirose K, Ishima T, Ishii S. Intra-articular injection of high molecular weight hyaluronan after arthrocentesis as treatment for rheumatoid knees with joint effusion. Rheumatol Int. 2002 Aug;22(4):151-4.	NR	5	Suvenyl
86	Matsuno H, Nakamura H, Katayama K, Hayashi S, Kano S, Yudoh K, Kiso Y. Effects of an oral administration of glucosamine-chondroitin-quercetin glucoside on the synovial fluid properties in patients with osteoarthritis and rheumatoid arthritis. Biosci Biotechnol Biochem. 2009 Feb;73(2):288-92.	NR	4	
87	de Campos GC, Rezende MU, Pailo AF, Frucchi R, Camargo OP. Adding triamcinolone improves viscosupplementation: a randomized clinical trial. Clin Orthop Relat Res. 2013 Feb;471(2):613-20.	NR	5	hylan G-F 20 6 ml
88	Alpaslan C, Bilgihan A, Alpaslan GH, Güner B, Ozgür Yis M, Erbaş D. Effect of arthrocentesis and sodium hyaluronate injection on nitrite, nitrate, and thiobarbituric acid-reactive substance levels in the synovial fluid. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2000 Jun;89(6):686-90.	NR	6	
89	Wu MX, Li XH, Lin MN, Jia XR, Mu R, Wan WR, Chen RH, Chen LH, Lin WQ, Huang CY, Zhang XR, Hong KD, Li L, Liu XX. Clinical study on the treatment of knee osteoarthritis of Shen-Sui insufficiency syndrome type by electroacupuncture. Chin J Integr Med. 2010 Aug;16(4):291-7.	NR	4	
90	Payne MW, Petrella RJ. Viscosupplementation effect on proprioception in the osteoarthritic knee. Arch Phys Med Rehabil. 2000 May;81(5):598-603.	NR	5	Suplasyn
91	**Calis M, Demir H, Ulker S, Kirnap M, Duygulu F, Calis HT. Is intraarticular sodium hyaluronate injection an alternative treatment in patients with adhesive capsulitis? Rheumatol Int. 2006 Apr;26(6):536-40.**	**R**	**9**	**Orthovisc**
92	Huang MH, Yang RC, Lee CL, Chen TW, Wang MC. Preliminary results of integrated therapy for patients with knee osteoarthritis. Arthritis Rheum. 2005 Dec 15;53(6):812-20.	NR	5	Hyalgan
93	Christensson B, Ryd L, Dahlberg L, Lohmander S. Candida albicans arthritis in a nonimmunocompromised patient. Complication of placebo intraarticular injections. Acta Orthop Scand. 1993 Dec;64(6):695-8.	NR	4	
94	Yoshida M, Funasaki H, Saito M, Kajitani K, Fujii K. Pathologic gene expression in adhesive subacromial bursae of human shoulder. Clin Orthop Relat Res. 2003 Jul;(412):57-64.	NR	4	
95	Mathies B. Effects of Viscoseal, a synovial fluid substitute, on recovery after arthroscopic partial meniscectomy and joint lavage. Knee Surg Sports Traumatol Arthrosc. 2006 Jan;14(1):32-9.	NR	5	Viscoseal
96	Hess H, Rothhaar J, Thiel W. [Clinical studies of intra-articular injections of Arteparon. Retrospective study following the treatment of 754 patients]. Fortschr Med. 1982 Sep 16;100(35):1624-7. German.	NR	4	
97	Sharif M, Salisbury C, Taylor DJ, Kirwan JR. Changes in biochemical markers of joint tissue metabolism in a randomized controlled trial of glucocorticoid in early rheumatoid arthritis. Arthritis Rheum. 1998 Jul;41(7):1203-9.	NR	4	

7.1.2 User query # 9

Results are ordered according their relevance (high to low).

User query # 9: "Ostenil Plus" OR "Osteonil Plus" OR Ost Plus" OR "Maxiostenil Plus" OR "Hyaject Plus"				
Citation		**Relevance NR=non-relevant R=relevant**	**Reason for non-relevance or Appraisal**	
1	Waters AM, Farrell LJ, Zimmer-Gembeck MJ, Milliner E, Tiralongo E, Donovan CL, McConnell H, Bradley BP, Mogg K, Ollendick TH. Augmenting one-session treatment of children's specific phobias with attention training to positive stimuli. Behav Res Ther. 2014 Nov;62:107-19. doi: 10.1016/j.brat.2014.07.020. Epub 2014 Aug 8. PubMed PMID: 25156398.	NR	4	
2	Brown R, Gassman M, Hetzel S, Berger L. Community-based treatment for opioid dependent offenders: a pilot study. Am J Addict. 2013 Sep-Oct;22(5):500-2. doi: 10.1111/j.1521-0391.2013.12049.x. Epub 2013 Apr 3. PubMed PMID: 23952897; PubMed Central PMCID: PMC3748386.	NR	4	
3	Day E, Copello A, Seddon JL, Christie M, Bamber D, Powell C, George S, Ball A, Frew E, Freemantle N. Pilot study of a social network intervention for heroin users in opiate substitution treatment: study protocol for a randomized controlled trial. Trials. 2013 Aug 19;14:264. doi: 10.1186/1745-6215-14-264. PubMed PMID: 23958332; PubMed Central PMCID: PMC3765136.	NR	4	
4	Porschen R, Arkenau HT, Kubicka S, Greil R, Seufferlein T, Freier W, Kretzschmar A, Graeven U, Grothey A, Hinke A, Schmiegel W, Schmoll HJ; AIO Colorectal Study Group. Phase III study of capecitabine plus oxaliplatin compared with fluorouracil and leucovorin plus oxaliplatin in metastatic colorectal cancer: a final report of the AIO Colorectal Study Group. J Clin Oncol. 2007 Sep 20;25(27):4217-23. Epub 2007 Jun 4. PubMed PMID: 17548840.	NR	4	
5	Hellström-Lindberg E, Negrin R, Stein R, Krantz S, Lindberg G, Vardiman J, Ost A, Greenberg P. Erythroid response to treatment with G-CSF plus erythropoietin for the anaemia of patients with myelodysplastic syndromes: proposal for a predictive model. Br J Haematol. 1997 Nov;99(2):344-51. PubMed PMID: 9375752.	NR	4	
6	Wolffsohn JS, Hunt OA, Chowdhury A. Objective clinical performance of 'comfort-enhanced' daily disposable soft contact lenses. Cont Lens Anterior Eye. 2010 Apr;33(2):88-92. doi: 10.1016/j.clae.2010.01.004. Epub 2010 Feb 9. PubMed PMID: 20149716.	NR	4	
7	Miniero R, Brach del Prever A, Vassallo E, Nesi F, Busca A, Fagioli F, Albiani R, Picci P, Bacci G, Madon E. Feasibility of high-dose chemotherapy and autologous peripheral blood stem cell transplantation in children with high grade osteosarcoma. Bone Marrow Transplant. 1998 Dec;22 Suppl 5:S37-40. PubMed PMID: 9989888.	NR	4	
8	Hurley M, Yao W, Lane NE. Changes in serum fibroblast growth factor 2 in patients with glucocorticoid-induced osteoporosis treated with human parathyroid hormone (1-34). Osteoporos Int. 2005 Dec;16(12):2080-4. Epub 2005 Aug 19. PubMed PMID: 16133640.	NR	4	
9	Ruckser R, Kier P, Buxhofer V, Kittl E, Tatzreiter G, Vedovelli H, Zelenka P, Hübl G, Hinterberger W. [High dosage chemotherapy with autologous stem cell transplantation in multiple myeloma]. Acta Med Austriaca Suppl. 2000;52:40-2. German. PubMed PMID: 11261278.	NR	4	

7.1.3 User query # 14

Results are ordered according their relevance (high to low).

User query # 14: (("Osteoarthritis/drug therapy"[Mesh] OR "Osteoarthritis/therapy"[Mesh])) AND ("Hyaluronic Acid/therapeutic use"[Mesh] OR "Hyaluronic Acid/therapy"[Mesh])				
Citation		**Relevance NR=non-relevant R=relevant**	**Reason for non-relevance or Appraisal**	
1	Yan CH, Chan WL, Yuen WH, Yung PS, Ip KY, Fan JC, Chiu KY. Efficacy and safety of hylan G-F 20 injection in treatment of knee osteoarthritis in Chinese patients: results of a prospective, multicentre, longitudinal study. Hong Kong Med J. 2015 Aug;21(4):327-32. doi: 10.12809/hkmj144329. Epub 2015 Jun 19. PubMed PMID: 26087755.	NR	5	hylan G-F 20

User query # 14: (("Osteoarthritis/drug therapy"[Mesh] OR "Osteoarthritis/therapy"[Mesh])) AND ("Hyaluronic Acid/therapeutic use"[Mesh] OR "Hyaluronic Acid/therapy"[Mesh])				
Citation		**Relevance NR=non-relevant R=relevant**	**Reason for non-relevance or Appraisal**	
2	**van der Weegen W, Wullems JA, Bos E, Noten H, van Drumpt RA. No difference between intra-articular injection of hyaluronic acid and placebo for mild to moderate knee osteoarthritis: a randomized, controlled, double-blind trial. J Arthroplasty. 2015 May;30(5):754-7. doi: 10.1016/j.arth.2014.12.012. Epub 2014 Dec 13. PubMed PMID: 25548079.**	**R**	**9**	**Fermathron Plus 30mg/2ml (1.5%)**
3	Zhang H, Zhang K, Zhang X, Zhu Z, Yan S, Sun T, Guo A, Jones J, Steen RG, Shan B, Zhang J, Lin J. Comparison of two hyaluronic acid formulations for safety and efficacy (CHASE) study in knee osteoarthritis: a multicenter, randomized, double-blind, 26-week non-inferiority trial comparing Durolane to Artz. Arthritis Res Ther. 2015 Mar 10;17:51. doi: 10.1186/s13075-015-0557-x. PubMed PMID: 25889322; PubMed Central PMCID: PMC4391669.	NR	5	Durolane, Artz
4	Monfort J, Rotés-Sala D, Segalés N, Montañes FJ, Orellana C, Llorente-Onaindia J, Mojal S, Padró I, Benito P. Comparative efficacy of intra-articular hyaluronic acid and corticoid injections in osteoarthritis of the first carpometacarpal joint: results of a 6-month single-masked randomized study. Joint Bone Spine. 2015 Mar;82(2):116-21. doi: 10.1016/j.jbspin.2014.08.008. Epub 2014 Oct 11. PubMed PMID: 25311256.	NR	5	Suplasyn
5	Petrella RJ, Emans PJ, Alleyne J, Dellaert F, Gill DP, Maroney M. Safety and performance of Hydros and Hydros-TA for knee osteoarthritis: a prospective, multicenter, randomized, double-blind feasibility trial. BMC Musculoskelet Disord. 2015 Mar 18;16:57. doi: 10.1186/s12891-015-0513-6. PubMed PMID: 25887932; PubMed Central PMCID: PMC4367821.	NR	5	Hydros, Hydros TA, hylan G-F 20
6	Tang AC, Tang SF, Hong WH, Chen HC. Kinetics features changes before and after intra-articular hyaluronic acid injections in patients with knee osteoarthritis. Clin Neurol Neurosurg. 2015 Feb;129 Suppl 1:S21-6. doi: 10.1016/S0303-8467(15)30007-X. PubMed PMID: 25683308.	NR	5	Artz
7	Tang AC, Hong WH, Chen HC, Tang SF. Intra-articular intervention by hyaluronic acid for knee osteoarthritis can modify locomotor pattern of muscle activity. Clin Neurol Neurosurg. 2015 Feb;129 Suppl 1:S16-20. doi: 10.1016/S0303-8467(15)30006-8. PubMed PMID: 25683307.	NR	5	Artz
8	Yang L, Zhang J, Wang G. The effect of sodium hyaluronate treating knee osteoarthritis on synovial fluid interleukin -1β and clinical treatment mechanism. Pak J Pharm Sci. 2015 Jan;28(1 Suppl):407-10. PubMed PMID: 25631505.	NR	6	
9	Nelson FR, Zvirbulis RA, Zonca B, Li KW, Turner SM, Pasierb M, Wilton P, Martinez-Puig D, Wu W. The effects of an oral preparation containing hyaluronic acid (Oralvisc®) on obese knee osteoarthritis patients determined by pain, function, bradykinin, leptin, inflammatory cytokines, and heavy water analyses. Rheumatol Int. 2015 Jan;35(1):43-52. doi: 10.1007/s00296-014-3047-6. Epub 2014 Jun 5. Erratum in: Rheumatol Int. 2015 Jan;35(1):53. PubMed PMID: 24899570.	NR	4	
10	Gencer ZK, Özkiriş M, Okur A, Korkmaz M, Saydam L. A comparative study on the impact of intra-articular injections of hyaluronic acid, tenoxicam and betametazon on the relief of temporomandibular joint disorder complaints. J Craniomaxillofac Surg. 2014 Oct;42(7):1117-21. doi: 10.1016/j.jcms.2014.01.041. Epub 2014 Feb 4. PubMed PMID: 24853591.	NR	5	Hyalgan
11	Housman L, Arden N, Schnitzer TJ, Birbara C, Conrozier T, Skrepnik N, Wei N, Bockow B, Waddell D, Tahir H, Hammond A, Goupille P, Sanson BJ, Elkins C, Bailleul F. Intra-articular hylastan versus steroid for knee osteoarthritis. Knee Surg Sports Traumatol Arthrosc. 2014 Jul;22(7):1684-92. doi: 10.1007/s00167-013-2438-7. Epub 2013 Feb 16. PubMed PMID: 23417236.	NR	5	Hylastan
12	Chareancholvanich K, Pornrattanamaneewong C, Narkbunnam R. Increased cartilage volume after injection of hyaluronic acid in osteoarthritis knee patients who underwent high tibial osteotomy. Knee Surg Sports Traumatol Arthrosc. 2014 Jun;22(6):1415-23. doi: 10.1007/s00167-013-2735-1. Epub 2013 Oct 27. PubMed PMID: 24162762; PubMed Central PMCID: PMC4028547.	NR	5	Hyalgan
13	**Giarratana LS, Marelli BM, Crapanzano C, De Martinis SE, Gala L,**	**R**	**9**	**Hyalubrix**

User query # 14: (("Osteoarthritis/drug therapy"[Mesh] OR "Osteoarthritis/therapy"[Mesh])) AND ("Hyaluronic Acid/therapeutic use"[Mesh] OR "Hyaluronic Acid/therapy"[Mesh])				
Citation		**Relevance NR=non-relevant R=relevant**	**Reason for non-relevance or Appraisal**	
	Ferraro M, Marelli N, Albisetti W. A randomized double-blind clinical trial on the treatment of knee osteoarthritis: the efficacy of polynucleotides compared to standard hyaluronian viscosupplementation. Knee. 2014 Jun;21(3):661-8. doi: 10.1016/j.knee.2014.02.010. Epub 2014 Feb 24. PubMed PMID: 24703391.			
14	**Migliore A, Massafra U, Bizzi E, Tormenta S, Cassol M, Granata M. Duration of symptom relief after intra-articular injection of hyaluronic acid combined with sorbitol (anti-ox-vs) in symptomatic hip osteoarthritis. Int J Immunopathol Pharmacol. 2014 Apr-Jun;27(2):245-52. PubMed PMID: 25004836.**	**R**	**9**	**Synolis V-A**
15	Yu CJ, Ko CJ, Hsieh CH, Chien CT, Huang LH, Lee CW, Jiang CC. Proteomic analysis of osteoarthritic chondrocyte reveals the hyaluronic acid-regulated proteins involved in chondroprotective effect under oxidative stress. J Proteomics. 2014 Mar 17;99:40-53. doi: 10.1016/j.jprot.2014.01.016. Epub 2014 Jan 27. PubMed PMID: 24480285.	NR	3	
16	Arden NK, Åkermark C, Andersson M, Todman MG, Altman RD. A randomized saline-controlled trial of NASHA hyaluronic acid for knee osteoarthritis. Curr Med Res Opin. 2014 Feb;30(2):279-86. doi: 10.1185/03007995.2013.855631. Epub 2013 Nov 5. PubMed PMID: 24168077.	NR	5	NASHA
17	Khalaj N, Abu Osman NA, Mokhtar AH, George J, Abas WA. Effect of intra-articular hyaluronic injection on postural stability and risk of fall in patients with bilateral knee osteoarthritis. ScientificWorldJournal. 2014;2014:815184. doi: 10.1155/2014/815184. Epub 2014 Jun 19. PubMed PMID: 25136689; PubMed Central PMCID: PMC4090518.	NR	5	Hyalgan
18	Leighton R, Akermark C, Therrien R, Richardson JB, Andersson M, Todman MG, Arden NK; DUROLANE Study Group. NASHA hyaluronic acid vs. methylprednisolone for knee osteoarthritis: a prospective, multi-centre, randomized, non-inferiority trial. Osteoarthritis Cartilage. 2014 Jan;22(1):17-25. doi: 10.1016/j.joca.2013.10.009. Epub 2013 Nov 1. PubMed PMID: 24185114.	NR	5	NASHA
19	Habib G, Jabbour A, Artul S, Hakim G. Intra-articular methylprednisolone acetate injection at the knee joint and the hypothalamic-pituitary-adrenal axis: a randomized controlled study. Clin Rheumatol. 2014 Jan;33(1):99-103. doi: 10.1007/s10067-013-2374-4. Epub 2013 Aug 28. PubMed PMID: 23982564.	NR	5	Suplasyn
20	Ishijima M, Nakamura T, Shimizu K, Hayashi K, Kikuchi H, Soen S, Omori G, Yamashita T, Uchio Y, Chiba J, Ideno Y, Kubota M, Kurosawa H, Kaneko K; Research Group of Cartilage Metabolism. Intra-articular hyaluronic acid injection versus oral non-steroidal anti-inflammatory drug for the treatment of knee osteoarthritis: a multi-center, randomized, open-label, non-inferiority trial. Arthritis Res Ther. 2014 Jan 21;16(1):R18. doi: 10.1186/ar4446. PubMed PMID: 24443804; PubMed Central PMCID: PMC3979073.	NR	6	
21	Witteveen AG, Kok A, Sierevelt IN, Kerkhoffs GM, van Dijk CN. The optimal injection technique for the osteoarthritic ankle: a randomized, cross-over trial. Foot Ankle Surg. 2013 Dec;19(4):283-8. doi: 10.1016/j.fas.2013.07.003. Epub 2013 Aug 8. PubMed PMID: 24095239.	NR	4	hylan G-F 20
22	**Heisel J, Kipshoven C. Safety and efficacy findings from a non-interventional study of a new hyaluronic acid/sorbitol formulation (GO-ON® matrix) for intra-articular injection to relieve pain and disability in osteoarthritis patients. Drug Res (Stuttg). 2013 Sep;63(9):445-9. doi: 10.1055/s-0033-1343425. Epub 2013 Apr 18. PubMed PMID: 23599036.**	**R**	**9**	**Go-On matrix**
23	Ostałowska A, Nowak D, Święchowicz S, Birkner E, Brenk A, Kasperczyk S, Dobrakowski M, Machoń A. Assessment of knee function and biochemical parameters of articular fluid and peripheral blood in gonarthrosis patients following intra-articular administration of hyaluronic acid. Pol Orthop Traumatol. 2013 Aug 16;78:173-81. PubMed PMID: 23959433.	NR	5	Euflexxa
24	Henrotin Y, Chevalier X, Deberg M, Balblanc JC, Richette P, Mulleman	NR	5	hylan G-F 20

User query # 14: (("Osteoarthritis/drug therapy"[Mesh] OR "Osteoarthritis/therapy"[Mesh])) AND ("Hyaluronic Acid/therapeutic use"[Mesh] OR "Hyaluronic Acid/therapy"[Mesh])				
Citation		**Relevance NR=non-relevant R=relevant**	**Reason for non-relevance or Appraisal**	
	D, Maillet B, Rannou F, Piroth C, Mathieu P, Conrozier T; Osteoarthritis Group of French Society of Rheumatology. Early decrease of serum biomarkers of type II collagen degradation (Coll2-1) and joint inflammation (Coll2-1 NO_2) by hyaluronic acid intra-articular injections in patients with knee osteoarthritis: a research study part of the Biovisco study. J Orthop Res. 2013 Jun;31(6):901-7. doi: 10.1002/jor.22297. Epub 2013 Feb 19. PubMed PMID: 23423846.			
25	Mei-Dan O, Carmont M, Laver L, Mann G, Maffulli N, Nyska M. Intra-articular injections of hyaluronic acid in osteoarthritis of the subtalar joint: a pilot study. J Foot Ankle Surg. 2013 Mar-Apr;52(2):172-6. doi: 10.1053/j.jfas.2012.12.008. Epub 2013 Jan 17. PubMed PMID: 23333279.	NR	5	Euflexxa
26	Palmieri B, Rottigni V, Iannitti T. Preliminary study of highly cross-linked hyaluronic acid-based combination therapy for management of knee osteoarthritis-related pain. Drug Des Devel Ther. 2013;7:7-12. doi: 10.2147/DDDT.S37330. Epub 2013 Jan 7. PubMed PMID: 23326188; PubMed Central PMCID: PMC3544341.	NR	5	Variofill
27	Cerza F, Carnì S, Carcangiu A, Di Vavo I, Schiavilla V, Pecora A, De Biasi G, Ciuffreda M. Comparison between hyaluronic acid and platelet-rich plasma, intra-articular infiltration in the treatment of gonarthrosis. Am J Sports Med. 2012 Dec;40(12):2822-7. doi: 10.1177/0363546512461902. Epub 2012 Oct 25. PubMed PMID: 23104611.	NR	5	Hyalgan
28	Guarda-Nardini L, Cadorin C, Frizziero A, Ferronato G, Manfredini D. Comparison of 2 hyaluronic acid drugs for the treatment of temporomandibular joint osteoarthritis. J Oral Maxillofac Surg. 2012 Nov;70(11):2522-30. doi: 10.1016/j.joms.2012.07.020. Epub 2012 Aug 29. PubMed PMID: 22939642.	NR	5	Hyalgan, Sinovial
29	Iannitti T, Rottigni V, Palmieri B. A pilot study to compare two different hyaluronic acid compounds for treatment of knee osteoarthritis. Int J Immunopathol Pharmacol. 2012 Oct-Dec;25(4):1093-8. PubMed PMID: 23298499.	NR	5	hylan G-F 20, Variofill
30	Khanasuk Y, Dechmaneenin T, Tanavalee A. Prospective randomized trial comparing the efficacy of single 6-ml injection of hylan G-F 20 and hyaluronic acid for primary knee arthritis: a preliminary study. J Med Assoc Thai. 2012 Oct;95 Suppl 10:S92-7. PubMed PMID: 23451445.	NR	5	Hyalgan, hylan G-F 20 (Synvisc)
31	Berenbaum F, Grifka J, Cazzaniga S, D'Amato M, Giacovelli G, Chevalier X, Rannou F, Rovati LC, Maheu E. A randomised, double-blind, controlled trial comparing two intra-articular hyaluronic acid preparations differing by their molecular weight in symptomatic knee osteoarthritis. Ann Rheum Dis. 2012 Sep;71(9):1454-60. doi: 10.1136/annrheumdis-2011-200972. Epub 2012 Jan 31. PubMed PMID: 22294639; PubMed Central PMCID: PMC3414228.	NR	5	Go-On, Hyalgan
32	DeCaria JE, Montero-Odasso M, Wolfe D, Chesworth BM, Petrella RJ. The effect of intra-articular hyaluronic acid treatment on gait velocity in older knee osteoarthritis patients: a randomized, controlled study. Arch Gerontol Geriatr. 2012 Sep-Oct;55(2):310-5. doi: 10.1016/j.archger.2011.11.007. Epub 2011 Dec 9. PubMed PMID: 22169699.	NR	5	1% HA
33	Hegab AF, Ali HE, Elmasry M, Khallaf MG. Platelet-Rich Plasma Injection as an Effective Treatment for Temporomandibular Joint Osteoarthritis. J Oral Maxillofac Surg. 2015 Sep;73(9):1706-13. doi: 10.1016/j.joms.2015.03.045. Epub 2015 Mar 24. PubMed PMID: 25882438.	NR	4	
34	Henrotin Y, Hauzeur JP, Bruel P, Appelboom T. Intra-articular use of a medical device composed of hyaluronic acid and chondroitin sulfate (Structovial CS): effects on clinical, ultrasonographic and biological parameters. BMC Res Notes. 2012 Aug 4;5:407. doi: 10.1186/1756-0500-5-407. PubMed PMID: 22862789; PubMed Central PMCID: PMC3477095.	NR	5	
35	**Paoloni M, Di Sante L, Dimaggio M, Bernetti A, Mangone M, Di Renzo S, Santilli V. Kinematic and kinetic modifications in walking pattern of hip osteoarthritis patients induced by intra-articular injections of hyaluronic acid. Clin Biomech (Bristol, Avon). 2012**	**R**	**9**	**Hyalubrix**

User query # 14: (("Osteoarthritis/drug therapy"[Mesh] OR "Osteoarthritis/therapy"[Mesh])) AND ("Hyaluronic Acid/therapeutic use"[Mesh] OR "Hyaluronic Acid/therapy"[Mesh])				
Citation		**Relevance NR=non-relevant R=relevant**	**Reason for non-relevance or Appraisal**	
	Aug;27(7):661-5. doi: 10.1016/j.clinbiomech.2012.02.004. Epub 2012 Mar 11. PubMed PMID: 22410192.			
36	**Filardo G, Di Matteo B, Di Martino A, Merli ML, Cenacchi A, Fornasari P, Marcacci M, Kon E. Platelet-Rich Plasma Intra-articular Knee Injections Show No Superiority Versus Viscosupplementation: A Randomized Controlled Trial. Am J Sports Med. 2015 Jul;43(7):1575-82. doi: 10.1177/0363546515582027. Epub 2015 May 7. PubMed PMID: 25952818.**	**R**	**9**	**Hyalubrix**
37	Spaková T, Rosocha J, Lacko M, Harvanová D, Gharaibeh A. Treatment of knee joint osteoarthritis with autologous platelet-rich plasma in comparison with hyaluronic acid. Am J Phys Med Rehabil. 2012 May;91(5):411-7. doi: 10.1097/PHM.0b013e3182aab72. PubMed PMID: 22513879.	NR	5	Erectus
38	Strand V, Baraf HS, Lavin PT, Lim S, Hosokawa H. A multicenter, randomized controlled trial comparing a single intra-articular injection of Gel-200, a new cross-linked formulation of hyaluronic acid, to phosphate buffered saline for treatment of osteoarthritis of the knee. Osteoarthritis Cartilage. 2012 May;20(5):350-6. doi: 10.1016/j.joca.2012.01.013. Epub 2012 Feb 1. PubMed PMID: 22342928.	NR	5	Gel-200
39	Conrozier T, Balblanc JC, Richette P, Mulleman D, Maillet B, Henrotin Y, Rannou F, Piroth C, Hilliquin P, Mathieu P, Walliser-Lohse A, Rousselot I, Plattner V, Maillefert JF, Vignon E, Chevalier X; Osteoarthritis Group of the French Society of Rheumatology. Early effect of hyaluronic acid intra-articular injections on serum and urine biomarkers in patients with knee osteoarthritis: An open-label observational prospective study. J Orthop Res. 2012 May;30(5):679-85. doi: 10.1002/jor.21580. Epub 2011 Oct 24. PubMed PMID: 22025307.	NR	5	hylan G-F 20
40	Ip D, Fu NY. Can combined use of low-level lasers and hyaluronic acid injections prolong the longevity of degenerative knee joints? Clin Interv Aging. 2015 Aug 5;10:1255-8. doi: 10.2147/CIA.S86907. eCollection 2015. PubMed PMID: 26346122; PubMed Central PMCID: PMC4531024.	NR	5	Hyalgan
41	Kubový P, Mensíková L, Kůrková E, Lopot F, Hojka V, Jelen K. Influence of SYSADOA group chemicals on progression of human knee joint osteoarthritis: new objective evaluation method - measuring of rheological properties in vivo. Neuro Endocrinol Lett. 2012;33(6):651-9. PubMed PMID: 23160228.	NR	4	
42	Bum Park Y, Ah Choi W, Kim YK, Chul Lee S, Hae Lee J. Accuracy of blind versus ultrasound-guided suprapatellar bursal injection. J Clin Ultrasound. 2012 Jan;40(1):20-5. doi: 10.1002/jcu.20890. Epub 2011 Oct 28. PubMed PMID: 22033897.	NR	4	
43	DeGroot H 3rd, Uzunishvili S, Weir R, Al-omari A, Gomes B. Intra-articular injection of hyaluronic acid is not superior to saline solution injection for ankle arthritis: a randomized, double-blind, placebo-controlled study. J Bone Joint Surg Am. 2012 Jan 4;94(1):2-8. doi: 10.2106/JBJS.J.01763. PubMed PMID: 22218376.	NR	5	Supartz
44	Pavelka K, Uebelhart D. Efficacy evaluation of highly purified intra-articular hyaluronic acid (Sinovial(®)) vs hylan G-F20 (Synvisc(®)) in the treatment of symptomatic knee osteoarthritis. A double-blind, controlled, randomized, parallel-group non-inferiority study. Osteoarthritis Cartilage. 2011 Nov;19(11):1294-300. doi: 10.1016/j.joca.2011.07.016. Epub 2011 Aug 16. PubMed PMID: 21875678.	NR	5	Sinovial, hylan G-F 20
45	Navarro-Sarabia F, Coronel P, Collantes E, Navarro FJ, de la Serna AR, Naranjo A, Gimeno M, Herrero-Beaumont G; AMELIA study group. A 40-month multicentre, randomised placebo-controlled study to assess the efficacy and carry-over effect of repeated intra-articular injections of hyaluronic acid in knee osteoarthritis: the AMELIA project. Ann Rheum Dis. 2011 Nov;70(11):1957-62. doi: 10.1136/ard.2011.152017. Epub 2011 Aug 17. PubMed PMID: 21852252; PubMed Central PMCID: PMC3184238.	NR	5	Adant
46	Altman RD, Rosen JE, Bloch DA, Hatoum HT. Safety and efficacy of retreatment with a bioengineered hyaluronate for painful osteoarthritis of the knee: results of the open-label Extension Study of the FLEXX	NR	5	Euflexxa

User query # 14: (("Osteoarthritis/drug therapy"[Mesh] OR "Osteoarthritis/therapy"[Mesh])) AND ("Hyaluronic Acid/therapeutic use"[Mesh] OR "Hyaluronic Acid/therapy"[Mesh])				
Citation		**Relevance NR=non-relevant R=relevant**	**Reason for non-relevance or Appraisal**	
	Trial. Osteoarthritis Cartilage. 2011 Oct;19(10):1169-75. doi: 10.1016/j.joca.2011.07.001. Epub 2011 Jul 23. PubMed PMID: 21820521.			
47	Munteanu SE, Zammit GV, Menz HB, Landorf KB, Handley CJ, Elzarka A, Deluca J. Effectiveness of intra-articular hyaluronan (Synvisc, hylan G-F 20) for the treatment of first metatarsophalangeal joint osteoarthritis: a randomised placebo-controlled trial. Ann Rheum Dis. 2011 Oct;70(10):1838-41. doi: 10.1136/ard.2011.153049. Epub 2011 Jul 25. PubMed PMID: 21791454.	NR	5	hylan G-F 20
48	Huang TL, Chang CC, Lee CH, Chen SC, Lai CH, Tsai CL. Intra-articular injections of sodium hyaluronate (Hyalgan®) in osteoarthritis of the knee. a randomized, controlled, double-blind, multicenter trial in the Asian population. BMC Musculoskelet Disord. 2011 Oct 6;12:221. doi: 10.1186/1471-2474-12-221. PubMed PMID: 21978211; PubMed Central PMCID: PMC3203101.	NR	5	Hyalgan
49	**Foti C, Cisari C, Carda S, Giordan N, Rocco A, Frizziero A, Della Bella G. A prospective observational study of the clinical efficacy and safety of intra-articular sodium hyaluronate in synovial joints with osteoarthritis. Eur J Phys Rehabil Med. 2011 Sep;47(3):407-15. PubMed PMID: 21946401.**	**R**	**9**	**Hyalubrix**
50	Sun SF, Hsu CW, Sun HP, Chou YJ, Li HJ, Wang JL. The effect of three weekly intra-articular injections of hyaluronate on pain, function, and balance in patients with unilateral ankle arthritis. J Bone Joint Surg Am. 2011 Sep 21;93(18):1720-6. doi: 10.2106/JBJS.J.00315. PubMed PMID: 21938376.	NR	5	Hyalgan
51	Habib GS, Miari W. The effect of intra-articular triamcinolone preparations on blood glucose levels in diabetic patients: a controlled study. J Clin Rheumatol. 2011 Sep;17(6):302-5. doi: 10.1097/RHU.0b013e31822acd7c. PubMed PMID: 21869712.	NR	4	
52	Wang Y, Hall S, Hanna F, Wluka AE, Grant G, Marks P, Feletar M, Cicuttini FM. Effects of Hylan G-F 20 supplementation on cartilage preservation detected by magnetic resonance imaging in osteoarthritis of the knee: a two-year single-blind clinical trial. BMC Musculoskelet Disord. 2011 Aug 24;12:195. doi: 10.1186/1471-2474-12-195. PubMed PMID: 21861935; PubMed Central PMCID: PMC3201041.	NR	5	hylan G-F 20
53	**Battaglia M, Guaraldi F, Vannini F, Rossi G, Timoncini A, Buda R, Giannini S. Efficacy of ultrasound-guided intra-articular injections of platelet-rich plasma versus hyaluronic acid for hip osteoarthritis. Orthopedics. 2013 Dec;36(12):e1501-8. PubMed PMID: 24579221.**	**R**	**9**	**Hyalubrix**
54	Maheu E, Zaim M, Appelboom T, Jeka S, Trc T, Berenbaum F, Maasalu K, Berenbaum F. Comparative efficacy and safety of two different molecular weight (MW) hyaluronans F60027 and Hylan G-F20 in symptomatic osteoarthritis of the knee (KOA). Results of a non inferiority, prospective, randomized, controlled trial. Clin Exp Rheumatol. 2011 May-Jun;29(3):527-35. Epub 2011 Jun 29. PubMed PMID: 21722501.	NR	5	Structovial, hylan G-F 20
55	Decaria J, Petrella R, Petrella R, Wolfe D, Chesworth BM, Montero-Odasso M. Effect of intra-articular hyaluronic acid on gait variability in older adults with knee osteoarthritis. J Am Geriatr Soc. 2011 May;59(5):949-51. doi: 10.1111/j.1532-5415.2011.03375.x. PubMed PMID: 21568973.	NR	6	letter
56	Vaquerizo V, Plasencia MÁ, Arribas I, Seijas R, Padilla S, Orive G, Anitua E. Comparison of intra-articular injections of plasma rich in growth factors (PRGF-Endoret) versus Durolane hyaluronic acid in the treatment of patients with symptomatic osteoarthritis: a randomized controlled trial. Arthroscopy. 2013 Oct;29(10):1635-43. doi: 10.1016/j.arthro.2013.07.264. PubMed PMID: 24075613.	NR	5	Durolane
57	Chen WL, Hsu WC, Lin YJ, Hsieh LF. Comparison of intra-articular hyaluronic acid injections with transcutaneous electric nerve stimulation for the management of knee osteoarthritis: a randomized controlled trial. Arch Phys Med Rehabil. 2013 Aug;94(8):1482-9. doi: 10.1016/j.apmr.2013.04.009. Epub 2013 Apr 27. PubMed PMID: 23628378.	NR	5	Artz

User query # 14: (("Osteoarthritis/drug therapy"[Mesh] OR "Osteoarthritis/therapy"[Mesh])) AND ("Hyaluronic Acid/therapeutic use"[Mesh] OR "Hyaluronic Acid/therapy"[Mesh])				
Citation		**Relevance NR=non-relevant R=relevant**	**Reason for non-relevance or Appraisal**	
58	Lee SC, Rha DW, Chang WH. Rapid analgesic onset of intra-articular hyaluronic acid with ketorolac in osteoarthritis of the knee. J Back Musculoskelet Rehabil. 2011;24(1):31-8. doi: 10.3233/BMR-2011-0272. PubMed PMID: 21248398.	NR	5	combination
59	Atchia I, Kane D, Reed MR, Isaacs JD, Birrell F. Efficacy of a single ultrasound-guided injection for the treatment of hip osteoarthritis. Ann Rheum Dis. 2011 Jan;70(1):110-6. doi: 10.1136/ard.2009.127183. Epub 2010 Nov 10. PubMed PMID: 21068096.	NR	5	Durolane
60	Lester DK, Zhang K. Gait analysis of knee arthritis treated with hyaluronic acid. J Arthroplasty. 2010 Dec;25(8):1290-4. doi: 10.1016/j.arth.2009.09.001. Epub 2009 Dec 21. PubMed PMID: 20022450.	NR	5	Supartz
61	**Witteveen AG, Sierevelt IN, Blankevoort L, Kerkhoffs GM, van Dijk CN. Intra-articular sodium hyaluronate injections in the osteoarthritic ankle joint: effects, safety and dose dependency. Foot Ankle Surg. 2010 Dec;16(4):159-63. doi: 10.1016/j.fas.2009.10.003. Epub 2009 Nov 8. PubMed PMID: 21047602.**	**R**	**9**	**Orthovisc**
62	van Tiel J, Reijman M, Bos PK, Hermans J, van Buul GM, Bron EE, Klein S, Verhaar JA, Krestin GP, Bierma-Zeinstra SM, Weinans H, Kotek G, Oei EH. Delayed gadolinium-enhanced MRI of cartilage (dGEMRIC) shows no change in cartilage structural composition after viscosupplementation in patients with early-stage knee osteoarthritis. PLoS One. 2013 Nov 6;8(11):e79785. doi: 10.1371/journal.pone.0079785. eCollection 2013. PubMed PMID: 24223194; PubMed Central PMCID: PMC3819245.	NR	5	hylan G-F 20
63	**Colen S, van den Bekerom MP, Bellemans J, Mulier M. Comparison of intra-articular injections of hyaluronic acid and corticosteroid in the treatment of osteoarthritis of the hip in comparison with intra-articular injections of bupivacaine. Design of a prospective, randomized, controlled study with blinding of the patients and outcome assessors. BMC Musculoskelet Disord. 2010 Nov 16;11:264. doi: 10.1186/1471-2474-11-264. PubMed PMID: 21080920; PubMed Central PMCID: PMC2998460.**	**R**	**9**	**Ostenil Plus**
64	Say F, Gürler D, Yener K, Bülbül M, Malkoc M. Platelet-rich plasma injection is more effective than hyaluronic acid in the treatment of knee osteoarthritis. Acta Chir Orthop Traumatol Cech. 2013;80(4):278-83. PubMed PMID: 24119476.	NR	5	HA 1%
65	Eyigör C, Pirim A, Eyigör S, Uyar M. Efficacy of intraarticular hyaluronic acid injection through a lateral approach under fluoroscopic control for advanced hip osteoarthritis. Agri. 2010 Oct;22(4):139-44. PubMed PMID: 21153931.	NR	5	Adant
66	**Filardo G, Kon E, Di Martino A, Di Matteo B, Merli ML, Cenacchi A, Fornasari PM, Marcacci M. Platelet-rich plasma vs hyaluronic acid to treat knee degenerative pathology: study design and preliminary results of a randomized controlled trial. BMC Musculoskelet Disord. 2012 Nov 23;13:229. doi: 10.1186/1471-2474-13-229. PubMed PMID: 23176112; PubMed Central PMCID: PMC3532098.**	**R**	**9**	**Hyalubrix**
67	Vanelli R, Costa P, Rossi SM, Benazzo F. Efficacy of intra-articular polynucleotides in the treatment of knee osteoarthritis: a randomized, double-blind clinical trial. Knee Surg Sports Traumatol Arthrosc. 2010 Jul;18(7):901-7. doi: 10.1007/s00167-009-1039-y. Epub 2010 Jan 29. PubMed PMID: 20111953.	NR	5	Sinovial
68	Jørgensen A, Stengaard-Pedersen K, Simonsen O, Pfeiffer-Jensen M, Eriksen C, Bliddal H, Pedersen NW, Bødtker S, Hørslev-Petersen K, Snerum LØ, Egund N, Frimer-Larsen H. Intra-articular hyaluronan is without clinical effect in knee osteoarthritis: a multicentre, randomised, placebo-controlled, double-blind study of 337 patients followed for 1 year. Ann Rheum Dis. 2010 Jun;69(6):1097-102. doi: 10.1136/ard.2009.118042. Epub 2010 May 6. PubMed PMID: 20447955.	NR	5	Hyalgan
69	Chen R, Chen M, Kang M, Xiong J, Chi Z, Zhang B, Fu Y. The design and protocol of heat-sensitive moxibustion for knee osteoarthritis: a multicenter randomized controlled trial on the rules of selecting	NR	2	

User query # 14: (("Osteoarthritis/drug therapy"[Mesh] OR "Osteoarthritis/therapy"[Mesh])) AND ("Hyaluronic Acid/therapeutic use"[Mesh] OR "Hyaluronic Acid/therapy"[Mesh])				
Citation		**Relevance NR=non-relevant R=relevant**	**Reason for non-relevance or Appraisal**	
	moxibustion location. BMC Complement Altern Med. 2010 Jun 25;10:32. doi: 10.1186/1472-6882-10-32. PubMed PMID: 20576162; PubMed Central PMCID: PMC2911404.			
70	Bellamy N, Bell MJ, Goldsmith CH, Lee S, Maschio M, Raynauld JP, Torrance GW, Tugwell P. BLISS index using WOMAC index detects between-group differences at low-intensity symptom states in osteoarthritis. J Clin Epidemiol. 2010 May;63(5):566-74. doi: 10.1016/j.jclinepi.2009.07.011. Epub 2009 Nov 6. PubMed PMID: 19896801.	NR	5	hylan G-F 20
71	Manfredini D, Rancitelli D, Ferronato G, Guarda-Nardini L. Arthrocentesis with or without additional drugs in temporomandibular joint inflammatory-degenerative disease: comparison of six treatment protocols*. J Oral Rehabil. 2012 Apr;39(4):245-51. doi: 10.1111/j.1365-2842.2011.02265.x. Epub 2011 Oct 15. PubMed PMID: 21999138.	NR	5	Hyalgan, hylan G-F 20
72	Guarda-Nardini L, Ferronato G, Manfredini D. Two-needle vs. single-needle technique for TMJ arthrocentesis plus hyaluronic acid injections: a comparative trial over a six-month follow up. Int J Oral Maxillofac Surg. 2012 Apr;41(4):506-13. doi: 10.1016/j.ijom.2011.11.007. Epub 2011 Dec 16. PubMed PMID: 22178274.	NR	5	Hyalgan
73	**Kul-Panza E, Berker N. Is hyaluronate sodium effective in the management of knee osteoarthritis? A placebo-controlled double-blind study. Minerva Med. 2010 Apr;101(2):63-72. PubMed PMID: 20467406.**	**R**	**9**	**Orthovisc**
74	Brander VA, Gomberawalla A, Chambers M, Bowen M, Nuber G. Efficacy and safety of hylan G-F 20 for symptomatic glenohumeral osteoarthritis: a prospective, pilot study. PM R. 2010 Apr;2(4):259-67. doi: 10.1016/j.pmrj.2010.02.010. PubMed PMID: 20430327.	NR	5	hylan G-F 20
75	Tang YL, Zhu GQ, Hu L, Zheng M, Zhang JY, Shi ZD, Liang XH. Effects of intra-articular administration of sodium hyaluronate on plasminogen activator system in temporomandibular joints with osteoarthritis. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2010 Apr;109(4):541-7. doi: 10.1016/j.tripleo.2009.11.007. Epub 2010 Feb 24. PubMed PMID: 20185343.	NR	5	Sofast
76	Mei-Dan O, Kish B, Shabat S, Masarawa S, Shteren A, Mann G, Nyska M. Treatment of osteoarthritis of the ankle by intra-articular injections of hyaluronic acid: a prospective study. J Am Podiatr Med Assoc. 2010 Mar-Apr;100(2):93-100. PubMed PMID: 20237359.	NR	5	Adant
77	**Kon E, Mandelbaum B, Buda R, Filardo G, Delcogliano M, Timoncini A, Fornasari PM, Giannini S, Marcacci M. Platelet-rich plasma intra-articular injection versus hyaluronic acid viscosupplementation as treatments for cartilage pathology: from early degeneration to osteoarthritis. Arthroscopy. 2011 Nov;27(11):1490-501. doi: 10.1016/j.arthro.2011.05.011. Epub 2011 Aug 10. PubMed PMID: 21831567.**	**R**	**9**	**HMW HA (30 mg/2 mL, 1.5%, 1,000-2,900 kDa)** and LMW HA (20 mg/2 mL, 1%, 500-730 kDa).
78	Shimizu M, Higuchi H, Takagishi K, Shinozaki T, Kobayashi T. Clinical and biochemical characteristics after intra-articular injection for the treatment of osteoarthritis of the knee: prospective randomized study of sodium hyaluronate and corticosteroid. J Orthop Sci. 2010 Jan;15(1):51-6. doi: 10.1007/s00776-009-1421-0. Epub 2010 Feb 12. PubMed PMID: 20151251.	NR	5	Artz dispo
79	Chevalier X, Jerosch J, Goupille P, van Dijk N, Luyten FP, Scott DL, Bailleul F, Pavelka K. Single, intra-articular treatment with 6 ml hylan G-F 20 in patients with symptomatic primary osteoarthritis of the knee: a randomised, multicentre, double-blind, placebo controlled trial. Ann Rheum Dis. 2010 Jan;69(1):113-9. doi: 10.1136/ard.2008.094623. Epub . PubMed PMID: 19304567; PubMed Central PMCID: PMC2789938.	NR	5	hylan G-F 20
80	Noël E, Hardy P, Hagena FW, Laprelle E, Goebel F, Faure C, Favard L, Gaudin P, Christ R, Baudot C, Dietl J, Goupille P. Efficacy and safety of Hylan G-F 20 in shoulder osteoarthritis with an intact rotator cuff. Open-label prospective multicenter study. Joint Bone Spine. 2009 Dec;76(6):670-3. doi: 10.1016/j.jbspin.2009.10.008. Epub . PubMed PMID: 19945321.	NR	5	hylan G-F 20
81	Skwara A, Peterlein CD, Tibesku CO, Rosenbaum D, Fuchs-Winkelmann S. Changes of gait patterns and muscle activity after	NR	5	Ostenil

User query # 14: (("Osteoarthritis/drug therapy"[Mesh] OR "Osteoarthritis/therapy"[Mesh])) AND ("Hyaluronic Acid/therapeutic use"[Mesh] OR "Hyaluronic Acid/therapy"[Mesh])				
Citation		**Relevance NR=non-relevant R=relevant**	**Reason for non-relevance or Appraisal**	
	intraarticular treatment of patients with osteoarthritis of the knee: a prospective, randomised, doubleblind study. Knee. 2009 Dec;16(6):466-72. doi: 10.1016/j.knee.2009.03.003. Epub 2009 Apr 10. PubMed PMID: 19362003.			
82	Migliore A, Bizzi E, Massafra U, Vacca F, Alimonti A, Iannessi F, Tormenta S. Viscosupplementation: a suitable option for hip osteoarthritis in young adults. Eur Rev Med Pharmacol Sci. 2009 Nov-Dec;13(6):465-72. PubMed PMID: 20085128.	NR	5	hylan G-F 20
83	Diraçoğlu D, Alptekin K, Teksöz B, Yağci I, Ozçakar L, Aksoy C. Knee vs hip single-joint intra-articular hyaluronic acid injection in patients with both hip and knee osteoarthritis: a pilot study. Clin Rheumatol. 2009 Sep;28(9):1021-4. doi: 10.1007/s10067-009-1199-7. Epub 2009 May 20. PubMed PMID: 19455363.	NR	5	hylan G-F 20
84	Mandl LA, Hotchkiss RN, Adler RS, Lyman S, Daluiski A, Wolfe SW, Katz JN. Injectable hyaluronan for the treatment of carpometacarpal osteoarthritis: open label pilot trial. Curr Med Res Opin. 2009 Sep;25(9):2103-8. doi: 10.1185/03007990903084016. PubMed PMID: 19601706; PubMed Central PMCID: PMC2761209.	NR	5	hylan G-F 20
85	Altman RD, Rosen JE, Bloch DA, Hatoum HT, Korner P. A double-blind, randomized, saline-controlled study of the efficacy and safety of EUFLEXXA for treatment of painful osteoarthritis of the knee, with an open-label safety extension (the FLEXX trial). Semin Arthritis Rheum. 2009 Aug;39(1):1-9. doi: 10.1016/j.semarthrit.2009.04.001. Epub 2009 Jun 17. PubMed PMID: 19539353.	NR	5	Euflexxa (1%)
86	Manfredini D, Bonnini S, Arboretti R, Guarda-Nardini L. Temporomandibular joint osteoarthritis: an open label trial of 76 patients treated with arthrocentesis plus hyaluronic acid injections. Int J Oral Maxillofac Surg. 2009 Aug;38(8):827-34. doi: 10.1016/j.ijom.2009.03.715. Epub 2009 Apr 29. PubMed PMID: 19406617.	NR	5	Hyalgan
87	Rossini M, Viapiana O, Ramonda R, Bianchi G, Olivieri I, Lapadula G, Adami S. Intra-articular clodronate for the treatment of knee osteoarthritis: dose ranging study vs hyaluronic acid. Rheumatology (Oxford). 2009 Jul;48(7):773-8. doi: 10.1093/rheumatology/kep084. Epub 2009 Apr 30. PubMed PMID: 19406908.	NR	6	HA 20mg Fidia
88	Krocker D, Matziolis G, Tuischer J, Funk J, Tohtz S, Buttgereit F, Perka C. [Reduction of arthrosis associated knee pain through a single intra-articular injection of synthetic hyaluronic acid]. Z Rheumatol. 2006 Jul;65(4):327-31. German. PubMed PMID: 16794845.	NR	5	Durolane
89	Auerbach B, Melzer C. [Cross-linked hyaluronic acid in the treatment of osteoarthritis of the knee--results of a prospective randomized trial]. Zentralbl Chir. 2002 Oct;127(10):895-9. German. PubMed PMID: 12410458.	NR	5	hylan G-F 20
90	Diracoglu D, Vural M, Baskent A, Dikici F, Aksoy C. The effect of viscosupplementation on neuromuscular control of the knee in patients with osteoarthritis. J Back Musculoskelet Rehabil. 2009;22(1):1-9. doi: 10.3233/BMR-2009-0207. PubMed PMID: 20023357.	NR	5	hylan G-F 20
91	**Migliore A, Massafra U, Bizzi E, Vacca F, Martin-Martin S, Granata M, Alimonti A, Tormenta S. Comparative, double-blind, controlled study of intra-articular hyaluronic acid (Hyalubrix) injections versus local anesthetic in osteoarthritis of the hip. Arthritis Res Ther. 2009;11(6):R183. doi: 10.1186/ar2875. Epub 2009 Dec 9. PubMed PMID: 20003205; PubMed Central PMCID: PMC3003515.**	**R**	**9**	**Hyalubrix**
92	Salini V, De Amicis D, Abate M, Natale MA, Di Iorio A. Ultrasound-guided hyaluronic acid injection in carpometacarpal osteoarthritis: short-term results. Int J Immunopathol Pharmacol. 2009 Apr-Jun;22(2):455-60. PubMed PMID: 19505398.	NR	5	0.8% HA
93	Skwara A, Ponelis R, Tibesku CO, Rosenbaum D, Fuchs-Winkelmann S. Gait patterns after intraarticular treatment of patients with osteoarthritis of the knee--hyaluronan versus triamcinolone: a prospective, randomized, doubleblind, monocentric study. Eur J Med Res. 2009 Apr 16;14(4):157-64. PubMed PMID: 19380288; PubMed Central PMCID: PMC3401005.	NR	5	Ostenil
94	Bahadir C, Onal B, Dayan VY, Gürer N. Comparison of therapeutic	NR	5	Ostenil

User query # 14: (("Osteoarthritis/drug therapy"[Mesh] OR "Osteoarthritis/therapy"[Mesh])) AND ("Hyaluronic Acid/therapeutic use"[Mesh] OR "Hyaluronic Acid/therapy"[Mesh])				
Citation		**Relevance NR=non-relevant R=relevant**	**Reason for non-relevance or Appraisal**	
	effects of sodium hyaluronate and corticosteroid injections on trapeziometacarpal joint osteoarthritis. Clin Rheumatol. 2009 May;28(5):529-33. doi: 10.1007/s10067-008-1079-6. Epub 2009 Jan 10. PubMed PMID: 19137353.			
95	Luciani D, Cadossi M, Tesei F, Chiarello E, Giannini S. Viscosupplementation for grade II osteoarthritis of the ankle: a prospective study at 18 months' follow-up. Chir Organi Mov. 2008 Dec;92(3):155-60. doi: 10.1007/s12306-008-0066-z. Epub 2008 Dec 6. PubMed PMID: 19067120.	NR	5	hylan G-F 20
96	Cohen MM, Altman RD, Hollstrom R, Hollstrom C, Sun C, Gipson B. Safety and efficacy of intra-articular sodium hyaluronate (Hyalgan) in a randomized, double-blind study for osteoarthritis of the ankle. Foot Ankle Int. 2008 Jul;29(7):657-63. PubMed PMID: 18785414.	NR	5	Hyalgan
97	Birchall D, Ismail AM, Peat G. Clinical outcomes from a physiotherapist-led intra-articular hyaluronic acid injection clinic. Musculoskeletal Care. 2008 Sep;6(3):135-49. doi: 10.1002/msc.130. Erratum in: Musculoskeletal Care. 2008 Dec;6(4):267. PubMed PMID: 18729065.	NR	5	Hyalgan
98	Karatosun V, Unver B, Ozden A, Ozay Z, Gunal I. Intra-articular hyaluronic acid compared to exercise therapy in osteoarthritis of the ankle. A prospective randomized trial with long-term follow-up. Clin Exp Rheumatol. 2008 Mar-Apr;26(2):288-94. PubMed PMID: 18565251.	NR	5	Adant
99	Raman R, Dutta A, Day N, Sharma HK, Shaw CJ, Johnson GV. Efficacy of Hylan G-F 20 and Sodium Hyaluronate in the treatment of osteoarthritis of the knee -- a prospective randomized clinical trial. Knee. 2008 Aug;15(4):318-24. doi: 10.1016/j.knee.2008.02.012. Epub 2008 Apr 21. PubMed PMID: 18430574.	NR	5	Hyalgan, hylan G-F 20 (Synvisc)
100	Lundsgaard C, Dufour N, Fallentin E, Winkel P, Gluud C. Intra-articular sodium hyaluronate 2 mL versus physiological saline 20 mL versus physiological saline 2 mL for painful knee osteoarthritis: a randomized clinical trial. Scand J Rheumatol. 2008 Mar-Apr;37(2):142-50. doi: 10.1080/03009740701813103. PubMed PMID: 18415773.	NR	5	Hyalgan
101	Anandacoomarasamy A, Bagga H, Ding C, Burkhardt D, Sambrook PN, March LM. Predictors of clinical response to intraarticular Hylan injections -- a prospective study using synovial fluid measures, clinical outcomes, and magnetic resonance imaging. J Rheumatol. 2008 Apr;35(4):685-90. Epub 2008 Feb 15. PubMed PMID: 18278831.	NR	5	hylan G-F 20
102	Sugimoto H, Yamada H, Terada N, Kanaji A, Kato S, Date H, Ichinose H, Miyazaki K. Intraarticular injection of high molecular weight hyaluronan for osteoarthritis of the knee - prediction of effectiveness with biological markers. J Rheumatol. 2006 Dec;33(12):2527. PubMed PMID: 17143987.	NR	5	Artz
103	Conrozier T, Bertin P, Bailleul F, Mathieu P, Charlot J, Vignon E, Treves R, Chevalier X. Clinical response to intra-articular injections of hylan G-F 20 in symptomatic hip osteoarthritis: the OMERACT-OARSI criteria applied to the results of a pilot study. Joint Bone Spine. 2006 Dec;73(6):705-9. Epub 2006 Aug 30. PubMed PMID: 16997602.	NR	5	hylan G-F 20
104	Karalezli N, Ogun TC, Kartal S, Saracgil SN, Yel M, Tuncay I. The pain associated with intraarticular hyaluronic acid injections for trapeziometacarpal osteoarthritis. Clin Rheumatol. 2007 Apr;26(4):569-71. Epub 2006 Jun 24. PubMed PMID: 16799752.	NR	4	Ostenil, hylan G-F 20
105	Bagga H, Burkhardt D, Sambrook P, March L. Longterm effects of intraarticular hyaluronan on synovial fluid in osteoarthritis of the knee. J Rheumatol. 2006 May;33(5):946-50. PubMed PMID: 16652425.	NR	5	hylan G-F 20
106	Lee PB, Kim YC, Lim YJ, Lee CJ, Sim WS, Ha CW, Bin SI, Lim KB, Choi SS, Lee SC. Comparison between high and low molecular weight hyaluronates in knee osteoarthritis patients: open-label, randomized, multicentre clinical trial. J Int Med Res. 2006 Jan-Feb;34(1):77-87. PubMed PMID: 16604827.	NR	6	Hyruan Plus, Hyal
107	**Stahl S, Karsh-Zafrir I, Ratzon N, Rosenberg N. Comparison of intraarticular injection of depot corticosteroid and hyaluronic acid for treatment of degenerative trapeziometacarpal joints. J Clin Rheumatol. 2005 Dec;11(6):299-302. PubMed PMID: 16371798.**	**R**	**9**	**Orthovisc**
108	Kirchner M, Marshall D. A double-blind randomized controlled trial comparing alternate forms of high molecular weight hyaluronan for the	NR	5	Euflexxa (1%), hylan G-F 20

User query # 14: (("Osteoarthritis/drug therapy"[Mesh] OR "Osteoarthritis/therapy"[Mesh])) AND ("Hyaluronic Acid/therapeutic use"[Mesh] OR "Hyaluronic Acid/therapy"[Mesh])				
Citation		**Relevance NR=non-relevant R=relevant**	**Reason for non-relevance or Appraisal**	
	treatment of osteoarthritis of the knee. Osteoarthritis Cartilage. 2006 Feb;14(2):154-62. Epub 2005 Oct 19. PubMed PMID: 16242361.			(Synvisc)
109	Migliore A, Tormenta S, Massafra U, Carloni E, Padalino C, Iannessi F, Alimonti A, Martin LS, Granata M. Repeated ultrasound-guided intra-articular injections of 40 mg of Hyalgan may be useful in symptomatic relief of hip osteoarthritis. Osteoarthritis Cartilage. 2005 Dec;13(12):1126-7. Epub 2005 Oct 19. PubMed PMID: 16242357.	NR	5	Hyalgan
110	Fuchs S, Mönikes R, Wohlmeiner A, Heyse T. Intra-articular hyaluronic acid compared with corticoid injections for the treatment of rhizarthrosis. Osteoarthritis Cartilage. 2006 Jan;14(1):82-8. Epub 2005 Oct 19. PubMed PMID: 16242353.	NR	5	Ostenil Mini
111	**Neustadt D, Caldwell J, Bell M, Wade J, Gimbel J. Clinical effects of intraarticular injection of high molecular weight hyaluronan (Orthovisc) in osteoarthritis of the knee: a randomized, controlled, multicenter trial. J Rheumatol. 2005 Oct;32(10):1928-36. PubMed PMID: 16206349.**	**R**	**9**	**Orthovisc**
112	**Kotevoglu N, Iyibozkurt PC, Hiz O, Toktas H, Kuran B. A prospective randomised controlled clinical trial comparing the efficacy of different molecular weight hyaluronan solutions in the treatment of knee osteoarthritis. Rheumatol Int. 2006 Feb;26(4):325-30. Epub 2005 Jun 15. PubMed PMID: 15959784.**	**R**	**9**	hylan G-F 20 6 ml, **Orthovisc**
113	**Karatay S, Kiziltunc A, Yildirim K, Karanfil RC, Senel K. Effects of different hyaluronic acid products on synovial fluid NO levels in knee osteoarthritis. Clin Rheumatol. 2005 Sep;24(5):497-501. Epub 2005 May 20. PubMed PMID: 15906109.**	**R**	**9**	**Orthovisc**, hylan G-F 20 (Synvisc)
114	Tang SF, Chen CP, Chen MJ, Hong WH, Yu TY, Tsai WC. Improvement of muscle strength in osteoarthritic knee patients after intraarticular knee injection of hyaluronan. Am J Phys Med Rehabil. 2005 Apr;84(4):274-7. PubMed PMID: 15785260.	NR	6	1% HA
115	Bellamy N, Bell MJ, Goldsmith CH, Pericak D, Walker V, Raynauld JP, Torrance GW, Tugwell P, Polisson R. The effectiveness of hylan G-F 20 in patients with knee osteoarthritis: an application of two sets of response criteria developed by the OARSI and one set developed by OMERACT-OARSI. Osteoarthritis Cartilage. 2005 Feb;13(2):104-10. PubMed PMID: 15694571.	NR	5	hylan G-F 20
116	Tikiz C, Unlü Z, Sener A, Efe M, Tüzün C. Comparison of the efficacy of lower and higher molecular weight viscosupplementation in the treatment of hip osteoarthritis. Clin Rheumatol. 2005 Jun;24(3):244-50. Epub 2005 Jan 13. PubMed PMID: 15647968.	NR	5	Ostenil
117	Cubukçu D, Ardiç F, Karabulut N, Topuz O. Hylan G-F 20 efficacy on articular cartilage quality in patients with knee osteoarthritis: clinical and MRI assessment. Clin Rheumatol. 2005 Aug;24(4):336-41. Epub 2004 Dec 14. PubMed PMID: 15599642.	NR	5	hylan G-F 20
118	Bellamy N, Bell MJ, Goldsmith CH, Pericak D, Walker V, Raynauld JP, Torrance GW, Tugwell P, Polisson R. Evaluation of WOMAC 20, 50, 70 response criteria in patients treated with hylan G-F 20 for knee osteoarthritis. Ann Rheum Dis. 2005 Jun;64(6):881-5. Epub 2004 Nov 25. PubMed PMID: 15564311; PubMed Central PMCID: PMC1755531.	NR	5	hylan G-F 20
119	Altman RD, Akermark C, Beaulieu AD, Schnitzer T; Durolane International Study Group. Efficacy and safety of a single intra-articular injection of non-animal stabilized hyaluronic acid (NASHA) in patients with osteoarthritis of the knee. Osteoarthritis Cartilage. 2004 Aug;12(8):642-9. PubMed PMID: 15262244.	NR	5	NASHA
120	Tang SF, Chen CP, Chen MJ, Pei YC, Lau YC, Leong CP. Changes in sagittal ground reaction forces after intra-articular hyaluronate injections for knee osteoarthritis. Arch Phys Med Rehabil. 2004 Jun;85(6):951-5. PubMed PMID: 15179649.	NR	5	Artz
121	Berg P, Olsson U. Intra-articular injection of non-animal stabilised hyaluronic acid (NASHA) for osteoarthritis of the hip: a pilot study. Clin Exp Rheumatol. 2004 May-Jun;22(3):300-6. PubMed PMID: 15144123.	NR	5	NASHA
122	Caglar-Yagci H, Unsal S, Yagci I, Dulgeroglu D, Ozel S. Safety and efficacy of ultrasound-guided intra-articular hylan G-F 20 injection in osteoarthritis of the hip: a pilot study. Rheumatol Int. 2005 Jun;25(5):341-4. Epub 2004 Mar 5. PubMed PMID: 15004721.	NR	5	hylan G-F 20

User query # 14: (("Osteoarthritis/drug therapy"[Mesh] OR "Osteoarthritis/therapy"[Mesh])) AND ("Hyaluronic Acid/therapeutic use"[Mesh] OR "Hyaluronic Acid/therapy"[Mesh])				
Citation		**Relevance NR=non-relevant R=relevant**	**Reason for non-relevance or Appraisal**	
123	Kahan A, Lleu PL, Salin L. Prospective randomized study comparing the medicoeconomic benefits of Hylan GF-20 vs. conventional treatment in knee osteoarthritis. Joint Bone Spine. 2003 Aug;70(4):276-81. PubMed PMID: 12951310.	NR	5	hylan G-F 20
124	**Bayramoğlu M, Karataş M, Cetin N, Akman N, Sözay S, Dilek A. Comparison of two different viscosupplements in knee osteoarthritis -- a pilot study. Clin Rheumatol. 2003 May;22(2):118-22. PubMed PMID: 12740676.**	**R**	**9**	**Orthovisc**, hylan G-F 20
125	Karlsson J, Sjögren LS, Lohmander LS. Comparison of two hyaluronan drugs and placebo in patients with knee osteoarthritis. A controlled, randomized, double-blind, parallel-design multicentre study. Rheumatology (Oxford). 2002 Nov;41(11):1240-8. PubMed PMID: 12421996.	NR	5	Artzal, hylan G-F 20
126	Raynauld JP, Torrance GW, Band PA, Goldsmith CH, Tugwell P, Walker V, Schultz M, Bellamy N; Canadian Knee OA Study Group. A prospective, randomized, pragmatic, health outcomes trial evaluating the incorporation of hylan G-F 20 into the treatment paradigm for patients with knee osteoarthritis (Part 1 of 2): clinical results. Osteoarthritis Cartilage. 2002 Jul;10(7):506-17. PubMed PMID: 12127830.	NR	5	hylan G-F 20
127	Bunyaratavej N, Chan KM, Subramanian N. Treatment of painful osteoarthritis of the knee with hyaluronic acid. Results of a multicenter Asian study. J Med Assoc Thai. 2001 Oct;84 Suppl 2:S576-81. PubMed PMID: 11853284.	NR	5	Hyalgan
128	Evanich JD, Evanich CJ, Wright MB, Rydlewicz JA. Efficacy of intraarticular hyaluronic acid injections in knee osteoarthritis. Clin Orthop Relat Res. 2001 Sep;(390):173-81. PubMed PMID: 11550864.	NR	5	hylan G-F 20
129	Tamir E, Robinson D, Koren R, Agar G, Halperin N. Intra-articular hyaluronan injections for the treatment of osteoarthritis of the knee: a randomized, double blind, placebo controlled study. Clin Exp Rheumatol. 2001 May-Jun;19(3):265-70. PubMed PMID: 11407078.	NR	5	BioHy
130	Guidolin DD, Ronchetti IP, Lini E, Guerra D, Frizziero L. Morphological analysis of articular cartilage biopsies from a randomized, clinical study comparing the effects of 500-730 kDa sodium hyaluronate (Hyalgan) and methylprednisolone acetate on primary osteoarthritis of the knee. Osteoarthritis Cartilage. 2001 May;9(4):371-81. PubMed PMID: 11399102.	NR	5	Hyalgan
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134	Wobig M, Dickhut A, Maier R, Vetter G. Viscosupplementation with hylan G-F 20: a 26-week controlled trial of efficacy and safety in the osteoarthritic knee. Clin Ther. 1998 May-Jun;20(3):410-23. PubMed PMID: 9663358.	NR	5	hylan G-F 20
135	Adams ME, Atkinson MH, Lussier AJ, Schulz JI, Siminovitch KA, Wade JP, Zummer M. The role of viscosupplementation with hylan G-F 20 (Synvisc) in the treatment of osteoarthritis of the knee: a Canadian multicenter trial comparing hylan G-F 20 alone, hylan G-F 20 with non-steroidal anti-inflammatory drugs (NSAIDs) and NSAIDs alone. Osteoarthritis Cartilage. 1995 Dec;3(4):213-25. PubMed PMID: 8689457.	NR	5	hylan G-F 20
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User query # 14: (("Osteoarthritis/drug therapy"[Mesh] OR "Osteoarthritis/therapy"[Mesh])) AND ("Hyaluronic Acid/therapeutic use"[Mesh] OR "Hyaluronic Acid/therapy"[Mesh])				
Citation		**Relevance NR=non-relevant R=relevant**	**Reason for non-relevance or Appraisal**	
	1995;17(4):129-32. PubMed PMID: 8867642.			
137	Puhl W, Bernau A, Greiling H, Köpcke W, Pförringer W, Steck KJ, Zacher J, Scharf HP. Intra-articular sodium hyaluronate in osteoarthritis of the knee: a multicenter, double-blind study. Osteoarthritis Cartilage. 1993 Oct;1(4):233-41. PubMed PMID: 15449510.	NR	5	1% HA
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139	Grecomoro G, Martorana U, Di Marco C. Intra-articular treatment with sodium hyaluronate in gonarthrosis: a controlled clinical trial versus placebo. Pharmatherapeutica. 1987;5(2):137-41. PubMed PMID: 3310017.	NR	5	Hyalgan
140	Kawasaki T, Kurosawa H, Ikeda H, Takazawa Y, Ishijima M, Kubota M, Kajihara H, Maruyama Y, Kim SG, Kanazawa H, Doi T. Therapeutic home exercise versus intraarticular hyaluronate injection for osteoarthritis of the knee: 6-month prospective randomized open-labeled trial. J Orthop Sci. 2009 Mar;14(2):182-91. doi: 10.1007/s00776-008-1312-9. Epub 2009 Apr 1. PubMed PMID: 19337810.	NR	5	Artz
141	Richette P, Ravaud P, Conrozier T, Euller-Ziegler L, Mazières B, Maugars Y, Mulleman D, Clerson P, Chevalier X. Effect of hyaluronic acid in symptomatic hip osteoarthritis: a multicenter, randomized, placebo-controlled trial. Arthritis Rheum. 2009 Mar;60(3):824-30. doi: 10.1002/art.24301. PubMed PMID: 19248105.	NR	5	Adant
142	Figen Ayhan F, Ustün N. The evaluation of efficacy and tolerability of Hylan G-F 20 in bilateral thumb base osteoarthritis: 6 months follow-up. Clin Rheumatol. 2009 May;28(5):535-41. doi: 10.1007/s10067-008-1080-0. Epub 2009 Jan 10. PubMed PMID: 19137352.	NR	5	hylan G-F 20
143	Kirkley A, Birmingham TB, Litchfield RB, Giffin JR, Willits KR, Wong CJ, Feagan BG, Donner A, Griffin SH, D'Ascanio LM, Pope JE, Fowler PJ. A randomized trial of arthroscopic surgery for osteoarthritis of the knee. N Engl J Med. 2008 Sep 11;359(11):1097-107. doi: 10.1056/NEJMoa0708333. Erratum in: N Engl J Med. 2009 Nov 12;361(20):2004. PubMed PMID: 18784099.	NR	4	
144	Conrozier T, Jerosch J, Beks P, Kemper F, Euller-Ziegler L, Bailleul F, Chevalier X. Prospective, multi-centre, randomised evaluation of the safety and efficacy of five dosing regimens of viscosupplementation with hylan G-F 20 in patients with symptomatic tibio-femoral osteoarthritis: a pilot study. Arch Orthop Trauma Surg. 2009 Mar;129(3):417-23. doi: 10.1007/s00402-008-0601-2. Epub 2008 Mar 26. PubMed PMID: 18365224.	NR	5	hylan G-F 20
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147	Møystad A, Mork-Knutsen BB, Bjørnland T. Injection of sodium hyaluronate compared to a corticosteroid in the treatment of patients with temporomandibular joint osteoarthritis: a CT evaluation. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2008 Feb;105(2):e53-60. doi: 10.1016/j.tripleo.2007.08.024. PubMed PMID: 18230379.	NR	5	hylan G-F 20
148	Kalman DS, Heimer M, Valdeon A, Schwartz H, Sheldon E. Effect of a natural extract of chicken combs with a high content of hyaluronic acid (Hyal-Joint) on pain relief and quality of life in subjects with knee osteoarthritis: a pilot randomized double-blind placebo-controlled trial. Nutr J. 2008 Jan 21;7:3. doi: 10.1186/1475-2891-7-3. PubMed PMID: 18208600; PubMed Central PMCID: PMC2245974.	NR	6	Hyal-Joint®
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User query # 14: (("Osteoarthritis/drug therapy"[Mesh] OR "Osteoarthritis/therapy"[Mesh])) AND ("Hyaluronic Acid/therapeutic use"[Mesh] OR "Hyaluronic Acid/therapy"[Mesh])				
Citation		**Relevance NR=non-relevant R=relevant**	**Reason for non-relevance or Appraisal**	
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150	Jüni P, Reichenbach S, Trelle S, Tschannen B, Wandel S, Jordi B, Züllig M, Guetg R, Häuselmann HJ, Schwarz H, Theiler R, Ziswiler HR, Dieppe PA, Villiger PM, Egger M; Swiss Viscosupplementation Trial Group. Efficacy and safety of intraarticular hylan or hyaluronic acids for osteoarthritis of the knee: a randomized controlled trial. Arthritis Rheum. 2007 Nov;56(11):3610-9. PubMed PMID: 17968921.	NR	5	Ostenil
151	Bjørnland T, Gjaerum AA, Møystad A. Osteoarthritis of the temporomandibular joint: an evaluation of the effects and complications of corticosteroid injection compared with injection with sodium hyaluronate. J Oral Rehabil. 2007 Aug;34(8):583-9. PubMed PMID: 17650168.	NR	5	hylan G-F 20
152	Roux C, Fontas E, Breuil V, Brocq O, Albert C, Euller-Ziegler L. Injection of intra-articular sodium hyaluronidate (Sinovial) into the carpometacarpal joint of the thumb (CMC1) in osteoarthritis. A prospective evaluation of efficacy. Joint Bone Spine. 2007 Jul;74(4):368-72. Epub 2007 May 24. PubMed PMID: 17590369.	NR	5	Sinovial
153	Paker N, Tekdös D, Kesiktas N, Soy D. Comparison of the therapeutic efficacy of TENS versus intra-articular hyaluronic acid injection in patients with knee osteoarthritis: a prospective randomized study. Adv Ther. 2006 Mar-Apr;23(2):342-53. PubMed PMID: 16751166.	NR	5	hylan G-F 20
154	Petrella RJ, Petrella M. A prospective, randomized, double-blind, placebo controlled study to evaluate the efficacy of intraarticular hyaluronic acid for osteoarthritis of the knee. J Rheumatol. 2006 May;33(5):951-6. PubMed PMID: 16652426.	NR	5	Suplasyn
155	Sun SF, Chou YJ, Hsu CW, Hwang CW, Hsu PT, Wang JL, Hsu YW, Chou MC. Efficacy of intra-articular hyaluronic acid in patients with osteoarthritis of the ankle: a prospective study. Osteoarthritis Cartilage. 2006 Sep;14(9):867-74. Epub 2006 Apr 24. PubMed PMID: 16635582.	NR	5	Artz
156	Salk RS, Chang TJ, D'Costa WF, Soomekh DJ, Grogan KA. Sodium hyaluronate in the treatment of osteoarthritis of the ankle: a controlled, randomized, double-blind pilot study. J Bone Joint Surg Am. 2006 Feb;88(2):295-302. PubMed PMID: 16452740.	NR	5	Hyalgan
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158	Yavuzer G, Sonel B, Süldür N, Ergin S. Effects of intra-articular hylan G-F 20 injections on clinical and biomechanical characteristics of the knee in osteoarthritis. Int J Rehabil Res. 2005 Dec;28(4):371-4. PubMed PMID: 16319566.	NR	5	hylan G-F 20
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161	Migliore A, Tormenta S, Martin Martin LS, Iannessi F, Massafra U, Carloni E, Monno D, Alimonti A, Granata M. The symptomatic effects of intra-articular administration of hylan G-F 20 on osteoarthritis of the hip: clinical data of 6 months follow-up. Clin Rheumatol. 2006 May;25(3):389-93. Epub 2005 Oct 25. PubMed PMID: 16249827.	NR	5	hylan G-F 20
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User query # 14: (("Osteoarthritis/drug therapy"[Mesh] OR "Osteoarthritis/therapy"[Mesh])) AND ("Hyaluronic Acid/therapeutic use"[Mesh] OR "Hyaluronic Acid/therapy"[Mesh])				
Citation		**Relevance NR=non-relevant R=relevant**	**Reason for non-relevance or Appraisal**	
	Oct;24(10):1391-5. PubMed PMID: 16179623.			
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165	Novaes AC, Schaiquevich P, Nasswetter G; Latin American Group of Quality of Life in Rheumatology. Multicenter study of hyaluronic acid obtained by biotechnology to evaluate clinical efficacy and safety in knee osteoarthritis. Int J Clin Pharmacol Res. 2005;25(1):1-7. PubMed PMID: 15864872.	NR	5	1% HA
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168	**Ozturk C, Atamaz F, Hepguler S, Argin M, Arkun R. The safety and efficacy of intraarticular hyaluronan with/without corticosteroid in knee osteoarthritis: 1-year, single-blind, randomized study. Rheumatol Int. 2006 Feb;26(4):314-9. Epub 2005 Feb 10. PubMed PMID: 15703953.**	**R**	**9**	**Orthovisc**
169	Raynauld JP, Goldsmith CH, Bellamy N, Torrance GW, Polisson R, Belovich D, Pericak D, Tugwell P. Effectiveness and safety of repeat courses of hylan G-F 20 in patients with knee osteoarthritis. Osteoarthritis Cartilage. 2005 Feb;13(2):111-9. PubMed PMID: 15694572.	NR	5	hylan G-F 20
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174	**Sezgin M, Demirel AC, Karaca C, Ortancil O, Ulkar GB, Kanik A, Cakçi A. Does hyaluronan affect inflammatory cytokines in knee osteoarthritis? Rheumatol Int. 2005 May;25(4):264-9. Epub 2004 Mar 4. PubMed PMID: 14999424.**	**R**	**9**	**Orthovisc**
175	Caborn D, Rush J, Lanzer W, Parenti D, Murray C; Synvisc 901 Study Group. A randomized, single-blind comparison of the efficacy and tolerability of hylan G-F 20 and triamcinolone hexacetonide in patients with osteoarthritis of the knee. J Rheumatol. 2004 Feb;31(2):333-43. PubMed PMID: 14760806.	NR	5	hylan G-F 20
176	Magilavy D, Polisson R, Parenti D. Re: Karlsson et al. Comparison of two hyaluronan drugs and placebo in patients with knee osteoarthritis. A controlled, randomized, double-blind, parallel-design multicentre study. Rheumatology (Oxford). 2003 Oct;42(10):1262; author reply 1262-3. PubMed PMID: 14508044.	NR	2	
177	Jubb RW, Piva S, Beinat L, Dacre J, Gishen P. A one-year, randomised, placebo (saline) controlled clinical trial of 500-730 kDa sodium	NR	5	Hyalgan

User query # 14: (("Osteoarthritis/drug therapy"[Mesh] OR "Osteoarthritis/therapy"[Mesh])) AND ("Hyaluronic Acid/therapeutic use"[Mesh] OR "Hyaluronic Acid/therapy"[Mesh])				
Citation		**Relevance NR=non-relevant R=relevant**	**Reason for non-relevance or Appraisal**	
	hyaluronate (Hyalgan) on the radiological change in osteoarthritis of the knee. Int J Clin Pract. 2003 Jul-Aug;57(6):467-74. PubMed PMID: 12918884.			
178	Vad VB, Sakalkale D, Sculco TP, Wickiewicz TL. Role of hylan G-F 20 in treatment of osteoarthritis of the hip joint. Arch Phys Med Rehabil. 2003 Aug;84(8):1224-6. PubMed PMID: 12917864.	NR	5	hylan G-F 20
179	Leopold SS, Redd BB, Warme WJ, Wehrle PA, Pettis PD, Shott S. Corticosteroid compared with hyaluronic acid injections for the treatment of osteoarthritis of the knee. A prospective, randomized trial. J Bone Joint Surg Am. 2003 Jul;85-A(7):1197-203. PubMed PMID: 12851342.	NR	5	hylan G-F 20
180	**Tascioglu F, Oner C. Efficacy of intra-articular sodium hyaluronate in the treatment of knee osteoarthritis. Clin Rheumatol. 2003 May;22(2):112-7. PubMed PMID: 12740675.**	**R**	**9**	**Orthovisc**
181	Miltner O, Schneider U, Siebert CH, Niedhart C, Niethard FU. Efficacy of intraarticular hyaluronic acid in patients with osteoarthritis--a prospective clinical trial. Osteoarthritis Cartilage. 2002 Sep;10(9):680-6. PubMed PMID: 12202120.	NR	5	Hyalart
182	Brocq O, Tran G, Breuil V, Grisot C, Flory P, Euller-Ziegler L. Hip osteoarthritis: short-term efficacy and safety of viscosupplementation by hylan G-F 20. An open-label study in 22 patients. Joint Bone Spine. 2002 Jun;69(4):388-91. PubMed PMID: 12184436.	NR	5	hylan G-F 20
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184	Petrella RJ, DiSilvestro MD, Hildebrand C. Effects of hyaluronate sodium on pain and physical functioning in osteoarthritis of the knee: a randomized, double-blind, placebo-controlled clinical trial. Arch Intern Med. 2002 Feb 11;162(3):292-8. PubMed PMID: 11822921.	NR	5	Suplasyn
185	Grecomoro G, La Sala F, Francavilla G. Rheologic changes in the synovial fluid of patients with gonarthritis induced by intraarticular infiltration of hyaluronic acid. Int J Tissue React. 2001;23(2):67-71. PubMed PMID: 11447776.	NR	5	Hyalart
186	Herrero-Beaumont G, Guerrero R, Sánchez-Pernaute O, Acebes C, Palacios I, Mas S, Rodriguez I, Egido J, Vivanco F. Cartilage and bone biological markers in the synovial fluid of osteoarthritic patients after hyaluronan injections in the knee. Clin Chim Acta. 2001 Jun;308(1-2):107-15. PubMed PMID: 11412822.	NR	5	Adant
187	**Brandt KD, Block JA, Michalski JP, Moreland LW, Caldwell JR, Lavin PT. Efficacy and safety of intraarticular sodium hyaluronate in knee osteoarthritis. ORTHOVISC Study Group. Clin Orthop Relat Res. 2001 Apr;(385):130-43. PubMed PMID: 11302304.**	**R**	**9**	**Orthovisc**
188	Altman RD, Moskowitz R. A randomized clinical trial of intra-articular sodium hyaluronate in patients with osteoarthritis of the knee: a summary. Am J Orthop (Belle Mead NJ). 1999 Nov;28(11 Suppl):3-4. PubMed PMID: 10587244.	NR	5	Hyalgan
189	Huskisson EC, Donnelly S. Hyaluronic acid in the treatment of osteoarthritis of the knee. Rheumatology (Oxford). 1999 Jul;38(7):602-7. PubMed PMID: 10461471.	NR	5	Hyalgan
190	Altman RD, Moskowitz R. Intraarticular sodium hyaluronate (Hyalgan) in the treatment of patients with osteoarthritis of the knee: a randomized clinical trial. Hyalgan Study Group. J Rheumatol. 1998 Nov;25(11):2203-12. Erratum in: J Rheumatol 1999 May;26(5):1216. PubMed PMID: 9818665.	NR	5	Hyalgan
191	Listrat V, Ayral X, Patarnello F, Bonvarlet JP, Simonnet J, Amor B, Dougados M. Arthroscopic evaluation of potential structure modifying activity of hyaluronan (Hyalgan) in osteoarthritis of the knee. Osteoarthritis Cartilage. 1997 May;5(3):153-60. PubMed PMID: 9219678.	NR	5	Hyalgan
192	Wu JJ, Shih LY, Hsu HC, Chen TH. The double-blind test of sodium hyaluronate (ARTZ) on osteoarthritis knee. Zhonghua Yi Xue Za Zhi (Taipei). 1997 Feb;59(2):99-106. PubMed PMID: 9175299.	NR	5	Artz

User query # 14: (("Osteoarthritis/drug therapy"[Mesh] OR "Osteoarthritis/therapy"[Mesh])) AND ("Hyaluronic Acid/therapeutic use"[Mesh] OR "Hyaluronic Acid/therapy"[Mesh])				
Citation		**Relevance NR=non-relevant R=relevant**	**Reason for non-relevance or Appraisal**	
193	Lohmander LS, Dalén N, Englund G, Hämäläinen M, Jensen EM, Karlsson K, Odensten M, Ryd L, Sernbo I, Suomalainen O, Tegnander A. Intra-articular hyaluronan injections in the treatment of osteoarthritis of the knee: a randomised, double blind, placebo controlled multicentre trial. Hyaluronan Multicentre Trial Group. Ann Rheum Dis. 1996 Jul;55(7):424-31. PubMed PMID: 8774159; PubMed Central PMCID: PMC1010204.	NR	5	Artzal
194	Jones AC, Pattrick M, Doherty S, Doherty M. Intra-articular hyaluronic acid compared to intra-articular triamcinolone hexacetonide in inflammatory knee osteoarthritis. Osteoarthritis Cartilage. 1995 Dec;3(4):269-73. PubMed PMID: 8689462.	NR	5	Hyalgan
195	Henderson EB, Smith EC, Pegley F, Blake DR. Intra-articular injections of 750 kD hyaluronan in the treatment of osteoarthritis: a randomised single centre double-blind placebo-controlled trial of 91 patients demonstrating lack of efficacy. Ann Rheum Dis. 1994 Aug;53(8):529-34. PubMed PMID: 7944639; PubMed Central PMCID: PMC1005394.	NR	5	Hyalgan
196	Creamer P, Sharif M, George E, Meadows K, Cushnaghan J, Shinmei M, Dieppe P. Intra-articular hyaluronic acid in osteoarthritis of the knee: an investigation into mechanisms of action. Osteoarthritis Cartilage. 1994 Jun;2(2):133-40. PubMed PMID: 11548229.	NR	5	Hyalgan
197	Graf J, Neusel E, Schneider E, Niethard FU. Intra-articular treatment with hyaluronic acid in osteoarthritis of the knee joint: a controlled clinical trial versus mucopolysaccharide polysulfuric acid ester. Clin Exp Rheumatol. 1993 Jul-Aug;11(4):367-72. PubMed PMID: 8403580.	NR	5	1% HA
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199	Leardini G, Mattara L, Franceschini M, Perbellini A. Intra-articular treatment of knee osteoarthritis. A comparative study between hyaluronic acid and 6-methyl prednisolone acetate. Clin Exp Rheumatol. 1991 Jul-Aug;9(4):375-81. PubMed PMID: 1934686.	NR	5	Hyalgan
200	Dixon AS, Jacoby RK, Berry H, Hamilton EB. Clinical trial of intra-articular injection of sodium hyaluronate in patients with osteoarthritis of the knee. Curr Med Res Opin. 1988;11(4):205-13. PubMed PMID: 3063436.	NR	5	Hyalgan
201	Thein R, Haviv B, Kidron A, Bronak S. Intra-articular injection of hyaluronic acid following arthroscopic partial meniscectomy of the knee. Orthopedics. 2010 Oct 11;33(10):724. doi: 10.3928/01477447-20100826-11. PubMed PMID: 20954664.	NR	4	Viscoseal
202	Westrich G, Schaefer S, Walcott-Sapp S, Lyman S. Randomized prospective evaluation of adjuvant hyaluronic acid therapy administered after knee arthroscopy. Am J Orthop (Belle Mead NJ). 2009 Dec;38(12):612-6. PubMed PMID: 20145786.	NR	4	
203	Miltner O, Schneider U, Siebert CH, Wirtz DC, Niethard FU. [Measuring isokinetic force in patients with gonarthrosis before and after hyaluronic acid therapy]. Z Orthop Ihre Grenzgeb. 2001 Jul-Aug;139(4):340-5. German. PubMed PMID: 11558053.	NR	5	Hyalart
204	Schneider U, Miltner O, Graf J, Thomsen M, Niethard FU. [Mechanism of action of hyaluronic acid in gonarthrosis of both knee joints in a right/left comparison. Study with dynamometry, oxygen partial pressure, temperature and Lequesne score]. Z Orthop Ihre Grenzgeb. 1997 Jul-Aug;135(4):341-7. German. PubMed PMID: 9381772.	NR	5	Hyalart
205	Carpenter B, Motley T. The role of viscosupplementation in the ankle using hylan G-F 20. J Foot Ankle Surg. 2008 Sep-Oct;47(5):377-84. doi: 10.1053/j.jfas.2008.06.013. PubMed PMID: 18725116.	NR	5	hylan G-F 20
206	Huskin JP, Vandekerckhove B, Delincé P, Verdonk R, Dubuc JE, Willems S, Hardy P, Blanco FJ, Charrois O, Handelberg F. Multicentre, prospective, open study to evaluate the safety and efficacy of hylan G-F 20 in knee osteoarthritis subjects presenting with pain following arthroscopic meniscectomy. Knee Surg Sports Traumatol Arthrosc. 2008 Aug;16(8):747-52. doi: 10.1007/s00167-008-0556-4. Epub 2008 Jun 7. PubMed PMID: 18536906; PubMed Central PMCID: PMC2516182.	NR	5	hylan G-F 20
207	Stitik TP, Blacksin MF, Stiskal DM, Kim JH, Foye PM, Schoenherr L,	NR	5	Hyalgan

User query # 14: (("Osteoarthritis/drug therapy"[Mesh] OR "Osteoarthritis/therapy"[Mesh])) AND ("Hyaluronic Acid/therapeutic use"[Mesh] OR "Hyaluronic Acid/therapy"[Mesh])				
Citation		**Relevance NR=non-relevant R=relevant**	**Reason for non-relevance or Appraisal**	
	Choi ES, Chen B, Saunders HJ, Nadler SF. Efficacy and safety of hyaluronan treatment in combination therapy with home exercise for knee osteoarthritis pain. Arch Phys Med Rehabil. 2007 Feb;88(2):135-41. PubMed PMID: 17270509.			
208	Gobbi A, Kon E, Berruto M, Francisco R, Filardo G, Marcacci M. Patellofemoral full-thickness chondral defects treated with Hyalograft-C: a clinical, arthroscopic, and histologic review. Am J Sports Med. 2006 Nov;34(11):1763-73. Epub 2006 Jul 10. PubMed PMID: 16832129.	NR	4	
209	Huang MH, Yang RC, Lee CL, Chen TW, Wang MC. Preliminary results of integrated therapy for patients with knee osteoarthritis. Arthritis Rheum. 2005 Dec 15;53(6):812-20. PubMed PMID: 16342083.	NR	5	Hyalgan
210	Wobig M, Bach G, Beks P, Dickhut A, Runzheimer J, Schwieger G, Vetter G, Balazs E. The role of elastoviscosity in the efficacy of viscosupplementation for osteoarthritis of the knee: a comparison of hylan G-F 20 and a lower-molecular-weight hyaluronan. Clin Ther. 1999 Sep;21(9):1549-62. PubMed PMID: 10509850.	NR	5	Artz, hylan G-F 20
211	Witteveen AG, Giannini S, Guido G, Jerosch J, Lohrer H, Vannini F, Donati L, Schulz A, Scholl J, Sierevelt IN, van Dijk CN. A prospective multi-centre, open study of the safety and efficacy of hylan G-F 20 (Synvisc) in patients with symptomatic ankle (talo-crural) osteoarthritis. Foot Ankle Surg. 2008;14(3):145-52. doi: 10.1016/j.fas.2008.01.001. Epub 2008 Mar 4. PubMed PMID: 19083633.	NR	5	hylan G-F 20
212	Baltzer AW, Moser C, Jansen SA, Krauspe R. Autologous conditioned serum (Orthokine) is an effective treatment for knee osteoarthritis. Osteoarthritis Cartilage. 2009 Feb;17(2):152-60. doi: 10.1016/j.joca.2008.06.014. Epub 2008 Jul 31. PubMed PMID: 18674932.	NR	5	HYA-Ject
213	Aydogan NH, Baydar ML, Atay T, Perktas I, Baykal BY, Ozmeric A. The effect of arthroscopic surgery and intraarticular drug injection to the antioxidation system and lipid peroxidation at osteoarthritis of knee. Saudi Med J. 2008 Mar;29(3):397-402. PubMed PMID: 18327367.	NR	5	hylan G-F 20
214	Guarda-Nardini L, Stifano M, Brombin C, Salmaso L, Manfredini D. A one-year case series of arthrocentesis with hyaluronic acid injections for temporomandibular joint osteoarthritis. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2007 Jun;103(6):e14-22. Epub 2007 Apr 6. PubMed PMID: 17419078.	NR	5	Hyalgan
215	Hempfling H. Intra-articular hyaluronic acid after knee arthroscopy: a two-year study. Knee Surg Sports Traumatol Arthrosc. 2007 May;15(5):537-46. Epub 2006 Dec 23. PubMed PMID: 17187274.	NR	5	Viscoseal
216	Karatosun V, Unver B, Gocen Z, Sen A, Gunal I. Intra-articular hyaluranic acid compared with progressive knee exercises in osteoarthritis of the knee: a prospective randomized trial with long-term follow-up. Rheumatol Int. 2006 Feb;26(4):277-84. Epub 2005 Mar 18. PubMed PMID: 15776267.	NR	5	hylan G-F 20
217	Forster MC, Straw R. A prospective randomised trial comparing intra-articular Hyalgan injection and arthroscopic washout for knee osteoarthritis. Knee. 2003 Sep;10(3):291-3. PubMed PMID: 12893153.	NR	5	Hyalgan
218	Payne MW, Petrella RJ. Viscosupplementation effect on proprioception in the osteoarthritic knee. Arch Phys Med Rehabil. 2000 May;81(5):598-603. PubMed PMID: 10807098.	NR	5	Suplasyn
219	Adams ME. An analysis of clinical studies of the use of crosslinked hyaluronan, hylan, in the treatment of osteoarthritis. J Rheumatol Suppl. 1993 Aug;39:16-8. PubMed PMID: 8410879.	NR	5	hylan G-F 20

7.2 PMC Search

Results are sorted by default order.

Search query: hyaluron* AND osteoarthritis AND "synovial joint" AND intraarticular AND human AND "clinical trial"				
Citation		**Relevance NR=non-relevant R=relevant**	**Reason for non-relevance or Appraisal**	
1	Tamer TM. Hyaluronan and synovial joint: function, distribution and healing. Interdiscip Toxicol. 2013 September; 6(3): 111–125. Published online 2013 September.	NR	1	
2	Reid MC. Viscosupplementation for Osteoarthritis: a Primer for Primary Care Physicians. Adv Ther. Author manuscript; available in PMC 2015 March 6.Published in final edited form as: Adv Ther. 2013 November; 30(11): 967–986. Published online 2013 November 8.	NR	1	
3	Goldberg VM, Laura Goldberg. Intra-articular hyaluronans: the treatment of knee pain in osteoarthritis. J Pain Res. 2010; 3: 51–56.	NR	1	
4	Altman RD, A. Manjoo, A. Fierlinger, F. Niazi, M. Nicholls. The mechanism of action for hyaluronic acid treatment in the osteoarthritic knee: a systematic review. BMC Musculoskelet Disord. 2015; 16: 321.	NR	1	
5	Chou LW, John Wang, Pei-Lin Chang, Yueh-Ling Hsieh. Hyaluronan modulates accumulation of hypoxia-inducible factor-1 alpha, inducible nitric oxide synthase, and matrix metalloproteinase-3 in the synovium of rat adjuvant-induced arthritis model. Arthritis Res Ther. 2011; 13(3): R90.	NR	3	
6	Lu HS, Ming-Thau Sheu, Yung-Feng Lin, Jai Lan, Yi-Ping Chin, Ming-Shium Hsieh, Chao-Wen Cheng, Chien-Ho Chen. Injectable hyaluronic-acid-doxycycline hydrogel therapy in experimental rabbit osteoarthritis. BMC Vet Res. 2013; 9: 68	NR	3	
7	Igarashi T, Norimasa Iwasaki, Daisuke Kawamura, Yukinori Tsukuda, Yasuhiko Kasahara, Masahiro Todoh, Shigeru Tadano, Akio Minami. Therapeutic Effects of Intra-Articular Ultrapurified Low Endotoxin Alginate Administration on Experimental Osteoarthritis in Rabbits. Cartilage. 2012 January; 3(1): 70–78.	NR	4	
8	Trigkilidas D, A Anand. The effectiveness of hyaluronic acid intra-articular injections in managing osteoarthritic knee pain. Ann R Coll Surg Engl. 2013 November; 95(8): 545–551. Published online 2013 November.	NR	1	
9	Zhang W, Hongwei Ouyang, Crispin R Dass, Jiake Xu. Current research on pharmacologic and regenerative therapies for osteoarthritis. Bone Res. 2016; 4: 15040.	NR	1	
10	Sharma A, Amar Singh Rana, Gaurav Jain, Puneet Kalra, Deepak Gupta, Siddharth Sharma. Evaluation of efficacy of arthrocentesis (with normal saline) with or without sodium hyaluronate in treatment of internal derangement of TMJ – A prospective randomized study in 20 patients. J Oral Biol Craniofac Res. 2013 Sep-Dec; 3(3): 112–119.	NR	6	
11	Sofat N, Anasuya Kuttapitiya. Future directions for the management of pain in osteoarthritis. Int J Clin Rheumtol. Int J Clin Rheumtol. 2014 April; 9(2): 197–276.	NR	1	
12	Kuyinu EL, Ganesh Narayanan, Lakshmi S. Nair, Cato T. Laurencin. Animal models of osteoarthritis: classification, update, and measurement of outcomes. J Orthop Surg Res. 2016;11:19.	NR	1	
13	Meszaros E, Charles J. Malemud. Prospects for treating osteoarthritis: enzyme–protein interactions regulating matrix metalloproteinase activity. Ther Adv Chronic Dis. 2012 September; 3(5): 219–229.	NR	4	
14	Scanzello CR, Steven R. Goldring. The Role of Synovitis in Osteoarthritis pathogenesis. Bone. Author manuscript; available in PMC 2013 August 1.Published in final edited form as: Bone. 2012 August; 51(2): 249–257.	NR	4	
15	Liu-Bryan R, Robert Terkeltaub. Emerging regulators of the inflammatory process in osteoarthritis. Nat Rev Rheumatol. Author manuscript; available in PMC 2015 March 26.Published in final edited form as: Nat Rev Rheumatol. 2015 January; 11(1): 35–44. Published online 2014 September 30.	NR	4	
16	Xie X, Changqing Zhang, Rocky S Tuan. Biology of platelet-rich plasma and its clinical application in cartilage repair. Arthritis Res Ther. 2014; 16(1): 204. Published online 2014 February 25.	NR	4	
17	Hunter DJ, W. Zhang, Philip G. Conaghan, K. Hirko, L. Menashe, L. Li, W.M. Reichmann, E. Losina. Systematic review of the concurrent and predictive validity of MRI biomarkers in OA. Osteoarthritis Cartilage. Author manuscript; available in PMC 2012 May 1.Published in final edited form as: Osteoarthritis Cartilage. 2011 May; 19(5): 557–588. Published online 2011 March 23.	NR	4	
18	Leong DJ, Marwa Choudhury, David M. Hirsh, John A. Hardin, Neil J. Cobelli, Hui B. Sun. Nutraceuticals: Potential for Chondroprotection and Molecular Targeting of Osteoarthritis. Int J Mol Sci. 2013 November; 14(11): 23063–23085. Published online 2013 November 21.	NR	4	
19	Lotz M. Osteoarthritis year 2011 in review: biology. Osteoarthritis Cartilage. Author manuscript; available in PMC 2013 March 1.Published in final edited form as: Osteoarthritis Cartilage. 2012 March; 20(3): 192–196. Published online 2011	NR	1	

Search query: hyaluron* AND osteoarthritis AND "synovial joint" AND intraarticular AND human AND "clinical trial"				
Citation		**Relevance NR=non-relevant R=relevant**	**Reason for non-relevance or Appraisal**	
	December 1.			
20	Hunter DJ. Focusing Osteoarthritis Management on Modifiable Risk Factors and Future Therapeutic Prospects. Ther Adv Musculoskelet Dis. 2009 February; 1(1): 35–47.	NR	1	
21	Todd JR. Lawrence, James Birmingham, Alison P. Toth. Emerging Ideas: Prevention of Posttraumatic Arthritis Through Interleukin-1 and Tumor Necrosis Factor-alpha Inhibition. Clin Orthop Relat Res. 2011 December; 469(12): 3522–3526.	NR	4	
22	Rainbow R, Weiping Ren, Li Zeng. Inflammation and Joint Tissue Interactions in OA: Implications for Potential Therapeutic Approaches. Arthritis. 2012; 2012: 741582.	NR	1	
23	Blalock D, Andrew Miller, Michael Tilley, Jinxi Wang. Joint Instability and Osteoarthritis Clin Med Insights Arthritis Musculoskelet Disord. 2015; 8: 15–23.	NR	1	
24	Evans CH. Advances in Regenerative Orthopaedics. Mayo Clin Proc. Author manuscript; available in PMC 2014 November 1.Published in final edited form as: Mayo Clin Proc. 2013 November; 88(11): 1323–1339.	NR	1	
25	Lee JK, Donald J. Responte, Derek D. Cissell, Jerry C. Hu, Jan A. Nolta, Kyriacos A. Athanasiou. Clinical translation of stem cells: insight for cartilage therapies. Crit Rev Biotechnol. Author manuscript; available in PMC 2015 March 1.Published in final edited form as: Crit Rev Biotechnol. 2014 March; 34(1): 89–100. Published online 2013 October 1.	NR	1	
26	Goodrich LR, Jennifer N Phillips, C Wayne McIlwraith, Stacey B Foti, Joshua C Grieger, Steven J Gray, R Jude Samulski. Optimization of scAAVIL-1ra In Vitro and In Vivo to Deliver High Levels of Therapeutic Protein for Treatment of Osteoarthritis. Mol Ther Nucleic Acids. 2013 February; 2(2): e70. Published online 2013 February 5.	NR	4	
27	2nd International meeting on synovium cell biology, physiology and pathology. Canterbury, United Kingdom, 21-23 September 1994. Proceedings and abstracts. Ann Rheum Dis. 1995 June; 54(6): 501–528.	NR	1	
28	Myers KR, N. A. Sgaglione, D. A. Grande. Trends in biological joint resurfacing. Bone Joint Res. 2013 September; 2(9): 193–199. Published online 2013 September 1.	NR	1	
29	Roelofs AJ, J.P.J. Rocke, C. De Bari. Cell-based approaches to joint surface repair: a research perspective. Osteoarthritis Cartilage. 2013 July; 21(7): 892–900.	NR	1	
30	Kimmerling KA, B.D. Furman, D.S. Mangiapani, M.A. Moverman, S.M. Sinclair, J.L. Huebner, A. Chilkoti, V.B. Kraus, L.A. Setton, F. Guilak, S.A. Olson. SUSTAINED INTRA-ARTICULAR DELIVERY OF IL-1RA FROM A THERMALLY-RESPONSIVE ELASTIN-LIKE POLYPEPTIDE AS A THERAPY FOR POST-TRAUMATIC ARTHRITIS. Eur Cell Mater. Author manuscript; available in PMC 2015 March 13.Published in final edited form as: Eur Cell Mater. 2015; 29: 124–140. Published online 2015 January 31.	NR	5	
31	Shimizu R, Naosuke Kamei, Nobuo Adachi, Michio Hamanishi, Goki Kamei, Elhussein Elbadry Mahmoud, Tomohiro Nakano, Takanori Iwata, Masayuki Yamato, Teruo Okano, Mitsuo Ochi. Repair Mechanism of Osteochondral Defect Promoted by Bioengineered Chondrocyte Sheet. Tissue Eng Part A. 2015 March 1; 21(5-6): 1131–1141.	NR	4	
32	Middleton K, David E. Fish. Lumbar spondylosis: clinical presentation and treatment approaches. Curr Rev Musculoskelet Med. 2009 June; 2(2): 94–104. Published online 2009 March 25.	NR	1	

7.3 Cartilage

Results 1-12 of 12 found for cartilage and tissue engineering in all fields are ordered according to relevance.

Search query: hyaluron* AND osteoarthritis AND "synovial joint" AND intraarticular AND human AND "clinical trial"

Citation		Relevance NR=non-relevant R=relevant	Reason for non-relevance or Appraisal	
1	Lee PB, Kim YC, Lim YJ, Lee CJ, Sim WS, Ha CW, Bin SI, Lim KB, Choi SS, Lee SC. Comparison between high and low molecular weight hyaluronates in knee osteoarthritis patients: open-label, randomized, multicentre clinical trial. J Int Med Res. 2006;34(1):77-87.	NR	5	
2	Hunter DJ. Focusing osteoarthritis management on modifiable risk factors and future therapeutic prospects. Ther Adv Musculoskelet Dis. 2009 Feb;1(1):35-47.	NR	1	
3	Huskisson EC. Modern management of mild-to-moderate joint pain due to osteoarthritis: a holistic approach. J Int Med Res. 2010 Jul-Aug;38(4):1175-212.	NR	1	
4	Henrotin Y, Pesesse L, Lambert C. Targeting the synovial angiogenesis as a novel treatment approach to osteoarthritis. Ther Adv Musculoskelet Dis. 2014;6:20-34.	NR	1	
5	Osterman C, McCarthy MB, Cote MP, Beitzel K, Bradley J, Polkowski G, Mazzocca AD. Platelet-Rich Plasma Increases Anti-inflammatory Markers in a Human Coculture Model for Osteoarthritis. Am J Sports Med. 2015 Jun;43(6):1474-84.	NR	4	
6	de Windt TS, Vonk LA, Brittberg M, Saris DB. Treatment and Prevention of (Early) Osteoarthritis Using Articular Cartilage Repair—Fact or Fiction? A Systematic Review. Cartilage. 2013;4:5S-12S.	NR	1	
7	Extended Abstracts	NR	6	
8	Posters	NR	6	
9	Schreiner MM, Mlynarik V, Zbýň S, Szomolanyi P, Apprich S, Windhager R, Trattnig S. New Technology in Imaging Cartilage of the Ankle. Cartilage 2016 March 3; doi: 10.1177/1947603516632848	NR	4	
10	Haskin CL, Milam SB, Cameron IL. Pathogenesis of degenerative joint disease in the human temporomandibular joint. Crit Rev Oral Biol Med. 1995;6(3):248-77.	NR	1	
11	Bekkers JE, Creemers LB, Dhert WJ, Saris DB. Diagnostic Modalities for Diseased Articular Cartilage—From Defect to Degeneration: A Review. Cartilage. 2010;1:157-164.	NR	1	
12	Mithoefer K, Saris DB, Farr J, Kon E, Zaslav K, Cole BJ, Ranstam J, Yao J, Shive M, Levine D, Dalemans W, Brittberg M. Guidelines for the Design and Conduct of Clinical Studies in Knee Articular Cartilage Repair: International Cartilage Repair Society Recommendations Based on Current Scientific Evidence and Standards of Clinical Care. Cartilage. 2011;2(2):100-121.	NR	1	

7.4 CENTRAL

Results are ordered according their relevance (high to low).

User query # 1: (hyaluronan OR hyaluronic) AND osteoarthritis AND intraarticular AND human AND "clinical trial"

Citation		Relevance NR=non-relevant R=relevant	Reason for non-relevance or Appraisal	
1	Miltner O , Schneider U , Siebert CH , Niedhart C and Niethard FU.Efficacy of intraarticular hyaluronic acid in patients with osteoarthritis --a prospective clinical trial . Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society, 2002, 10(9), 680	NR	5	Hyalart
2	Karlsson J, Sjogren LS, Lohmander LS. Comparison of two hyaluronan drugs and placebo in patients with knee osteoarthritis. A controlled, randomized, double-blind, parallel-design multicentre study. Rheumatology (Oxford). 2002;41(11):1240-8.	NR	5	Artzal, hylan G-F 20
3	Yentur EA , Okcu G and Yegul I. The role of trigger point therapy in knee osteoarthritis. Pain Clinic, 2003, 15(4), 385	NR	4	
4	Lucangeli A , Gugelmetto M and Primon D.Physical therapy and intraarticular hyaluronic acid in the treatment of osteoarthritis . [Italian] Rivista Italiana di Biologia e Medicina, 2001, 21(1-2), 5	NR	6	italian
5	**Neustadt D , Caldwell J , Bell M , Wade J and Gimbel J.Clinical effects of intraarticular injection of high molecular weight hyaluronan (Orthovisc) in osteoarthritis of the knee: a randomized, controlled, multicenter trial. The Journal of rheumatology, 2005,**	**R**	**9**	**Orthovisc**

User query # 1: (hyaluronan OR hyaluronic) AND osteoarthritis AND intraarticular AND human AND "clinical trial"				
Citation		**Relevance NR=non-relevant R=relevant**	**Reason for non-relevance or Appraisal**	
	32(10), 1928			
6	Petrella RJ, Decaria J and Petrella MJ. Long term efficacy and safety of a combined low and high molecular weight hyaluronic acid in the treatment of osteoarthritis of the knee. Rheumatology Reports, 2011, 3(1), 16	NR	5	dual molecular weight HA
7	Strand V , Baraf HSB , Lavin PT , Lim S and Hosokawa H.A multicenter, randomized controlled trial comparing a single intra-articular injection of Gel-200, a new cross-linked formulation of hyaluronic acid, to phosphate buffered saline for treatment of osteoarthritis of the knee. Osteoarthritis and Cartilage, 2012, 20(5), 350	NR	5	Gel2000
8	Pavelka K and Uebelhart D.Efficacy evaluation of highly purified intra-articular hyaluronic acid (Sinovial) vs hylan G-F20 (Synvisc) in the treatment of symptomatic knee osteoarthritis . A double-blind, controlled, randomized, parallel-group non-inferiority study. Osteoarthritis and cartilage, 2011, 19(11), 1294	NR	5	hylan G-F 20
9	**Atamaz F, Kirazli Y, Akkoc Y. A comparison of two different intra-articular hyaluronan drugs and physical therapy in the management of knee osteoarthritis. Rheumatol Int. 2006;26(10):873-8.**	**R**	**9**	hylan G-F 20, **Orthovisc**
10	Tikiz C, Ünlü Z, Şener A, Efe M, Tüzün Ç. Comparison of the efficacy of lower and higher molecular weight viscosupplementation in the treatment of hip osteoarthritis. Clin Rheumatol. 2005;24(3):244-50.	NR	5	Ostenil
11	**Ozturk C , Atamaz F , Hepguler S , Argin M and Arkun R.The safety and efficacy of intraarticular hyaluronan with/without corticosteroid in knee osteoarthritis : 1-year, single-blind, randomized study. Rheumatology international, 2006, 26(4), 314**	**R**	**9**	**Orthovisc**
12	Petrella RJ , Cogliano A and Decaria J.Combining two hyaluronic acids in osteoarthritis of the knee: a randomized, double-blind, placebo-controlled trial. Clinical rheumatology, 2008, 27(8), 975	NR	5	combination of two HA sizes
13	Aslan A, Kirdemir V, Atay T, Baykal YB, Aytekin O, Aydogan FC. The efficacy of intra-articular injection of hyaluronic acid with supplemental peroral vitamin e following arthroscopic debridement in the treatment of knee osteoarthritis: A prospective, randomized, controlled study. Turkiye Fiziksel Tip ve Rehabilitasyon Dergisi, 2012, 58(3), 199	NR	6	turkish
14	Schneider U , Miltner O , Graf J , Thomsen M and Niethard FU.The efficacy of hyaluronic acid in patients with osteoarthritis of both knees in right/left-comparison - Examination with dynamometry, synovial oxygen partial pressure, intraarticular temperature and Lequesne-score. <ORIGINAL> WIRKUNGSWEISE VON HYALURONSAURE BEI GONARTHROSE BEIDER KNIEGELENKE IM RECHTS/LINKS-VERGLEICH - UNTERSUCHUNG MIT DYNAMOMETRIE, SAUERSTOFFPARTIALDRUCK, TEMPERATUR UND LEQUESNE-SCORE Zeitschrift fur Orthopadie und ihre Grenzgebiete, 1997, 135(4), 341	NR	5	Hyalart
15	Schneider U , Miltner O , Graf J , Thomsen M and Niethard FU.[The efficacy of hyaluronic acid in patients with osteoarthritis of both knees in right/left-comparison - Examination with dynamometry, synovial oxygen partial pressure, intraarticular temperature and Lequesne-score.] Zeitschrift fur Orthopadie und ihre Grenzgebiete, 1997, 135(4), 341	NR	5	
16	Hashemi SM, Madadi F, Razavi S, Nikooseresht M, Kiyabi FH, Nasiripour S. Intra-articular hyaluronic acid injections Vs. dextrose prolotherapy in the treatment of osteoarthritic knee pain. Tehran University Medical Journal, 2012, 70(2), 119	NR	6	arabian
17	Auerbach B and Melzer C.[Cross-linked hyaluronic acid in the treatment of osteoarthritis of the knee--results of a prospective randomized trial]. Zentralblatt für Chirurgie, 2002, 127(10), 895	NR	5	hylan G-F 20
18	Vaquerizo V , Plasencia MA , Arribas I , Seijas R , Padilla S , Orive G and Anitua E. Comparison of intra-articular injections of plasma rich in growth factors (PRGF-Endoret) versus durolane hyaluronic acid in the treatment of patients with symptomatic osteoarthritis : A randomized controlled trial. Arthroscopy - Journal of Arthroscopic and Related Surgery, 2013, 29(10), 1635	NR	5	Durolane, crosslinked
19	**Polacco A, Beomonte Zobel B, Polacco M, Scarlata S, Gasparro F, DelVescovo R, Scarciolla L. The effect of intra-articular hyaluronic**	**R**	**9**	**Sinovial One**

User query # 1: (hyaluronan OR hyaluronic) AND osteoarthritis AND intraarticular AND human AND "clinical trial"				
Citation		**Relevance NR=non-relevant R=relevant**	**Reason for non-relevance or Appraisal**	
	acid (Sinovial One) on knee osteoarthritis : A preliminary study. European Journal of Inflammation. 2013;11(3):847-853			
20	Navarro-Sarabia F, Coronel P, Blanco F, Rodriguez De La Serna A, Gimeno M, Herrero-Beaumont G. Efficacy and safety of long-term repeated, intraarticular injections of hyaluronic acid in knee osteoarthritis: Final results of the amelia trial. Osteoarthritis and cartilage. 2012;20:S28	NR	5	Adant
21	McDonald C, Hantel S, Strohmeier M. A randomised, controlled study to compare the performance and safety of two sources of sodium hyaluronate given as a viscosupplement by intra-articular injection to patients with osteoarthritis of the knee. Journal of Clinical Research. 2000;3(41-50):41	NR	5	Hyalart
22	**Giarratana LS , Marelli BM , Crapanzano C , DeMartinis SE , Gala L , Ferraro M , Marelli N and Albisetti W.A randomized double-blind clinical trial on the treatment of knee osteoarthritis : the efficacy of polynucleotides compared to standard hyaluronian viscosupplementation. The Knee. 2014;21(3):661-8**	**R**	**9**	**Hyalubrix**
23	Saeed K, Khan SA, Ahmed I. Efficacy of intra articular hyaluronic acid versus arthroscopic debridement in terms of improvement in pain score in Kellgran -Lawrence Grading II & III osteoarthritis of knee joint. Pakistan Journal of Medical and Health Sciences. 2015;9(3):1011	NR	6	
24	Lee PB , Kim YC , Lim YJ , Lee CJ , Sim WS , Ha CW , Bin SI , Lim KB , Choi SS and Lee SC.Comparison between high and low molecular weight hyaluronates in knee osteoarthritis patients: open-label, randomized, multicentre clinical trial . The Journal of international medical research, 2006, 34(1), 77	NR	5	Hyruan plus, Hyal
25	**Paoloni M, Di Sante L, Dimaggio M, Bernetti A, Mangone M, Di Renzo S, Santilli V. Kinematic and kinetic modifications in walking pattern of hip osteoarthritis patients induced by intra-articular injections of hyaluronic acid. Clin Biomech (Bristol, Avon). 2012 Aug;27(7):661-5.**	**R**	**9**	**Hyalubrix**
26	Arensi F. Comparison of efficacy and therapeutic safety of two treatments based on hyaluronic acid (Go-On and Hyalgan) in knee osteoarthritis . Minerva Ortopedica e Traumatologica, 2006, 57(3), 105	NR	5	Go-on, Hyalgan
27	Stitik TP, Blacksin MF, Stiskal DM, Kim JH, Foye PM, Schoenherr L, Choi ES, Chen B, Saunders HJ, Nadler SF. Efficacy and safety of hyaluronan treatment in combination therapy with home exercise for knee osteoarthritis pain. Arch Phys Med Rehabil. 2007 Feb;88(2):135-41. PubMed PMID: 17270509.	NR	5	Hyalgan
28	Al-Omran A, Azam Q. Efficacy of viscosupplementation in knee osteoarthritis : A clinical trial of three agents. Bahrain Medical Bulletin. 2014;36(3):150	NR	5	Osteonil
29	Skwara A , Peterlein CD , Tibesku CO , Rosenbaum D and Fuchs-Winkelmann S.Changes of gait patterns and muscle activity after intraarticular treatment of patients with osteoarthritis of the knee: a prospective, randomised, doubleblind study. The Knee, 2009, 16(6), 466	NR	5	Ostenil
30	**Alberto M , Umberto M , Emanuele B , Bruno L , Valentina G , Prisco P , Mauro G and Sandro T.Intra-articular injection of hyaluronic acid (MW 1,500-2,000 kDa; HyalOne) in symptomatic osteoarthritis of the hip: A prospective cohort study. Archives of orthopaedic and trauma surgery, 2011, 131(12), 1677**	**R**	**9**	**Hyalone**
31	Diracoglu D , Vural M , Baskent A , Dikici F and Aksoy C.The effect of viscosupplementation on neuromuscular control of the knee in patients with osteoarthritis . Journal of back and musculoskeletal rehabilitation, 2009, 22(1), 1	NR	5	hylan G-F 20
32	Raeissadat SA, Rayegani SM, Hassanabadi H, Fathi M, Ghorbani E, Babaee M, Azma K. Knee Osteoarthritis Injection Choices: Platelet- Rich Plasma (PRP) Versus Hyaluronic Acid (A one-year randomized clinical trial). Clin Med Insights Arthritis Musculoskelet Disord. 2015;8:1-8.	NR	5	Hyalgan
33	Therrien R , Richardson JB , Andersson M , Todman MG , Arden NK , Ther-rien R , Bell M , Thorne C , Bensen W , Cividino A , Olszynski W , Khraishi M , Dobson C , Leighton R , Werle J , Alleyne J , Litchfield R , Stanish W , Chow A , Wilson D , Arden N , Birrel F , Richardson J , Scott D , Akermark C , Isacson J , Ericsater J , Adalberth T and Melberg P-E.	NR	5	NASHA

User query # 1: (hyaluronan OR hyaluronic) AND osteoarthritis AND intraarticular AND human AND "clinical trial"				
Citation		**Relevance NR=non-relevant R=relevant**	**Reason for non-relevance or Appraisal**	
	NASHA hyaluronic acid vs methylprednisolone for knee osteoarthritis : A prospective, multi-centre, randomized, non-inferiority trial. Osteoarthritis and cartilage, 2014, 22(1), 17			
34	Qvistgaard E , Christensen R , Torp-Pedersen S and Bliddal H.Intra-articular treatment of hip osteoarthritis : a randomized trial of hyaluronic acid, corticosteroid, and isotonic saline. Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society, 2006, 14(2), 163	NR	5	Hyalgan
35	Fuchs S , Mönikes R , Wohlmeiner A and Heyse T.Intra-articular hyaluronic acid compared with corticoid injections for the treatment of rhizarthrosis. Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society, 2006, 14(1), 82	NR	5	Ostenil Mini
36	Listrat V , Ayral X , Patarnello F , Bonvarlet J-P , Simonnet J , Amor B and Dougados M.Arthroscopic evaluation of potential structure modifying activity of hyaluronan (Hyalgan (R)) in osteoarthritis of the knee Osteoarthritis and cartilage, 1997, 5(3), 153	NR	5	Hyalgan
37	Chen W-L , Hsu W-C , Lin Y-J and Hsieh L-F.Comparison of intra-articular hyaluronic acid injections with transcutaneous electric nerve stimulation for the management of knee osteoarthritis : A randomized controlled trial. Archives of Physical Medicine and Rehabilitation, 2013, 94(8), 1482	NR	5	Artz
38	Davalillo CAT , Vasavilbaso CT , Alvarez JMN , Granado PC , Jimenez OAG , delSol MG and Orbezo FG.Clinical efficacy of intra-articular injections in knee osteoarthritis : A prospective randomized study comparing hyaluronic acid and betamethasone. Open Access Rheumatology: Research and Reviews, 2015, 7, 9	NR	5	Suprahyal=Adant
39	**Karatosun V, Unver B, Gocen Z, Sen A. Comparison of two hyaluronan drugs in patients with advanced osteoarthritis of the knee. A prospective, randomized, double-blind study with long term follow-up. Clin Exp Rheumatol. 2005 Mar-Apr;23(2):213-8.**	**R**	**9**	**Orthovisc**, hylan G-F 20 (Synvisc)
40	De Campos GC , Rezende MU , Pailo AF , Frucchi R and Camargo OP.Adding triamcinolone improves viscosupplementation: A randomized clinical trial knee. Clinical orthopaedics and related research, 2013, 471(2), 613	NR	5	hylan G-F 20 6 ml
41	Ucar D , Diracoglu D , Suleyman T and Capan N.Intra-articular hyaluronic acid as treatment in elderly and middle-aged patients with knee osteoarthritis . Open rheumatology journal, 2013, 7(1), 38	NR	6	
42	Zhang H , Zhang K , Zhang X , Zhu Z , Yan S , Sun T , Guo A , Jones J , Steen RG , Shan B , Zhang J and Lin J.Comparison of two hyaluronic acid formulations for safety and efficacy (CHASE) study in knee osteoarthritis : A multicenter, randomized, double-blind, 26-week non-inferiority trial comparing Durolane to Artz. Arthritis research & therapy, 2015, 17(1)	NR	5	Durolane, Artz
43	Chareancholvanich K , Pornrattanamaneewong C and Narkbunnam R.Increased cartilage volume after injection of hyaluronic acid in osteoarthritis knee patients who underwent high tibial osteotomy. Knee surgery, sports traumatology, arthroscopy : official journal of the ESSKA, 2014, 22(6), 1415	NR	5	Hyalgan
44	Paker N , Tekdös D , Kesiktas N and Soy D.Comparison of the therapeutic efficacy of TENS versus intra-articular hyaluronic acid injection in patients with knee osteoarthritis : a prospective randomized study. Advances in therapy, 2006, 23(2), 342	NR	5	hylan G-F 20
45	Toda Y and Tsukimura N.A comparison of intra-articular hyaluronan injection accuracy rates between three approaches based on radiographic severity of knee osteoarthritis Osteoarthritis and cartilage, 2008, 16(9), 980	NR	5	Suvenyl
46	Ishijima M , Nakamura T , Shimizu K , Hayashi K , Kikuchi H , Soen S , Omori G , Yamashita T , Uchio Y , Chiba J , Ideno Y , Kubota M , Kurosawa H and Kaneko K.Intra-articular hyaluronic acid injection versus oral non-steroidal anti-inflammatory drug for the treatment of knee osteoarthritis : A multi-center, randomized, open-label, non-inferiority trial. Arthritis research & therapy, 2014, 16(1)	NR	6	high molecular weight 2,700 kDa HA (25 mg)
47	**Karatay S , Kiziltunc A , Yildirim K , Karanfil RC and Senel K.Effects of different hyaluronic acid products on synovial fluid levels of intercellular adhesion molecule-1 and vascular cell adhesion**	**R**	**9**	**Orthovisc**, hylan G-F 20 (Synvisc)

User query # 1: (hyaluronan OR hyaluronic) AND osteoarthritis AND intraarticular AND human AND "clinical trial"				
Citation		**Relevance NR=non-relevant R=relevant**	**Reason for non-relevance or Appraisal**	
	molecule-1 in knee osteoarthritis . Annals of clinical and laboratory science, 2004, 34(3), 330			
48	**Battaglia M, Guaraldi F, Vannini F, Rossi G, Timoncini A, Buda R, Giannini S. Efficacy of ultrasound-guided intra-articular injections of platelet-rich plasma versus hyaluronic acid for hip osteoarthritis. Orthopedics. 2013 Dec;36(12):e1501-8. PubMed PMID: 24579221.**	**R**	**9**	**Hyalubrix**
49	Campisi M , Galesso D , Mero A and Pasut G.Development of a new hyaluronic acid-calcitonin conjugate for the local treatment of osteoarthritis . Osteoarthritis and cartilage, 2014, 22, S475	NR	5	HA crosslinked
50	Karatosun V, Unver B, Gocen Z, Sen A, Gunal I. Intra-articular hyaluranic acid compared with progressive knee exercises in osteoarthritis of the knee: a prospective randomized trial with long-term follow-up. Rheumatol Int. 2006 Feb;26(4):277-84.	NR	5	hylan G-F 20
51	Unsal S , Caglar-Yagci H , Kaya K , Sahin-Onat S and Ozel S.Comparison of effectiveness of intraarticular sodium hyaluronat and physical therapy applications in patients with knee osteoarthritis : Randomized prospective study. [Turkish] Journal of Rheumatology and Medical Rehabilitation, 2008, 19(1), 16	NR	6	turkish
52	Martin Martin LS , Massafra U , Bizzi E and Migliore A.A double blind randomized active-controlled clinical trial on the intra-articular use of Md-Knee versus sodium hyaluronate in patients with knee osteoarthritis ("Joint"). BMC musculoskeletal disorders, 2016, 17(1) (no pagination)	NR	5	Supartz
53	Padilla S , Aguirre J , Prado R , Orive G and Anitua E.Clinical efficacy of plasma rich in growth factors intraarticular infiltrations in the treatment of knee osteoarthritis : A systematic review. Osteoarthritis and cartilage, 2014, 22, S195	NR	1	
54	Hatoum HT , Fierlinger AL , Lin S-J and Altman RD.Cost-effectiveness analysis of intra-Articular injections of a high molecular weight bioengineered hyaluronic acid for the treatment of osteoarthritis knee pain. Journal of medical economics, 2014, 17(5), 326	NR	4	
55	Cubukçu D , Ardiç F , Karabulut N and Topuz O.Hylan G-F 20 efficacy on articular cartilage quality in patients with knee osteoarthritis : clinical and MRI assessment. Clinical rheumatology, 2005, 24(4), 336	NR	5	hylan G-F 20
56	DeCaria JE, Montero-Odasso M, Wolfe D, Chesworth BM, Petrella RJ. The effect of intra-articular hyaluronic acid treatment on gait velocity in older knee osteoarthritis patients: a randomized, controlled study. Arch Gerontol Geriatr. 2012 Sep-Oct;55(2):310-5.	NR	5	1% HA
57	Hu JZ , Luo CY , Kang M , Lü HB , Lei GH and Dai Z.[Therapeutic effects of intraarticular injection of ligustrazine on knee osteoarthritis]. Zhong nan da xue xue bao. Yi xue ban = Journal of Central South University. Medical sciences, 2006, 31(4), 591	NR	6	chinese
58	Ip D and Fu NY.Can combined use of low-level lasers and hyaluronic acid injections prolong the longevity of degenerative knee joints?. Clinical interventions in aging, 2015, 10, 1255	NR	5	Hyalgan
59	Altman RD and Moskowitz R.Intraarticular sodium hyaluronate (Hyalgan) in the treatment of patients with osteoarthritis of the knee: a randomized clinical trial. Hyalgan Study Group. The Journal of Rheumatology, 1998, 25(11), 2203	NR	5	Hyalgan
60	Navarro-Sarabia F , Toyos FJ , Herrero-Beaumont G , Coronel P , Gimeno M and Hernandez-Cruz B.Knee joint space width progression: Results of a 3.3 years randomized, double blind clinical trial with hyaluronic acid. the AMELIA project. Osteoarthritis and cartilage, 2012, 20, S168	NR	5	Adant
61	Thein R , Haviv B , Kidron A and Bronak S.Intra-articular injection of hyaluronic acid following arthroscopic partial meniscectomy of the knee. Orthopedics, 2010, 33(10), 724	NR	4	Viscoseal
62	Paterson KL , Nicholls M , Bennell KL and Bates D.Intra-articular injection of photo-activated platelet-rich plasma in patients with knee osteoarthritis : A double-blind, randomized controlled pilot study. BMC musculoskeletal disorders, 2016, 17(1) (no pagination)	NR	5	hylan G-F 20
63	Dickson DJ , Hosie G and English JR.A double-blind, placebo-controlled comparison of hylan G-F 20 against diclofenac in knee osteoarthritis . Journal of Clinical Research, 2001, 4(41-52), 41	NR	5	hylan G-F 20

User query # 1: (hyaluronan OR hyaluronic) AND osteoarthritis AND intraarticular AND human AND "clinical trial"				
Citation		**Relevance NR=non-relevant R=relevant**	**Reason for non-relevance or Appraisal**	
64	Salk RS, Chang TJ, D'Costa WF, Soomekh DJ, Grogan KA. Sodium hyaluronate in the treatment of osteoarthritis of the ankle: a controlled, randomized, double-blind pilot study. J Bone Joint Surg Am. 2006 Feb;88(2):295-302.	NR	5	Hyalgan
65	Hermans J , Bierma-Zeinstra SM , Niesten D , Verhaar JA and Reijman M.The visk study: A pragmatic randomized clinical trialfor the effectiveness of intra articular hyaluronic acid for knee osteoarthritis . Osteoarthritis and cartilage, 2013, 21, S148	NR	6	abstract
66	Wong H , Yuan W-Q , Zhao Y-X and Li Y-J.External application of reparil-gel accompanied with intra-articular injection of sodium hyaluronate for treatment of knee osteoarthritis . [Chinese] Chinese Journal of Clinical Rehabilitation, 2006, 10(15), 39	NR	6	chinese
67	VanTiel J , Reijman M , Bos PK , Hermans J , VanBuul GM , Bron EE , Klein S , Verhaar JAN , Krestin GP , Bierma-Zeinstra SMA , Weinans H , Kotek G and Oei EHG.Delayed gadolinium-enhanced MRI of cartilage (dGEMRIC) shows no change in cartilage structural composition after viscosupplementation in patients with early-stage knee osteoarthritis . PloS one, 2013, 8(11)	NR	5	hylan G-F 20
68	**Brandt KD , Block JA , Michalski JP , Moreland LW , Caldwell JR and Lavin PT.Efficacy and safety of intra-articular sodium hyaluronate in knee osteoarthritis . Clinical orthopaedics and related research, 2001, 385, 130**	**R**	**9**	**Orthovisc**
69	**Witteveen AG, Sierevelt IN, Blankevoort L, Kerkhoffs GM, van Dijk CN. Intra-articular sodium hyaluronate injections in the osteoarthritic ankle joint: effects, safety and dose dependency. Foot Ankle Surg. 2010 Dec;16(4):159-63.**	**R**	**9**	**Orthovisc**
70	Kolarz G , Kotz R , Broll H , Dunky A , Landsiedl F , Mayrhofer F , Rainer F , Ramach W , Singer F and Metz M.Hyaluronic acid in the treatment of osteoarthritis of the knee joint: Interim results of a comparative clinical study. European Journal of Rheumatology and Inflammation., 1995, 15(1), 39	NR	5	Hyalgan
71	Witteveen AG , Kok A , Sierevelt IN , Kerkhoffs GM and vanDijk CN.The optimal injection technique for the osteoarthritic ankle: a randomized, cross-over trial. Foot and ankle surgery : official journal of the European Society of Foot and Ankle Surgeons, 2013, 19(4), 283	NR	4	hylan G-F 20
72	Arden NK , Åkermark C , Andersson M , Todman MG and Altman RD.A randomized saline-controlled trial of NASHA hyaluronic acid for knee osteoarthritis . Current medical research and opinion, 2014, 30(2), 279	NR	5	NASHA
73	Kawasaki T , Kurosawa H , Ikeda H , Takazawa Y , Ishijima M , Kubota M , Kajihara H , Maruyama Y , Kim SG , Kanazawa H and Doi T.Therapeutic home exercise versus intraarticular hyaluronate injection for osteoarthritis of the knee: 6-month prospective randomized open-labeled trial. Journal of orthopaedic science : official journal of the Japanese Orthopaedic Association, 2009, 14(2), 182	NR	5	Artz
74	Housman L , Arden N , Schnitzer TJ , Birbara C , Conrozier T , Skrepnik N , Wei N , Bockow B , Waddell D , Tahir H , Hammond A , Goupille P , Sanson BJ , Elkins C and Bailleul F.Intra-articular hylastan versus steroid for knee osteoarthritis . Knee surgery, sports traumatology, arthroscopy : official journal of the ESSKA, 2014, 22(7), 1684	NR	5	Hylastan
75	Adams ME , Atkinson MH , Lussier AJ , Schulz J , Siminovitch KA , Wade JP and Zummer M.The role of viscosupplementation with hylan G-F 20 (Synviscregistered trade mark) in the treatment of osteoarthritis of the knee: A Canadian multicenter trial comparing hylan G-F 20 alone, hylan G-F 20 with non-steroidal anti-inflammatory drugs (NSAIDs) and NSAIDs alone. Osteoarthritis and Cartilage., 1995, 3(4), 213	NR	5	hylan G-F 20
76	Watik A , Rachidi W , Janani S , Nassar K , Mkinsi O , Serhier Z and Othmani MB.Intra-articular use of sodium hyaluronate (2,2-2,7 MDa) in the treatment of Moroccan patients with knee osteoarthritis : Randomized controlled trial. [French] Revue medicale de Bruxelles, 2014, 35(6), 469	NR	6	french
77	Strand V , Baraf HSB , Lavin PT , Lim S and Hosokawa H.Effectiveness and Safety of a Multicenter Extension and Retreatment Trial of Gel-200 in Patients with Knee Osteoarthritis . Cartilage, 2012, 3(4), 297	NR	5	Gel2000
78	Vega A , Martín-Ferrero MA , DelCanto F , Alberca M , García V , Munar	NR	5	Durolane

User query # 1: (hyaluronan OR hyaluronic) AND osteoarthritis AND intraarticular AND human AND "clinical trial"				
Citation		**Relevance NR=non-relevant R=relevant**	**Reason for non-relevance or Appraisal**	
	A , Orozco L , Soler R , Fuertes JJ , Huguet M , Sánchez A and García-Sancho J.Treatment of Knee Osteoarthritis With Allogeneic Bone Marrow Mesenchymal Stem Cells: A Randomized Controlled Trial. Transplantation, 2015, 99(8), 1681			
79	Kang J-G , Wang M-L and Zhang X-N.Treatment of knee osteoarthritis with arthroscopic debridement and intra-articular sodium hyaluronate injection. [Chinese] Journal of Jilin University Medicine Edition, 2005, 31(5), 802	NR	6	chinese
80	Huang T-L , Chang C-C , Lee C-H , Chen S-C , Lai C-H and Tsai C-L.Intra-articular injections of sodium hyaluronate (Hyalgan) in osteoarthritis of the knee. a randomized, controlled, double-blind, multicenter trial in the asian population. BMC musculoskeletal disorders, 2011, 12	NR	5	Hyalgan
81	Hatoum HT , Rosen JE , Fierlinger AL , Lin S-J and Altman RD.Assessment of the health-related quality of life impact of euflexxa (1% SODIUM HYALURONATE) using the short form (SF)-36 data collected in a randomized clinical trial . Osteoarthritis and cartilage, 2013, 21, S246	NR	5	Euflexxa
82	Xin Y , Jianhao L , Tiansheng S , Yongqiang H , Weimin F , Ming C , Tiezheng S , Jianhua Y , Liang X , Xiaoyuan G and Yongping C.The efficacy and safety of sodium hyaluronate injection (Adant) in treating degenerative osteoarthritis : A multi-center, randomized, double-blind, positive-drug parallel-controlled and non-inferiority clinical study. International journal of rheumatic diseases, 2016, 19(3), 271	NR	5	Adant, Artz
83	Saw K-Y , Anz A , Siew-Yoke Jee C , Merican S , Ching-Soong Ng R , Roohi SA and Ragavanaidu K.Articular cartilage regeneration with autologous peripheral blood stem cells versus hyaluronic acid: A randomized controlled trial. Arthroscopy - Journal of Arthroscopic and Related Surgery, 2013, 29(4), 684	NR	6	
84	Habib G , Jabbour A , Artul S and Hakim G.Intra-articular methylprednisolone acetate injection at the knee joint and the hypothalamic-pituitary-adrenal axis: a randomized controlled study. Clinical rheumatology, 2014, 33(1), 99	NR	5	Suplasyn
85	Wong KL , Lee KB , Tai BC , Law P , Lee EH and Hui JH.Injectable cultured bone marrow-derived mesenchymal stem cells in varus knees with cartilage defects undergoing high tibial osteotomy: a prospective, randomized controlled clinical trial with 2 years' follow-up. Arthroscopy : the journal of arthroscopic & related surgery : official publication of the Arthroscopy Association of North America and the International Arthroscopy Association, 2013, 29(12), 2020	NR	4	
86	Tang X , Pei F-X , Zhou Z-K , Liu G , Shen B , Kang P-D , Li J , Zhao X-D , Li Q and Li Y.A randomized, single-blind comparison of the efficacy and tolerability of hyaluronate acid and meloxicam in adult patients with Kashin-Beck disease of the knee. Clinical rheumatology, 2012, 31(7), 1079	NR	5	1% HA
87	Scale D , Wobig LM and Wolpert W.Viscosupplementation of osteoarthritic knees with hylan: A treatment schedule study. Current therapeutic research, clinical and experimental, 1994, 55(3), 220	NR	5	hylan G-F 20
88	Jevtic T , Mejdi Z , Vukomanovic J , Milovanovic D and Jevtic M.Application of methylprednisolone suspension by iontophoresis in patients with arthrosis of the knee. Serbian Journal of Experimental and Clinical Research, 2008, 9(1), 13	NR	5	

7.5 DIMDI

No information concerning sort order displayed.

User query # 1: (hyaluron* AND osteoarthritis AND "synovial joint" AND intraarticular AND human AND "clinical trial"				
Citation		**Relevance NR=non-relevant R=relevant**	**Reason for non-relevance or Appraisal**	
1	Kraus VB, Birmingham J, Stabler TV, Feng S, Taylor DC, Moorman CT 3rd, Garrett WE, Toth AP. Effects of intraarticular IL1-Ra for acute anterior cruciate ligament knee injury: a randomized controlled pilot trial (NCT00332254). Osteoarthritis Cartilage. 2012 Apr;20(4):271-8.	NR	4	
2	Palmieri B, Rottigni V, Iannitti T. Preliminary study of highly cross-linked hyaluronic acid-based combination therapy for management of knee osteoarthritis-related pain. Drug Des Devel Ther. 2013,7:7-12	NR	5	Variofill
3	Atchia I, Kane D, Reed MR, Isaacs JD, Birrell F. Efficacy of a single ultrasound-guided injection for the treatment of hip osteoarthritis. Ann Rheum Dis 2011:70:110-116.	NR	5	Durolane
4	Mariani E, Canella V, Cattini L, Kon E, Marcacci M, Di Matteo B, Pulsatelli L, Filardo G.Leukocyte-Rich Platelet-Rich Plasma Injections Do Not Up-Modulate Intra-Articular Pro-Inflammatory Cytokines in the Osteoarthritic Knee. PLoS One. 2016 Jun 3;11(6):e0156137.	NR	4	
5	Schiraldi C, Stellavato A, de Novellis F, La Gatta A, De Rosa M. Hyaluronan viscosupplementation: state of the art and insight into the novel cooperative hybrid complexes based on high and low molecular weight HA of potential interest in osteoarthritis treatment. Clin Cases Miner Bone Metab. 2016 Jan-Apr;13(1):36-7.	NR	1	
6	**Rivera F. Single intra-articular injection of high molecular weight hyaluronic acid for hip osteoarthritis. J Orthop Traumatol. 2016;17:21-6.**	**R**	**9**	**Coxarthrum**
7	Iannitti T, Rottigni V, Palmieri B. A pilot study to compare two different hyaluronic acid compounds for treatment of knee osteoarthritis. Int J Immunopathol Pharmacol. 2012 Oct-Dec;25(4):1093-8.	NR	5	Variofill, Synvisc
8	Wen ZH, Chang YC, Jean YH. Excitatory amino acid glutamate: role in peripheral nociceptive transduction and inflammation in experimental and clinical osteoarthritis. Osteoarthritis Cartilage. 2015 Nov;23(11):2009-16	NR	5	
9	Yu SP, Hunter DJ. Emerging drugs for the treatment of knee osteoarthritis. Expert Opin Emerg Drugs. 2015 Sep;20(3):361-78.	NR	1	
10	Legre-Boyer V. Viscosupplementation: Techniques, indications, results. Orthop Traumatol Surg Res. 2015;101:S101-S108.	NR	1	
11	Kandel L, Dolev Y, Shimonov R, Rivkin G, Liebergall M, Mattan Y, Chevalier X. Safety and efficacy of liposome intra-articular injection in moderate knee osteoarthritis a prospective randomized double-blinded study. American College of Rheumatology ACR Annual Meeting 2014. Abstract 2234	NR	2	
12	Campisi M, Galesso D, Mero A, Pasut G. Development of a new hyaluronic acid-calcitonin conjugate for the local treatment of osteoarthritis. Osteoarthritis and Cartilage. 2014;22(Suppl):S475-S476 DOI: http://dx.doi.org/10.1016/j.joca.2014.02.903	NR	5	HA crosslinked
13	Anitua E, Sánchez M, Aguirre JJ, Prado R, Padilla S, Orive G. Efficacy and safety of plasma rich in growth factors intra-articular infiltrations in the treatment of knee osteoarthritis. Arthroscopy. 2014 Aug;30(8):1006-17.	NR	1	5
14	Kandel L, Dolev Y, Rivkind G, Liebergall M, Mattan Y, Barenholz Y, Shimonov R, Chevalier X. Safety and efficacy of MM-II, an intra-articular injection of liposomes, in moderate knee osteoarthritis. Prospective randomized double-blinded study. Osteoarthritis and cartilage 2014;22 (Suppl):S193	NR	4	
15	Chevalier X., Migliore A. Safety and tolerability of intra-articular hyaluronic acid injection (Sinovial®) in experimental and clinical practice. European Journal of Inflammation. 2013;11(3):573-580	NR	5	Sinovial
16	Orth P. Current perspectives in stem cell research for knee cartilage repair. Stem Cells Cloning. 2014;7:1-17.	NR	1	
17	Shen X. The safety and efficacy of intra-articular dual molecular weighted hyaluronic Acid in the treatment of knee osteoarthritis: the I.d.e.h.a. Study. Orthop Rev (Pavia). 2013;5:e33.	NR	5	RenehaVis
18	Evans CH. Progress in intra-articular therapy. Nat Rev Rheumatol.	NR	1	

User query # 1: (hyaluron* AND osteoarthritis AND "synovial joint" AND intraarticular AND human AND "clinical trial"				
Citation		**Relevance NR=non-relevant R=relevant**	**Reason for non-relevance or Appraisal**	
	2014;10:11-22.			
19	Reid MC. Viscosupplementation for osteoarthritis: a primer for primary care physicians. Adv Ther. 2013;30:967-86.	NR	1	
20	"In vitro effects of hyaluronate on adipose tissue-derived mesenchymal stem cells." No author and source available.	NR	3	4
21	Shusharin AG, Polovinka MP, Shevela AI, Vlasov V. Evaluating the effectiveness of combined therapy of patients with hip osteoarthritis and concomitant osteoporosis. IOF Regionals - 3rd Asia-Pacific Osteoporosis Meeting, 2012:S829	NR	6	
22	Manara M, Bortoluzzi A, Favero M, Prevete I, Sciré CA, Bagnato G, Bianchi G, Ceruso M, Checchia GA, D'Avola GM, Di Giacinto G, Frediani B, Lombardi A, Mannoni A, Mascheroni G, Matucci Cerinic M, Punzi L, Richelmi P, Scarpellini M, Torretta F, Migliore A, Ramonda R, Minisola G; Italian Society for Rheumatology. Italian Society for Rheumatology recommendations for the management of hand osteoarthritis. Reumatismo. 2013 Oct 31;65(4):167-85	NR	1	
23	Barry F, Murphy M. Mesenchymal stem cells in joint disease and repair. Nat Rev Rheumatol. 2013 Oct;9(10):584-94.	NR	1	
24	Cianflocco AJ. Viscosupplementation in patients with osteoarthritis of the knee. Postgrad Med. 2013;125:97-105.	NR	1	
25	de Campos GC, Rezende MU, Pailo AF, Frucchi R, Camargo OP. Adding Triamcinolone Improves Viscosupplementation: A Randomized Clinical Trial. Clin Orthop Relat Res. 2013,471:613–620	NR	5	hylan G-F 20
26	Courtney P, Doherty M. Joint aspiration and injection and synovial fluid analysis. Best Practice & Research Clinical Rheumatology 2009,23:161–192	NR	1	
27	Oliviero F, Ramonda R, Punzi L. New horizons in osteoarthritis. Swiss Med Wkly. 2010 Sep 17,140:w13098.	NR	1	
28	Clegg TE, Caborn D, Mauffrey C. Viscosupplementation with hyaluronic acid in the treatment for cartilage lesions: a review of current evidence and future directions. Eur J Orthop Surg Traumatol. 2013 Feb,23(2):119-24.	NR	1	
29	Hirsch G, Kitas G, Klocke R. Intra-articular corticosteroid injection in osteoarthritis of the knee and hip: factors predicting pain relief--a systematic review. Semin Arthritis Rheum. 2013 Apr;42(5):451-73.	NR	1	
30	Vlad V, Iagnocco A. Ultrasound of the knee in rheumatology. Med Ultrason. 2012 Dec;14(4):318-25.	NR	4	
31	Guermazi A, Roemer FW, Haugen IK, Crema MD, Hayashi D. MRI-based semiquantitative scoring of joint pathology in osteoarthritis. Nat Rev Rheumatol. 2013 Apr;9(4):236-51.	NR	4	
32	Frizziero A, Giannotti E, Oliva F, Masiero S, Maffulli N. Autologous conditioned serum for the treatment of osteoarthritis and other possible applications in musculoskeletal disorders. Br Med Bull. 2013;105:169-84	NR	4	
33	Hochberg M, Chevalier X, Henrotin Y, Hunter DJ, Uebelhart D. Symptom and structure modification in osteoarthritis with pharmaceutical-grade chondroitin sulfate: what's the evidence? Curr Med Res Opin. 2013,29(3):259–267	NR	1	
34	Eyles J, Lucas BR, Hunter DJ. Targeting care: tailoring nonsurgical management according to clinical presentation. Rheum Dis Clin North Am. 2013 Feb;39(1):213-33.	NR	1	
35	Schaible HG. Mechanisms of Chronic Pain in Osteoarthritis. Curr Rheumatol Rep. 2012 Jul 15. [Epub ahead of print]	NR	1	
36	IBSA. The pathway of pain - from basic science to clinical approach. EULAR congress 2011	NR	2	
37	Bennell KL, Hunter DJ, Hinman RS. Management of osteoarthritis of the knee. BMJ. 2012;345:e4934	NR	1	
38	Bono JV, Robbins CE, Mehio AK, Aghazadeh M, Talmo CT. Pharmacologic pain management before and after total joint replacement of the hip and knee. Clin Geriatr Med. 2012 Aug;28(3):459-70.	NR	1	
39	Rousseau JC, Delmas PD. Biological markers in osteoarthritis. Nat Clin Pract Rheumatol. 2007;3(6):346-56.	NR	1	
40	Tuncer T, Fatih H, Kacar C, Altan L, Atik OS, Aydin AT, Ayhan FF, Cörekci Yanik B, Durmaz B, Eskiyurt N, Genc H, Gökce Kutsal Y, Günaydin R, Hepgüler S, Hizmetli S, Kaya T, Kurtais Y, Ölmez N, Saridogan M, Sindel D, Sonel Tur B, Sütbeyaz S, Sendur ÖF, Ugurlu H, Ünlü Z. Evidence-	NR	1	

User query # 1: (hyaluron* AND osteoarthritis AND "synovial joint" AND intraarticular AND human AND "clinical trial"				
Citation		**Relevance NR=non-relevant R=relevant**	**Reason for non-relevance or Appraisal**	
	based recommendations for the management of knee osteoarthritis: A consensus report of the Turkish league against rheumatism. Turk J Rheumatol 2012;27(1):1-17			
41	Kraus VB, Birmingham J, Stabler TV, Feng S, Taylor DC, Moorman CT 3rd, Garrett WE, Toth AP. Effects of intraarticular IL1-Ra for acute anterior cruciate ligament knee injury: a randomized controlled pilot trial (NCT00332254). Osteoarthritis Cartilage. 2012 Apr;20(4):271-8.	NR	4	
42	Baker JF, Solayar GN, Byrne DP, Moran R, Mulhall KJ. Analgesic Control and Functional Outcome After Knee Arthroscopy: Results of a Randomized Double-Blinded Trial Comparing a Hyaluronic Acid Supplement With Bupivacaine. Clin J Sport Med 2012,22:109–115	NR	4	post-arthrocopy
43	Tan YK, Conaghan PG. Insights into osteoarthritis from MRI. Int J Rheum Dis. 2012 Feb;15(1):1-7.	NR	4	
44	Mandel NS, Mandel GS, Carroll DJ, Halverson PB. Calcium pyrophosphate crystal deposition. An in vitro study using a gelatin matrix model. Arthritis Rheum. 1984 Jul;27(7):789-96.	NR	4	
45	Peng PW, Cheng P. Ultrasound-guided interventional procedures in pain medicine: a review of anatomy, sonoanatomy, and procedures. Part III: shoulder. Reg Anesth Pain Med. 2011 Nov-Dec;36(6):592-605.	NR	1	
46	Matthews GL, Hunter DJ. Emerging drugs for osteoarthritis. Expert Opin Emerg Drugs. 2011	NR	1	
47	Migliore A, Granata M, Tormenta S, Laganà B, Piscitelli P, Bizzi E, Massafra U, Alimonti A, Maggi C, De Chiara R, Iannessi F, Sanfilippo A, Sotera R, Scapato P, Carducci S, Persod P, Denaro S, Camminiti M, Pagano MG, Bagnato G, Iolascon G. Hip viscosupplementation under ultra-sound guidance riduces NSAID consumption in symptomatic hip osteoarthritis patients in a long follow-up. Data from Italian registry. Eur Rev Med Pharmacol Sci. 2011 Jan;15(1):25-34.	NR	5	hylan G-F 20
48	Wang HM, Liu JN, Zhao Y. Progress on integrated Chinese and Western medicine in the treatment of osteoarthritis. Chin J Integr Med. 2010 Aug;16(4):378-84.	NR	1	
49	Wu MX, Li XH, Lin MN, Jia XR, Mu R, Wan WR, Chen RH, Chen LH, Lin WQ, Huang CY, Zhang XR, Hong KD, Li L, Liu XX. Clinical study on the treatment of knee osteoarthritis of Shen-Sui insufficiency syndrome type by electroacupuncture. Chin J Integr Med. 2010 Aug;16(4):291-7.	NR	4	
50	Migliore A, Giovannangeli F, Bizzi E, Massafra U, Alimonti A, Laganà B, Diamanti Picchianti A, Germano V, Granata M, Piscitelli P. Viscosupplementation in the management of ankle osteoarthritis: a review. Arch Orthop Trauma Surg 2011,131:139–147	NR	1	
51	Sapundzhiev L, Lambova S. Current views on the role of viscosupplementation in osteoarthritis with different localizations.	NR	1	
52	Migliore A, Giovannangeli F, Granata M, Laganà B. Hylan g-f 20: review of its safety and efficacy in the management of joint pain in osteoarthritis. Clin Med Insights Arthritis Musculoskelet Disord. 2010 Sep 20,3:55-68.	NR	5	hylan G-F 20
53	Thein R, Haviv B, Kidron A, Bronak S. Intra-articular injection of hyaluronic acid following arthroscopic partial meniscectomy of the knee. Orthopedics. 2010 Oct 11,33(10).	NR	5	Viscoseal
54	Shimizu M, Higuchi H, Takagishi K, Shinozaki T, Kobayashi T. Clinical and biochemical characteristics after intra-articular injection for the treatment of osteoarthritis of the knee: prospective randomized study of sodium hyaluronate and corticosteroid. J Orthop Sci. 2010 Jan,15(1):51-6.	NR	5	Artz dispo
55	Malemud CJ. Anticytokine therapy for osteoarthritis: evidence to date. Drugs Aging. 2010 Feb 1;27(2):95-115.	NR	4	
56	Mulvaney SW. A review of viscosupplementation for osteoarthritis of the hip and a description of an ultrasound-guided hip injection technique. Curr Sports Med Rep. 2009 Nov-Dec,8(6):291-4.	NR	1	
57	Habib GS, Saliba W, Nashashibi M. Local effects of intra-articular corticosteroids. Clin Rheumatol. 2010 Apr,29(4):347-56.	NR	4	
58	Abate M, Pulcini D, Di Iorio A, Schiavone C. Viscosupplementation with intra-articular hyaluronic acid for treatment of osteoarthritis in the elderly. Curr Pharm Des. 2010,16(6):631-40. Review.	NR	1	
59	Radecki J, Kim SS, Vad VB. Synvisc-One® for the treatment of knee osteoarthritis. Int J Clin Rheumatol. 2009;4(6):631-639	NR	5	Synvisc One
60	Altman RD. Non-avian-derived hyaluronan for the treatment of	NR	1	

User query # 1: (hyaluron* AND osteoarthritis AND "synovial joint" AND intraarticular AND human AND "clinical trial"				
Citation		**Relevance NR=non-relevant R=relevant**	**Reason for non-relevance or Appraisal**	
	osteoarthritis of the knee. Expert Rev Clin Immunol. 2010 Jan,6(1):21-7. Review.			
61	Conduah AH, Baker L III, Baker CL jr. Managing joint pain in osteoarthritis: safety and efficacy of hylan G-F 20. Journal of Pain Research 2009,2:87–98	NR	1	
62	Valdes AM. Molecular pathogenesis and genetics of osteoarthritis: Implications for personalized medicine. Future Medicine 2010;7(1):49-63	NR	1	
63	Ostałowska A, Nowak D, Święchowicz S, Birkner E, Brenk A, Kasperczyk S, Dobrakowski M, Machoń A. Assessment of knee function and biochemical parameters of articular fluid and peripheral blood in gonarthrosis patients following intra-articular administration of hyaluronic acid. Pol Orthop Traumatol. 2013;78:173-81.	NR	5	Euflexxa
64	Chareancholvanich K, Pornrattanamaneewong C, Narkbunnam R. Increased cartilage volume after injection of hyaluronic acid in osteoarthritis knee patients who underwent high tibial osteotomy. Knee Surg Sports Traumatol Arthrosc. 2014 Jun;22(6):1415-23.	NR	5	Hyalgan
65	Bum Park Y, Ah Choi W, Kim YK, Chul Lee S, Hae Lee J. Accuracy of blind versus ultrasound-guided suprapatellar bursal injection. J Clin Ultrasound. 2012 Jan,40(1):20-5.	NR	4	
66	Gadek A, Miśkowiec K, Wordliczek J, Liszka H. [Effectiveness and safety of intra-articular use of hyaluronic acid (Suplasyn) in the treatment of knee osteoarthritis]. [Article in Polish]. Przegl Lek. 2011;68(6):307-10.	NR	6	
67	Thein R, Haviv B, Kidron A, Bronak S. Intra-articular injection of hyaluronic acid following arthroscopic partial meniscectomy of the knee. Orthopedics. 2010 Oct 11,33(10).	NR	5	Viscoseal
68	**Foti C, Cisari C, Carda S, Giordan N, Rocco A, Frizziero A, Della Bella G. A prospective observational study of the clinical efficacy and safety of intra-articular sodium hyaluronate in synovial joints with osteoarthritis. Eur J Phys Rehabil Med. 2011,47:407-15**	**R**	**9**	Hyalubrix
69	Tang YL, Zhu GQ, Hu L, Zheng M, Zhang JY, Shi ZD, Liang XH. Effects of intra-articular administration of sodium hyaluronate on plasminogen activator system in temporomandibular joints with osteoarthritis. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2010 Apr,109(4):541-7	NR	5	Sofast
70	Succar P, Medynskyj M, Breen EJ, Batterham T, Molloy MP, Herbert BR. Priming Adipose-Derived Mesenchymal Stem Cells with Hyaluronan Alters Growth Kinetics and Increases Attachment to Articular Cartilage. Stem Cells Int. 2016;2016:9364213.	NR	3	
71	Schroeppel JP, Crist JD, Anderson HC, Wang J. Molecular regulation of articular chondrocyte function and its significance in osteoarthritis. Histol Histopathol. 2011;26(3):377-94.	NR	1	

7.6 Clinicaltrials.gov

No information concerning sort order displayed.

Search query: Osteoarthritis hyaluronan				
Citation		**Relevance NR=non-relevant R=relevant**	**Reason for non-relevance or Appraisal**	
Study: 1	Title: Effects of Hyaluronic Acid vs. Hyaluronic Acid on Knee Osteoarthritis Recruitment: Active, not recruiting Study Results: No Results Available Conditions: Physical Activity Interventions: Other: hyaluronic acid|Other: hyaluronic acid combined corticosteroid URL: https://ClinicalTrials.gov/show/NCT02625727	NR	6	
Study: 2	Title: Platelet Rich Plasma vs Hyaluronic-Acid in Hip OA (Osteoarthritis) Recruitment: Enrolling by invitation Study Results: No Results Available Conditions: Hip Osteoarthritis Interventions:	NR	5	Supartz

Search query: Osteoarthritis hyaluronan				
Citation		**Relevance NR=non-relevant R=relevant**	**Reason for non-relevance or Appraisal**	
	Biological: PRP|Device: Hyaluronic Acid URL: https://ClinicalTrials.gov/show/NCT01920152			
Study: 3	Title: Hyaluronan Versus NaCl 20 Ml Versus Placebo in Knee Osteoarthritis Recruitment: Active, not recruiting Study Results: No Results Available Conditions: Osteoarthritis, Knee Interventions: Drug: Injection of Hyaluronan or Saline URL: https://ClinicalTrials.gov/show/NCT00144820	NR	6	
Study: 4	Title: Cingal Study for Knee Osteoarthritis Recruitment: Completed Study Results: No Results Available Conditions: Knee Osteoarthritis Interventions: Device: Hyaluronic Acid and TH|Device: Hyaluronic Acid|Device: Saline URL: https://ClinicalTrials.gov/show/NCT01891396	NR	5	crosslinked
Study: 5	Title: Comparative Study of Safety and Efficacy of Two Hyaluronic Acids for the Treatment of Knee Osteoarthritis Recruitment: Completed Study Results: No Results Available Conditions: Knee Osteoarthritis Interventions: Device: Hyaluronic acid, stabilized|Device: Hyaluronic acid URL: https://ClinicalTrials.gov/show/NCT01295580	NR	5	Durolane, Artz
Study: 6	Title: A Study of Hyaluronan for the Treatment of Osteoarthritis in the Thumb Recruitment: Completed Study Results: No Results Available Conditions: Osteoarthritis Interventions: Drug: Synvisc (Hylan G-F20; hyaluronan injection)|Drug: Bupivicaine (local anesthesia injection)|Drug: Kenalog (triamcinolone; corticosteroid injection) URL: https://ClinicalTrials.gov/show/NCT00398866	NR	5	hylan G-F 20
Study: 7	Title: A Study of the Efficacy and Safety of EUFLEXXA™ for Treatment of Painful Osteoarthritis of the Knee Recruitment: Completed Study Results: Has Results Conditions: Osteoarthritis, Knee Interventions: Device: EUFLEXXA™|Device: placebo URL: https://ClinicalTrials.gov/show/NCT00379236	NR	5	Eufelxxa
Study: 8	Title: Investigation of 1.2% Sodium Hyaluronate for Treatment of Painful Chronic Osteoarthritis of the Knee Recruitment: Completed Study Results: Has Results Conditions: Osteoarthritis of the Knee Interventions: Device: 1.2% Sodium Hyaluronate|Device: Buffered Saline URL: https://ClinicalTrials.gov/show/NCT00988091	NR	5	1.2% HA
Study: 9	Title: Gel-One Treatment in Knee Osteoarthritis Recruitment: Completed Study Results: No Results Available Conditions: Osteoarthritis Knee Interventions: Device: Gel-One|Device: PBS URL: https://ClinicalTrials.gov/show/NCT01934218	NR	5	crosslinked
Study: 10	Title: The Efficacy Study of Sodium Hyaluronate to Treat Symptomatic Hip Osteoarthritis Recruitment: Terminated Study Results: No Results Available Conditions: Symptomatic Hip Osteoarthritis Interventions: Drug: Sodium hyaluronate|Drug: placebo injection URL: https://ClinicalTrials.gov/show/NCT00330135	NR	5	Adant
Study: 11	Title: Prediction of Response to Intra-articular Injections of Hyaluronic Acid for Knee Osteoarthritis Recruitment: Completed Study Results: Has Results Conditions: Osteoarthritis, Knee Interventions: Device: hylan G-F 20|Device: 1% sodium hyaluronate URL: https://ClinicalTrials.gov/show/NCT01557868	NR	5	
Study: 12	Title: Gait Patterns After Intraarticular Treatment of Patients With Osteoarthritis of the Knee Recruitment: Completed Study Results: No Results Available Conditions: Osteoarthritis Interventions: Drug: hyaluronic acid|Drug: triamcinolone URL: https://ClinicalTrials.gov/show/NCT00731289	NR	5	Durolane
Study: 13	Title: Comparative Effectiveness of Hyaluronic Acid Injections for Management of Knee Osteoarthritis Recruitment: Not yet recruiting Study Results: No Results Available Conditions: Knee Osteoarthritis Interventions: Drug: Hyaluronic Acid injections URL: https://ClinicalTrials.gov/show/NCT02671565	NR	6	Orthovisc, Euflexxa, Monovisc, Hyglan or Supartz
Study: 14	Title: Effectiveness of Two Hyaluronic Acids in Osteoarthritis of the Knee Recruitment: Terminated Study Results: No Results Available Conditions: Knee Osteoarthritis Interventions: Device: 3ml hyaluronic acid (DUROLANE)|Device: 2ml hyaluronic acid, (HYALGAN) URL: https://ClinicalTrials.gov/show/NCT01543737	NR	5	Durolane, Hyalgan

Search query: Osteoarthritis hyaluronan				
Citation		**Relevance NR=non-relevant R=relevant**	**Reason for non-relevance or Appraisal**	
Study: 15	Title: Efficacy of 3 Weekly Injections of Hyaluronate in Patients With Ankle Osteoarthritis Recruitment: Completed Study Results: Has Results Conditions: Osteoarthritis Interventions: Drug: sodium hyaluronate URL: https://ClinicalTrials.gov/show/NCT00918736	NR	5	Hyalgan
Study: 16	Title: Efficacy and Safety of Intraarticular Injections of Hyalgan in the Treatment of Osteoarthritis of the Knee Recruitment: Completed Study Results: No Results Available Conditions: Osteoarthritis Interventions: Device: Hyalgan|Device: sterile normal saline URL: https://ClinicalTrials.gov/show/NCT01319461	NR	5	Hyalgan
Study: 17	Title: Efficacy and Safety of 3 Different Dosage Regimens of Hyaluronic Acid in Patients With Knee Osteoarthritis (OA) Recruitment: Completed Study Results: No Results Available Conditions: Osteoarthritis of the Knee Interventions: Drug: Hyaluronic acid 5 x 2.5 ml|Drug: Hyaluronic acid 1 x 5 ml|Drug: Hyaluronic acid 2 x 5 ml URL: https://ClinicalTrials.gov/show/NCT01290497	NR	5	Adant
Study: 18	Title: Hyaluronic Acid vs Platelet Rich Plasma: Effects on Clinical Outcomes and Intra-articular Biology for the Treatment of Knee Osteoarthritis Recruitment: Completed Study Results: No Results Available Conditions: Osteoarthritis, Knee Interventions: Biological: Platelet-rich Plasma (PRP)|Biological: Hyaluronic Acid URL: https://ClinicalTrials.gov/show/NCT02588872	NR	5	0.8% HA
Study: 19	Title: Intra-articular Hyaluronic Acid in Mild to Moderate Knee Osteoarthritis Recruitment: Completed Study Results: No Results Available Conditions: Osteoarthritis Interventions: Drug: Hyaluronic Acid URL: https://ClinicalTrials.gov/show/NCT01239810	NR	5	Ostenil
Study: 20	Title: Comparison of Autologous Platelet-rich Plasma With Hyaluronic Acid for the Treatment of Osteoarthritis of the Knee Joint Recruitment: Completed Study Results: No Results Available Conditions: Osteoarthritis, Knee Interventions: Biological: PRP|Drug: Hyaluronic acid URL: https://ClinicalTrials.gov/show/NCT02211521	NR	6	
Study: 21	Title: Treatment of Knee Osteoarthritis With Allogenic Mesenchymal Stem Cells Recruitment: Completed Study Results: Has Results Conditions: Osteoarthritis, Knee|Arthritis of Knee|Knee Osteoarthritis Interventions: Other: Allogenic mesenchymal stromal cells injection|Drug: Hyaluronic Acid URL: https://ClinicalTrials.gov/show/NCT01586312	NR	5	Durolane
Study: 22	Title: Comparative Assessment of Viscosupplementation With Polynucleotides and Hyaluronic Acid Recruitment: Recruiting Study Results: No Results Available Conditions: Osteoarthritis Interventions: Device: Polynucleotide - PNHA - Newart|Device: Hyaluronic acid - HA - Ialart URL: https://ClinicalTrials.gov/show/NCT02417610	NR	5	Hyalart
Study: 23	Title: Efficacy and Safety Study in Patients Suffering From Knee Osteoarthritis Recruitment: Withdrawn Study Results: No Results Available Conditions: Knee Osteoarthritis Interventions: Device: Chondroitin sulfate and sodium hyaluronate|Drug: Hyaluronan URL: https://ClinicalTrials.gov/show/NCT01469507	NR	5	Hyalgan
Study: 24	Title: SUPARTZ Versus Placebo in Osteoarthritis of the Shoulder Recruitment: Completed Study Results: No Results Available Conditions: Osteoarthritis of the Shoulder Interventions: Device: SUPARTZ|Device: Phosphate Buffered Saline URL: https://ClinicalTrials.gov/show/NCT00479687	NR	5	Supartz
Study: 25	**Title: ORTHOVISC Shoulder RCT Recruitment: Completed Study Results: Has Results Conditions: Glenohumeral Osteoarthritis Interventions: Device: Orthovisc|Drug: Control|Drug: Control URL: https://ClinicalTrials.gov/show/NCT00436969 No publication found. Study results posted.**	**R**	**6**	**Orthovisc**
Study: 26	Title: Effect Of Plasma Rich In Growth Factors In Knee Osteoarthritis Recruitment: Completed Study Results: No Results Available Conditions: Knee Osteoarthritis Interventions: Biological:	NR	5	Durolane

Search query: Osteoarthritis hyaluronan				
Citation		**Relevance NR=non-relevant R=relevant**	**Reason for non-relevance or Appraisal**	
	Plasma rich in growth factors|Drug: Hyaluronic Acid URL: https://ClinicalTrials.gov/show/NCT02039531			
Study: 27	**Title: Treatment of Knee Osteoarthritis by Intra-articular Injection of Bone Marrow Mesenchymal Stem Cells Recruitment: Active, not recruiting Study Results: No Results Available Conditions: Osteoarthritis Interventions: Drug: Hyaluronic acid|Biological: 10 million Bone marrow mesenchimal stem cells|Biological: 100 million Bone marrow mesenchimal stem cells URL: https://ClinicalTrials.gov/show/NCT02123368 No publication found. No study results posted.**	**R**	**6**	**HyalOne**
Study: 28	Title: A Double-blind RCT of a Single Dose of Hyaluronan in the Treatment of Osteoarthritis of the Ankle Recruitment: Completed Study Results: No Results Available Conditions: Osteoarthritis Interventions: Device: hyaluronate intra-articular injection|Device: placebo injection URL: https://ClinicalTrials.gov/show/NCT01243814	NR	5	Supartz
Study: 29	Title: Trial to Assess the Structural Effect and Long-term Symptomatic Relief of Intra-articular Injections of Hyaluronic Acid in Primary Knee OA Recruitment: Recruiting Study Results: No Results Available Conditions: Osteoarthritis Of Knee Interventions: Device: Intra-Articular Hyaluronic Acid|Device: Placebo URL: https://ClinicalTrials.gov/show/NCT02280538	NR	5	hylan G-F 20
Study: 30	Title: Medical Chitosan or Sodium Hyaluronate for Knee Osteoarthritis (CHOOSE) Recruitment: Recruiting Study Results: No Results Available Conditions: Osteoarthritis, Knee Interventions: Device: Medical Chitosan|Drug: Sodium Hyaluronate Injection URL: https://ClinicalTrials.gov/show/NCT02323451	NR	5	1% HA
Study: 31	Title: Daily Activity and Gait Analysis After Viscosupplement Injection Among Hip Osteoarthritis Patients Recruitment: Recruiting Study Results: No Results Available Conditions: Hip Osteoarthritis Interventions: Drug: Hyaluronan|Drug: Bupivacaine URL: https://ClinicalTrials.gov/show/NCT02086474	NR	5	Neovisc
Study: 32	Title: Safety and Effectiveness of Agilus (Hyaluronic Acid) for Ankle Osteoarthritis Recruitment: Terminated Study Results: No Results Available Conditions: OSTEOARTHRITIS Interventions: Device: Agilus|Device: Normal saline URL: https://ClinicalTrials.gov/show/NCT00642382	NR	6	Agilus
Study: 33	Title: A Study of Hyaluronate Injectable Viscosupplement for Treatment of Osteoarthritis of the Knee Recruitment: Active, not recruiting Study Results: No Results Available Conditions: Osteoarthritis Interventions: Device: Hyaluronate Injectable Viscosupplement|Device: Euflexxa IA injection|Device: Placebo URL: https://ClinicalTrials.gov/show/NCT02495857	NR	5	Eufelxxa
Study: 34	Title: TREAD-20: Trial of Hyalgan Three Injection-Regimen for the Treatment of Knee Pain Due to Osteoarthritis Recruitment: Completed Study Results: No Results Available Conditions: Osteoarthritis Interventions: Drug: Hyalgan (sodium hyaluronate) URL: https://ClinicalTrials.gov/show/NCT00130468	NR	5	
Study: 35	**Title: Intra-Articular Autologous Bone Marrow Mesenchymal Stem Cells Transplantation to Treat Mild to Moderate Osteoarthritis Recruitment: Recruiting Study Results: No Results Available Conditions: Osteoarthritis Interventions: Drug: Hyaluronic Acid|Biological: Autologous bone marrow-derived mesenchymal stem cells URL: https://ClinicalTrials.gov/show/NCT01459640 No publication found. No study results posted.**	**R**	**6**	**Orthovisc**
Study: 36	Title: The Impact of Hyaluronic Acid Injections on Osteoarthritic Knee Mechanics Recruitment: Active, not recruiting Study Results: No Results Available Conditions: Osteoarthritis, Knee Interventions: Device: Hyaluronic acid|Device: Placebo (Saline injection) URL: https://ClinicalTrials.gov/show/NCT00778076	NR	5	Suplasyn
Study: 37	Title: Identification and Characterization of the Biomarker in Synovial Fluid for Hyaluronic Acid Therapy in Osteoarthritis	NR	6	

Search query: Osteoarthritis hyaluronan				
Citation		**Relevance NR=non-relevant R=relevant**	**Reason for non-relevance or Appraisal**	
	Recruitment: Completed Study Results: No Results Available Conditions: Osteoarthritis Interventions: Other: proteomic analysis URL: https://ClinicalTrials.gov/show/NCT01813916			
Study: 38	Title: Safety and Effectiveness Study of Hyaluronic Acid for Osteoarthritis of the Knee Recruitment: Completed Study Results: No Results Available Conditions: Osteoarthritis Interventions: Device: MONOVISC URL: https://ClinicalTrials.gov/show/NCT00653432	NR	5	Monovisc
Study: 39	Title: Three Injections of EUFLEXXA (Sodium Hyaluronate) for Treatment of Chronic Shoulder Pain Associated With Osteoarthritis (OA) Recruitment: Completed Study Results: Has Results Conditions: Osteoarthritis Interventions: Drug: EUFLEXXA URL: https://ClinicalTrials.gov/show/NCT00969501	NR	5	Euflexxa
Study: 40	Title: A Study Comparing Viscosupplementation and Corticosteroid Injections for Knee Osteoarthritis Recruitment: Enrolling by invitation Study Results: No Results Available Conditions: Osteoarthritis, Knee Interventions: Device: Hylan G-F 20 (Synvisc One)|Drug: Methylprednisolone (Corticosteroid) URL: https://ClinicalTrials.gov/show/NCT01132677	NR	5	hylan G-F 20
Study: 41	**Title: Comparison of Hyaluronic Acid and Corticosteroid Intra-articular Injections for the Treatment of Osteoarthritis of the Hip Recruitment: Not yet recruiting Study Results: No Results Available Conditions: Coxarthrosis Interventions: Drug: Corticosterone URL: https://ClinicalTrials.gov/show/NCT01079455 Colen S 2010 published**	**R**	**9**	**HA 2%**
Study: 42	**Title: Study of Evaluating the Duration of Efficacy of One Intra Articular Injection of Sodium Hyaluronate 2.0% in Patients With Painful Osteoarthritis of the Knee Recruitment: Completed Study Results: No Results Available Conditions: Osteoarthritis Patient Interventions: Drug: Ostenil plus URL: https://ClinicalTrials.gov/show/NCT01288001 Abstract available. Siriraj Hospital; Bangkoknoi, Bangkok, Thailand**	**R**	**9**	**Ostenil Plus**
Study: 43	Title: Effects of Intraarticular Botulinum Toxin A in Ankle Osteoarthritis Recruitment: Completed Study Results: No Results Available Conditions: Ankle Osteoarthritis Interventions: Drug: Botulinum Toxin A (Allergan, Inc, Irvine CA)|Drug: Hyalgan (Hyalgan, Fidia , Italy) URL: https://ClinicalTrials.gov/show/NCT01760577	NR	5	Hyalgan
Study: 44	Title: Platelet Rich Plasma (PRP) as a Treatment for Knee Osteoarthritis PRP as a Treatment for Knee Osteoarthritis Recruitment: Not yet recruiting Study Results: No Results Available Conditions: Osteoarthritis of the Knee Interventions: Biological: Platelet Rich Plasma (Preparation Rich in Growth Factors)|Drug: Hyaluronic acid URL: https://ClinicalTrials.gov/show/NCT01270412	NR	5	Arthrease
Study: 45	Title: Efficacy and Safety of Repeated Intraarticular Injections of Hyaluronic Acid in Patients With OA of the Knee Recruitment: Completed Study Results: Has Results Conditions: Osteoarthritis of the Knee Interventions: Device: Hyaluronic acid|Other: Placebo URL: https://ClinicalTrials.gov/show/NCT00669032	NR	5	Adant
Study: 46	Title: Double-Blind,Randomized,Placebo-Controlled Efficacy & Safety Study of EUFLEXXA™ for Treatment of OA of the First CMC Recruitment: Completed Study Results: No Results Available Conditions: Osteoarthritis Interventions: Device: sodium hyaluronate|Device: placebo URL: https://ClinicalTrials.gov/show/NCT00423371	NR	5	Eufelxxa
Study: 47	Title: Efficacy Study of Intra-articular Hyaluronic Acid in the Knee Osteoarthritis Recruitment: Completed Study Results: No Results Available Conditions: Osteoarthritis, Knee Interventions: Device: Sinovial® (syringe containing sodium hyaluronate solution)|Device: Synvisc® (syringe containing Hylan G-F 20 solution) URL: https://ClinicalTrials.gov/show/NCT00556608	NR	5	hylan G-F 20
Study: 48	Title: Efficacy of Three Weekly Injections of a Bacterial-- Sourced	NR	5	Hyalgan

Search query: Osteoarthritis hyaluronan				
Citation		**Relevance NR=non-relevant R=relevant**	**Reason for non-relevance or Appraisal**	
	Hyaluronate on Pain and Function in Patients With Knee Osteoarthritis (OA) Recruitment: Completed Study Results: No Results Available Conditions: Hyaluronate|Osteoarthritis|Knee Interventions: Procedure: Hya-Joint|Procedure: Hyalgan URL: https://ClinicalTrials.gov/show/NCT01185444			
Study: 49	Title: TREAD-20 Extension - Treatment of Knee Pain Due to Osteoarthritis Recruitment: Completed Study Results: No Results Available Conditions: Osteoarthritis Interventions: Drug: Hyalgan (sodium hyaluronate) URL: https://ClinicalTrials.gov/show/NCT00830830	NR	5	Hyalgan
Study: 50	Title: Steroids, Hyaluronic Acid or Platelet Rich Plasma Versus Placebo for the Knee Osteoarthritis Recruitment: Recruiting Study Results: No Results Available Conditions: Osteoarthritis, Knee Interventions: Drug: Triamcort|Drug: Platelet-rich-plasma|Drug: Suplasyn1|Drug: Placebo URL: https://ClinicalTrials.gov/show/NCT02776514	NR	5	Suplasyn
Study: 51	Title: The Efficacy and Safety of Intraarticular Sodium Hyaluronate (Hyalgan) After Proximal Tibial Osteotomy in Treatment of Knee Osteoarthritis Patients Recruitment: Completed Study Results: No Results Available Conditions: Knee Osteoarthritis Interventions: Drug: Sodium Hyaluronate (Hyalgan)|Procedure: Osteotomy alone URL: https://ClinicalTrials.gov/show/NCT01267214	NR	5	Hyalgan
Study: 52	Title: Post-op Treatment With Hyaluronic Acid Injections Recruitment: Terminated Study Results: No Results Available Conditions: Meniscus Tear|Chondropathy/Degenerative Joint Disease (DJD) Interventions: Device: Euflexxa|Other: Saline URL: https://ClinicalTrials.gov/show/NCT01256788	NR	5	Eufelxxa
Study: 53	Title: To Look at the Characteristics of Synovial Fluid and Cartilage Matrix in Osteoarthritic Knee After Hyaluronic Acid Injection Recruitment: Recruiting Study Results: No Results Available Conditions: Knee Osteoarthritis Interventions: Drug: Euflexxa|Device: Magnetic Resonance Imaging (MRI) URL: https://ClinicalTrials.gov/show/NCT01895959	NR	5	Eufelxxa
Study: 54	Title: Intra-articular Corticosteroid Injection Compared With Single-Shot Hyaluronic Acid for Treatment of Osteoarthritis Knee Recruitment: Completed Study Results: No Results Available Conditions: Knee Osteoarthritis Interventions: Drug: Hylan G-F 20|Drug: Corticosteroid URL: https://ClinicalTrials.gov/show/NCT01874574	NR	5	hylan G-F 20
Study: 55	Title: Comparative Assessment of Intra-articular Knee Injections of Platelet-rich Plasma (PRP) and Hyaluronic Acid in the Treatment of Knee Osteoarthritis Recruitment: Recruiting Study Results: No Results Available Conditions: the Treatment of Knee Osteoarthritis Interventions: Drug: platelet-rich plasma|Drug: durolane URL: https://ClinicalTrials.gov/show/NCT01697423	NR	5	Durolane
Study: 56	Title: Non-Inferiority Study Comparing 3 Weekly Injections of SUPARTZ® vs 3 Weekly Injections of Euflexxa® for Knee OA Recruitment: Completed Study Results: Has Results Conditions: Osteoarthritis Interventions: Device: Supartz|Device: Euflexxa URL: https://ClinicalTrials.gov/show/NCT02110238	NR	5	Eufelxxa, Supartz
Study: 57	Title: Efficacy Study of "Go On" in Magnetic Resonance Imaging (MRI) Improvement in Osteoarthritis (OA) Knee Recruitment: Completed Study Results: No Results Available Conditions: Osteoarthritis Interventions: Drug: 25 mg sodium hyaluronate "GO ON"|Drug: normal saline,2 ml., intraarticular weekly for 5 weeks URL: https://ClinicalTrials.gov/show/NCT00750724	NR	5	Go-on
Study: 58	Title: A Study to Assess Safety and Efficacy of Umbilical Cord-derived Mesenchymal Stromal Cells in Knee Osteoarthritis Recruitment: Recruiting Study Results: No Results Available Conditions: Osteoarthritis Interventions: Biological: umbilical-cord mesenchymal stromal cells|Drug: Hyaluronic Acid URL: https://ClinicalTrials.gov/show/NCT02580695	NR	5	Durolane
Study: 59	Title: Gait, Stair Climbing and Postural Stability in Knee Osteoarthritis Patients After Hyaluronic Acid Injection Recruitment: Completed Study Results: No Results Available Conditions:	NR	5	Hyalgan

Search query: Osteoarthritis hyaluronan				
Citation		**Relevance NR=non-relevant R=relevant**	**Reason for non-relevance or Appraisal**	
	Bilateral Knee Osteoarthritis Interventions: Other: Hyaluronic acid URL: https://ClinicalTrials.gov/show/NCT02063373			
Study: 60	Title: Prospective Assessment of the Efficacy of Hyaluronate Knee Injections in Patients With Osteoarthritis Recruitment: Terminated Study Results: No Results Available Conditions: Knee Osteoarthritis Interventions: Drug: Hyalgan URL: https://ClinicalTrials.gov/show/NCT00323778	NR	5	Hyalgan
Study: 61	Title: Comparison Between Four Types of Single Dose Hyaluronic Acid Injection in Patients With Knee Osteoarthritis Recruitment: Recruiting Study Results: No Results Available Conditions: Osteoarthritis Interventions: Drug: Crespine gel|Drug: Intragel|Drug: Crespine plus gel|Drug: Monovisc URL: https://ClinicalTrials.gov/show/NCT01998308	NR	5	Monovisc
Study: 62	Title: Hymovis™ Versus Placebo in Knee Osteoarthritis Recruitment: Completed Study Results: No Results Available Conditions: Knee Osteoarthritis Interventions: Device: Hymovis Intra-articular Injection|Procedure: Phosphate Buffered Saline Injection URL: https://ClinicalTrials.gov/show/NCT01372475	NR	5	Hymovis
Study: 63	Title: Comparing One Intraarticular Injection of a Novel HYAJOINT Plus With Synvisc-One for the Treatment of Knee OA Recruitment: Completed Study Results: No Results Available Conditions: Knee Osteoarthritis Interventions: Device: HYAJOINT Plus|Device: Synvisc-One URL: https://ClinicalTrials.gov/show/NCT02686047	NR	5	Hya-Joint, hyalgan G-F 20
Study: 64	Title: HUPS: Hyalgan Use in Painful Shoulder Recruitment: Completed Study Results: No Results Available Conditions: Osteoarthritis of Shoulder Interventions: Drug: sodium hyaluronate URL: https://ClinicalTrials.gov/show/NCT00377624	NR	5	Hyalgan
Study: 65	Title: Repeat Injection of Cingal® for Osteoarthritis of the Knee Recruitment: Completed Study Results: No Results Available Conditions: Osteoarthritis of the Knee Interventions: Device: Cingal® URL: https://ClinicalTrials.gov/show/NCT02381652	NR	5	HA+steroid combination
Study: 66	Title: Intraarticular Injections of Platelet-rich Plasma in Pain's Treatment of the Osteoarthritic Knee Recruitment: Completed Study Results: No Results Available Conditions: Knee Osteoarthritis Interventions: Biological: Platelet rich plasma|Drug: Hyaluronic acid URL: https://ClinicalTrials.gov/show/NCT02448407	NR	5	Adant
Study: 67	**Title: Platelet-rich Plasma vs Viscosupplementation in the Treatment of Knee Articular Degenerative Pathology Recruitment: Completed Study Results: No Results Available Conditions: Knee Chondropathy|Osteoarthritis, Knee Interventions: Biological: PRP|Device: Hyaluronic acid URL: https://ClinicalTrials.gov/show/NCT01670578 Published: Filardo G 2015, Mariani E 2016**	**R**	**9**	**Hyalubrix**
Study: 68	Title: Clinical Trial of Autologous Adipose Tissue-Derived Mesenchymal Progenitor Cells (MPCs) Therapy for Knee Osteoarthritis Recruitment: Recruiting Study Results: No Results Available Conditions: Knee Osteoarthritis Interventions: Biological: Mesenchymal progenitor cells|Biological: Sodium Hyaluronate URL: https://ClinicalTrials.gov/show/NCT02162693	NR	6	
Study: 69	Title: Safety and Efficacy of an Injectable Medical Device to Treat Knee Osteoarthritis Recruitment: Completed Study Results: No Results Available Conditions: Knee Osteoarthritis Interventions: Device: MM-II|Device: DurolaneTM URL: https://ClinicalTrials.gov/show/NCT01365260	NR	5	Durolane
Study: 70	Title: Functional and Quality of Life Outcomes Following Viscosupplementation for Knee Osteoarthritis Recruitment: Terminated Study Results: No Results Available Conditions: Knee Osteoarthritis Interventions: Other: Subject outcomes following viscosupplementation of the knee URL: https://ClinicalTrials.gov/show/NCT01447303	NR	6	
Study: 71	Title: Effects of Synvisc on Cartilage in Knee Osteoarthritis (OA) Recruitment: Completed Study Results: No Results Available Conditions: Osteoarthritis Interventions: Device: Synvisc URL:	NR	5	hylan G-F 20

Search query: Osteoarthritis hyaluronan				
Citation		**Relevance NR=non-relevant R=relevant**	**Reason for non-relevance or Appraisal**	
	https://ClinicalTrials.gov/show/NCT00949494			
Study: 72	**Title: Effectiveness of a Knee Brace When Combined With Viscosupplementation in the Treatment of Knee Osteoarthritis Recruitment: Terminated Study Results: No Results Available Conditions: Knee Osteoarthritis Interventions: Other: Orthovisc|Device: DonJoy HA lite knee brace|Device: Orthovisc injections and DonJoy HA lite knee brace URL: https://ClinicalTrials.gov/show/NCT01478386 No publication found. No study results posted.**	**R**	**6**	**Orthovisc**
Study: 73	Title: The Effect of Intraaricular Knee Injections of Hyaluronic Acid (HA) on Bone and Cartilaginous Debris, as a Therapeutic Indicator Recruitment: Not yet recruiting Study Results: No Results Available Conditions: Osteoarthritis of the Knee Interventions: Drug: Sodium hyaluronate (hyaluronic acid) URL: https://ClinicalTrials.gov/show/NCT00422643	NR	5	Arthrease
Study: 74	Title: Safety and Effectiveness Study of a Non-Crosslinked HA Alkylamide HYADD(TM) 4 Hydrogel for Osteoarthritis of the Knee Recruitment: Active, not recruiting Study Results: No Results Available Conditions: Knee Osteoarthritis Interventions: Device: HYMOVIS|Device: Placebo URL: https://ClinicalTrials.gov/show/NCT02187549	NR	5	Hymovis
Study: 75	Title: An Investigation of ReNu™ Knee Injection in Patients With Osteoarthritis Recruitment: Recruiting Study Results: No Results Available Conditions: Osteoarthritis Interventions: Procedure: Knee injection|Device: ReNu amniotic allograft|Device: placebo saline|Device: Hyaluronic Acid URL: https://ClinicalTrials.gov/show/NCT02318511	NR	6	
Study: 76	Title: The Influence of Hyaluronic Acid Injection Following Knee Arthroscopy Recruitment: Not yet recruiting Study Results: No Results Available Conditions: Cartilage Damage Interventions: Drug: Sodium Hyaluronate 1%|Drug: Placebo URL: https://ClinicalTrials.gov/show/NCT02640144	NR	4	
Study: 77	Title: Sodium Hyaluronate Injection and Corticosteroids in Trochanteric Bursitis: a Randomized Controlled Study. Recruitment: Not yet recruiting Study Results: No Results Available Conditions: Osteoarthritis Interventions: Drug: Corticosteroids|Device: Hyaluronic acid URL: https://ClinicalTrials.gov/show/NCT02039804	NR	4	
Study: 78	Title: An Open Label Trial for Treating Carpometacarpal Osteoarthritis of the Thumb: Pilot Study Recruitment: Completed Study Results: Has Results Conditions: Carpometacarpal Osteoarthritis Interventions: Device: Synvisc (hylan G-F20) URL: https://ClinicalTrials.gov/show/NCT00198029	NR	5	hylan G-F 20
Study: 79	Title: A Clinical Trial to Evaluate the Safety and Efficacy of Retreatment With Intra-articular LBSA0103 Injections in the Patients With Osteoarthritis of the Knee Recruitment: Completed Study Results: No Results Available Conditions: Osteoarthritis of Knee Interventions: Drug: LBSA0103 (BDDE cross-linked sodium hyaluronate gel) URL: https://ClinicalTrials.gov/show/NCT02122601	NR	5	crosslinked
Study: 80	Title: Allogeneic Mesenchymal Stem Cells in Osteoarthritis Recruitment: Completed Study Results: No Results Available Conditions: Osteoarthritis of Knee Interventions: Biological: Ex-vivo cultured adult allogeneic MSCs|Biological: Plasmalyte-A URL: https://ClinicalTrials.gov/show/NCT01453738	NR	4	
Study: 81	Title: A Phase I, Prospective, Randomized, Open-label, Active-Controlled Clinical Trial for Safety Evaluation of Intra-articular Injection of RegenoGel-SP for the Treatment of Moderate to Severe Osteoarthritis Recruitment: Recruiting Study Results: No Results Available Conditions: Osteoarthritis Interventions: Device: intra-articular administration of RegenoGel-SP or hyaluronic acid (HA) URL: https://ClinicalTrials.gov/show/NCT02188771	NR	5	Euflexxa
Study: 82	Title: Autologous Plasma Rich in Growth Factors (PRGF) Treating the Symptomatic Knee OA Recruitment: Completed Study Results: No Results Available Conditions: Joint Disease	NR	5	Euflexxa

Search query: Osteoarthritis hyaluronan				
Citation		**Relevance NR=non-relevant R=relevant**	**Reason for non-relevance or Appraisal**	
	Interventions: Device: PRGF Intraarticular injection|Device: Hyaluronic Acid Intraarticular injection URL: https://ClinicalTrials.gov/show/NCT00782197			
Study: 83	Title: UCMSC Transplantation in the Treatment of Cartilage Damage Recruitment: Not yet recruiting Study Results: No Results Available Conditions: Cartilage Damage|Degenerative Osteoarthritis Interventions: Biological: umbilical cord mesenchymal stem cells|Device: Hyaluronic acid URL: https://ClinicalTrials.gov/show/NCT02776943	NR	6	
Study: 84	Title: Comparison of Two Application Regimens for Viscosupplementation Recruitment: Completed Study Results: No Results Available Conditions: Osteoarthritis Interventions: Drug: viscosupplementation 1+1+1|Drug: viscosupplementation 3 at once URL: https://ClinicalTrials.gov/show/NCT01824485	NR	5	Osteonil
Study: 85	Title: PRP vs HA Intra-articular Knee Injections for Cartilage Defects Recruitment: Not yet recruiting Study Results: No Results Available Conditions: Osteoarthritis Interventions: Procedure: HA|Procedure: PRP URL: https://ClinicalTrials.gov/show/NCT02012530	NR	6	
Study: 86	Title: Safety and Efficacy Study of MSB-CAR001 in Subjects 6 Weeks Post an Anterior Cruciate Ligament Reconstruction Recruitment: Active, not recruiting Study Results: No Results Available Conditions: Anterior Cruciate Ligament Injury|Osteoarthritis Interventions: Biological: MSB-CAR001 Combined With Hyaluronan|Drug: Hyaluronan URL: https://ClinicalTrials.gov/show/NCT01088191	NR	6	
Study: 87	**Title: The Knee Usual Care Evaluation Study Recruitment: Terminated Study Results: No Results Available Conditions: Knee Osteoarthritis Interventions: URL: https://ClinicalTrials.gov/show/NCT01905358 No publication found. No study results posted.**	**R**	**6**	**Synvisc®, Orthrovisc®, Euflexxa**
Study: 88	Title: Pilot Study of Therapy With Hylan G-F 20 Exercise Capacity Recruitment: Terminated Study Results: No Results Available Conditions: Knee Osteoarthritis Interventions: Device: Hylan G-F 20|Other: Control URL: https://ClinicalTrials.gov/show/NCT01810848	NR	5	hylan G-F 20
Study: 89	Title: A Safety Study of Hylan GF-20 to Treat Shoulder Osteoarthritis Recruitment: Active, not recruiting Study Results: No Results Available Conditions: Painful Shoulder Osteoarthritis Interventions: Device: Hylan GF-20 URL: https://ClinicalTrials.gov/show/NCT00253799	NR	5	hylan G-F 20
Study: 90	Title: Preparation Rich in Growth Factors (PRGF) Treatment for Osteoarthritis of the Knee Recruitment: Completed Study Results: No Results Available Conditions: Osteoarthritis of the Knee Interventions: Biological: PRGF|Drug: hyaluronic acid|Drug: placebo URL: https://ClinicalTrials.gov/show/NCT00728611	NR	5	Arthrease
Study: 91	Title: Microdrilling Surgery for Full Thickness Chondral Lesions of the Knee Augmented With Concentrated Bone Marrow Aspirate, Platelet Rich Plasma and Hyaluronic Acid Recruitment: Active, not recruiting Study Results: No Results Available Conditions: Unilateral Primary Osteoarthritis of Knee|Osteoarthritis Knee|Degeneration; Articular Cartilage, Knee|Degenerative Lesion of Articular Cartilage of Knee Interventions: Procedure: Microdrilling Surgery|Biological: Injections of BMAC + PRP + HA URL: https://ClinicalTrials.gov/show/NCT02285725	NR	5	HA+PRP
Study: 92	Title: Different Volumes of Durolane in Knee OA Recruitment: Completed Study Results: Has Results Conditions: Knee Osteoarthritis Interventions: Device: Durolane 3 ml, Durolane 4,5 ml, Durolane 6 ml URL: https://ClinicalTrials.gov/show/NCT01265459	NR	5	Durolane
Study: 93	Title: Prospective Single Center Open Label Study of Shoulder OA Pain Recruitment: Recruiting Study Results: No Results Available Conditions: Osteoarthritis Interventions: Device: Durolane URL: https://ClinicalTrials.gov/show/NCT02610504	NR	5	Durolane

Search query: Osteoarthritis hyaluronan				
Citation		**Relevance NR=non-relevant R=relevant**	**Reason for non-relevance or Appraisal**	
Study: 94	Title: Early Viscosupplementation After Partial Meniscectomy: a Randomized Controlled Trial Recruitment: Active, not recruiting Study Results: No Results Available Conditions: Meniscus Lesion Interventions: Device: hyaluronic acid|Procedure: meniscectomy alone URL: https://ClinicalTrials.gov/show/NCT02629380	NR	4	
Study: 95	Title: Allogeneic Mesenchymal Stem Cells for Osteoarthritis Recruitment: Completed Study Results: No Results Available Conditions: Osteoarthritis of Knee Joint Interventions: Biological: Ex- vivo cultured adult allogeneic MSCs|Biological: Plasmalyte-A URL: https://ClinicalTrials.gov/show/NCT01448434	NR	4	
Study: 96	Title: Durolane Versus Phosphate Buffered Saline (PBS) in Knee Osteoarthritis Recruitment: Terminated Study Results: No Results Available Conditions: Knee Osteoarthritis Interventions: Device: Durolane|Device: PBS URL: https://ClinicalTrials.gov/show/NCT01753830	NR	5	Durolane
Study: 97	Title: Platelet-Rich Plasma Intra-Articular Injection in Treating Hemophilic Arthropathy Recruitment: Completed Study Results: No Results Available Conditions: Hemophilia|Hemophilic Arthropathy Interventions: Biological: Platelet-Rich Plasma Intra-Articular Injection|Drug: Hyaluronic Acid Viscosupplementation URL: https://ClinicalTrials.gov/show/NCT02601170	NR	4	
Study: 98	Title: Clinical Trial to Evaluate the Use of Platelet Rich Plasma in Front Hyaluronic Acid in Coxarthrosis Recruitment: Recruiting Study Results: No Results Available Conditions: Coxarthrosis Interventions: Drug: Platelet rich plasma|Drug: Hylan G-F 20 URL: https://ClinicalTrials.gov/show/NCT02694146	NR	5	HA+PRP combination
Study: 99	Title: Intra-articular Hyaluronic Acid Injection for Therapy-resistant Patellofemoral Pain Syndrome Recruitment: Recruiting Study Results: No Results Available Conditions: Patellofemoral Pain Syndrome Interventions: Device: Hylan G-F 20 URL: https://ClinicalTrials.gov/show/NCT02613247	NR	5	hylan G-F 20
Study: 100	Title: Effectiveness Trial for Evaluating IAHA for PFPS Recruitment: Recruiting Study Results: No Results Available Conditions: Patellofemoral Pain Syndrome Interventions: Device: Intra-Articular Hyaluronic Acid-Euflexxa URL: https://ClinicalTrials.gov/show/NCT01811654	NR	5	Euflexxa
Study: 101	Title: The Efficacy of Viscosupplementation for Early Knee Osteoarthritis Recruitment: Recruiting Study Results: No Results Available Conditions: Knee Osteoarthritis Interventions: Device: Synvisc One|Other: Routine management URL: https://ClinicalTrials.gov/show/NCT01210742	NR	5	hylan G-F 20
Study: 102	Title: Randomized Evaluation of the Efficacy of Synvisc-One® for the Treatment of Patellofemoral Chondromalacia Recruitment: Recruiting Study Results: No Results Available Conditions: Chondromalacia Patella|Patellofemoral Pain Syndrome Interventions: Device: Synvisc-One™|Other: Sham Treatment URL: https://ClinicalTrials.gov/show/NCT01771952	NR	5	hylan G-F 20
Study: 103	Title: Safety and Efficacy Study of HYTOP® in the Treatment of Focal Chondral Defects. Recruitment: Recruiting Study Results: No Results Available Conditions: Focal Chondral Defect in Femoro-tibial Compartment of the Knee Joint. Interventions: Device: HYTOP® URL: https://ClinicalTrials.gov/show/NCT01791062	NR	4	
Study: 104	Title: ActaVisc and ActaVisc Mx Intra-articular Injection for Pain Associated With Osteoarthritis in the Knee Recruitment: Terminated Study Results: No Results Available Conditions: Osteoarthritis Interventions: Other: ActaVisc and ActaVisc Mx Intra-articular Injection URL: https://ClinicalTrials.gov/show/NCT00665574	NR	6	
Study: 105	Title: HyaloFAST Trial for Repair of Articular Cartilage in the Knee Recruitment: Recruiting Study Results: No Results Available Conditions: Defect of Articular Cartilage Interventions: Device: Hyalofast|Procedure: Microfracture URL: https://ClinicalTrials.gov/show/NCT02659215	NR	4	

Search query: Osteoarthritis hyaluronan				
Citation		**Relevance NR=non-relevant R=relevant**	**Reason for non-relevance or Appraisal**	
Study: 106	Title: The Effectiveness of Hylan GF-20 on Joint Reaction Forces and Kinematic Patterns During Gait in Patients With Knee Osteoarthritis Recruitment: Active, not recruiting Study Results: No Results Available Conditions: Osteoarthritis Interventions: Device: Hylan G-F 20 URL: https://ClinicalTrials.gov/show/NCT00147186	NR	5	hylan G-F 20
Study: 107	Title: The VENUS Clinical Study (Verifying the Effectiveness of the NUsurface® System) Recruitment: Recruiting Study Results: No Results Available Conditions: Meniscectomy|Osteoarthritis Interventions: Device: NUsurface® Meniscus Implant|Drug: NSAID's and Non-surgical Treatment Options|Drug: Intra-Articular Injections with Corticosteroids|Drug: Intra-Articular Injections with Hyaluronic Acid (HA) URL: https://ClinicalTrials.gov/show/NCT02136901	NR	5	hylan G-F 20
Study: 108	Title: Verifying the Effectiveness of the NUsurface® System Recruitment: Recruiting Study Results: No Results Available Conditions: Meniscectomy|Osteoarthritis Interventions: Device: NUsurface® Meniscus Implant|Drug: NSAID's and Non-surgical Treatment Options|Drug: Intra-Articular Injections with Corticosteroids|Drug: Intra-Articular Injections with Hyaluronic Acid (HA) URL: https://ClinicalTrials.gov/show/NCT02108496	NR	5	hylan G-F 20
Study: 109	Title: Viscosupplementation in Patients With Hemophilic Arthropathy Recruitment: Completed Study Results: No Results Available Conditions: Osteoarthritis|Hemarthrosis|Hemophilia A|Hemophilia B Interventions: Procedure: Joint lavage and viscosupplementation URL: https://ClinicalTrials.gov/show/NCT01748201	NR	4	
Study: 110	Title: Human Autologous MSCs for the Treatment of Mid to Late Stage Knee OA Recruitment: Recruiting Study Results: No Results Available Conditions: Osteoarthritis of Knee Interventions: Biological: 1 x 10^6 MSCs|Biological: 10 x 10^6 MSCs|Biological: 50 x 10^6 MSCs URL: https://ClinicalTrials.gov/show/NCT02351011	NR	4	
Study: 111	Title: Efficacy and Safety of LBSA0103 Versus Hyruan Plus Injection in Patients With Knee Osteoarthritis Recruitment: Completed Study Results: No Results Available Conditions: Osteoarthritis of the Knee Interventions: Drug: Placebo|Drug: Hyruan Plus|Drug: LBSA0103 URL: https://ClinicalTrials.gov/show/NCT01510535	NR	5	Hyruan Plus
Study: 112	Title: A Study on Visco-antalgic Intra-articular Administration in Symptomatic Knee Osteoarthritis Recruitment: Recruiting Study Results: No Results Available Conditions: Knee Osteoarthritis Interventions: Drug: JTA-004 intra-articular injection|Device: Reference product intra-articular injection URL: https://ClinicalTrials.gov/show/NCT02740231	NR	6	
Study: 113	Title: Outcome Following Hylan F- 20 (Synvisc) + Corticosteroid Injections for the Treatment of Osteoarthritis of the Knee Recruitment: Completed Study Results: No Results Available Conditions: Osteoarthritis, Knee Interventions: Drug: Hylan F- 20 URL: https://ClinicalTrials.gov/show/NCT00312533	NR	5	hylan G-F 20
Study: 114	Title: The Effect of Platelet-rich Plasma in Patients With Osteoarthritis of the Knee Recruitment: Completed Study Results: No Results Available Conditions: Osteoarthritis Interventions: Biological: PRP injection|Biological: Placebo URL: https://ClinicalTrials.gov/show/NCT01926327	NR	4	
Study: 115	Title: A Phase 2 Study to Evaluate the Efficacy and Safety of JointStem in Treatment of Osteoarthritis Recruitment: Recruiting Study Results: No Results Available Conditions: Osteoarthritis, Knee Interventions: Drug: JointStem|Drug: Synvisc-One URL: https://ClinicalTrials.gov/show/NCT02674399	NR	5	hylan G-F 20
Study: 116	Title: Platelet-Rich Plasma vs Corticosteroid Injection as Treatment for Degenerative Pathology of the Temporomandibular Joint Recruitment: Withdrawn Study Results: No Results Available Conditions: Degenerative Joint Disease Interventions: Drug: Group A (corticosteroid injection group)|Biological: Group B	NR	4	

Search query: Osteoarthritis hyaluronan				
Citation		**Relevance NR=non-relevant R=relevant**	**Reason for non-relevance or Appraisal**	
	(platelet rich plasma injection group) URL: https://ClinicalTrials.gov/show/NCT01920373			
Study: 117	Title: Anti-inflammatory Effect of Serum of Osteoarthritis Patients After Administration of the Oléogrape®SEED, an Extract of Grape and Olive Recruitment: Completed Study Results: No Results Available Conditions: Osteoarthritis Interventions: Drug: Extract of grape and olive|Drug: Lactose URL: https://ClinicalTrials.gov/show/NCT02566798	NR	4	
Study: 118	Title: Evaluation of the Effect of Adding Corticosteroid to Viscosupplementation Recruitment: Completed Study Results: No Results Available Conditions: Osteoarthritis Interventions: Drug: Hylan GF-20 alone|Drug: Triamcinolone URL: https://ClinicalTrials.gov/show/NCT01335321	NR	5	hylan G-F 20
Study: 119	**Title: Platelet-rich Plasma (PRP) vs Viscosupplementation for the Treatment of Early Knee Articular Degenerative Pathology Recruitment: Recruiting Study Results: No Results Available Conditions: Knee Chondropathy|Knee Early Osteoarthritis Interventions: Biological: PRP URL: https://ClinicalTrials.gov/show/NCT02135367 Recruiting**	**R**	**6**	**Hyalubrix**
Study: 120	Title: Durolane Versus Methylprednisolone in Knee Osteoarthritis Recruitment: Completed Study Results: No Results Available Conditions: Knee Osteoarthritis Interventions: Device: Durolane is a device, methylprednisolone in a drug URL: https://ClinicalTrials.gov/show/NCT01209364	NR	5	Durolane
Study: 121	Title: Hip Viscosupplementation: What is the Best Dosage? Recruitment: Recruiting Study Results: No Results Available Conditions: Osteoarthritis Interventions: Procedure: articular lavage with saline injection|Drug: 1 ampoule of Hylan GF-20|Drug: 2 ampoules of Hylan GF-20|Drug: 3 ampoules of Hylan GF-20 URL: https://ClinicalTrials.gov/show/NCT01810809	NR	5	hylan G-F 20
Study: 122	Title: Viscosupplementation in the Hip Following Hip Arthroscopy Recruitment: Not yet recruiting Study Results: No Results Available Conditions: Osteoarthritis Interventions: Drug: Monovisc URL: https://ClinicalTrials.gov/show/NCT02476903	NR	4	Monovisc
Study: 123	Title: A Study of the Safety and Efficacy of Hylan G-F 20 (Synvisc) in Patients With Symptomatic Osteoarthritis of the Knee Recruitment: Completed Study Results: Has Results Conditions: Osteoarthritis, Knee|Musculoskeletal Diseases Interventions: Device: hylan G-F 20|Other: Phosphate Buffered Saline URL: https://ClinicalTrials.gov/show/NCT00131352	NR	5	hylan G-F 20
Study: 124	Title: A Study of the Efficacy and Safety of Synvisc® in Chinese Subjects With Symptomatic Osteoarthritis of the Knee(s) Recruitment: Completed Study Results: Has Results Conditions: Osteoarthritis Interventions: Drug: Hylan G-F 20 URL: https://ClinicalTrials.gov/show/NCT01586338	NR	5	hylan G-F 20
Study: 125	Title: Study of Safety and Efficacy of 6 mL Synvisc-One (Hylan G-F 20) in Indian Patients With Symptomatic Osteoarthritis of Knee(s) After Initial and Repeat Treatment Recruitment: Completed Study Results: Has Results Conditions: Osteoarthritis Interventions: Drug: Synvisc-One URL: https://ClinicalTrials.gov/show/NCT02389452	NR	5	hylan G-F 20
Study: 126	Title: Synvisc-One for Younger, Active Patients With Osteoarthritis Recruitment: Recruiting Study Results: No Results Available Conditions: Osteoarthritis Interventions: Device: Synvisc-One (G-F 20) URL: https://ClinicalTrials.gov/show/NCT01625013	NR	5	hylan G-F 20
Study: 127	Title: Effectiveness Study of Hylan G-F 20 to Preserve Cartilage in Osteoarthritis of the Knee Recruitment: Recruiting Study Results: No Results Available Conditions: Osteoarthritis Interventions: Drug: intra-articular injection of Hylan G-F 20 URL: https://ClinicalTrials.gov/show/NCT00393393	NR	5	hylan G-F 20
Study: 128	Title: Hyaluronate Injection for Lateral Epicondylitis Recruitment: Not yet recruiting Study Results: No Results Available Conditions: Tennis Elbow Interventions: Drug: Arthrease|Drug: Intragel|Drug: Saline URL: https://ClinicalTrials.gov/show/NCT02258295	NR	5	Arthrease

Search query: Osteoarthritis hyaluronan				
Citation		**Relevance NR=non-relevant R=relevant**	**Reason for non-relevance or Appraisal**	
Study: 129	Title: Intra-articular Betamethasone and the Hypothalamic-pituitary-adrenal Axis Recruitment: Completed Study Results: No Results Available Conditions: Adrenal Suppression Interventions: URL: https://ClinicalTrials.gov/show/NCT01799408	NR	4	
Study: 130	Title: A Study of the Safety and Effectiveness of Synvisc-One® (Hylan G-F 20) in Patients With Primary Osteoarthritis of the Hip Recruitment: Completed Study Results: No Results Available Conditions: Osteoarthritis, Hip Interventions: Device: Synvisc-One (hylan G-F 20)|Device: Saline Placebo URL: https://ClinicalTrials.gov/show/NCT01618708	NR	5	hylan G-F 20
Study: 131	Title: Optimization of Synvisc-One for Knee OA Recruitment: Recruiting Study Results: No Results Available Conditions: Knee Osteoarthritis Interventions: Device: Synvisc-One Injection|Other: Sham Injection URL: https://ClinicalTrials.gov/show/NCT02029703	NR	5	hylan G-F 20
Study: 132	Title: Evaluation of Safety and Exploratory Efficacy of CARTISTEM®, a Cell Therapy Product for Articular Cartilage Defects Recruitment: Active, not recruiting Study Results: No Results Available Conditions: Degeneration Articular Cartilage Knee Interventions: Biological: CARTISTEM® URL: https://ClinicalTrials.gov/show/NCT01733186	NR	4	

7.7 International Clinical Trials Registry Platform (ICTRP) who.int/ictrp/en/

Search query: Osteoarthritis hyaluronan					
	Main ID	**Public title**	**Relevance NR=non-relevant R=relevant**	**Reason for non-relevance or Appraisal**	
1	NCT02776943	UCMSC Transplantation in the Treatment of Cartilage Damage	NR	4	
2	IRCT2016021710507N4	Evaluation of Effectiveness of Intra-Articular Injection of Stem Cells on Knee Arthrosis	NR	4	
3	CTRI/2016/02/006587	Comparision of various drugs used inknee osteoarthritis	NR	5	oral HA
4	NCT02671565	Comparative Effectiveness of Hyaluronic Acid Injections for Management of Knee Osteoarthritis	NR	6	observational study Not yet open for recruitment.
5	ISRCTN93862496	Clinical trial on the intra-articular efficacy of MD-Knee (collagen medical device-knee) versus sodium hyaluronate in patients with knee osteoarthritis	NR	5	Artz
6	KCT0001699	Clinical Trial to Evaluate the Efficacy and Safety of Intra-articular DA-5202 in Patients with Osteoarthritis of the Knee	NR	6	
7	CTRI/2015/11/006350	Action of Rhus tox in primary osteo arthritis	NR	4	
8	NCT02588872	Hyaluronic Acid vs Platelet Rich Plasma: Effects on Clinical Outcomes and Intra-articular Biology for the Treatment of Knee Osteoarthritis	NR	8	HA?
9	NCT02580695	A Study to Assess Safety and Efficacy of Umbilical Cord-derived Mesenchymal Stromal Cells in Knee Osteoarthritis	NR	8	
10	ChiCTR-IOR-15006942	RCT mesenchymal stem cells versus hyaluronic acid in OA knee	NR	6	
11	IRCT201504141479N4	The effects of Hyaluronic acid and Atorvastatin on knee arthrosis	NR	5	Hyaluron® HEXAL, Germany,20mg/2

Search query: Osteoarthritis hyaluronan					
	Main ID	**Public title**	**Relevance NR=non-relevant R=relevant**	**Reason for non-relevance or Appraisal**	
					cc
12	IRCT2015031421460N1	Hyaluronic Acid Compared with Corticosteroid Injections for the Treatment of Osteoarthritis of the knee	NR	5	Hyalgan
13	NCT02495857	A Study of Hyaluronate Injectable Viscosupplement for Treatment of Osteoarthritis of the Knee	NR	8	EUFLEXXA
14	JPRN-UMIN000017962	Prospective Randomized Trial of Hyaluronan Injection Efficacy for Long-term Prognosis in Knee Osteoarthritis	NR	6	
15	IRCT2015041213828N6	Effect of Hyaluronic acid in the treatment of knee osteoarthritis	NR	6	
16	ChiCTR-ICR-15006376	Intra-articular injection of Autologous conditioned plasma to treat Knee Osteoarthritis A randomized clinical trial	NR	4	
17	NCT02554240	Study to Evaluate the Efficacy and Safety of Intra-articular DA-5202 in Patients With Osteoarthritis of the Knee	NR	6	Recruiting
18	ACTRN12615000345583	Evaluating the effects on function and pain of two gels applied over the knee in people with mild to moderate osteoarthritis: a 2-week randomised control trial. The KnEe Guard (KEG) trial.	NR	4	HA combination
19	NCT02417610	Comparative Assessment of Viscosupplementation With Polynucleotides and Hyaluronic Acid	NR	8	Ialart Recruiting
20	NCT02323451	Medical Chitosan or Sodium Hyaluronate for Knee Osteoarthritis (CHOOSE)	NR	8	(10mg/ml)
21	NCT02318511	An Investigation of ReNu™ Knee Injection in Patients With Osteoarthritis	NR	8	HA? Recruiting
22	EUCTR2014-004435-40-CZ	Study with random distribution of treatments (fasitibant and placebo given in combination with sodium hyaluronate), where neither the investigator nor the patients know the treatment taken, to evaluate efficacy of the drug when injected into the knee joint in the patients with osteoarthritis of the knee.	NR	4	HA combination
23	ChiCTR-IPR-14005607	A study on effects of acupoint injection on factors in synovial fluid related to cartilage degeneration	NR	6	
24	JPRN-UMIN000015585	Molecular biological and physical analysis of hyaluronan injection with mechanical stress on osteoarthritis	NR	6	
25	JPRN-UMIN000015666	A phase II study on periarticular injection of Anti-cytokine therapy Magnetic for the treatment of osteoarthritic knee pain.	NR	6	
26	NCT02280538	Trial to Assess the Structural Effect and Long-term Symptomatic Relief of Intra-articular Injections of Hyaluronic Acid in Primary Knee OA	NR	8	Recruiting
27	ACTRN12614001044617	Knee Osteoarthritis and Non-expanded Stem Cell Study	NR	6	
28	ISRCTN81261986	Effects of intra-articular administration of Hymovis on the expression and activity of matrix metalloproteinases in synovial fluids of patients affected by osteoarthritis of the knee	NR	5	Hymovis, hylan G-F 20
29	NCT02211521	Comparison of Autologous Platelet-rich Plasma With Hyaluronic Acid for the Treatment of Osteoarthritis of the Knee Joint	NR	8	
30	NCT02188771	A Phase I, Prospective, Randomized,	NR	8	Recruiting

Search query: Osteoarthritis hyaluronan					
	Main ID	**Public title**	**Relevance NR=non-relevant R=relevant**	**Reason for non-relevance or Appraisal**	
		Open-label, Active-Controlled Clinical Trial for Safety Evaluation of Intra-articular Injection of RegenoGel-SP for the Treatment of Moderate to Severe Osteoarthritis			
31	IRCT2012080510507N1	Evaluation of efficacy of treatment with stem cells (SCs) and platelet-rich plasma (PRP) in patients with knee arthrosis	NR	4	
32	NCT02136901	The VENUS Clinical Study (Verifying the Effectiveness of the NUsurface® System)	NR	8	hylan G-F 20
33	NCT02122601	A Clinical Trial to Evaluate the Safety and Efficacy of Retreatment With Intra-articular LBSA0103 Injections in the Patients With Osteoarthritis of the Knee	NR	8	LBSA0103 (BDDE cross-linked sodium hyaluronate gel)
34	NCT02108496	Verifying the Effectiveness of the NUsurface® System	NR	8	hylan G-F 20
35	NCT02162693	Clinical Trial of Autologous Adipose Tissue-Derived Mesenchymal Progenitor Cells (MPCs) Therapy for Knee Osteoarthritis	NR	8	
36	ChiCTR-TRC-14004351	Efficacy of ultrasound-guided intra-articular injections of platelet-rich plasma for knee osteoarthritis: a randomized controlled trial.	NR	6	
37	NCT02086474	Daily Activity and Gait Analysis After Viscosupplement Injection Among Hip Osteoarthritis Patients	NR	8	Neovisc 1%
38	NCT02063373	Gait, Stair Climbing and Postural Stability in Knee Osteoarthritis Patients After Hyaluronic Acid Injection	NR	8	hyalgan
39	IRCT20140121134442N5	cCmparison of Platelet Rich Plasma and Hyaluronic acid in patients with knee osteoarthritis	NR	6	
40	NCT02039531	Effect Of Plasma Rich In Growth Factors In Knee Osteoarthritis	NR	8	Durolane
41	EUCTR2013-001303-36-ES	Treatment of osteoarthritis knee pain injection concentrate a patient's own plasma	NR	4	
42	NCT01920152	Platelet Rich Plasma vs Hyaluronic-Acid in Hip OA (Osteoarthritis)	NR	8	Supartz
43	NCT02039804	Sodium Hyaluronate Injection and Corticosteroids in Trochanteric Bursitis: a Randomized Controlled Study.	NR	8	
44	NCT01891396	Cingal Study for Knee Osteoarthritis	NR	8	crosslinked HA
45	NCT01670578	Platelet-rich Plasma vs Viscosupplementation in the Treatment of Knee Articular Degenerative Pathology	NR	8	Hyalubrix
46	JPRN-UMIN000008260	Open-label, randomized parallel group trial on the efficacy and safety of intra-articular administration of bevacizumab for knee osteoarthritis.	NR	6	
47	NCT01586312	Treatment of Knee Osteoarthritis With Allogenic Mesenchymal Stem Cells	NR	8	Durolane
48	NCT01557868	Prediction of Response to Intra-articular Injections of Hyaluronic Acid for Knee Osteoarthritis	NR	8	hylan G-F 20, EUFLEXXA
49	ISRCTN83189455	Study of sodium hyaluronate injections for trapeziometacarpal osteoarthritis	NR	5	Hyalgan
50	NCT01543737	Effectiveness of Two Hyaluronic Acids in Osteoarthritis of the Knee	NR	8	Durolane, Hyalgan
51	EUCTR2011-005254-53-DE	A placebo-controlled study assessing the tolerability and plasma concentrations of	NR	5	Hyalart combination

Search query: Osteoarthritis hyaluronan					
	Main ID	**Public title**	**Relevance NR=non-relevant R=relevant**	**Reason for non-relevance or Appraisal**	
		ascending doses of fasitibant in patients with osteoarthritis of the knee.			
52	EUCTR2011-005321-51-ES	Treatment of osteoarthritis with allogeneic mesenchymal cells (MSV*).	NR	5	Durolane
53	NCT01469507	Efficacy and Safety Study in Patients Suffering From Knee Osteoarthritis	NR	8	Hyalgan
54	NCT01459640	Intra-Articular Autologous Bone Marrow Mesenchymal Stem Cells Transplantation to Treat Mild to Moderate Osteoarthritis	NR	8	Orthovisc
55	JPRN-UMIN000006178	Effect of home-based quadriceps muscle strengthening and range of motion exercises for knee osteoarthritis, A randomized controlled trial ; motor function in lower extrimities, ADL and mental state	NR	6	
56	JPRN-UMIN000005643	Effects of COX-2 selective inhibitor and hyaluronan acid to prevent cartilage degeneration in patients with knee osteoarthritis	NR	6	
57	NCT01295580	Comparative Study of Safety and Efficacy of Two Hyaluronic Acids for the Treatment of Knee Osteoarthritis	NR	8	Durolane, Artz
58	NCT01290497	Efficacy and Safety of 3 Different Dosage Regimens of Hyaluronic Acid in Patients With Knee Osteoarthritis (OA)	NR	8	Adant
59	NCT01267214	The Efficacy and Safety of Intraarticular Sodium Hyaluronate (Hyalgan) After Proximal Tibial Osteotomy in Treatment of Knee Osteoarthritis Patients	NR	8	Hyalgan
60	NCT01270412	Platelet Rich Plasma (PRP) as a Treatment for Knee Osteoarthritis PRP as a Treatment for Knee Osteoarthritis	NR	8	Arthrease
61	EUCTR2009-017624-72-ES	Tratamiento de la Artrosis mediante la inyección intra-articular de Células Madre Mesenquimales de Médula Ósea	NR	5	Durolane
62	NCT01243814	A Double-blind RCT of a Single Dose of Hyaluronan in the Treatment of Osteoarthritis of the Ankle	NR	8	Supartz
63	NCT01239810	Intra-articular Hyaluronic Acid in Mild to Moderate Knee Osteoarthritis	NR	8	Ostenil
64	**ISRCTN32694665**	**Intra-articular injection of hyaluronic acid (MW 1500-2000 KDa; HyalOne®) in symptomatic osteoarthritis of the hip** **Published:** **Migliore A, Massafra U, Bizzi E, Laganà B, Germano V, Piscitelli P, Granata M, Tormenta S. Intra-articular injection of hyaluronic acid (MW 1,500-2,000 kDa, HyalOne(®)) in symptomatic osteoarthritis of the hip: a prospective cohort study. Arch Orthop Trauma Surg. 2011;131:1677–1685.**	**R**	**9**	**HyalOne**
65	NCT01088191	Safety and Efficacy Study of MSB-CAR001 in Subjects 6 Weeks Post an Anterior Cruciate Ligament Reconstruction	NR	8	

7.8 Manual search

Citations are sorted in descending year of publication.

Maheu E 2016 published data from the same clinical study performed by Dreiser RL 2015 but with a different focus of data analysis.

Citation		Relevance NR=non-relevant R=relevant	Reason for non-relevance or Appraisal	
1	**Dreiser RL, Avouac B, Bardin T. Efficacy of One Intra-Articular Injection of 2% Natural Sodium Hyaluronate Is Non-Inferior To Chemically Crosslinked Hylan G-F 20 In The Treatment Of Painful Tbiofemoral Osteoarthritis. Abstract publication: Osteoporos Int 2015;26(Suppl 1): P308 Ann Rheum Dis 2015;74(Suppl 2):376.**	**R**	**9**	**Ostenil Plus**
2	**Maheu E, Dreiser RL, Avouac B, Bardin T. Comparison of Therapeutic Response Rates, Using Various Response Definitions in a Prospective Randomized Non-Inferiority Trial Comparing Two Intra-Articular Hyaluronic Acid Preparations (1-Shot IAHA) in Isymptomatic Knee Osteoarthritis (OA), And Predictive Factors of a Better Response. SAT0443 EULAR congress 2016 London, UK. Abstract**	**R**	**9**	**Ostenil Plus**
3	**Guler O, Mutlu S, Isyar M, Seker A, Kayaalp ME, Mahirogullari M. Comparison of short-term results of intraarticular platelet-rich plasma (PRP) and hyaluronic acid treatments in early-stage gonarthrosis patients. Eur J Orthop Surg Traumatol. 2015;25:509-13.**	**R**	**9**	**Osteonil Plus (=Ostenil plus)**
4	**Borrás-Verdera A, Calcedo-Bernal V, Ojeda-Levenfeld J, Clavel-Sainz C. Efficacy and safety of a single intra-articular injection of 2% hyaluronic acid plus mannitol in knee osteoarthritis over a 6-month period. Rev Esp Cir Ortop Traumatol. 2011;56:274-80.**	**R**	**9**	**Ostenil Plus**
5	**Frobenius K. A new high-dose treatment with intraarticular hyaluronic acid facilitates the management of osteoarthritis. Orthopädische Praxis. 2009;46(5):252-7**	**R**	**9**	**Ostenil Plus**

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Citations from hand search in Infotehna for osteoarthritis	Relevance
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Wen DY. Intra-articular hyaluronic acid injections for knee osteoarthritis. Am Fam Physician 2000;62:565–70 [72].	BI
Zhang W, Doherty M, Arden N, Bannwarth B, Bijlsma J, Gunther KP, Hauselmann HJ, Herrero-Beaumont G, Jordan K, Kaklamanis P, Leeb B, Lequesne M, Lohmander S, Mazieres B, Martin-Mola E, Pavelka K, Pendleton A, Punzi L, Swoboda B, Varatojo R, Verbruggen G, Zimmermann-Gorska I, Dougados M; EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). EULAR evidence based recommendations for the management of hip osteoarthritis: report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). Ann Rheum Dis. 2005 May;64(5):669-81.	BI
Zhang W, Doherty M, Leeb BF, Alekseeva L, Arden NK, Bijlsma JW, Dinçer F, Dziedzic K, Häuselmann HJ, Herrero-Beaumont G, Kaklamanis P, Lohmander S, Maheu E, Martín-Mola E, Pavelka K, Punzi L, Reiter S, Sautner J, Smolen J, Verbruggen G, Zimmermann-Górska I. EULAR evidence based recommendations for the management of hand osteoarthritis: report of a Task Force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). Ann Rheum Dis. 2007 Mar;66(3):377-88.	BI
Zhang W, Doherty M, Peat G, Bierma-Zeinstra SM, Arden NK, Bresnihan B, Herrero-Beaumont G, Kirschner S, Leeb BF, Lohmander LS, Mazières B, Pavelka K, Punzi L, So AK, Tuncer T, Watt I, Bijlsma JW. EULAR evidence based recommendations for the diagnosis of knee osteoarthritis. Ann Rheum Dis. 2010;69:483-9.	BI
Zhang W, Nuki G, Moskowitz RW, Abramson S, Altman RD, Arden NK, Bierma-Zeinstra S, Brandt KD, Croft P, Doherty M, Dougados M, Hochberg M, Hunter DJ, Kwoh K, Lohmander LS, Tugwell P. OARSI recommendations for the management of hip and knee osteoarthritis: part III: Changes in evidence following systematic cumulative update of research published through January 2009. Osteoarthritis Cartilage. 2010;18(4):476-99.	BI

*Background information

8. Relevant Literature

65 Publications were judged as ‘relevant’ and are – after cleareance from duplicates and publications with missing data – 37 were further evaluated in the clinical evaluation report.

Relevance was obtained by:

- in the indication: osteoarthritis
- with the intervention(s): intra-articular HA injection
- with the use of: linear (not crosslinked) HA ≥1.5%

Relevant literature:

	Source	N° in scource	Citation	Reason for non-relevance or Appraisal	Product
1	Medline	9	Foti C, Cisari C, Carda S, Giordan N, Rocco A, Frizziero A, Della Bella G. A prospective observational study of the clinical efficacy and safety of intra-articular sodium hyaluronate in synovial joints with osteoarthritis. Eur J Phys Rehabil Med. 2011 Sep;47(3):407-15.	9	Hyalubrix
2	Medline	15	Karatay S, Kiziltunc A, Yildirim K, Karanfil RC, Senel K. Effects of different hyaluronic acid products on synovial fluid NO levels in knee osteoarthritis. Clin Rheumatol. 2005 Sep;24(5):497-501.	9	Orthovisc, hylan G-F 20 (Synvisc)
3	Medline	21	Karatay S, Kiziltunc A, Yildirim K, Karanfil RC, Senel K. Effects of different hyaluronic acid products on synovial fluid levels of intercellular adhesion molecule-1 and vascular cell adhesion molecule-1 in knee osteoarthritis. Ann Clin Lab Sci. 2004 Summer;34(3):330-5.	9	Orthovisc, hylan G-F 20 (Synvisc)
4	Medline	29	Kotevoglu N, Iyibozkurt PC, Hiz O, Toktas H, Kuran B. A prospective randomised controlled clinical trial comparing the efficacy of different molecular weight hyaluronan solutions in the treatment of knee osteoarthritis. Rheumatol Int. 2006 Feb;26(4):325-30.	9	hylan G-F 20 6 ml, Orthovisc
5	Medline	32	Stahl S, Karsh-Zafrir I, Ratzon N, Rosenberg N. Comparison of intraarticular injection of depot corticosteroid and hyaluronic acid for treatment of degenerative trapeziometacarpal joints. J Clin Rheumatol. 2005 Dec;11(6):299-302.	9	Orthovisc
6	Medline	36	Brandt KD, Block JA, Michalski JP, Moreland LW, Caldwell JR, Lavin PT. Efficacy and safety of intraarticular sodium hyaluronate in knee osteoarthritis. ORTHOVISC Study Group. Clin Orthop Relat Res. 2001 Apr;(385):130-43.	9	Orthovisc
7	Medline	39	Neustadt D, Caldwell J, Bell M, Wade J, Gimbel J. Clinical effects of intraarticular injection of high molecular weight hyaluronan (Orthovisc) in osteoarthritis of the knee: a randomized, controlled, multicenter trial. J Rheumatol. 2005 Oct;32(10):1928-36.	9	Orthovisc
8	Medline	56	Ozturk C, Atamaz F, Hepguler S, Argin M, Arkun R. The safety and efficacy of intraarticular hyaluronan with/without corticosteroid in knee osteoarthritis: 1-year, single-blind, randomized study. Rheumatol Int. 2006 Feb;26(4):314-9.	9	Orthovisc
9	Medline	75	Sezgin M, Demirel AC, Karaca C, Ortancil O, Ulkar GB, Kanik A, Cakçi A. Does hyaluronan affect inflammatory cytokines in knee osteoarthritis? Rheumatol Int. 2005 May;25(4):264-9.	9	Orthovisc
10	Medline	91	Calis M, Demir H, Ulker S, Kirnap M, Duygulu F, Calis HT. Is intraarticular sodium hyaluronate injection an alternative treatment in patients with adhesive capsulitis? Rheumatol Int. 2006 Apr;26(6):536-40.	9	Orthovisc
11	MeSH Medline	2	van der Weegen W, Wullems JA, Bos E, Noten H, van Drumpt RA. No difference between intra-articular injection of hyaluronic acid and placebo for mild to moderate knee osteoarthritis: a randomized, controlled, double-blind trial. J Arthroplasty. 2015 May;30(5):754-7. doi: 10.1016/j.arth.2014.12.012. Epub 2014 Dec 13. PubMed PMID: 25548079.	9	Fermathron Plus
12	MeSH Medline	13	Giarratana LS, Marelli BM, Crapanzano C, De Martinis SE, Gala L, Ferraro M, Marelli N, Albisetti W. A randomized double-blind clinical trial on the treatment of knee osteoarthritis: the efficacy of polynucleotides compared to standard hyaluronian	9	Hyalubrix

	Source	N° in scource	Citation	Reason for non-relevance or Appraisal	Product
			viscosupplementation. Knee. 2014 Jun;21(3):661-8. doi: 10.1016/j.knee.2014.02.010. Epub 2014 Feb 24. PubMed PMID: 24703391.		
13	MeSH Medline	14	Migliore A, Massafra U, Bizzi E, Tormenta S, Cassol M, Granata M. Duration of symptom relief after intra-articular injection of hyaluronic acid combined with sorbitol (anti-ox-vs) in symptomatic hip osteoarthritis. Int J Immunopathol Pharmacol. 2014 Apr-Jun;27(2):245-52. PubMed PMID: 25004836.	9	Synolis V-A
14	MeSH Medline	22	Heisel J, Kipshoven C. Safety and efficacy findings from a non-interventional study of a new hyaluronic acid/sorbitol formulation (GO-ON® matrix) for intra-articular injection to relieve pain and disability in osteoarthritis patients. Drug Res (Stuttg). 2013 Sep;63(9):445-9. doi: 10.1055/s-0033-1343425. Epub 2013 Apr 18. PubMed PMID: 23599036.	9	Go-On matrix
15	MeSH Medline	35	Paoloni M, Di Sante L, Dimaggio M, Bernetti A, Mangone M, Di Renzo S, Santilli V. Kinematic and kinetic modifications in walking pattern of hip osteoarthritis patients induced by intra-articular injections of hyaluronic acid. Clin Biomech (Bristol, Avon). 2012 Aug;27(7):661-5. doi: 10.1016/j.clinbiomech.2012.02.004. Epub 2012 Mar 11. PubMed PMID: 22410192.	9	Hyalubrix
16	MeSH Medline	36	Filardo G, Di Matteo B, Di Martino A, Merli ML, Cenacchi A, Fornasari P, Marcacci M, Kon E. Platelet-Rich Plasma Intra-articular Knee Injections Show No Superiority Versus Viscosupplementation: A Randomized Controlled Trial. Am J Sports Med. 2015 Jul;43(7):1575-82. doi: 10.1177/0363546515582027. Epub 2015 May 7. PubMed PMID: 25952818.	9	Hyalubrix
17	MeSH Medline	49	Foti C, Cisari C, Carda S, Giordan N, Rocco A, Frizziero A, Della Bella G. A prospective observational study of the clinical efficacy and safety of intra-articular sodium hyaluronate in synovial joints with osteoarthritis. Eur J Phys Rehabil Med. 2011 Sep;47(3):407-15. PubMed PMID: 21946401.	8	Hyalubrix
18	MeSH Medline	53	Battaglia M, Guaraldi F, Vannini F, Rossi G, Timoncini A, Buda R, Giannini S. Efficacy of ultrasound-guided intra-articular injections of platelet-rich plasma versus hyaluronic acid for hip osteoarthritis. Orthopedics. 2013 Dec;36(12):e1501-8. PubMed PMID: 24579221.	9	Hyalubrix
19	MeSH Medline	61	Witteveen AG, Sierevelt IN, Blankevoort L, Kerkhoffs GM, van Dijk CN. Intra-articular sodium hyaluronate injections in the osteoarthritic ankle joint: effects, safety and dose dependency. Foot Ankle Surg. 2010 Dec;16(4):159-63. doi: 10.1016/j.fas.2009.10.003. Epub 2009 Nov 8. PubMed PMID: 21047602.	9	Orthovisc
20	MeSH Medline	63	Colen S, van den Bekerom MP, Bellemans J, Mulier M. Comparison of intra-articular injections of hyaluronic acid and corticosteroid in the treatment of osteoarthritis of the hip in comparison with intra-articular injections of bupivacaine. Design of a prospective, randomized, controlled study with blinding of the patients and outcome assessors. BMC Musculoskelet Disord. 2010 Nov 16;11:264. doi: 10.1186/1471-2474-11-264. PubMed PMID: 21080920; PubMed Central PMCID: PMC2998460.	9	Ostenil Plus Study protocol, biostatistical report is available
21	MeSH Medline	66	Filardo G, Kon E, Di Martino A, Di Matteo B, Merli ML, Cenacchi A, Fornasari PM, Marcacci M. Platelet-rich plasma vs hyaluronic acid to treat	9	Hyalubrix

	Source	N° in scource	Citation	Reason for non-relevance or Appraisal	Product
			knee degenerative pathology: study design and preliminary results of a randomized controlled trial. BMC Musculoskelet Disord. 2012 Nov 23;13:229. doi: 10.1186/1471-2474-13-229. PubMed PMID: 23176112; PubMed Central PMCID: PMC3532098.		
22	MeSH Medline	73	Kul-Panza E, Berker N. Is hyaluronate sodium effective in the management of knee osteoarthritis? A placebo-controlled double-blind study. Minerva Med. 2010 Apr;101(2):63-72. PubMed PMID: 20467406.	9	Orthovisc
23	MeSH Medline	77	Kon E, Mandelbaum B, Buda R, Filardo G, Delcogliano M, Timoncini A, Fornasari PM, Giannini S, Marcacci M. Platelet-rich plasma intra-articular injection versus hyaluronic acid viscosupplementation as treatments for cartilage pathology: from early degeneration to osteoarthritis. Arthroscopy. 2011 Nov;27(11):1490-501. doi: 10.1016/j.arthro.2011.05.011. Epub 2011 Aug 10. PubMed PMID: 21831567.	9	HMW HA (30 mg/2 mL, 1.5%, 1,000-2,900 kDa) and LMW HA (20 mg/2 mL, 1%, 500-730 kDa).
24	MeSH Medline	91	Migliore A, Massafra U, Bizzi E, Vacca F, Martin-Martin S, Granata M, Alimonti A, Tormenta S. Comparative, double-blind, controlled study of intra-articular hyaluronic acid (Hyalubrix) injections versus local anesthetic in osteoarthritis of the hip. Arthritis Res Ther. 2009;11(6):R183. doi: 10.1186/ar2875. Epub 2009 Dec 9. PubMed PMID: 20003205; PubMed Central PMCID: PMC3003515.	9	Hyalubrix
25	MeSH Medline	107	Stahl S, Karsh-Zafrir I, Ratzon N, Rosenberg N. Comparison of intraarticular injection of depot corticosteroid and hyaluronic acid for treatment of degenerative trapeziometacarpal joints. J Clin Rheumatol. 2005 Dec;11(6):299-302. PubMed PMID: 16371798.	8	Orthovisc
26	MeSH Medline	111	Neustadt D, Caldwell J, Bell M, Wade J, Gimbel J. Clinical effects of intraarticular injection of high molecular weight hyaluronan (Orthovisc) in osteoarthritis of the knee: a randomized, controlled, multicenter trial. J Rheumatol. 2005 Oct;32(10):1928-36. PubMed PMID: 16206349.	8	Orthovisc
27	MeSH Medline	112	Kotevoglu N, Iyibozkurt PC, Hiz O, Toktas H, Kuran B. A prospective randomised controlled clinical trial comparing the efficacy of different molecular weight hyaluronan solutions in the treatment of knee osteoarthritis. Rheumatol Int. 2006 Feb;26(4):325-30. Epub 2005 Jun 15. PubMed PMID: 15959784.	8	hylan G-F 20 6 ml, Orthovisc
28	MeSH Medline	113	Karatay S, Kiziltunc A, Yildirim K, Karanfil RC, Senel K. Effects of different hyaluronic acid products on synovial fluid NO levels in knee osteoarthritis. Clin Rheumatol. 2005 Sep;24(5):497-501. Epub 2005 May 20. PubMed PMID: 15906109.	8	Orthovisc, hylan G-F 20 (Synvisc)
29	MeSH Medline	124	Bayramoğlu M, Karataş M, Cetin N, Akman N, Sözay S, Dilek A. Comparison of two different viscosupplements in knee osteoarthritis -- a pilot study. Clin Rheumatol. 2003 May;22(2):118-22. PubMed PMID: 12740676.	9	Orthovisc, hylan G-F 20 (Synvisc)
30	MeSH Medline	157	Atamaz F, Kirazli Y, Akkoc Y. A comparison of two different intra-articular hyaluronan drugs and physical therapy in the management of knee osteoarthritis. Rheumatol Int. 2006 Aug;26(10):873-8. Epub 2006 Jan 14. PubMed PMID: 16416102.	9	hylan G-F 20, Orthovisc
31	MeSH Medline	164	Karatosun V, Unver B, Gocen Z, Sen A.	9	Orthovisc, hylan

	Source	N° in scource	Citation	Reason for non-relevance or Appraisal	Product
			Comparison of two hyaluronan drugs in patients with advanced osteoarthritis of the knee. A prospective, randomized, double-blind study with long term follow-up. Clin Exp Rheumatol. 2005 Mar-Apr;23(2):213-8. PubMed PMID: 15895892.		G-F 20 (Synvisc)
32	MeSH Medline	168	Ozturk C, Atamaz F, Hepguler S, Argin M, Arkun R. The safety and efficacy of intraarticular hyaluronan with/without corticosteroid in knee osteoarthritis: 1-year, single-blind, randomized study. Rheumatol Int. 2006 Feb;26(4):314-9. Epub 2005 Feb 10. PubMed PMID: 15703953.	8	Orthovisc
33	MeSH Medline	171	Karatay S, Kiziltunc A, Yildirim K, Karanfil RC, Senel K. Effects of different hyaluronic acid products on synovial fluid levels of intercellular adhesion molecule-1 and vascular cell adhesion molecule-1 in knee osteoarthritis. Ann Clin Lab Sci. 2004 Summer;34(3):330-5. PubMed PMID: 15487709.	8	Orthovisc, hylan G-F 20 (Synvisc)
34	MeSH Medline	174	Sezgin M, Demirel AC, Karaca C, Ortancil O, Ulkar GB, Kanik A, Cakçi A. Does hyaluronan affect inflammatory cytokines in knee osteoarthritis? Rheumatol Int. 2005 May;25(4):264-9. Epub 2004 Mar 4. PubMed PMID: 14999424.	8	Orthovisc
35	MeSH Medline	180	Tascioglu F, Oner C. Efficacy of intra-articular sodium hyaluronate in the treatment of knee osteoarthritis. Clin Rheumatol. 2003 May;22(2):112-7. PubMed PMID: 12740675.	9	Orthovisc
36	MeSH Medline	187	Brandt KD, Block JA, Michalski JP, Moreland LW, Caldwell JR, Lavin PT. Efficacy and safety of intraarticular sodium hyaluronate in knee osteoarthritis. ORTHOVISC Study Group. Clin Orthop Relat Res. 2001 Apr;(385):130-43. PubMed PMID: 11302304.	8	Orthovisc
37	CENTRAL	5	Neustadt D , Caldwell J , Bell M , Wade J and Gimbel J.Clinical effects of intraarticular injection of high molecular weight hyaluronan (Orthovisc) in osteoarthritis of the knee: a randomized, controlled, multicenter trial. The Journal of rheumatology, 2005, 32(10), 1928	8	Orthovisc
38	CENTRAL	9	Atamaz F, Kirazli Y, Akkoc Y. A comparison of two different intra-articular hyaluronan drugs and physical therapy in the management of knee osteoarthritis. Rheumatol Int. 2006;26(10):873-8.	8	hylan G-F 20, Orthovisc
39	CENTRAL	11	Ozturk C , Atamaz F , Hepguler S , Argin M and Arkun R.The safety and efficacy of intraarticular hyaluronan with/without corticosteroid in knee osteoarthritis : 1-year, single-blind, randomized study. Rheumatology international, 2006, 26(4), 314	8	Orthovisc
40	CENTRAL	19	Polacco A, Beomonte Zobel B, Polacco M, Scarlata S, Gasparro F, DelVescovo R, Scarciolla L. The effect of intra-articular hyaluronic acid (Sinovial One) on knee osteoarthritis : A preliminary study. European Journal of Inflammation. 2013;11(3):847-853	9	Sinovial One
41	CENTRAL	22	Giarratana LS , Marelli BM , Crapanzano C , DeMartinis SE , Gala L , Ferraro M , Marelli N and Albisetti W.A randomized double-blind clinical trial on the treatment of knee osteoarthritis : the efficacy of polynucleotides compared to standard hyaluronian viscosupplementation. The Knee. 2014;21(3):661-8	8	Hyalubrix
42	CENTRAL	25	Paoloni M, Di Sante L, Dimaggio M, Bernetti A, Mangone M, Di Renzo S, Santilli V. Kinematic and kinetic modifications in walking pattern of hip osteoarthritis patients induced by intra-articular	8	Hyalubrix

	Source	N° in scource	Citation	Reason for non-relevance or Appraisal	Product
			injections of hyaluronic acid. Clin Biomech (Bristol, Avon). 2012 Aug;27(7):661-5.		
43	CENTRAL	30	Alberto M , Umberto M , Emanuele B , Bruno L , Valentina G , Prisco P , Mauro G and Sandro T.Intra-articular injection of hyaluronic acid (MW 1,500-2,000 kDa; HyalOne) in symptomatic osteoarthritis of the hip: A prospective cohort study. Archives of orthopaedic and trauma surgery, 2011, 131(12), 1677 Migliore A, Massafra U, Bizzi E, Laganà B, Germano V, Piscitelli P, Granata M, Tormenta S. Intra-articular injection of hyaluronic acid (MW 1,500-2,000 kDa, HyalOne(®)) in symptomatic osteoarthritis of the hip: a prospective cohort study. Arch Orthop Trauma Surg. 2011;131:1677–1685.	9	Hyalone
44	CENTRAL	39	Karatosun V, Unver B, Gocen Z, Sen A. Comparison of two hyaluronan drugs in patients with advanced osteoarthritis of the knee. A prospective, randomized, double-blind study with long term follow-up. Clin Exp Rheumatol. 2005 Mar-Apr;23(2):213-8.	8	Orthovisc, hylan G-F 20 (Synvisc)
45	CENTRAL	47	Karatay S , Kiziltunc A , Yildirim K , Karanfil RC and Senel K.Effects of different hyaluronic acid products on synovial fluid levels of intercellular adhesion molecule-1 and vascular cell adhesion molecule-1 in knee osteoarthritis . Annals of clinical and laboratory science, 2004, 34(3), 330	8	Orthovisc, hylan G-F 20 (Synvisc)
46	CENTRAL	48	Battaglia M, Guaraldi F, Vannini F, Rossi G, Timoncini A, Buda R, Giannini S. Efficacy of ultrasound-guided intra-articular injections of platelet-rich plasma versus hyaluronic acid for hip osteoarthritis. Orthopedics. 2013 Dec;36(12):e1501-8. PubMed PMID: 24579221.	8	Hyalubrix
47	CENTRAL	68	Brandt KD , Block JA , Michalski JP , Moreland LW , Caldwell JR and Lavin PT.Efficacy and safety of intra-articular sodium hyaluronate in knee osteoarthritis . Clinical orthopaedics and related research, 2001, 385, 130	8	Orthovisc
48	CENTRAL	69	Witteveen AG, Sierevelt IN, Blankevoort L, Kerkhoffs GM, van Dijk CN. Intra-articular sodium hyaluronate injections in the osteoarthritic ankle joint: effects, safety and dose dependency. Foot Ankle Surg. 2010 Dec;16(4):159-63.	8	Orthovisc
49	DIMDI	6	Rivera F. Single intra-articular injection of high molecular weight hyaluronic acid for hip osteoarthritis. J Orthop Traumatol. 2016;17:21-6.	9	Coxarthrum
50	DIMDI	68	Foti C, Cisari C, Carda S, Giordan N, Rocco A, Frizziero A, Della Bella G. A prospective observational study of the clinical efficacy and safety of intra-articular sodium hyaluronate in synovial joints with osteoarthritis. Eur J Phys Rehabil Med. 2011,47:407-15	8	Hyalubrix
51	Clinicaltrials.gov	25	Title: ORTHOVISC Shoulder RCT Recruitment: Completed Study Results: Has Results Conditions: Glenohumeral Osteoarthritis Interventions: Device: Orthovisc|Drug: Control|Drug: Control URL: https://ClinicalTrials.gov/show/NCT00436969 No publication found. Study results posted.	6	Orthovisc
52	Clinicaltrials.gov	27	Title: Treatment of Knee Osteoarthritis by Intra-articular Injection of Bone Marrow Mesenchymal Stem Cells Recruitment: Active, not recruiting Study Results: No Results Available Conditions: Osteoarthritis Interventions: Drug: Hyaluronic acid|Biological: 10 million Bone marrow	6	HyalOne

	Source	N° in scource	Citation	Reason for non-relevance or Appraisal	Product
			mesenchimal stem cells|Biological: 100 million Bone marrow mesenchimal stem cells URL: https://ClinicalTrials.gov/show/NCT02123368 No publication found. No study results posted.		
53	Clinicaltrials.gov	35	Title: Intra-Articular Autologous Bone Marrow Mesenchymal Stem Cells Transplantation to Treat Mild to Moderate Osteoarthritis Recruitment: Recruiting Study Results: No Results Available Conditions: Osteoarthritis Interventions: Drug: Hyaluronic Acid|Biological: Autologous bone marrow-derived mesenchymal stem cells URL: https://ClinicalTrials.gov/show/NCT01459640 No publication found. No study results posted.	6	Orthovisc
54	Clinicaltrials.gov	41	Title: Comparison of Hyaluronic Acid and Corticosteroid Intra-articular Injections for the Treatment of Osteoarthritis of the Hip Recruitment: Not yet recruiting Study Results: No Results Available Conditions: Coxarthrosis Interventions: Drug: Corticosterone URL: https://ClinicalTrials.gov/show/NCT01079455 Colen S 2010 published	8	HA 2%
55	Clinicaltrials.gov	42	Title: Study of Evaluating the Duration of Efficacy of One Intra Articular Injection of Sodium Hyaluronate 2.0% in Patients With Painful Osteoarthritis of the Knee Recruitment: Completed Study Results: No Results Available Conditions: Osteoarthritis Patient Interventions: Drug: Ostenil plus URL: https://ClinicalTrials.gov/show/NCT01288001 Abstract available. Siriraj Hospital; Bangkoknoi, Bangkok, Thailand, 10700; NCT01288001;	9	Ostenil Plus
56	Clinicaltrials.gov	67	Title: Platelet-rich Plasma vs Viscosupplementation in the Treatment of Knee Articular Degenerative Pathology Recruitment: Completed Study Results: No Results Available Conditions: Knee Chondropathy|Osteoarthritis, Knee Interventions: Biological: PRP|Device: Hyaluronic acid URL: https://ClinicalTrials.gov/show/NCT01670578 Published: Filardo 2015, Mariani E 2016	8	Hyalubrix
57	Clinicaltrials.gov	72	Title: Effectiveness of a Knee Brace When Combined With Viscosupplementation in the Treatment of Knee Osteoarthritis Recruitment: Terminated Study Results: No Results Available Conditions: Knee Osteoarthritis Interventions: Other: Orthovisc|Device: DonJoy HA lite knee brace|Device: Orthovisc injections and DonJoy HA lite knee brace URL: https://ClinicalTrials.gov/show/NCT01478386 No publication found. No study results posted.	6	Orthovisc
58	Clinicaltrials.gov	87	Title: The Knee Usual Care Evaluation Study Recruitment: Terminated Study Results: No Results Available Conditions: Knee Osteoarthritis Interventions: URL: https://ClinicalTrials.gov/show/NCT01905358 No publication found. No study results posted.	6	Synvisc®, Orthrovisc®, Euflexxa
59	Clinicaltrials.gov	119	Title: Platelet-rich Plasma (PRP) vs Viscosupplementation for the Treatment of Early Knee Articular Degenerative Pathology Recruitment: Recruiting Study Results: No Results Available Conditions: Knee Chondropathy|Knee Early Osteoarthritis Interventions: Biological: PRP URL: https://ClinicalTrials.gov/show/NCT02135367	6	Hyalubrix

	Source	N° in scource	Citation	Reason for non-relevance or Appraisal	Product
			Recruiting		
60	ICTRP	64	Intra-articular injection of hyaluronic acid (MW 1500-2000 KDa; HyalOne®) in symptomatic osteoarthritis of the hip Published: Migliore A, Massafra U, Bizzi E, Laganà B, Germano V, Piscitelli P, Granata M, Tormenta S. Intra-articular injection of hyaluronic acid (MW 1,500-2,000 kDa, HyalOne(®)) in symptomatic osteoarthritis of the hip: a prospective cohort study. Arch Orthop Trauma Surg. 2011;131:1677–1685.	9	HyalOne
61	Manual search	1	Guler O, Mutlu S, Isyar M, Seker A, Kayaalp ME, Mahirogullari M. Comparison of short-term results of intraarticular platelet-rich plasma (PRP) and hyaluronic acid treatments in early-stage gonarthrosis patients. Eur J Orthop Surg Traumatol. 2015;25:509-13.	9	Ostenil Plus (Osteonil plus) knee OA
62	Manual search	2	Borrás-Verdera A, Calcedo-Bernal V, Ojeda-Levenfeld J, Clavel-Sainz C. Efficacy and safety of a single intra-articular injection of 2% hyaluronic acid plus mannitol in knee osteoarthritis over a 6-month period. Rev Esp Cir Ortop Traumatol. 2011;56:274-80.	9	Ostenil Plus
63	Manual search	3	Frobenius K. A new high-dose treatment with intraarticular hyaluronic acid facilitates the management of osteoarthritis. Orthopädische Praxis. 2009;46(5):252-7	9	Ostenil Plus
64	Manual search	4	Dreiser RL, Avouac B, Bardin T. Efficacy of One Intra-Articular Injection of 2% Natural Sodium Hyaluronate Is Non-Inferior To Chemically Crosslinked Hylan G-F 20 In The Treatment Of Painful Tbiofemoral Osteoarthritis. WCO-IOF-ESCEO World Congress on Osteoporosis, Osteoarthritis and Musculoskeletal Diseases. 26–29 March 2015, Milan, Italy. 2015;-:-. Abstract publication: Osteoporos Int 2015;26(Suppl 1): P308 Ann Rheum Dis 2015;74(Suppl 2):376.	9	Ostenil Plus
65	Manual search	5	Maheu E, Dreiser RL, Avouac B, Bardin T. Comparison of Therapeutic Response Rates, Using Various Response Definitions in a Prospective Randomized Non-Inferiority Trial Comparing Two Intra-Articular Hyaluronic Acid Preparations (1-Shot IAHA) in Isymptomatic Knee Osteoarthritis (OA), And Predictive Factors of a Better Response. SAT0443 EULAR congress 2016 London, UK. Abstract *Further evaluation from Dreiser data.*	9	Ostenil Plus

Relevant Literature, without doublettes and publications with missing data:

	Source	N° in scource	Citation	Reason for non-relevance or Appraisal	Product
1	Medline	9	Foti C, Cisari C, Carda S, Giordan N, Rocco A, Frizziero A, Della Bella G. A prospective observational study of the clinical efficacy and safety of intra-articular sodium hyaluronate in synovial joints with osteoarthritis. Eur J Phys	9	Hyalubrix

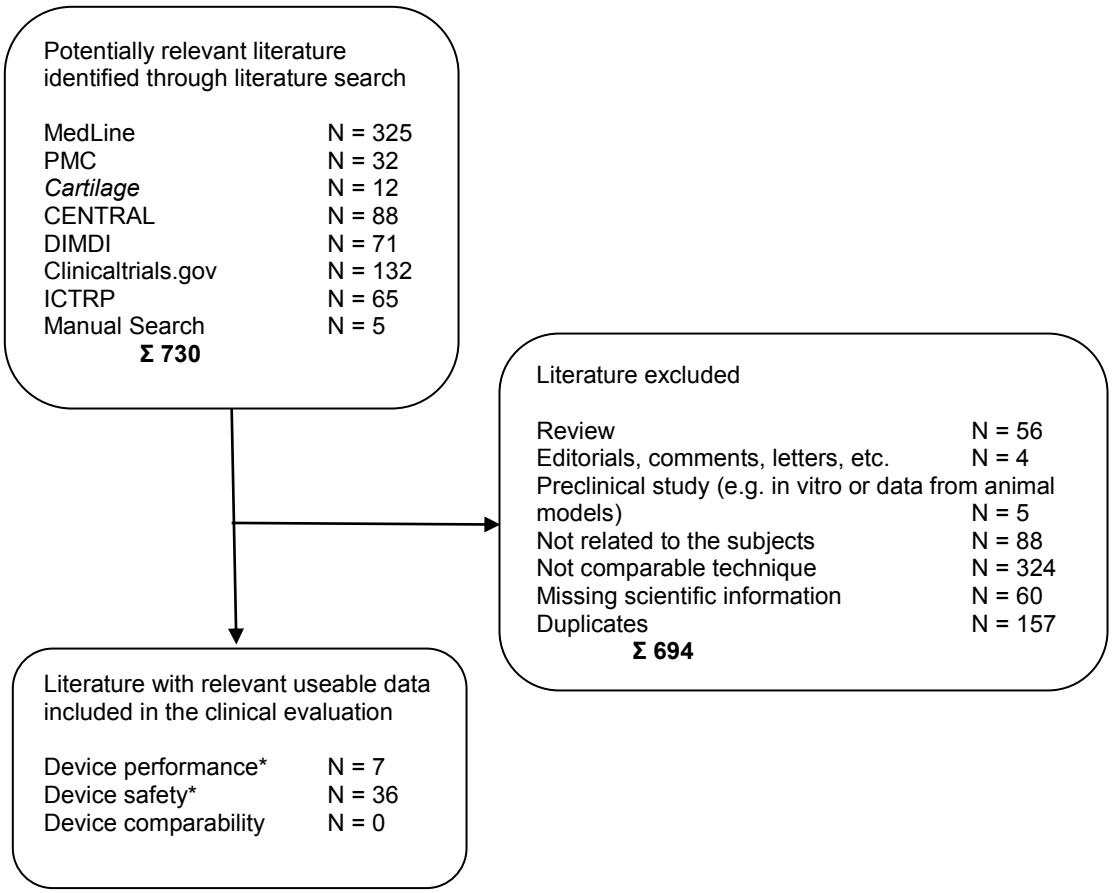
	Source	N° in scource	Citation	Reason for non-relevance or Appraisal	Product
			Rehabil Med. 2011 Sep;47(3):407-15.		
2	Medline	15	Karatay S, Kiziltunc A, Yildirim K, Karanfil RC, Senel K. Effects of different hyaluronic acid products on synovial fluid NO levels in knee osteoarthritis. Clin Rheumatol. 2005 Sep;24(5):497-501.	9	Orthovisc, hylan G-F 20 (Synvisc)
3	Medline	21	Karatay S, Kiziltunc A, Yildirim K, Karanfil RC, Senel K. Effects of different hyaluronic acid products on synovial fluid levels of intercellular adhesion molecule-1 and vascular cell adhesion molecule-1 in knee osteoarthritis. Ann Clin Lab Sci. 2004 Summer;34(3):330-5.	9	Orthovisc, hylan G-F 20 (Synvisc)
4	Medline	29	Kotevoglu N, Iyibozkurt PC, Hiz O, Toktas H, Kuran B. A prospective randomised controlled clinical trial comparing the efficacy of different molecular weight hyaluronan solutions in the treatment of knee osteoarthritis. Rheumatol Int. 2006 Feb;26(4):325-30.	9	hylan G-F 20 6 ml, Orthovisc
5	Medline	32	Stahl S, Karsh-Zafrir I, Ratzon N, Rosenberg N. Comparison of intraarticular injection of depot corticosteroid and hyaluronic acid for treatment of degenerative trapeziometacarpal joints. J Clin Rheumatol. 2005 Dec;11(6):299-302.	9	Orthovisc
6	Medline	36	Brandt KD, Block JA, Michalski JP, Moreland LW, Caldwell JR, Lavin PT. Efficacy and safety of intraarticular sodium hyaluronate in knee osteoarthritis. ORTHOVISC Study Group. Clin Orthop Relat Res. 2001 Apr;(385):130-43.	9	Orthovisc
7	Medline	39	Neustadt D, Caldwell J, Bell M, Wade J, Gimbel J. Clinical effects of intraarticular injection of high molecular weight hyaluronan (Orthovisc) in osteoarthritis of the knee: a randomized, controlled, multicenter trial. J Rheumatol. 2005 Oct;32(10):1928-36.	9	Orthovisc
8	Medline	56	Ozturk C, Atamaz F, Hepguler S, Argin M, Arkun R. The safety and efficacy of intraarticular hyaluronan with/without corticosteroid in knee osteoarthritis: 1-year, single-blind, randomized study. Rheumatol Int. 2006 Feb;26(4):314-9.	9	Orthovisc
9	Medline	75	Sezgin M, Demirel AC, Karaca C, Ortancil O, Ulkar GB, Kanik A, Cakçi A. Does hyaluronan affect inflammatory cytokines in knee osteoarthritis? Rheumatol Int. 2005 May;25(4):264-9.	9	Orthovisc
10	Medline	91	Calis M, Demir H, Ulker S, Kirnap M, Duygulu F, Calis HT. Is intraarticular sodium hyaluronate injection an alternative treatment in patients with adhesive capsulitis? Rheumatol Int. 2006 Apr;26(6):536-40.	9	Orthovisc
11	MeSH Medline	2	van der Weegen W, Wullems JA, Bos E, Noten H, van Drumpt RA. No difference between intra-articular injection of hyaluronic acid and placebo for mild to moderate knee osteoarthritis: a randomized, controlled, double-blind trial. J Arthroplasty. 2015 May;30(5):754-7. doi: 10.1016/j.arth.2014.12.012. Epub 2014 Dec 13. PubMed PMID: 25548079.	9	Fermathron Plus
12	MeSH Medline	13	Giarratana LS, Marelli BM, Crapanzano C, De Martinis SE, Gala L, Ferraro M, Marelli N, Albisetti W. A randomized double-blind clinical trial on the treatment of knee osteoarthritis: the efficacy of polynucleotides compared to standard hyaluronian viscosupplementation. Knee. 2014 Jun;21(3):661-8. doi: 10.1016/j.knee.2014.02.010. Epub 2014 Feb 24. PubMed PMID: 24703391.	9	Hyalubrix
13	MeSH Medline	14	Migliore A, Massafra U, Bizzi E, Tormenta S, Cassol M, Granata M. Duration of symptom relief	9	Synolis V-A

	Source	N° in scource	Citation	Reason for non-relevance or Appraisal	Product
			after intra-articular injection of hyaluronic acid combined with sorbitol (anti-ox-vs) in symptomatic hip osteoarthritis. Int J Immunopathol Pharmacol. 2014 Apr-Jun;27(2):245-52. PubMed PMID: 25004836.		
14	MeSH Medline	22	Heisel J, Kipshoven C. Safety and efficacy findings from a non-interventional study of a new hyaluronic acid/sorbitol formulation (GO-ON® matrix) for intra-articular injection to relieve pain and disability in osteoarthritis patients. Drug Res (Stuttg). 2013 Sep;63(9):445-9. doi: 10.1055/s-0033-1343425. Epub 2013 Apr 18. PubMed PMID: 23599036.	9	Go-On matrix
15	MeSH Medline	35	Paoloni M, Di Sante L, Dimaggio M, Bernetti A, Mangone M, Di Renzo S, Santilli V. Kinematic and kinetic modifications in walking pattern of hip osteoarthritis patients induced by intra-articular injections of hyaluronic acid. Clin Biomech (Bristol, Avon). 2012 Aug;27(7):661-5. doi: 10.1016/j.clinbiomech.2012.02.004. Epub 2012 Mar 11. PubMed PMID: 22410192.	9	Hyalubrix
16	MeSH Medline	36	Filardo G, Di Matteo B, Di Martino A, Merli ML, Cenacchi A, Fornasari P, Marcacci M, Kon E. Platelet-Rich Plasma Intra-articular Knee Injections Show No Superiority Versus Viscosupplementation: A Randomized Controlled Trial. Am J Sports Med. 2015 Jul;43(7):1575-82. doi: 10.1177/0363546515582027. Epub 2015 May 7. PubMed PMID: 25952818.	9	Hyalubrix
17	MeSH Medline	53	Battaglia M, Guaraldi F, Vannini F, Rossi G, Timoncini A, Buda R, Giannini S. Efficacy of ultrasound-guided intra-articular injections of platelet-rich plasma versus hyaluronic acid for hip osteoarthritis. Orthopedics. 2013 Dec;36(12):e1501-8. PubMed PMID: 24579221.	9	Hyalubrix
18	MeSH Medline	61	Witteveen AG, Sierevelt IN, Blankevoort L, Kerkhoffs GM, van Dijk CN. Intra-articular sodium hyaluronate injections in the osteoarthritic ankle joint: effects, safety and dose dependency. Foot Ankle Surg. 2010 Dec;16(4):159-63. doi: 10.1016/j.fas.2009.10.003. Epub 2009 Nov 8. PubMed PMID: 21047602.	9	Orthovisc
19	MeSH Medline	63	Colen S, van den Bekerom MP, Bellemans J, Mulier M. Comparison of intra-articular injections of hyaluronic acid and corticosteroid in the treatment of osteoarthritis of the hip in comparison with intra-articular injections of bupivacaine. Design of a prospective, randomized, controlled study with blinding of the patients and outcome assessors. BMC Musculoskelet Disord. 2010 Nov 16;11:264. doi: 10.1186/1471-2474-11-264. PubMed PMID: 21080920; PubMed Central PMCID: PMC2998460.	9	Ostenil Plus Study protocol, biostatistical report is available
20	MeSH Medline	66	Filardo G, Kon E, Di Martino A, Di Matteo B, Merli ML, Cenacchi A, Fornasari PM, Marcacci M. Platelet-rich plasma vs hyaluronic acid to treat knee degenerative pathology: study design and preliminary results of a randomized controlled trial. BMC Musculoskelet Disord. 2012 Nov 23;13:229. doi: 10.1186/1471-2474-13-229. PubMed PMID: 23176112; PubMed Central PMCID: PMC3532098.	9	Hyalubrix
21	MeSH Medline	73	Kul-Panza E, Berker N. Is hyaluronate sodium effective in the management of knee osteoarthritis? A placebo-controlled double-blind study. Minerva Med. 2010 Apr;101(2):63-72. PubMed PMID: 20467406.	9	Orthovisc

	Source	N° in scource	Citation	Reason for non-relevance or Appraisal	Product
22	MeSH Medline	77	Kon E, Mandelbaum B, Buda R, Filardo G, Delcogliano M, Timoncini A, Fornasari PM, Giannini S, Marcacci M. Platelet-rich plasma intra-articular injection versus hyaluronic acid viscosupplementation as treatments for cartilage pathology: from early degeneration to osteoarthritis. Arthroscopy. 2011 Nov;27(11):1490-501. doi: 10.1016/j.arthro.2011.05.011. Epub 2011 Aug 10. PubMed PMID: 21831567.	9	HMW HA (30 mg/2 mL, 1.5%, 1,000-2,900 kDa) and LMW HA (20 mg/2 mL, 1%, 500-730 kDa).
23	MeSH Medline	91	Migliore A, Massafra U, Bizzi E, Vacca F, Martin-Martin S, Granata M, Alimonti A, Tormenta S. Comparative, double-blind, controlled study of intra-articular hyaluronic acid (Hyalubrix) injections versus local anesthetic in osteoarthritis of the hip. Arthritis Res Ther. 2009;11(6):R183. doi: 10.1186/ar2875. Epub 2009 Dec 9. PubMed PMID: 20003205; PubMed Central PMCID: PMC3003515.	9	Hyalubrix
24	MeSH Medline	124	Bayramoğlu M, Karataş M, Cetin N, Akman N, Sözay S, Dilek A. Comparison of two different viscosupplements in knee osteoarthritis -- a pilot study. Clin Rheumatol. 2003 May;22(2):118-22. PubMed PMID: 12740676.	9	Orthovisc, hylan G-F 20 (Synvisc)
25	MeSH Medline	157	Atamaz F, Kirazli Y, Akkoc Y. A comparison of two different intra-articular hyaluronan drugs and physical therapy in the management of knee osteoarthritis. Rheumatol Int. 2006 Aug;26(10):873-8. Epub 2006 Jan 14. PubMed PMID: 16416102.	9	hylan G-F 20, Orthovisc
26	MeSH Medline	164	Karatosun V, Unver B, Gocen Z, Sen A. Comparison of two hyaluronan drugs in patients with advanced osteoarthritis of the knee. A prospective, randomized, double-blind study with long term follow-up. Clin Exp Rheumatol. 2005 Mar-Apr;23(2):213-8. PubMed PMID: 15895892.	9	Orthovisc, hylan G-F 20 (Synvisc)
27	MeSH Medline	180	Tascioglu F, Oner C. Efficacy of intra-articular sodium hyaluronate in the treatment of knee osteoarthritis. Clin Rheumatol. 2003 May;22(2):112-7. PubMed PMID: 12740675.	9	Orthovisc
28	CENTRAL	19	Polacco A, Beomonte Zobel B, Polacco M, Scarlata S, Gasparro F, DelVescovo R, Scarciolla L. The effect of intra-articular hyaluronic acid (Sinovial One) on knee osteoarthritis : A preliminary study. European Journal of Inflammation. 2013;11(3):847-853	9	Sinovial One
29	CENTRAL	30	Alberto M , Umberto M , Emanuele B , Bruno L , Valentina G , Prisco P , Mauro G and Sandro T.Intra-articular injection of hyaluronic acid (MW 1,500-2,000 kDa; HyalOne) in symptomatic osteoarthritis of the hip: A prospective cohort study. Archives of orthopaedic and trauma surgery, 2011, 131(12), 1677 Migliore A, Massafra U, Bizzi E, Laganà B, Germano V, Piscitelli P, Granata M, Tormenta S. Intra-articular injection of hyaluronic acid (MW 1,500-2,000 kDa, HyalOne(®)) in symptomatic osteoarthritis of the hip: a prospective cohort study. Arch Orthop Trauma Surg. 2011;131:1677–1685.	9	Hyalone
30	DIMDI	6	Rivera F. Single intra-articular injection of high molecular weight hyaluronic acid for hip osteoarthritis. J Orthop Traumatol. 2016;17:21-6.	9	Coxarthrum
31	Clinicaltrials.gov	42	Title: Study of Evaluating the Duration of Efficacy of One Intra Articular Injection of Sodium Hyaluronate 2.0% in Patients With Painful Osteoarthritis of the Knee Recruitment: Completed Study Results: No Results Available Conditions:	9	Ostenil Plus

	Source	N° in scource	Citation	Reason for non-relevance or Appraisal	Product
			Osteoarthritis Patient Interventions: Drug: Ostenil plus URL: https://ClinicalTrials.gov/show/NCT01288001 Abstract available. Siriraj Hospital; Bangkoknoi, Bangkok, Thailand, 10700; NCT01288001;		
32	Manual search	1	Guler O, Mutlu S, Isyar M, Seker A, Kayaalp ME, Mahirogullari M. Comparison of short-term results of intraarticular platelet-rich plasma (PRP) and hyaluronic acid treatments in early-stage gonarthrosis patients. Eur J Orthop Surg Traumatol. 2015;25:509-13.	9	Ostenil Plus (Osteonil plus) knee OA
33	Manual search	2	Borrás-Verdera A, Calcedo-Bernal V, Ojeda-Levenfeld J, Clavel-Sainz C. Efficacy and safety of a single intra-articular injection of 2% hyaluronic acid plus mannitol in knee osteoarthritis over a 6-month period. Rev Esp Cir Ortop Traumatol. 2011;56:274-80.	9	Ostenil Plus
34	Manual search	3	Frobenius K. A new high-dose treatment with intraarticular hyaluronic acid facilitates the management of osteoarthritis. Orthopädische Praxis. 2009;46(5):252-7	9	Ostenil Plus
35	Manual search	4	Dreiser RL, Avouac B, Bardin T. Efficacy of One Intra-Articular Injection of 2% Natural Sodium Hyaluronate Is Non-Inferior To Chemically Crosslinked Hylan G-F 20 In The Treatment Of Painful Tbiofemoral Osteoarthritis. WCO-IOF-ESCEO World Congress on Osteoporosis, Osteoarthritis and Musculoskeletal Diseases. 26–29 March 2015, Milan, Italy. 2015;-:-. Abstract publication: Osteoporos Int 2015;26(Suppl 1): P308 Ann Rheum Dis 2015;74(Suppl 2):376.	9	Ostenil Plus
36	Manual search	5	Maheu E, Dreiser RL, Avouac B, Bardin T. Comparison of Therapeutic Response Rates, Using Various Response Definitions in a Prospective Randomized Non-Inferiority Trial Comparing Two Intra-Articular Hyaluronic Acid Preparations (1-Shot IAHA) in Isymptomatic Knee Osteoarthritis (OA), And Predictive Factors of a Better Response. SAT0443 EULAR congress 2016 London, UK. Abstract *Further evaluation from Dreiser data.*	9	Ostenil Plus

9. Flow Chart



* some literature will address issue of both performance and safety
** excluded if no relevance is found

Appendix A 3 Tables Literature Evaluation

Study Titel	**Efficacy of OSTENIL PLUS (hyaluronic acid) versus SYNVISC-ONE in patients with tibiofemoral osteoarthritis. A randomised, controlled, double-blind, parallel-group study with a 6-month follow-up.**
Coordinating investigator	**Professor Thomas Bardin**
Scientific committee	**Dr Renée Liliane Dreiser, APHP Bichat-Claude Bernard**
Source	**Clinical study report**
Year	**2017**
Study Design	☒ **RCT** ☐ **non-randomized** ☐ **uncontrolled** ☐ **other** *Comment:* A randomised, controlled, double-blind, parallel-group study.
Is the research ethical according to current criteria or, for recent studies, is there evidence of ethical approval by an appropriate body?	☒ **yes** ☐ **no** ☐ **not reported** *Comment*: Clinical Investigation Plan and Report are available. Prior to initiation of the study, the study p rotocol and the other documents essential for the performance of the study (including the patient information used to obtain informed consent) were submitted to the Ethical Committee for review and approval.
A. SELECTION BIAS	
1. Were the data generated from a patient group that is representative of the intended treatment population (e.g., age, sex, etc.) and clinical condition (i.e., disease, including state and severity)?	☒ **applicable** ☐ **limited** ☐ **different population** *Quote:* A total of 292 patients were included and randomised in the study by 49 evaluating doctors in 49 medical practices in France. One hundred and eight patients (27%) were preselected but not included since they did not fulfil the inclusion and exclusion criteria. Patients with from tibiofemoral osteoarthritis according to the American College of Rheumatology criteria (modified Kellgren Lawrence stage Ib - III) with a WOMAC A score of at least 40 mm were included into the study after verification of the pre-defined inclusion and exclusion criteria. *Comment:* Patient group is representative for the intended treatment population and clinical condition for the application of OSTENIL® PLUS
2. Adequate generation of randomization sequence?	☒ **yes** ☐ **no** ☐ **unclear** ☐ **not applicable** *Comment:* The randomisation list generated by a computer algorithm was produced by Genexion SA (Geneva, Switzerland).
3. Allocation concealment	☒ **yes** ☐ **no** ☐ **unclear** ☐ **not applicable** *Comment:* After verification of the inclusion and exclusion criteria, the evaluating doctors allocated a randomisation number according to the chronological order of enrolment of each patient at their site. The patient was then sent to the injecting doctor who gave an injection of the product corresponding to the randomisation number. To maintain the balance between the two groups each evaluating doctor undertook to recruit a multiple of four patients.
Risk of bias for this section: ☒ **low** ☐ **unclear** ☐ **high** *Comment:-*	
B. PERFORMANCE BIAS (Blinding of participants and personnel)	
1. Was (were) the patient(s) blinded to the intervention or exposure status of participants?	

☒ yes ☐ no ☐ not applicable ☐ not reported

Comment: To prevent the patients from knowing the nature of their treatment the study products were packed in identical neutral packs.

2. Was physician or attending person(s) blinded to the intervention or exposure status of participants?

☐ yes ☐ no ☐ not applicable ☐ not reported

Comment: The treatment was administered blind to the evaluating doctor and the patient but not to the injecting doctor.

Risk of bias for this section: ☒ low ☐ unclear ☐ high

Comment: -

C. DETECTION BIAS (Blinding of outcome assessment)

Was (were) the outcome assessor(s) blinded to the intervention or exposure status of participants?

☒ yes ☐ no ☐ not applicable ☐ not reported

Comment: -

Risk of bias: ☒ low ☐ unclear ☐ high

Comment: -

D. ATTRITION BIAS (Incomplete outcome data)

Is the number and reasons for withdrawals and outputs of participants mentioned?

☒ yes ☐ no

Quote: -

Risk of bias for this section: ☒ low ☐ unclear ☐ high

Comment: -

E. REPORTING BIAS (Selective Reporting)

Were results reported independently from outcome and completely?

☒ yes ☐ no ☐ unclear

Comment: Investigation Plan is available.

Risk of bias: ☒ low ☐ unclear ☐ high

Comment:

Investigation Plan is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way.

F. DATA COLLECTION METHODS

1. Was the design of the study appropriate to the research question?

☒ yes ☐ no

Comment: A RCT is appropriate to demonstrate the non-inferiority of the efficacy of an intra-articular injection of OSTENIL PLUS compared to that of an intra-articular injection of the reference product SYNVISC ONE in the treatment of symptomatic tibiofemoral osteoarthritis.

2. Do valid outcome measures reported reflect the intended performance of the device?

☒ yes ☐ no

Comment: Outcome measures used were appropriate to evaluate effectiveness of intervention(s) in the indication under investiagtion.

The indication of OSTENIL® PLUS is treatment of pain and restricted mobility in degenerative and traumatic changes of the knee joint and other synovial joints.

WOMAC patient questionnaire, Lequesne index, VAS pain and CGI, are appropriate methods to evaluate efficacy of treatments for pain and joint function in patients with knee arthrosis.

3. Were data collection tools known to be valid and reliable?

☒ yes ☐ no

Comment:

WOMAC (subjective measurement) is a validated composit scale[38] used to assess disability arising from OA which is recommended by the Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT).[37]

Outcomes were measured in the same way for all patients.

4. Do the reports or collations of data contain sufficient information to be able to undertake a rational and objective assessment?

☒ **high quality** ☐ **minor deficiencies** ☐ **insufficient information**

Comment: The Clinical Investigation Report is a complete and objective presentation of the results of the study. Valid and reliable outcome measures were used for this study. Author´s conclusions are substantiated by the available data.

5. Is the duration of follow-up long enough to demonstrate effects with regard to safety and efficacy?

☒ **yes** ☐ **no**

Comment: The 6 months follow-up period is long enough to demonstrate safety and short-term effects with regard to performance the test product.

Risk of bias for this section: ☒ **low** ☐ **unclear** ☐ **high**

*Comment: V*alid and reliable outcome measures were used.

G. ANALYSIS

1. Is there a sample size calculation or power calculation?

☒ **yes** ☐ **partially** ☐ **no**

Comment: The sample size was estimated by a unilateral approach; it is therefore at least 111 subjects in each treatment group. By anticipating a loss rate of ± 15% at six months and taking account of patients possibly leaving the study prematurely, it was decided to enrol a total of at least 260 (2 x 130) patients in this clinical study.

2. Was the magnitude of the treatment effect observed clinically significant?

☒ **yes** ☐ **no** ☐ **not reported**

Comment: A mean change of 34.4 mm in WOMAC pain score is regarded as clinically significant for the OSTENIL PLUS treatment group.

3. Are the statistical methods appropriate?

☒ **yes** ☐ **no** ☐ **not reported**

Comment: The statistical analysis was performed according to the ICH E9 requirements and according to the latest biometric methods.

4. Indicate the unit of analysis

☐ **study site** ☐ **sponsor** ☒ **external Institution** ☐ **other**

Comment: External biostatistician (Genexio SA, Geneva) performed data analysis.

5. Is the analysis performed by intervention allocation status (i.e. intention to treat ITT) rather than the actual intervention received?

☒ **yes** ☐ **no** ☐ **unclear** ☐ **not applicable**

Comment: -

6. Are there other comprehensive aspect leading to bias?

☐ **yes** ☒ **no** ☐ **unclear**

Risk of bias for this section: ☒ **low** ☐ **unclear** ☐ **high**

Comment: Adequate data analysis techniques were used to keep bias from data analysis low.

H. INTERVENTION INTEGRITY

1. Were the data generated from the device in question?

☒ **actual device** ☐ **comparable device** ☐ **other device**

Comment: OSTENIL® PLUS (TRB Chemedica).

2. Was the device used for the same intended purpose (e.g., methods of deployment, application, etc.)?

☒ **same purpose** ☐ **minor deviation** ☐ **major deviation**

Comment: Test product was used according to intended purpose.

3. Is it likely that subjects received an unintended intervention (contamination or co-intervention) that may influence the results?

☐ **yes** ☐ **no** ☒ **unclear**

Comment:

Intervention is clearly described and performed by physician. Concomitant treatment or co-intervention was not prescribed by physicians. Physician included compliant patients but due to outpatient study, general control of patients outside the study center was not possible.

Risk of bias for this section: ☐ **low** ☒ **unclear** ☐ **high**
Comment: Unclear risk of bias due to outpatient design.

I. CONFOUNDERS / OTHER BIAS

1. Prior to the intervention were there between group differences for important confounders reported in the paper?

☐ **yes** ☒ **no** ☐ **unclear** ☐ **not applicable**

Comment: No significant difference was found between the two treatment groups regarding the efficacy criteria at inclusion. The characteristics of the disease at inclusion were similar in both groups.
At inclusion the patients of both treatment groups had very similar demographic characteristics (age, weight, height, BMI); the only significant inter-group difference observed was in the male/female ratio (p = 0.028) with a greater proportion of men in the SYNVISC ONE group (OSTENIL PLUS: 27.3%; SYNVISC ONE: 39.5%).

2. If there were differences between groups for important confounders, were they adequately managed in the analysis?

☒ **yes** ☐ **no** ☐ **not applicable**

Comment: The influence of the demographic imbalance on the primary efficacy endpoint was adequately analyzed and managed in data analysis.

3. Were there important confounders / other bias not reported in the paper?

☐ **yes** ☒ **no**

Risk of bias for this section: ☒ **low** ☐ **unclear** ☐ **high**

J. BIAS RISK TABLE*

Selection bias (randomization)	+
Selection bias (allocation)	+
Performance bias	+
Detection bias	+
Attrition bias	+
Reporting bias	+

\- High risk
? Unclear risk
\+ Low risk

* Higgins JPT, Green S (2011) Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration. www.cochrane-handbook.org.

K. EVALUATORS CONCLUSION

The planning and conduct of this randomized controlled trial complies with modern standards. Appropriate inclusion and exclusion criteria as well as appropriate subjective and objective parameters were chosen before the start of the study. The study procedure is described in a clear manner. Approval of the local Ethics Commission was obtained before study start and written informed consent was obtained from each study participant before inclusion. The conclusions on the efficacy and safety of the test product, described in the study reports, can be designated as plausible.

Titel	**A new high-dose treatment with intraarticular hyaluronic acid facilitates the management of osteoarthritis.**
Author(s)	**Frobenius K.**
Source	**Orthopädische Praxis. 2009;46(5):252-7**
Year	**2009**
Type	Practice-orientated scientific journal in orthopedics.
Authors background	Dr. med. Klaus Frobenius is medical specialist in orthopedics, chiropractic, sports

and expertise	medicine and acupuncture and member of the Society for Orthopaedic Traumatologic Sports Medicine (GOTS).
Study Design	☐ **RCT** ☐ **non-randomized** ☒ **uncontrolled** ☐ **other** *Comment:* Uncontrolled, prospective pilot-study.
Is the research ethical according to current criteria or, for recent studies, is there evidence of ethical approval by an appropriate body?	☒ **yes** ☐ **no** ☐ **not reported** *Comment*: Clinical Investigation Plan is available. Prior to initiation of the study, the Study Protocol, Informed Consent Form and Clinical Investigator's Brochure along with the requested documents were submitted to the Ethical Committee for review and approval.
A. SELECTION BIAS	
1. Were the data generated from a patient group that is representative of the intended treatment population (e.g., age, sex, etc.) and clinical condition (i.e., disease, including state and severity)?	☒ **applicable** ☐ **limited** ☐ **different population** *Quote:* 25 patients with x-ray ascertained osteoarthritis of the knee or hip joint, which caused them considerable pain for at least three months were included into the study after verification of the pre-defined inclusion and exclusion criteria. *Comment:* Patient group is representative for the intended treatment population and clinical condition for the application of OSTENIL® PLUS
2. Adequate generation of randomization sequence?	☐ **yes** ☐ **no** ☐ **unclear** ☒ **not applicable** *Comment:* Uncontrolled case-series.
3. Allocation concealment	☐ **yes** ☐ **no** ☐ **unclear** ☒ **not applicable** *Comment:* Uncontrolled case-series.
Risk of bias for this section:	☒ **low** ☐ **unclear** ☐ **high** *Comment:* Selection bias due to study population, randomization and allocation concealment can be ruled out (uncontrolled case-series).
B. PERFORMANCE BIAS (Blinding of participants and personnel)	
1. Was (were) the patient(s) blinded to the intervention or exposure status of participants?	☐ **yes** ☐ **no** ☒ **not applicable** ☐ **not reported** *Comment:* Uncontrolled case series.
2. Was physician or attending person(s) blinded to the intervention or exposure status of participants?	☐ **yes** ☐ **no** ☒ **not applicable** ☐ **not reported** *Comment:* Uncontrolled case series.
Risk of bias for this section:	☒ **low** ☐ **unclear** ☐ **high** *Comment:* Case-series, no control group. All patients received a similar amount of attention, ancillary treatment and diagnostic investigation. Performance bias due to knowledge of the allocated interventions by participants and personnel during the study is unlikely.
C. DETECTION BIAS (Blinding of outcome assessment)	
Was (were) the outcome assessor(s) blinded to the intervention or exposure status of participants?	☐ **yes** ☐ **no** ☒ **not applicable** ☐ **not reported** *Comment:* Uncontrolled case series.
Risk of bias:	☒ **low** ☐ **unclear** ☐ **high** *Comment:* No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding.
D. ATTRITION BIAS (Incomplete outcome data)	
Is the number and reasons for withdrawals and outputs of participants mentioned?	☒ **yes** ☐ **no** *Quote: One patient was excluded from this analysis because he has received a treatment prohibited in the protocol (an intra-articular corticosteroid).*

Risk of bias for this section: ☒ **low** ☐ **unclear** ☐ **high**
Comment: Case-series, no control group. Attrition bias refers to systematic differences between groups in withdrawals from a study.

E. REPORTING BIAS (Selective Reporting)

Were results reported independently from outcome and completely?

☒ **yes** ☐ **no** ☐ **unclear**

Comment: Investigation Plan is available.

Risk of bias: ☒ **low** ☐ **unclear** ☐ **high**
Comment:
Investigation Plan is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way.

F. DATA COLLECTION METHODS

1. Was the design of the study appropriate to the research question?

☒ **yes** ☐ **no**

Comment: A prospective case-series is appropriate for pilot-studies.

2. Do valid outcome measures reported reflect the intended performance of the device?

☒ **yes** ☐ **no**

Comment: Outcome measures used were appropriate to evaluate effectiveness of intervention(s) in the indication under investiagtion.
The indication of OSTENIL® PLUS is treatment of pain and restricted mobility in degenerative and traumatic changes of the knee joint and other synovial joints.
WOMAC patient questionnaire, clinical parameters and CGI, are appropriate methods to evaluate efficacy of test treatment in patients with knee or hip arthrosis.

3. Were data collection tools known to be valid and reliable?

☒ **yes** ☐ **no**

Comment:
WOMAC (subjective measurement) is a validated composit scale[38] used to assess disability arising from OA which is recommended by the Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT).[37]
Outcomes were measured in the same way for all patients.

4. Do the reports or collations of data contain sufficient information to be able to undertake a rational and objective assessment?

☒ **high quality** ☐ **minor deficiencies** ☐ **insufficient information**

Comment: The publication is a complete and objective presentation of the results of the study. Valid and reliable outcome measures were used for this study. Author´s conclusions are substantiated by the available data.

5. Is the duration of follow-up long enough to demonstrate effects with regard to safety and efficacy?

☒ **yes** ☐ **no**

Comment: The 3 months follow-up period is long enough to demonstrate safety and short-term effects with regard to performance the test product.

Risk of bias for this section: ☒ **low** ☐ **unclear** ☐ **high**
*Comment: V*alid and reliable outcome measures were used.

G. ANALYSIS

1. Is there a sample size calculation or power calculation?

☐ **yes** ☐ **partially** ☒ **no**

Comment: Uncontrolled case-series.

2. Was the magnitude of the treatment effect observed clinically significant?

☒ **yes** ☐ **no** ☐ **not reported**

Comment: For WOMAC total score improvement for all patients was clinically significant ($p<0.0001$).

3. Are the statistical methods appropriate?

☒ **yes** ☐ **no** ☐ **not reported**

Comment: Within-group analysis using the Wilcoxon-Pratt test is appropriate for analysis of case-series.

4. Indicate the unit of analysis

☐ **study site** ☐ **sponsor** ☒ **external Institution** ☐ **other**

Comment: External biostatistician performed data analysis.

5. Is the analysis performed by intervention allocation status (i.e. intention to treat ITT) rather than the actual intervention received?

☐ **yes** ☐ **no** ☐ **unclear** ☒ **not applicable**

Comment: Uncontrolled case-series.

6. Are there other comprehensive aspect leading to bias?

☐ **yes** ☒ **no** ☐ **unclear**

Risk of bias for this section: ☒ **low** ☐ **unclear** ☐ **high**

Comment: Adequate data analysis techniques were used to keep bias from data analysis low.

H. INTERVENTION INTEGRITY

1. Were the data generated from the device in question?

☒ **actual device** ☐ **comparable device** ☐ **other device**

Comment: OSTENIL® PLUS (TRB Chemedica).

2. Was the device used for the same intended purpose (e.g., methods of deployment, application, etc.)?

☒ **same purpose** ☐ **minor deviation** ☐ **major deviation**

Comment: Test product was used according to intended purpose.

3. Is it likely that subjects received an unintended intervention (contamination or co-intervention) that may influence the results?

☐ **yes** ☐ **no** ☒ **unclear**

Comment:
Intervention is clearly described and performed by physician. Concomitant treatment or co-intervention was not prescribed by physicians. Physician included compliant patients but due to outpatient study, general control of patients outside the study center was not possible.

Risk of bias for this section: ☐ **low** ☒ **unclear** ☐ **high**

Comment: Unclear risk of bias due to outpatient design.

I. CONFOUNDERS / OTHER BIAS

1. Prior to the intervention were there between group differences for important confounders reported in the paper?

☐ **yes** ☐ **no** ☐ **unclear** ☒ **not applicable**

Comment: Uncontrolled case-series.

2. If there were differences between groups for important confounders, were they adequately managed in the analysis?

☐ **yes** ☐ **no** ☒ **not applicable**

Comment: Uncontrolled case-series.

3. Were there important confounders / other bias not reported in the paper?

☐ **yes** ☒ **no**

Risk of bias for this section: ☒ **low** ☐ **unclear** ☐ **high**

J. BIAS RISK TABLE*

Selection bias (randomization)	+
Selection bias (allocation)	+
Performance bias	+
Detection bias	+
Attrition bias	+
Reporting bias	+

-	High risk
?	Unclear risk
+	Low risk

* Higgins JPT, Green S (2011) Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration. www.cochrane-handbook.org.

K. EVALUATORS CONCLUSION

The planning and conduct of these open study complies with modern standards. Appropriate inclusion and exclusion criteria as well as appropriate subjective and objective parameters were chosen before the start of the study. The study procedure is described in a clear manner. Approval of the local Ethics Commission was obtained before study start and written informed consent was obtained from each study participant before inclusion. The conclusions on the efficacy and safety of the test product, described in the study reports, can be designated as plausible.

The reduced number of injections facilitated the application of i.a. HA in patients with a difficult access to the joint. Longer intervals between the individual injections also allow a useful, temporal flexibility in the planning and execution of the treatment.

Titel	**Comparison of short-term results of intraarticular platelet-rich plasma (PRP) and hyaluronic acid treatments in early-stage gonarthrosis patients.**
Author(s)	**Guler O, Mutlu S, Isyar M, Seker A, Kayaalp ME, Mahirogullari M.**
Source	**Eur J Orthop Surg Traumatol. 2015;25:509-13**
Year	**2015**
Type	---
Authors background and expertise	At time of publication Dr. Olcay Guler was working at the Orthopedics and Traumatology Department, Medical Faculty, Medipol University, Istanbul, Turkey.
Study Design	☐ **RCT** ☐ **non-randomized** ☐ **uncontrolled** ☒ **other** *Comment:* Retrospective study.
Is the research ethical according to current criteria or, for recent studies, is there evidence of ethical approval by an appropriate body?	☐ **yes** ☐ **no** ☒ **not reported**

A. SELECTION BIAS

1. Were the data generated from a patient group that is representative of the intended treatment population (e.g., age, sex, etc.) and clinical condition (i.e., disease, including state and severity)?

☒ **applicable** ☐ **limited** ☐ **different population**

Comment: Patient group is representative for the intended treatment population and clinical condition for the application of OSTENIL® PLUS.

2. Adequate generation of randomization sequence?

☐ **yes** ☐ **no** ☒ **unclear** ☐ **not applicable**

Comment: Retrospective study, random selection of data sets not described.

3. Allocation concealment

☐ **yes** ☐ **no** ☐ **unclear** ☒ **not applicable**

Comment: Retrospective comparison.

Risk of bias for this section: ☐ **low** ☒ **unclear** ☐ **high**

Comment: Retrospective comparison.

B. PERFORMANCE BIAS (Blinding of participants and personnel)

1. Was (were) the patient(s) blinded to the intervention or exposure status of participants?

☐ **yes** ☐ **no** ☒ **not applicable** ☐ **not reported**

Comment: Retrospective comparison.

2. Was physician or attending person(s) blinded to the intervention or exposure status of participants?

☐ **yes** ☐ **no** ☒ **not applicable** ☐ **not reported**

Comment: Retrospective comparison.

Risk of bias for this section: ☐ **low** ☒ **unclear** ☐ **high**

Comment: Retrospective comparison, lack of clarity about (standardized) co-interventions and no control over how the intervention was administered.

C. DETECTION BIAS (Blinding of outcome assessment)

Was (were) the outcome assessor(s) blinded to the intervention or exposure status of participants?

☐ **yes** ☐ **no** ☐ **not applicable** ☒ **not reported**

Comment: Retrospective comparison.
It is recommended that abstractors remain blind to the purpose of the study and the research questions that the retrospective chart review is attempting to address.[334]

Risk of bias: ☐ **low** ☒ **unclear** ☐ **high**

Comment: Retrospective comparison.

D. ATTRITION BIAS (Incomplete outcome data)

Is the number and reasons for withdrawals and outputs of participants mentioned?

☐ **yes** ☒ **no**

Comment: Retrospective comparison.

Risk of bias for this section: ☐ **low** ☒ **unclear** ☐ **high**

Comment: Retrospective comparison, differential losses to follow up can also bias retrospective studies.

E. REPORTING BIAS (Selective Reporting)

Were results reported independently from outcome and completely?

☐ **yes** ☐ **no** ☒ **unclear**

Comment: Retrospective comparison.

Risk of bias: ☐ **low** ☒ **unclear** ☐ **high**

F. DATA COLLECTION METHODS

1. Was the design of the study appropriate to the research question?

☐ **yes** ☒ **no**

Comment: A retrospective comparison is not regarded as appropriate. It is not certain if patients were treated and evaluated comparable.

2. Do valid outcome measures reported reflect the intended performance of the device?

☒ **yes** ☐ **no**

Comment: Outcome measures used were appropriate to evaluate effectiveness of intervention(s) in the indication under investigation.

Quote: The VAS scoring system was used to assess pre- and post-treatment degree of pain, which was scored from 0 (no pain) to 10 (extremely severe).
Comment: Contrary to stated VAS scoring (continuous scale), evaluation of pain by score from 0 to 10 describes an ordinary scale. Values for VAS pain listed in table 3 also indicate use of ordinal scale.

3. Were data collection tools known to be valid and reliable?

☒ **yes** ☐ **no**

Comment: KSS was rated as objective measurement to rate the knee and patient's functional abilities.[332]

4. Do the reports or collations of data contain sufficient information to be able to undertake a rational and objective assessment?

☒ **high quality** ☐ **minor deficiencies** ☐ **insufficient information**

Comment: Author´s conclusions are substantiated by the available data.

5. Is the duration of follow-up long enough to demonstrate effects with regard to safety and efficacy?

☒ **yes** ☐ **no**

Comment: The 6 months follow-up period is long enough to demonstrate safety and short-term effects with regard to performance the test product. The short follow-up time was stated as limitation of this study.

Risk of bias for this section: ☐ **low** ☒ **unclear** ☐ **high**

Comment: A retrospective study design bear the risk of absence of data on potential confounding factors if the data was recorded in the past.

G. ANALYSIS

1. Is there a sample size calculation or power calculation?

☐ **yes** ☐ **partially** ☒ **no**

Comment: Retrospective comparison.

2. Was the magnitude of the treatment effect observed clinically significant?

☒ **yes** ☐ **no** ☐ **not reported**

Comment: Increase in KSS score from baseline to post-treatment second month and from baseline to post-treatment sixth month was significant ($p<0.001$) in both treatment groups. Changes in KSS and VAS scores over time were clinically significant.

3. Are the statistical methods appropriate?

☒ **yes** ☐ **no** ☐ **not reported**

Quote: Chi-square test was used for paired group comparison of categorical variables. For the comparison of two independent groups, Mann–Whitney U test was used for non-normally distributed numerical variables. Repeated measures analysis was used to determine the differences between the groups over time for dependent numerical variables. A p value smaller than 0.05 was considered statistically significant.

Comment: Appropriate procedures are applied for the statistical evaluation of the study results.

4. Indicate the unit of analysis

☒ **study site** ☐ **sponsor** ☐ **external Institution** ☐ **other**

Comment: Data of gonarthrosis patients were obtained retrospectively from hospital records.

5. Is the analysis performed by intervention allocation status (i.e. intention to treat ITT) rather than the actual intervention received?

☐ **yes** ☐ **no** ☐ **unclear** ☒ **not applicable**

Comment: Retrospective comparison.

6. Are there other comprehensive aspect leading to bias?

☐ **yes** ☐ **no** ☒ **unclear**

Comment: Retrospective comparison.

Risk of bias for this section: ☐ **low** ☒ **unclear** ☐ **high**

Comment: Retrospective comparison.

H. INTERVENTION INTEGRITY

1. Were the data generated from the device in question?

☒ **actual device** ☐ **comparable device** ☐ **other device**

Comment: OSTENIL® PLUS (TRB Chemedica) was used as comparator.

2. Was the device used for the same intended purpose (e.g., methods of deployment, application, etc.)?

☒ **same purpose** ☐ **minor deviation** ☐ **major deviation**

Comment: Gonarthrosis patients, who were stage 1 or stage 2 according to Kellgren–Lawrence classification. As data were obtained retrospective, it is assumed that patients were treated according to instruction for use in daily hospital routine.

3. Is it likely that subjects received an unintended intervention (contamination or co-intervention) that may influence the results?

☐ **yes** ☐ **no** ☒ **unclear**

Comment: A disadvantage of retrospective evaluation is uncertainty of co-interventions. Further, unintended interventions cannaot ruled out due to outpatient design.

Risk of bias for this section: ☐ **low** ☒ **unclear** ☐ **high**

I. CONFOUNDERS / OTHER BIAS

1. Prior to the intervention were there between group differences for important confounders reported in the paper?

☐ **yes** ☒ **no** ☐ **unclear** ☐ **not applicable**

Quote: No significant difference was determined between the treatment groups in terms of gender, age, body mass index (BMI), distribution among stages, and unilateral/bilateral involvement.
Patients with diabetes mellitus, rheumatoid disease, hematological disease (coagulation disorder), major lower extremity axis disorder (varus<5, valgus<5°), severe cardiovascular diseases, infection, and immunosuppressive diseases, those receiving anticoagulant therapy, those who received anti-inflammatory drugs until 5 days before blood sampling, those with abnormal complete blood count, and those who could not be evaluated by scoring systems were excluded.

2. If there were differences between groups for important confounders, were they adequately managed in the analysis?

☐ **yes** ☐ **no** ☒ **not applicable**

3. Were there important confounders / other bias not reported in the paper?

☐ **yes** ☐ **no** ☒ **unclear**

Comment: Retrospective comparison.

Risk of bias for this section: ☐ **low** ☒ **unclear** ☐ **high**
Comment: Retrospective comparison.

J. BIAS RISK TABLE*

Selection bias (randomization)	?
Selection bias (allocation)	+
Performance bias	?
Detection bias	?
Attrition bias	?
Reporting bias	?

\- High risk
? Unclear risk
\+ Low risk

* Higgins JPT, Green S (2011) Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration. www.cochrane-handbook.org.

K. EVALUATORS CONCLUSION

The retrospective chart review, also known as a medical record review, is a type of research design in which pre-recorded, patient-centered data are used to answer one or more research questions.[333] Prospective studies seem to be more appropriate to demonstrate causal relationship, while record reviews may be more helpful in finding associations.[335] Although causality is difficult to demonstrate data support application of OSTENIL® PLUS in daily hospital routine showing efficacy and safety in its indication.

Data source was specified, study groups were representative of intended treatment population and

clinical conditions, generally available outcome parameters and length of follow-up were adequate. This study was judged to be relevant for appraisal but results were interpreted keeping in view their limitations.

Titel	**Eficacia y seguridad de una única inyección intraarticular de ácido hialurónico al 2% más manitol en artrosis de rodilla durante un periodo de 6 meses. [Efficacy and safety of a single intra-articular injection of 2% hyaluronic acid plus mannitol injection in knee osteoarthritis over a 6-month period.]**
Author(s)	**Borrás-Verdera A, Calcedo-Bernal V, Ojeda-Levenfeld J, Clavel-Sainz C.**
Source	**Rev Esp Cir Ortop Traumatol 2013;56(4):274-80**
Year	**2013**
Type	Bimonthly periodical.
Authors background and expertise	At time of publication Dr. Aurelio was working at Servicio de Cirugía Ortopédica y Traumatología, Hospital Universitario Virgen Macarena, Sevilla, Spain.
Study Design	☐ **RCT** ☐ **non-randomized** ☒ **uncontrolled** ☐ **other** *Quote:* Pilot, multicentre, open, non-comparative study
Is the research ethical according to current criteria or, for recent studies, is there evidence of ethical approval by an appropriate body?	☒ **yes** ☐ **no** ☐ **not reported** *Quote*: All subjects gave their written informed consent prior to participating in the study, which was approved by the Clinical Research Ethics Committees of each of the aforementioned centres.
A. SELECTION BIAS	
1. Were the data generated from a patient group that is representative of the intended treatment population (e.g., age, sex, etc.) and clinical condition (i.e., disease, including state and severity)?	☒ **applicable** ☐ **limited** ☐ **different population** *Comment:* Patient group is representative for the intended treatment population and clinical condition for the application of OSTENIL® PLUS.
2. Adequate generation of randomization sequence?	☐ **yes** ☐ **no** ☐ **unclear** ☒ **not applicable** *Comment*: Uncontrolled case-series.
3. Allocation concealment	☐ **yes** ☐ **no** ☐ **unclear** ☒ **not applicable** *Comment:* Uncontrolled case-series.
Risk of bias for this section: *Comment:* Uncontrolled case-series.	☒ **low** ☐ **unclear** ☐ **high**
B. PERFORMANCE BIAS (Blinding of participants and personnel)	
1. Was (were) the patient(s) blinded to the intervention or exposure status of participants?	☐ **yes** ☐ **no** ☒ **not applicable** ☐ **not reported** *Comment:* Uncontrolled case-series.
2. Was physician or attending person(s) blinded to the intervention or exposure status of participants?	☐ **yes** ☐ **no** ☒ **not applicable** ☐ **not reported** *Comment:* Uncontrolled case-series.
Risk of bias for this section: *Comment:* Uncontrolled case-series.	☒ **low** ☐ **unclear** ☐ **high**

C. DETECTION BIAS (Blinding of outcome assessment)

Was (were) the outcome assessor(s) blinded to the intervention or exposure status of participants?

☐ **yes** ☐ **no** ☒ **not applicable** ☐ **not reported**

Comment: Uncontrolled case-series.

Risk of bias: ☒ **low** ☐ **unclear** ☐ **high**

Comment: Uncontrolled case-series.

D. ATTRITION BIAS (Incomplete outcome data)

Is the number and reasons for withdrawals and outputs of participants mentioned?

☒ **yes** ☐ **no**

Comment: Reason for withdrawl is described for each patient mentioned.

Risk of bias for this section: ☒ **low** ☐ **unclear** ☐ **high**

Comment: Uncontrolled case-series, Attrition bias refers to systematic differences between groups in withdrawals from a study.

E. REPORTING BIAS (Selective Reporting)

Were results reported independently from outcome and completely?

☐ **yes** ☐ **no** ☒ **unclear**

Comment: Investigation Plan is not available.

Risk of bias: ☐ **low** ☒ **unclear** ☐ **high**

Comment: Insufficient information to permit judgement of 'low risk' or 'high risk'.

F. DATA COLLECTION METHODS

1. Was the design of the study appropriate to the research question?

☒ **yes** ☐ **no**

Comment: Study was performed as pilot study, case-series evaluation is appropriate.

2. Do valid outcome measures reported reflect the intended performance of the device?

☒ **yes** ☐ **no**

Comment: VAS pain and WOMAC questionnaire were appropriate to evaluate effectiveness of intervention(s) in the indication under investigation.

3. Were data collection tools known to be valid and reliable?

☒ **yes** ☐ **no**

Comment: Subjective pain evaluation was perfomed with valid and reliable VAS.[155,156] WOMAC (subjective measurement) is a validated composit scale[38] used to assess disability arising from OA which is recommended by the Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT).[37]

4. Do the reports or collations of data contain sufficient information to be able to undertake a rational and objective assessment?

☒ **high quality** ☐ **minor deficiencies** ☐ **insufficient information**

Comment: Valid and reliable outcome measures were used for this study. Author´s conclusions are substantiated by the available data.

5. Is the duration of follow-up long enough to demonstrate effects with regard to safety and efficacy?

☒ **yes** ☐ **no**

Comment: The 6 months follow-up period is long enough to demonstrate safety and mid-term effects with regard to performance the test product.

Risk of bias for this section: ☒ **low** ☐ **unclear** ☐ **high**

G. ANALYSIS

1. Is there a sample size calculation or power calculation?

☐ **yes** ☐ **partially** ☒ **no**

Comment: 80 patients are assumed to be enough to detect clinical relevant treatment effects.

2. Was the magnitude of the treatment effect observed clinically significant?

☒ **yes** ☐ **no** ☐ **not reported**

Quote: For the main efficacy parameters studied, the extent of joint pain assessed

by VAS showed a statistically significant decrease ($P < 0.001$) after the first follow-up visit (15 days) compared to the initial value (before HA infiltration). This decrease was maintained until the last visit (6 months).
Joint function improved by 38.7% on Day 30, reaching 47.5% on Day 180. Rescue medication use decreased from 58.2% at baseline to 2.5% on Day 90, increasing in the last visits.
Comment: Treatment effect was statistically significant and clinically relevant.

3. Are the statistical methods appropriate?

☒ **yes** ☐ **no** ☐ **not reported**

Comment: Computer program for data analysis was named and *a*ppropriate procedures were applied for the statistical evaluation of the study results, descriptive statistics fits to describe treatment effects.

4. Indicate the unit of analysis

☒ **study site** ☐ **sponsor** ☐ **external Institution** ☐ **other**

5. Is the analysis performed by intervention allocation status (i.e. intention to treat ITT) rather than the actual intervention received?

☐ **yes** ☐ **no** ☐ **unclear** ☒ **not applicable**

Comment: Uncontrolled case-series.

6. Are there other comprehensive aspect leading to bias?

☐ **yes** ☒ **no** ☐ **unclear**

Risk of bias for this section: ☒ **low** ☐ **unclear** ☐ **high**

H. INTERVENTION INTEGRITY

1. Were the data generated from the device in question?

☒ **actual device** ☐ **comparable device** ☐ **other device**

Comment: OSTENIL® PLUS (TRB Chemedica) was used.

2. Was the device used for the same intended purpose (e.g., methods of deployment, application, etc.)?

☒ **same purpose** ☐ **minor deviation** ☐ **major deviation**

Comment: Test product was used according to instruction for use.

3. Is it likely that subjects received an unintended intervention (contamination or co-intervention) that may influence the results?

☐ **yes** ☐ **no** ☒ **unclear**

Comment: Physician included compliant patients but due to outpatient study, general control of patients outside the study center was not possible.

Risk of bias for this section: ☐ **low** ☒ **unclear** ☐ **high**

I. CONFOUNDERS / OTHER BIAS

1. Prior to the intervention were there between group differences for important confounders reported in the paper?

☐ **yes** ☐ **no** ☐ **unclear** ☒ **not applicable**

Comment: Uncontrolled case series.

2. If there were differences between groups for important confounders, were they adequately managed in the analysis?

☐ **yes** ☐ **no** ☒ **not applicable**

Comment: Uncontrolled case series.

3. Were there important confounders / other bias not reported in the paper?

☐ **yes** ☒ **no**

Risk of bias for this section: ☒ **low** ☐ **unclear** ☐ **high**

Comment: This study appears to be free of other sources of bias.

J. BIAS RISK TABLE*

Selection bias (randomization)	+
Selection bias (allocation)	+
Performance bias	+
Detection bias	+
Attrition bias	+
Reporting bias	?

\- High risk
? Unclear risk
\+ Low risk

* Higgins JPT, Green S (2011) Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration. www.cochrane-handbook.org.

K. EVALUATORS CONCLUSION

The planning of this study complies with modern standards. Appropriate inclusion and exclusion criteria were chosen before the start of the study. The number of patients in this uncontrolled case series is high to obtain reliable results. The study procedure is described in a clear manner. Approval of the local Ethics Commission was obtained before study start. Study group was representative of intended treatment population and clinical conditions, generally available outcome parameters and length of follow-up were adequate to answer research question and to generalize results to everyday population. Outcomes show sufficient and scientific reliable information on the performance and safety of OSTENIL® PLUS to document the successful and safe application in patients with osteoarthritis. The conclusions on the test product, can be designated as plausible.

Titel	**Comparison of intra-articular injections of Hyaluronic Acid and Corticosteroid in the treatment of Osteoarthritis of the hip in comparison with intra-articular injections of Bupivacaine. Design of a prospective, randomized, controlled study with blinding of the patients and outcome assessors.**
Author(s)	**Colen S, van den Bekerom MP, Bellemans J, Mulier M.**
Source	**BMC Musculoskelet Disord. 2010;11(1):264**
Year	**2010**
Type	*BMC Musculoskeletal Disorders* is an open access, peer-reviewed journal that considers articles on all aspects of the prevention, diagnosis and management of musculoskeletal and associated disorders, as well as related molecular genetics, pathophysiology, and epidemiology.
Authors background and expertise	At time of publication Dr. Sascha Colen was working at the University of Leuven, Department of Orthopaedic Surgery, Pellenberg, Belgium.
Study Design	☒ **RCT** ☐ **non-randomized** ☐ **uncontrolled** ☐ **other** *Quote:* Randomized, controlled trial with a three-armed, parallel-group design
Is the research ethical according to current criteria or, for recent studies, is there evidence of ethical approval by an appropriate body?	☒ **yes** ☐ **no** ☐ **not reported** *Quote:* Ethical approval has been obtained from the ethical committee of the Catholic University, Leuven. Informed consent forms will be signed by the patients before inclusion into our study.

A. SELECTION BIAS

1. Were the data generated from a patient group that is representative of the intended treatment population (e.g., age, sex, etc.) and clinical condition (i.e., disease, including state and severity)?

☒ **applicable** ☐ **limited** ☐ **different population**

Comment: Inclusion and exclusion criteria are available on www.clinicaltrials.org (NCT01079455)
Patient group is representative for the intended treatment population and clinical condition for the application of OSTENIL® PLUS.

2. Adequate generation of randomization sequence?

☒ **yes** ☐ **no** ☐ **unclear** ☐ **not applicable**

Quote: A block randomization scheme, with a block size equal to 8, will be used for the randomization to avoid at random imbalances in group size. No stratification variables were considered in the randomization.

3. Allocation concealment

☐ **yes** ☐ **no** ☒ **unclear** ☐ **not applicable**

Comment: Not described.

Risk of bias for this section: ☐ **low** ☒ **unclear** ☐ **high**

B. PERFORMANCE BIAS (Blinding of participants and personnel)

1. Was (were) the patient(s) blinded to the intervention or exposure status of participants?

☐ **yes** ☐ **no** ☐ **not applicable** ☒ **not reported**

2. Was physician or attending person(s) blinded to the intervention or exposure status of participants?

☐ **yes** ☐ **no** ☐ **not applicable** ☒ **not reported**

Risk of bias for this section: ☐ **low** ☒ **unclear** ☐ **high**

C. DETECTION BIAS (Blinding of outcome assessment)

Was (were) the outcome assessor(s) blinded to the intervention or exposure status of participants?

☐ **yes** ☐ **no** ☐ **not applicable** ☒ **not reported**

Risk of bias: ☐ **low** ☒ **unclear** ☐ **high**

D. ATTRITION BIAS (Incomplete outcome data)

Is the number and reasons for withdrawals and outputs of participants mentioned?

☐ **yes** ☒ **no**

Risk of bias for this section: ☐ **low** ☐ **unclear** ☒ **high**

E. REPORTING BIAS (Selective Reporting)

Were results reported independently from outcome and completely?

☒ **yes** ☐ **no** ☐ **unclear**

Comment: Biostatistical report is available.

Risk of bias: ☒ **low** ☐ **unclear** ☐ **high**

Comment: Complete analysis of objective and subjective measurements for all groups independent from outcome.

F. DATA COLLECTION METHODS

1. Was the design of the study appropriate to the research question?

☒ **yes** ☐ **no**

Comment: A randomized controlled study design is appropriate to compare treatments. Unfortunately, it is not known if the study was performed in blind manner.

2. Do valid outcome measures reported reflect the intended performance of the device?

☒ **yes** ☐ **no**

Comment: Outcome measures used were appropriate to evaluate effectiveness of intervention(s) in the indication under investigation.

3. Were data collection tools known to be valid and reliable?

☒ **yes** ☐ **no**

Comment: Subjective pain evaluation was performed with valid and reliable VAS.[155,156] Harris hip score was shown to be responsive and has been validated for arthroplasty.[336,337,338]

4. Do the reports or collations of data contain sufficient information to be able to undertake a rational and objective assessment?

☐ **high quality** ☒ **minor deficiencies** ☐ **insufficient information**

Comment: Biostatistical analysis and report is available. Additional data analyses (e.g. inter-group comparisons) could have been performed.

5. Is the duration of follow-up long enough to demonstrate effects with regard to safety and efficacy?

☒ **yes** ☐ **no**

Comment: The 6 months follow-up period is long enough to demonstrate safety and short-term effects with regard to performance the test product.

Risk of bias for this section: ☒ **low** ☐ **unclear** ☐ **high**

G. ANALYSIS

1. Is there a sample size calculation or power calculation?

☒ **yes** ☐ **partially** ☐ **no**

Quote: A sample size calculation was performed to have at least 80% power to detect in both groups compared with placebo, a clinically meaningful difference in change (baseline-6 months) of 10 mm in VAS and 10 points in HSS.

2. Was the magnitude of the treatment effect observed clinically significant?

☒ **yes** ☐ **no** ☐ **not reported**

Comment: Biostatistical report is available. An improvement in VAS pain from baseline median 52.0 mm (range 0.0-100.0) to 34.0 (range 0.0-98.0) at 6 months post-treatment in HA-group was regarded as clinically relevant. 6 months post-treatment the Hip disability and Osteoarthritis Outcome Score improved from baseline 49.7 (range 7.5-93.8) to 55.1 (range 3.1-99.4) and the Harris hip score from 57.0 (range 20.0-88.0) to 74.5 (range 22.0-91.0) in HA-group.

3. Are the statistical methods appropriate?

☒ **yes** ☐ **no** ☐ **not reported**

Comment: Appropriate procedures are applied for the statistical evaluation of the study results.

4. Indicate the unit of analysis

☐ **study site** ☐ **sponsor** ☒ **external Institution** ☐ **other**

Comment: Statistical analysis was performed by the Group biomedical sciences, Dept. Public Health, Interuniversity Centre for Biostatistics and Statistical Bioinformatics.

5. Is the analysis performed by intervention allocation status (i.e. intention to treat ITT) rather than the actual intervention received?

☐ **yes** ☐ **no** ☒ **unclear** ☐ **not applicable**

Comment: Not mentioned in the report.

6. Are there other comprehensive aspect leading to bias?

☐ **yes** ☐ **no** ☒ **unclear**

Risk of bias for this section: ☐ **low** ☒ **unclear** ☐ **high**

H. INTERVENTION INTEGRITY

1. Were the data generated from the device in question?

☒ **actual device** ☐ **comparable device** ☐ **other device**

Comment: OSTENIL® PLUS (TRB Chemedica) was used.

2. Was the device used for the same intended purpose (e.g., methods of deployment, application, etc.)?

☒ **same purpose** ☐ **minor deviation** ☐ **major deviation**

Comment: Test product was used according to instruction for use.

3. Is it likely that subjects received an unintended intervention (contamination or co-intervention) that may influence the results?

☐ **yes** ☐ **no** ☒ **unclear**

Comment: Physician included compliant patients but due to outpatient study, general control of patients outside the study center was not possible.

Risk of bias for this section: ☐ **low** ☒ **unclear** ☐ **high**

I. CONFOUNDERS / OTHER BIAS

1. Prior to the intervention were there between group differences for important confounders reported in the paper?

☒ **yes** ☐ **no** ☐ **unclear** ☐ **not applicable**

Comment: Descriptive analysis in biostatistical report show that patients in different treatment groups were comparable with regard to demographics (age, gender, body size and weight, body mass index) and Kellgren Lawrence, baseline VAS pain and Harris Hip score.

2. If there were differences between groups for important confounders, were they adequately managed in the analysis?

☐ **yes** ☐ **no** ☒ **not applicable**

3. Were there important confounders / other bias not reported in the paper?

☐ **yes** ☐ **no** ☒ **unclear**

Risk of bias for this section: ☐ **low** ☒ **unclear** ☐ **high**

Comment: The biostatistical report contained insufficient information to assess whether an important risk of bias exists.

J. BIAS RISK TABLE*

Selection bias (randomization)	+
Selection bias (allocation)	?
Performance bias	?
Detection bias	?
Attrition bias	-
Reporting bias	+

-	High risk
?	Unclear risk
+	Low risk

* Higgins JPT, Green S (2011) Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration. www.cochrane-handbook.org.

K. EVALUATORS CONCLUSION

The planning of this study complies with modern standards (Colen S et al. 2010). Appropriate inclusion and exclusion criteria were chosen before the start of the study. The study procedure is described in a clear manner. Approval of the local Ethics Commission was obtained before study start. Study group(s) which were representative of intended treatment population and clinical conditions, generally available outcome parameters and length of follow-up were adequate to answer research question and to generalize results to everyday population. Outcomes show sufficient and scientific reliable information on the performance and safety of OSTENIL® PLUS to document the successful and safe application in patients with osteoarthritis. The conclusions on the test product, can be designated as plausible.

Tabular presentation of safety results from relevant literature:

Publication	Product	Information from publication
Foti C, Cisari C, Carda S, Giordan N, Rocco A, Frizziero A, Della Bella G. A prospective observational study of the clinical efficacy and safety of intra-articular sodium hyaluronate in synovial joints with osteoarthritis. Eur J Phys Rehabil Med. 2011 Sep;47(3):407-15.	Hyalubrix	In summary, this study has demonstrated that IA injections of sodium hyaluronate (MW 1500-2000 KDa; Hyalubrix®) are safe and well tolerated.
Karatay S, Kiziltunc A, Yildirim K, Karanfil RC, Senel K. Effects of different hyaluronic acid products on synovial fluid NO levels in knee osteoarthritis. Clin Rheumatol. 2005 Sep;24(5):497-501.	Orthovisc, hylan G-F 20 (Synvisc)	*Safety results not mentioned.*
Karatay S, Kiziltunc A, Yildirim K, Karanfil RC, Senel K. Effects of different hyaluronic acid products on synovial fluid levels of intercellular adhesion molecule-1 and vascular cell adhesion molecule-1 in knee osteoarthritis. Ann Clin Lab Sci. 2004 Summer;34(3):330-5.	Orthovisc, hylan G-F 20 (Synvisc)	*Safety results not mentioned.*
Kotevoglu N, Iyibozkurt PC, Hiz O, Toktas H, Kuran B. A prospective randomised controlled clinical trial comparing the efficacy of different molecular weight hyaluronan solutions in the treatment of knee osteoarthritis. Rheumatol Int. 2006 Feb;26(4):325-30.	hylan G-F 20 6 ml, Orthovisc	Local adverse events such as transient pain at injection site or warm knee lasting for one night were recorded in two patients (3%). *Not mentioned in which group.*
Stahl S, Karsh-Zafrir I, Ratzon N, Rosenberg N. Comparison of intraarticular injection of depot corticosteroid and hyaluronic acid for treatment of degenerative trapeziometacarpal joints. J Clin Rheumatol. 2005 Dec;11(6):299-302.	Orthovisc	*Safety results not mentioned.*
Brandt KD, Block JA, Michalski JP, Moreland LW, Caldwell JR, Lavin PT. Efficacy and safety of intraarticular sodium hyaluronate in knee osteoarthritis. ORTHOVISC Study Group. Clin Orthop Relat Res. 2001 Apr;(385):130-43.	Orthovisc	9 patients treated with HA (8%) and 11 patients treated with saline (10%) reported 32 adverse events that were attributed to treatment. The most common adverse events included injection site reactions, such as pain, local Mannnation, or ecchymosis (n = 12); musculoskeletal events, such as arthralgia or worsening arthritis (n 7); gastrointestinal events, such as nausea, diarrhea, dyspepsia, and abdorninal pain (n = 6); and general fatigue and pain (n = 3). In only 3 instances (in 3 patients) was arthralgia considered by the investigator to be related to treatment (HA in 1 patient, saline in 2 patients). No differences between the two treatment groups with respect to the nature of the adverse events were evident. None of the serious adverse events was thought by the investigator to have been related to treatment. A significant proportion of treatment related adverse events (9 events in 5 patients) were associated with the injection and involved a superficial localized intlammatory reaction or pain at the injection site. Only 1 patient reported severe injection site pain; all other injection site events were considered mild or moderate. No patient had acute synovitis develop or underwent arthrocentesis for effusion aller injection. All injection-related adverse events were of brief duration and resolved promptly after local application of an ice pack or the use of acetaminophen, or both, as permitted by the study protocol. The overall incidence of injection site

Publication	Product	Information from publication
		reactions was 1.2% for sodium hyaluronate and 1.5% for saline injections. The results indicate thal sodium hyaluronate treatment is well tolerated and produces statistically and clinically signilicant improvement of symptoms in patients with mild to moderate knee osteoarthrilis in whom pain in the contralateral knee is relatively modest.
Neustadt D, Caldwell J, Bell M, Wade J, Gimbel J. Clinical effects of intraarticular injection of high molecular weight hyaluronan (Orthovisc) in osteoarthritis of the knee: a randomized, controlled, multicenter trial. J Rheumatol. 2005 Oct;32(10):1928-36.	Orthovisc	Potential device-related adverse events were reported in 11 patients in the 04 group (4 weekly injections), 6 in the 03A1 group (3 weekly injections plus arthrocenthesis), and 4 in the A4 group (4 arthrocenthesis without injection; control). Adverse events directly related to the injection site (erythema, bruising, or pain) consisted of 5 events in 5 patients in the 04 group, 2 events in 2 patients in the 03A1 group, and 2 events in 2 patients in the A4 group. One patient in the A4 control group reported severe injection site pain; all other injection site events were considered slight to moderate. One patient in the 04 group reported severe joint swelling that was thought to be treatment-related. None of the serious adverse events were considered by the investigator to be related to Orthovisc® treatment. No unanticipated adverse device effect occurred during the study. Our results indicate that Orthovisc® has an excellent safety profile, highlighted by' a low rate of injection site rede¬tions. There were no device-related serious adverse events, and device-related adverse events in general were < 9% in 04 and 5% in 03A1; there was no statistical differente among the 04, 03A1, and A4 groups in any of the adverse event comparisons analyzed. The rate of injection site pain was L6% or less in 04 and 03A 1 groups. Arthralgia was noted in 12.5% of 04 patients; however, only one case was deemed. device-related. In conclusion. Orthovisc® is extremely safe, with low incidences of device-related adverse reactions and a safety profile comparable to the other approved viscosupplementation devices.
Ozturk C, Atamaz F, Hepguler S, Argin M, Arkun R. The safety and efficacy of intraarticular hyaluronan with/without corticosteroid in knee osteoarthritis: 1-year, single-blind, randomized study. Rheumatol Int. 2006 Feb;26(4):314-9.	Orthovisc	Two patients from group A (HA) and one from group B (HA+joint asoiration+steroid) reported adverse events after the third injection. All adverse effects were reported as local reactions, including mild swelling, warmth, and pain at the injection site without significant difference between groups. Moreover, these patients had relief within a few days after application of cold packs. No severe or systemic adverse events were observed in the patients during the study.
Sezgin M, Demirel AC, Karaca C, Ortancil O, Ulkar GB, Kanik A, Cakçi A. Does hyaluronan affect inflammatory cytokines in knee osteoarthritis? Rheumatol Int. 2005 May;25(4):264-9.	Orthovisc	HA was a safe treatment alternative in that it caused no local or systemic complications during the treatment or follow-up period.
Calis M, Demir H, Ulker S, Kirnap M, Duygulu F, Calis HT. Is intraarticular sodium hyaluronate injection an alternative treatment in patients with adhesive capsulitis? Rheumatol Int. 2006 Apr;26(6):536-40.	Orthovisc	*Safety results not mentioned.*
van der Weegen W, Wullems JA, Bos E, Noten H, van Drumpt RA. No difference between intra-articular injection of hyaluronic acid and placebo for mild to moderate knee osteoarthritis: a randomized, controlled, double-blind trial. J Arthroplasty. 2015 May;30(5):754-7. doi: 10.1016/j.arth.2014.12.012. Epub 2014 Dec 13. PubMed PMID: 25548079.	Fermathron Plus 30mg/2ml (1.5%)	There were no serious adverse events in either group. Mild to moderately transient increased knee pain and stiffness (1 to 3 days after injection) were reported in 23.2% in the HA group and in 15.6% in the placebo group (P = .13).
Giarratana LS, Marelli BM, Crapanzano C, De Martinis SE, Gala	Hyalubrix	No significant adverse events connected to the employment of both products were reported.

Publication	Product	Information from publication
L, Ferraro M, Marelli N, Albisetti W. A randomized double-blind clinical trial on the treatment of knee osteoarthritis: the efficacy of polynucleotides compared to standard hyaluronian viscosupplementation. Knee. 2014 Jun;21(3):661-8. doi: 10.1016/j.knee.2014.02.010. Epub 2014 Feb 24. PubMed PMID: 24703391.		
Heisel J, Kipshoven C. Safety and efficacy findings from a non-interventional study of a new hyaluronic acid/sorbitol formulation (GO-ON® matrix) for intra-articular injection to relieve pain and disability in osteoarthritis patients. Drug Res (Stuttg). 2013 Sep;63(9):445-9. doi: 10.1055/s-0033-1343425. Epub 2013 Apr 18. PubMed PMID: 23599036.	Go-On matrix	In total, 22 patients reported 24 ARs, all of which were in the SOC musculoskeletal and connective tissue disorders. The most commonly reported AR was injection site joint pain (n = 15). Overall, it can be concluded that the GO-ON ® matrix is effective and well tolerated in the treatment of pain and functional impairment in patients with radiologically confi rmed OA, providing fast acting and long-lasting pain relief and joint function.
Paoloni M, Di Sante L, Dimaggio M, Bernetti A, Mangone M, Di Renzo S, Santilli V. Kinematic and kinetic modifications in walking pattern of hip osteoarthritis patients induced by intra-articular injections of hyaluronic acid. Clin Biomech (Bristol, Avon). 2012 Aug;27(7):661-5. doi: 10.1016/j.clinbiomech.2012.02.004. Epub 2012 Mar 11. PubMed PMID: 22410192.	Hyalubrix	*Safety results not mentioned.*
Filardo G, Di Matteo B, Di Martino A, Merli ML, Cenacchi A, Fornasari P, Marcacci M, Kon E. Platelet-Rich Plasma Intra-articular Knee Injections Show No Superiority Versus Viscosupplementation: A Randomized Controlled Trial. Am J Sports Med. 2015 Jul;43(7):1575-82. doi: 10.1177/0363546515582027. Epub 2015 May 7. PubMed PMID: 25952818.	Hyalubrix	Two patients reported severe pain and swelling after the first HA injection, which led them to withdraw from the injective treatment.
Battaglia M, Guaraldi F, Vannini F, Rossi G, Timoncini A, Buda R, Giannini S. Efficacy of ultrasound-guided intra-articular injections of platelet-rich plasma versus hyaluronic acid for hip osteoarthritis. Orthopedics. 2013 Dec;36(12):e1501-8. PubMed PMID: 24579221.	Hyalubrix	Regarding side effects, 1 patient developed a superficial hematoma during the first infiltration due to transitional damage of a peripheral branch of the great saphenous vein presenting with an abnormal course, which spontaneously resolved in 2 weeks. No other major peri- or posttreatment complications occurred. Sixteen patients (10 in PRP group, 6 in HA group) reported moderate pain during or after treatment that spontaneously resolved in 1 to 2 days. Intra-articular PRP injections are as safe and efficacious as HA at 12-month follow-up in terms of functional improvement and pain reduction.
Witteveen AG, Sierevelt IN, Blankevoort L, Kerkhoffs GM, van Dijk CN. Intra-articular sodium hyaluronate injections in the osteoarthritic ankle joint: effects, safety and dose dependency. Foot Ankle Surg. 2010 Dec;16(4):159-63. doi: 10.1016/j.fas.2009.10.003. Epub 2009 Nov 8. PubMed PMID: 21047602.	Orthovisc	AEs were reported by 7 (27%) patients. One patient in the 1 ml dose group, 4 in the 2 ml, 1 in the 3 ml, and 1 in the 3x1 ml dose group. The adverse reactions mostly occurred shortly after the injection and consisted of swelling and increased pain in the injected ankle joint, sometimes associated with increased local temperature. Most of them were mild or moderate in severity and resolved within 3 days. One patient (dose 3x1 ml) experienced severe pain and diffuse swelling of the ankle for about a week after the first injection. These symptoms resolved without any intervention. This patient received his second and third injection 1 week later than planned to have the adverse reaction resolved before the next intra-articular injection would take place. Orthovisc viscosupplementation in the ankle joint is effective and well tolerated.
Colen S, van den Bekerom MP,	Ostenil Plus	--- *Study protocol. No AE mentioned in the statistical*

Publication	Product	Information from publication
Bellemans J, Mulier M. Comparison of intra-articular injections of hyaluronic acid and corticosteroid in the treatment of osteoarthritis of the hip in comparison with intra-articular injections of bupivacaine. Design of a prospective, randomized, controlled study with blinding of the patients and outcome assessors. BMC Musculoskelet Disord. 2010 Nov 16;11:264. doi: 10.1186/1471-2474-11-264. PubMed PMID: 21080920; PubMed Central PMCID: PMC2998460.		*analysis.*
Filardo G, Kon E, Di Martino A, Di Matteo B, Merli ML, Cenacchi A, Fornasari PM, Marcacci M. Platelet-rich plasma vs hyaluronic acid to treat knee degenerative pathology: study design and preliminary results of a randomized controlled trial. BMC Musculoskelet Disord. 2012 Nov 23;13:229. doi: 10.1186/1471-2474-13-229. PubMed PMID: 23176112; PubMed Central PMCID: PMC3532098.	Hyalubrix	No major complications related to the injections were observed during the treatment and follow-up period. *HA as control group.*
Kul-Panza E, Berker N. Is hyaluronate sodium effective in the management of knee osteoarthritis? A placebo-controlled double-blind study. Minerva Med. 2010 Apr;101(2):63-72. PubMed PMID: 20467406.	Orthovisc	No adverse effects (pain, warmth or swelling) potentially assiciated with treatment were observed. The only adverse effect was steril effusion in 1 patient from die HA group and a transient feeling of knee instability in 1 patient from the placebo group. These two patients continued the treatments thereafter.
Kon E, Mandelbaum B, Buda R, Filardo G, Delcogliano M, Timoncini A, Fornasari PM, Giannini S, Marcacci M. Platelet-rich plasma intra-articular injection versus hyaluronic acid viscosupplementation as treatments for cartilage pathology: from early degeneration to osteoarthritis. Arthroscopy. 2011 Nov;27(11):1490-501. doi: 10.1016/j.arthro.2011.05.011. Epub 2011 Aug 10. PubMed PMID: 21831567.	HMW HA (30 mg/2 mL, 1.5%, 1,000-2,900 kDa) and LMW HA (20 mg/2 mL, 1%, 500-730 kDa).	No complications related to the infiltrations were observed during the treatment and follow-up period.
Migliore A, Massafra U, Bizzi E, Vacca F, Martin-Martin S, Granata M, Alimonti A, Tormenta S. Comparative, double-blind, controlled study of intra-articular hyaluronic acid (Hyalubrix) injections versus local anesthetic in osteoarthritis of the hip. Arthritis Res Ther. 2009;11(6):R183. doi: 10.1186/ar2875. Epub 2009 Dec 9. PubMed PMID: 20003205; PubMed Central PMCID: PMC3003515.	Hyalubrix	Two adverse events were reported during the treatment phase. One HA-treated patient experienced moderate hip pain after the second injection that resolved within 7 days of treatment with paracetamol 2 g/day. One mepivacaine-treated patient had mildly intense injection site pain after the first injection, which lasted 36 hours without therapy after the second injection. No serious adverse events were reported during the study. This comparative study suggests a beneficial effect and safety of intra-articular HA in the management of hip OA.
Bayramoğlu M, Karataş M, Cetin N, Akman N, Sözay S, Dilek A. Comparison of two different viscosupplements in knee osteoarthritis -- a pilot study. Clin Rheumatol. 2003 May;22(2):118-22. PubMed PMID: 12740676.	Orthovisc, hylan G-F 20 (Synvisc)	*Safety results not mentioned.*
Atamaz F, Kirazli Y, Akkoc Y. A comparison of two different intra-articular hyaluronan drugs and physical therapy in the management of knee osteoarthritis. Rheumatol Int. 2006 Aug;26(10):873-8. Epub 2006 Jan 14. PubMed PMID: 16416102.	hylan G-F 20, Orthovisc	In conclusion, the results of this study support the PTA to be useful, safe and well-tolerated treatment for patients with knee OA, as well as hyaluronan therapy. No serious local or systemic effects were observed following injections.

Publication	Product	Information from publication
Karatosun V, Unver B, Gocen Z, Sen A. Comparison of two hyaluronan drugs in patients with advanced osteoarthritis of the knee. A prospective, randomized, double-blind study with long term follow-up. Clin Exp Rheumatol. 2005 Mar-Apr;23(2):213-8. PubMed PMID: 15895892.	Orthovisc, hylan G-F 20 (Synvisc)	Throughout the study no complications due to HA injection, such as pain, effusion, synovitis, haemarthrosis or septic arthritis were recorded. The data presented suggests that both HA preparations may present well tolerated alternatives to non-steroidal anti-inflammatory drugs or the intra-articular injection of corticosteroids.
Tascioglu F, Oner C. Efficacy of intra-articular sodium hyaluronate in the treatment of knee osteoarthritis. Clin Rheumatol. 2003 May;22(2):112-7. PubMed PMID: 12740675.	Orthovisc	No serious systemic adverse event was reported which could be related to the treatment. Six patients treated with Na HA (21%) and 5 patients treated with 6- MPA (18%) reported knee pain after the injection. One patient in the Na HA treated group experienced knee pain and swelling, which resolved 4 days later. No significant difference between groups was observed with respect to adverse events. This study suggests that intra-articular injections of Na HA is well-tolerated, provide pain relief and improved function and have a Jong-term beneficial effect in patients with knee osteoarthritis and gives further support to previous literature about the efficacy of HA.
Alberto M , Umberto M , Emanuele B , Bruno L , Valentina G , Prisco P , Mauro G and Sandro T.Intra-articular injection of hyaluronic acid (MW 1,500-2,000 kDa; HyalOne) in symptomatic osteoarthritis of the hip: A prospective cohort study. Archives of orthopaedic and trauma surgery, 2011, 131(12), 1677 Migliore A, Massafra U, Bizzi E, Laganà B, Germano V, Piscitelli P, Granata M, Tormenta S. Intra-articular injection of hyaluronic acid (MW 1,500-2,000 kDa, HyalOne(®)) in symptomatic osteoarthritis of the hip: a prospective cohort study. Arch Orthop Trauma Surg. 2011;131:1677–1685.	Hyalone	No systemic adverse events and septic complications were observed. Sixteen local pain adverse events were reported, out of 506 injections performed (3.19% per injection). All were mild and transient, lasted 2–7 days, and resolved spontaneously or after the use of oral analgesics. Patients' daily activities were unaffected by these events.
Rivera F. Single intra-articular injection of high molecular weight hyaluronic acid for hip osteoarthritis. J Orthop Traumatol. 2016;17:21-6.	Coxarthrum, 2800 kDa, 2.5 % (75 mg/3 mL)	No serious adverse event was noted; 12 cases (0.5 %) of pain associated with transient synovitis (during 24 h) are noteworthy. A single dose of HA (75 mg/3 mL) of high MW (2800 kDa) is proving to be safe and effective for pain control in patients with hip arthritis (Kellgren–Lawrence stages 2 and 3) before indications for hip arthroplasty.
Title: Study of Evaluating the Duration of Efficacy of One Intra Articular Injection of Sodium Hyaluronate 2.0% in Patients With Painful Osteoarthritis of the Knee Recruitment: Completed Study Results: No Results Available Conditions: Osteoarthritis Patient Interventions: Drug: Ostenil plus URL: https://ClinicalTrials.gov/show/NCT01288001 Abstract available.	Ostenil Plus	No serious adverse event was reported. This study demonstrated efficacy and safety of single dose intra-articular injection of 2% sodium hyaluronate for treatment in patients with knee osteoarthritis over a 24-week period.
Guler O, Mutlu S, Isyar M, Seker A, Kayaalp ME, Mahirogullari M. Comparison of short-term results of intraarticular platelet-rich plasma (PRP) and hyaluronic acid treatments in early-stage gonarthrosis patients. Eur J Orthop Surg Traumatol. 2015;25:509-13.	Ostenil Plus (Osteonil plus) knee OA	….none of the patients developed major complication. *HA as control group.*
Borrás-Verdera A, Calcedo-Bernal V, Ojeda-Levenfeld J, Clavel-Sainz C. Efficacy and safety of a single intra-articular injection of 2% hyaluronic acid plus mannitol in knee	Ostenil Plus	Regarding safety, no severe adverse effects were observed during the study. Mild adverse effects were reported in the second follow-up visit by 5.06% of patients (n = 4). These adverse effects consisted of mild pain and swelling in the area of infiltration in all cases, and disappeared during

Publication	Product	Information from publication
osteoarthritis over a 6-month period. Rev Esp Cir Ortop Traumatol. 2011;56:274-80.		subsequent visits. The excellent safety profile of the treatment resulted in a positive benefit/risk ratio for patients.
Frobenius K. A new high-dose treatment with intraarticular hyaluronic acid facilitates the management of osteoarthritis. Orthopädische Praxis. 2009;46(5):252-7	Ostenil Plus	The tolerability of Ostenil® Plus was assessed as very good in 94.7% of the cases and good in 5.3%. No adverse events that could be attributed to the test product were observed.
Dreiser RL, Avouac B, Bardin T. Efficacy of One Intra-Articular Injection of 2% Natural Sodium Hyaluronate Is Non-Inferior To Chemically Crosslinked Hylan G-F 20 In The Treatment Of Painful Tbiofemoral Osteoarthritis. WCO-IOF-ESCEO World Congress on Osteoporosis, Osteoarthritis and Musculoskeletal Diseases. 26–29 March 2015, Milan, Italy. 2015;-:-.	Ostenil Plus	Local reactions to the injection occurred only in 8.4% of patients in the SH group versus 13.0% in the hylan group. No serious reaction related to the injection was reported.
Maheu E, Dreiser RL, Avouac B, Bardin T. Comparison of Therapeutic Response Rates, Using Various Response Definitions in a Prospective Randomized Non-Inferiority Trial Comparing Two Intra-Articular Hyaluronic Acid Preparations (1-Shot IAHA) in Isymptomatic Knee Osteoarthritis (OA), And Predictive Factors of a Better Response. SAT0443 EULAR congress 2016 London, UK. Abstract	Ostenil Plus	*Safety results not mentioned, but identical to Dreiser RL 2015.*

Appendix A 4 Qualification - The authors' professional background

Manufacturer's justification of the choice of the evaluator and reviewer

The choice of the evaluator and the reviewer is justified through reference to qualifications and documented experience. Evaluator and reviewer understand the device technology and its application, research methodology for clinical investigations and biostatistics, and diagnosis and management of the device's indications for use.

Curriculum vitae of the Authors and Domain Experts

This clinical evaluation has been conducted and approved by members of the design and development, risk management and QA/RA team of OSTENIL® PLUS representative for the following capabilities:

- Device technology
- Risk management
- Biological safety evaluation
- Microbiological safety and performance evaluation
- Post-market surveillance
- Clinical evaluation
- Diagnosis and management of conditions of disorders intended to be treated

These capabilities were considered relevant as the clinical effectiveness and safety of OSTENIL® PLUS is directly related to the design of the products, its composition, and its compliance with intended indications.

Author: Dr. Petra Dobner	
Petra Dobner is a Dr. rer. biol. hum. Chemistry	
Background:	
University Education:	
1993	Chemistry, Diploma, Ludwig-Maximilians-University, Dept. of Chemistry, Munich
1997	Doctoral thesis at the institute of infectious- and tropical medicine of the Ludwig-Maximilians-University Munich („Genotypic differentiation of species and molecular characterisation of genes for drug resistance in mycobacteria")
Professional Experience:	

Since 01/2010	Head of Clinical Affairs, TRB Chemedica AG
03/2001 – 12/2009	Clinical Affairs, TRB Chemedica AG
02/2000 – 02/2001	Assistent Clinical Research / Regulatory Affairs, Chemedica AG
10/1998 – 01/2000	Clinical Research Associate, Sanofi Winthrop GmbH
05/1997 – 10/1998	Scientific collaboration in the area of arteriosclerosis at the physiological institute of the Ludwig-Maximilians-University Munich

Publikationsliste

Schütz A, Dobner P. [Effect of wrist arthroscopy with intraarticular hyaluronan substitution therapy: a randomised, controlled, prospective, non-blinded, single-centre, comparative trial]. Handchir Mikrochir Plast Chir 2013;45:277-84

Talke M, Dobner P, Naserke K. Eine neue Option bei der Arthrose des Daumensattelgelenks: intraartikuläre Hyaluronsäure. Orthop Praxis 2002;7:495-501.

Stoeckelhuber M, Dobner P, Baumgartner P, Ehlert J, Brandt E, Mentele R, Adam D, Engelmann B. Stimulation of cellular sphingomyelin import by the chemokine connective tissue-activating peptide III. J Biol Chem. 2000 Dec 1;275(48):37365-72.

Dobner P, Koller E, Engelmann B. Platelet high affinity low density lipoprotein binding and import of lipoprotein derived phospholipids. FEBS Lett. 1999 Feb 12;444(2-3):270-4.

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Engelmann B, Schaipp B, Dobner P, Stoeckelhuber M, Kogl C, Siess W, Hermetter A. Platelet agonists enhance the import of phosphatidylethanolamine into human platelets. J Biol Chem. 1998 Oct 23;273(43):27800-8.

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Munich, 17.02.2014

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Background:	
University Education:	
1998	Ph.D. at the Ludwig-Maximilian-University Munich Title: ß-Adrenoceptors on alveolar macrophages. A comparison of human and bovine subtypes.
1993 - 1997	Research study and dissertation at the Walter-Straub-Institute for pharmacology and toxicology of the Ludwig-Maximilians-University Munich
1993	State examination and approbation as pharmacist
1987 - 1992	Study of pharmacy Julius-Maximilians-University Würzburg and Ludwig-Maximilians-University Munich
Professional Experience:	
Since 09/2009	Manager Regulatory Affairs for Medical Devices at TRB Chemedica AG Role: - Deputy of Head of Regulatory Affairs
2004 - 2009	Manager Drug Safety at Winthrop Arzneimittel GmbH Fürstenfeldbruck, Germany Role: - Deputy of Affiliate's Pharmacovigilance Head and deputy of the Qualified Person of Pharmacovigilance AMG
1999 - 2004	Educational leave and pharmacy assistance
1996 - 1999	Manager Medical Information at Lichtenstein Pharmazeutica GmbH Puchheim, Germany Role: - Deputy of the Information Officer AMG
1993 - 1996	Pharmacist at the Merkur-Apotheke Munich
1992 - 1993	Practical training for pharmacists at the Odeons-Apotheke Munich

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Harald Binder is an approbated pharmacist.	
Background:	
University Education:	
1983	Pharmacy, State examination, Freie Universität Berlin
Professional Experience:	
Since 2009	Head quality assurance/regulatory affairs at TRB Chemedica AG Haar/Munich
2001 - 2005	Pharmacist at MDS Pharmaservices, Hoehenkirchen/Siegertsbrunn (clinical trials)
1997 - 2008	Pharmacist at Schützen-Apotheke Munich
1996 - 2008	Pharmaceutical consultant (e.g. quality control, quality assurance, production, clincal trials, expert reports) at several drug companies and pharmacies
1996 - 2008	Manager quality assurance/regulatory affairs at TRB Chemedica AG Haar/Munich
1996	Director quality control, head of production at BASF Generics GmbH Mannheim
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1993 – 1994	Head of laboratory, deputy director quality control/regulatory affairs at SAGITTA Arzneimittel GmbH Feldkirchen-Westerham
1992 – 1993	Pharmacist at Max-Weber-Platz Apotheke Munich
1991 – 1992	Trainee quality control at SAGITTA Arzneimittel GmbH, Feldkirchen-Westerham
1989	Additional training and certification: pharmacist for clinical pharmacy
1986 – 1991	Pharmacist at pharmacy of clinical center university of Munich, Grosshadern
1985	Pharmacist at Bahnhof-Apotheke Rottenburg/lower bavaria
1985	Approbation pharmacist
1983 – 1984	Pharmaceutical training Johannes-Apotheke Groebenzell/Munich