HYALUBRIX 60/ HYALONE

CLINICAL EVALUATION REPORT:

CRITICAL ANALYSIS OF LITERATURE

DATE	DESCRIPTION OF REVISION
March 2008	First certification
October 2010	Change Development of a specific dose rate of administration "HYALUBRIX 60 - HYALONE"
February 2011	Change to Knee injection
March 2011	Rational to support CER Oct 2010 dott. R. Minola
May 2011	Change Development of a specific dose rate of administration "HYALUBRIX 60 - HYALONE"
May 2011	Rationale to support Safety of repeated injections S. Spini.
June 2011	Addendum to CER May 2011 N. Giordan
July 2012	Renewal of the CE certificate
October 2016	Renewal of the CE certificate

INDEX

1. General details

1.1 Manufacturer

Fidia farmaceutici SpA – Via Ponte della fabbrica, 3/A - 35031 Abano Terme Padova – Italy

1.2 Scope of the clinical evaluation

The aim of this document is to analyze the available clinical data in order to assure the oversight of the safety profile and the performance of HYALUBRIX 60/ HYALONE. HYALUBRIX 60 and HYALONE are two different trademarks to designate the same product.

The present version has been written to attend the renewal of the CE certificate Annex III. This is a consolidated document which includes and covers all relevant clinical data available internally and in the literature since the product and similar devices were CE marked (as per Meddev 2.7/1 rev 4, June 2016).

HYALUBRIX 60/ HYALONE is considered an existing and well established technology and the clinical evaluation route used to support safety and performance of this device relies on the critical evaluation of the data relating to the safety, performance, design characteristics and intended purpose of the product. No new clinical investigation as per Annex X of Directive 93/42/EEC, was performed (Post Marketing Clinical Follow Up Plan_ HYALUBRIX 60/ HYALONE 2016).

The following sources were addressed:

- All available clinical data generated through literature search for the product and the similar devices.
- Any clinical experience related to the clinical use of the device and its similar devices such as any clinical investigations clinical database of governmental agency websites, and Fidia risk management system
- Clinical Data from Clinical Investigations conducted with HYALUBRIX 60/ HYALONE.

Essential requirements

The scope of this document is the periodical update related to the confirmation of conformity of HYALUBRIX 60/ HYALONE with the relevant Essential Requirements covering safety and performance. Specifically, from a clinical perspective, the following "CHECK-LIST OF ESSENTIAL REQUIREMENTS AND STANDARDS" points have been considered (Annex I of EC Directive 93/42/EEC) ER: 2, 3, 6, 6a, 13.1, 13.3 (f).

Therefore this document aims to confirm:

- The maintenance of the claimed characteristics and performances of the devices under the normal conditions of use not compromising the clinical condition or the safety of patients, provided that any risks which may be associated with their intended use constitute acceptable risks when weighed against the benefits to the patient and are compatible with a high level of protection of health and safety.
- The achievement of the intended clinical performance and safety.
- The assessment of the acceptability of the benefit/risk ratio.

2. Description of the device and composition

HYALUBRIX 60/ HYALONE is a sterile, non pyrogenic, viscoelastic solution manufactured with hyaluronic acid sodium salt, obtained by bacterial fermentation from a fraction of high molecular weight. Hyaluronic acid, a polysaccharide of the glycosaminoglycan family, is naturally present in many human tissues such as cartilage and synovial fluid; it is continuously secreted into the joint space and represents a major component of the synovial fluid, to which it provides its characteristic viscosity and elasticity. Such properties are fundamental for the lubricating and shock absorbing functions exerted by the fluid in normal joints to protect cartilage and soft tissues against mechanical injuries.

In traumatic and degenerative joint disorders, an insufficient amount of hyaluronic acid and a loss of viscosity occur in synovial fluid, resulting in an impairment of joint function and in a painful symptomatology. Extensive data in the literature indicate that intra-articular administration of hyaluronic acid is capable to restore the visco-elastic properties of the synovial fluid, with alleviation of pain and improvement of joint mobility.

As following the composition of HYALUBRIX 60/ HYALONE:

Principal component: Hyaluronic acid sodium salt 1.5%

Other components: Sodium chloride, Disodium hydrogen phosphate dodecahydrate, Sodium dihydrogen phosphate dihydrate, Water for injection.

Device classification

On the bases of the combination of its characteristics and its intended purpose HYALUBRIX 60/ HYALONE is a class III medical device, in accordance with the rules 8 (Annex IX of EC Directive 93/42).

GMDN: 44757

3. Intended use

HYALUBRIX60/ HYALONE is a 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.

4. Dosage and administration

Product administration shall be performed exclusively by qualified physicians. All the rules regarding the asepsis and the injection technique shall be followed. Remove any joint effusion, if present, before the administration. Further treatments after the first application may be needed to maintain the benefit of the treatment over time, depending from the individual patient needs. Inject HYALUBRIX60/ HYALONE using a suitable sterile needle (for example 18 or 20 G).

When HYALUBRIX60/ HYALONE is used in the hip, it is recommended to perform the injection under ultra-sound guidance. This is not necessary when HYALUBRIX60/ HYALONE is used in the knee.

The sterility also on the outer surface of the syringe makes the use of the product suitable for the operating room.

5. Contraindications

Do not administer to patients with ascertained individual hypersensitivity to the product components and in cases of infections or skin diseases in the area of the injection site.
There is no evidence of contraindications to repeat the treatment.

6. Warnings and Precautions

Although pre-clinical studies performed in experimental animals indicate that the product has no potential reproductive and developmental toxicity, HYALUBRIX60/ HYALONE has not been tested in pregnant women.
Do not use in case of package damage.
Do not use the product after the expiry date reported on the package.
The expiry date refers to the product kept in its original package at a temperature not exceeding 25° C.
The product is for single use, that means it is intended to be used once only for a single patient. The assembled syringe must be discarded immediately after use, regardless of whether or not the solution has been completely administered.
If this product is reprocessed and/or reused, Fidia Farmaceutici cannot guarantee performance, functionality, material structure, or cleanliness or sterility of the product. Reuse could lead to illness, infection and/or serious injury to the patient or user.
After use, dispose according to applicable national practice.
Keep out of reach of children.

7. Undesirable effects

Local pain, swelling, heat and redness may occur sporadically at the injection site. Such symptoms are generally mild and transient.

More marked inflammatory reactions, sometimes with sodium pyrophosphate crystals, have been occasionally reported in association with intra-articular injections of hyaluronate.
As for any intra-articular treatment, septic arthritis may rarely occur when general precautions for injections are not observed or the site of injection is not aseptic.

Interactions

Do not use concomitantly with disinfectants containing quaternary ammonium salts, because hyaluronic acid can precipitate in their presence.
In order to prevent any possible interactions, avoid the contemporary administration of HYALUBRIX 60/ HYALONE with other intra-articular products.

8. Product presentation

One pre-filled syringe containing 60 mg/4 ml hyaluronic acid sodium salt sterilised by using steam, in a blister sterilised by ethylene oxide.

9. Context of the evaluation and choice of clinical data types

The present document assesses a clinical perspective to current risk/benefit of on the basis of the safety/ performance data accumulated.
The high concentration of hyaluronic acid (HA) in synovial fluid is essential for normal joint function because HA confers exceptional viscoelasticity and lubricating properties to synovial fluid, particularly during high shear conditions. HA facilitates the transport of water and small solutes through synovial fluid to articular cartilage, from capillaries in the synovium and reduces fluid loss as intra-articular pressure is raised during joint flexion.
Physicochemical properties of HA arise from its unique macromolecular structure, an exceptionally long chain (up to 30 μm) of repeating disaccharide units of N-acetylglucosamine and glucuronic acid.
In the joint cavity the HA molecules are mainly synthesized by the type B synoviocytes, that release a polydispersed HA population with molecular weight (MW) ranging between $2X10^6$ and $10X10^6$ Da.

HA is produced in large quantities, leading to the formation of extensive macromolecular entanglements and networks that confer to the synovial fluid its characteristic rheological properties, i.e. the elasticity and viscosity responsible for shock absorption under conditions of high compression or shear, and lubrication in low load states.

Under dynamic loading of diarthrodial joints, shear thinning and a reduction in viscosity occur because of decreased physical entanglements of HA molecules and their realignment to directions more parallel with the axis of articulation. It is well known that joint arthropathies of traumatic and degenerative nature (such as osteoarthritis) are associated with a reduction of the molecular weight and concentration of hyaluronan in the synovial fluid. In fact, the presence of proinflammatory cytokines, free radicals and proteinases in the synovia can adversely affect the metabolism of the lining type B fibroblasts, leading to the biosynthesis of HA with abnormal MW, as has been shown by analysis of synovial fluid from pathologic joints.

The decline in HA molecular size coupled with its dilution by infiltration of plasma fluid and proteins (caused by increased synovial membrane permeability) reduce the rheological properties of synovial fluid from diseased joints. As a consequence, it was contended that cartilage attrition and subchondral bone remodeling was enhanced contributing to progression of pathology and clinical symptoms. Viscosupplementation is a therapeutical approach to osteoarthritis (OA) involving the replacement of the synovial fluid with highly purified HA, to restore (or supplement) synovial fluid viscoelasticity, to decrease symptoms, and improve joint functionality.

HYALUBRIX 60/ HYALONE is a 1.5% solution of non-modified HA (15 mg/ml) obtained from bacterial fermentation with molecular weight >1500 kDa. In order to obtain a physiologically compatible solution the formulation contains sodium chloride which gives to the product its isotonicity and a phosphate buffer consisting on a monobasic and dibasic phosphate which gives to the product its physiological PH value. HYALUBRIX 60/ HYALONE exhibits a behavior very similar to the synovial fluid that it replaces. In particular, it confers proper rheological properties, trans-synovial fluid buffering, and permeability to metabolites and macromolecules. Furthermore it is also characterized by a good residence time.

The safety profile of the viscous solution HYALUBRIX 60/ HYALONE (HA sodium salt 60 mg/4 ml) has been widely confirmed by preclinical data. In fact biocompatibility tests show that HYALUBRIX 60/ HYALONE can be considered non- toxic and with no sensitizing properties. Furthermore no

biological responses, inflammatory or degenerative lesions were observed after a single intra-articular injection in knee joint of rabbits. Additionally, HYALUBRIX 60/ HYALONE appears non-mutagenic and non-clastogenic (BER_ HYALONE-HYALUBRIX60, October 2016). Therefore the preclinical documentation is to be considered adequate to demonstrate the biocompatibility of HYALUBRIX60/ HYALONE and justify the clinical use of the product.

Additionally, collected human clinical trials results and post marketing surveillance data further confirm that the HA, in different preparations and with MW ranging between 500 and 2100 kDa, is safe and well tolerated by patients affected by OA, showing no systemic effects or alterations in standard laboratory tests. Altogether these results demonstrate the biocompatibility of the HA-based product HYALUBRIX 60/ HYALONE and justify the intra-articular use of the device.

Competitors

For temporary synovial fluid replacement for patients affected by degenerative or mechanical arthropathy of the hip and knee different products are present in the market and reported here below.

Table 1: Overview HYALUBRIX 60/ HYALONE competitors

Product	Company	Component	Intended use	Technical characteristics	Similar/Not similar
Orthovisc	Vita Research	Hyaluronic acid sodium salt	Orthovisc is similar to the fluid that surrounds the joints in your body. This fluid acts as a lubricant and shock absorber for the joints. Orthovisc is used to treat knee pain caused by osteoarthritis.	Viscoelastic solution (1500 kDa 1,5%)	Similar for: • Clinical characteristics: used for the same clinical condition, intended purpose, in a similar population and same site in the body. • Technical characteristics: Viscoelastic solution with similar principles of operation. • Biological characteristics: similar composition (HA based), temporary synovial fluid replacement.
Synvisc	Genzyme	Hyaluronic acid sodium salt	Synvisc is similar to the fluid that surrounds the joints in your body. This fluid acts as a lubricant and shock absorber for the joints. Synvisc is used to treat knee	Viscoelastic solution ≥6000 kDa 0,8%	Similar for: • Clinical characteristics: used for the same clinical condition, intended purpose, in a similar population and same site in the body. • Technical characteristics: Viscoelastic solution with similar principles of operation. • Biological characteristics: similar composition (HA based), temporary

			pain caused by osteoarthritis.		synovial fluid replacement.
Ostenil	TRB Chemedica	Hyaluronic acid sodium salt	For pain and restricted mobility in degenerative and traumatic changes of the knee joint and other synovial joints.	Viscoelastic solution 1.600 kDa N.A.	Similar for: • Clinical characteristics: used for the same clinical condition, intended purpose, in a similar population and same site in the body. • Technical characteristics: Viscoelastic solution with similar principles of operation. • Biological characteristics: similar composition (HA based), temporary synovial fluid replacement.

Similar products

As reported in Table 1 Orthovisc, Synvisc and Ostenil, can be considered as similar products of HYALUBRIX 60/ HYALONE for technical, biological characteristics (Hyaluronic acid based viscoelastic solution) and for clinical purpose and intended use. Therefore these HA-based products have been considered for the clinical data research to further support the safety and performance of HYALUBRIX 60/ HYALONE.

HYALUBRIX/ INARTRAL is another medical device produced and commercialized by Fidia since many years. HYALUBRIX 60/ HYALONE and HYALUBRIX/ INARTRAL differ only for the quantity of hyaluronic acid sodium salt solution contained in the prefilled syringes (60 mg/4ml in HYALUBRIX 60/ HYALONE whereas 30 mg/2ml in HYALUBRIX/ INARTRAL). Furthermore although they are used for a similar clinical purpose (degenerative or mechanical arthropathy), HYALUBRIX/ INARTRAL is administered as a course of 3 injections once a week whereas HYALUBRIX 60/ HYALONE (specifically used for arthropathy of the hip and knee) is administered by single injection.

Considering that both HYALUBRIX 60/ HYALONE and HYALUBRIX/ INARTRAL are constituted by HA which presents the same characteristics (same viscoelastic characteristics and same molecular weight), the available clinical evidences collected on HYALUBRIX/ INARTRAL have been considered in this clinical evaluation report to further support the efficacy and safety of HYALUBRIX 60/ HYALONE.

10. Clinical data appraisal

10.1 Data generated through Literature Search

Methods

HYALUBRIX60/ HYALONE own data have been considered. Furthermore, citations emerged from previous versions of CERs have been taken into consideration to examine their possible inclusion or exclusion in the present consolidated Clinical Evaluation Report. A search on available literature data and on internal clinical data publications was carried out on the base of their relevancy in supporting the rationale of this clinical evaluation report by Dr. F. Consolaro (Research and Development Dept. – Clinical Research). This clinical evaluation was performed through scientific databases like EBSCO (MEDLINE, Cochrane) and EMBASE (Pubmed) up to October 2016 including the following key words: hyaluronan/ hyaluronic acid AND osteoarthritis AND synovial fluid, knee OA, hip OA, Hyalubrix 60, Hyalone, Synvisc, Orthovisc, Ostenil.

The various citations obtained were screened and the publications containing relevant findings were considered. Suitable articles were evaluated and selected by assessment of type of the performed clinical study, study design, sample size of treated patients, the pathology treated and the statistical and clinical significance of results. The assessment and selection of articles suitable from both internal archive and literature was performed by using the '*Search and weighing of references for the clinical evaluation of medical device'* form (Annex 1) which takes in account the appropriateness of the device used and of the device application for the intended use, the appropriateness of the patient group if representative of the intended treatment population and clinical condition and the quality of presented clinical data if sufficient for an objective assessment. All publication with a total score ≤ 12 have been excluded.

Outputs

From the internal clinical data 10 studies have been collected over the years however only 4 of them (Ref 1-4, Table 2) have been considered and analyzed from both efficacy and safety point of view. All selected publications reached a score >12 in the assessment process (Annex 1). References 5- 10 were

excluded mainly because regarded data gained in devices different from what in question, with different technical characteristics or because papers contains data not sufficiently relevant (score ≤12).
Furthermore from literature database research 59 publications came out (see Search Protocol and Search Report, Annex 2 and Annex 3), however none of them have been considered mainly because no relevant for the aim of this document. The data selection process for screening and selection of clinical literature data is documented in the following flowchart (Figure 1) whereas the methods used for the assessment process is reported in Annex 1, Annex 2 and Annex 3.

Figure 1: Literature Data Selection Process

HYALUBRIX/INARTRAL own data have been considered. Furthermore, citations emerged from previous versions of CERs have been examined.

N° of internal clinical references emerged:10

Additionally a clinical literature research have been performed in so evaluating the state of the art. Key words included in the literature search: hyaluronan/ hyaluronic acid AND osteoarthritis AND synovial fluid, knee OA, hip OA, Hyalubrix 60, Hyalone, Synvisc, Orthovisc, Ostenil. All clinical data have been screened on the base of their relevancy.

N° of references emerged from literature:59 (see Search Protocol of Annex 2).

The screening has been done using the "Search and weighing of references for the clinical evaluation of medical device" form. All publication with a total score ≤ 12 have been excluded (Annex 1).

N° references excluded from literature :59

N° reference excluded from internal clinical data: 6

In addition to HYALUBRIX60/ HYALONE own data, no publication from literature search has been considered in the data analysis.
All literature with relevant useable data included a deep evaluation of:

- Device performance
- Device safety

N° internal clinical references considered: 4

The internal clinical articles available for HYALUBRIX 60/ HYALONE have been listed and summarized in the following Table 2. As previously explained only 4 of them (**Ref 1-4**) have been fully considered and examined to support the efficacy and safety of HYALUBRIX 60/ HYALONE.

Table 2: Relevant data considered from internal and literature review

Ref	Author	Title	Bibliography	Product	Considered/Not considered
1	Migliore Alberto, Massafra Umberto, Bizzi Emanuele, Laganà Bruno, Germano Valentina, Piscitelli Prisco, Granata Mauro, Tormenta Sandro	Intra-articular injection of hyaluronic acid (MW 1500 - 2000 KDa; HyalOne®) in symptomatic osteoarthritis of the hip: a prospective cohort study.	Arch. Orthop. Trauma Surg. 2011, 4 [epub ahead of print]	Hyalone	Considered Score:16,5
2	Migliore Alberto, Bella Antonino, Bisignani Massimariano, Calderaro Michele, DeAmicis Daniele, Logroscino Giandomenico, Mariottini Fabio, Moreschini Oreste, Massafra Umberto, Bizzi Emanuele, Laganà Bruno, Piscitelli Prisco, Tormenta Sandro	Total Hip Replacement rate in a Cohort of Patients affected by Symptomatic Hip Osteoarthritis Following Intra-articular Sodium Hyaluronate (MW 1500 - 2000 KDa; HyalOne®). ORTOBRIX study	Clin Rheumatol (2012) 1:1187–1196	Hyalone	Considered Score:13,5
3	Minola R.	Use of Hyalubrix 60/Hyalone for the treatment of the knee	Data on file, 2011	Hyalubrix 60	Considered Score:14
4	Vetro A. et al	Pain Relief and functional recovery over a six month period after intra-articular injection with sodium hyaluronate (MW 1500-2000KDA) in osteoarthritis of the knee	European journal of musculoskeletal diseases, Vole 3 2014	Hyalone	Considered Score:15,5
5	Alberto Migliore, Umberto Massafra, Emanuele Bizzi, Francesca Vacca, Severino Martin-Martin, Mauro Granata, Andrea Alimonti, Sandro Tormenta	Comparative, double-blind, controlled study of intra-articular hyaluronic acid (Hyalubrix®) injections versus local anesthetic in osteoarthritis of the hip	Arthritis Research & Therapy 2009, 11:R183	Hyalubrix	Not considered Score: 12

	(Reference cited in CER October 2010)				
6	F Navarro-Sarabia, P Coronel, E Collantes, F J Navarro, A Rodriguez de la Serna, A Naranjo, M Gimeno, G Herrero-Beaumont, on behalf of the AMELIA study group (Reference cited in CER July 2012)	A 40-month multicentre, randomised placebo controlled study to assess the effi cacy and carryover effect of repeated intra-articular injections of hyaluronic acid in knee osteoarthritis: the AMELIA project	Ann Rheum Dis 2011;70:1957–1962	Adant	Not considered Score:10
7	K. Pavelka, D. Uebelhart (Reference cited in CER July 2012)	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 19 (2011) 1294e1300	Synovial Vs Synvisc	Not considered Score:9,5
8	F. Schieb (Reference cited in CER June 2011)	Intra-Articular Injections Of Hyaluronic Acid In The Treatment Of Arthropathies.	Arthritis + Rheuma 2003;23 (6): 338-340	Hyalubrix	Not considered Score: 12
9	C. Smiderle, M. Scapin, M. Baldo, L. Ronconi, G. Marcolin, R. Villaminar (Reference cited in CER June 2011)	Gait analysis of changes in clinical and biomechanical parameters in osteoarthritis knee patients after intraarticular infiltration with high molecular weight hyaluronic acid.	Eur Med Phys 2007;43(Suppl. 1 to No. 3)	Hyalubrix	Not considered Score: 12
10	C. Foti , C. Cisari , S. Carda , N. Giordan , A. Rocco , A. Frizziero , G. Della Bella (Reference cited in CER June 2011)	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;47:1-9	Hyalubrix	Not considered Score: 12

10.2 Data generated through Clinical Experience

Methods

Fidia performs additional periodic web searches on Clinical Websites and/or Government database to monitor the safety profile of HYALUBRIX 60/ HYALONE and of similar medical devices present on the market. For this purpose, three similar medical devices have been considered and included in the research: Orthovisc, Synvisc and Ostenil. The web screening has been performed through the relevant Health Authority websites in which HYALUBRIX 60/ HYALONE is mainly marketed and the databases of the international Health Authorities: FDA, EMA (Safety Surveillance HYALUBRIX 60/ HYALONE - Reference Period 01 August 2009 - 30 June 2016; HYALUBRIX 60/ HYALONE PMS EQD2 rev.0).

Outputs

Relevant safety data emerged from Health Authority websites were summarized in the following section 12.2.2 and in the Post marketing Surveillance document (Safety Surveillance HYALUBRIX 60/ HYALONE - Reference Period 01 August 2009 - 30 June 2016; HYALUBRIX 60/ HYALONE PMS EQD2 rev.0).

11 Clinical data results

Fidia considered the similar products and HYALUBRIX 60/ HYALONE clinical publications and evidences to support the performance and safety profile of HYALUBRIX/ INARTRAL (Table 2).

The table below represents a summary of the results of the studies considered.

Ref	Subjects	Study	Indications	Treatments	Endpoint	Results
1	120	Prospective cohort clinical study	Hip Osteoarthritis	Hyalubrix 60 (4 ml) in the affected hip	Efficacy and safety with dose rate of injection of 1 injection after 6 months	This study investigated the long-term efficacy and tolerability of ultrasound-guided intra-articular sodium hyaluronate (MW 1500-2000 KDa; Hyalone®) injections in daily clinical practice. In this observational, cohort study of patients with hip osteoarthritis, Hyalone® was administered under

						ultrasound guidance, every six months, with the possibility of an additional injection at the intervening 3-month intervals on clinical request. The patients were followed up for 18 months after the first intra-articular injection. Data from 120 patients showed a statistically significant reduction in algofunctional indexes at 3 months after study product injection, while at 12 months 80% of patients achieved a decrease of at least 30% in symptoms. These results were maintained over time through cyclical and personalized repetition of ultrasound guided injections, at least one injection after six months. The study treatment reduced pain and improved mobility in osteoarthritis of the hip.
2	176	Retrospective study	Hip Osteoarthritis	Hyalubrix 60 (4 ml) In the affected hip	Efficacy safety and benefit in terms of delay total hip replacement surgery	This retrospective study involving a group of THR expert orthopedic surgeons to appraise the frequency and timing of THR in patients suffering from hip OA treated with ultrasound (US) guided intra-articular (IA) injections of HyalOne® and whether or not considered eligible for THR. Six orthopedists, not routinely performing hip IA injections, each independently assessed whether 176 patients suffering from hip OA treated with ultrasound guided intra-articular injections of Hyaluronic Acid were candidates for THR according to the clinical data. At 48 months 82% the study population survived THR. In the group of 93 patients considered candidates for THR (that is, in which 4, 5 or 6 orthopedic surgeons agreed that the patient was a suitable candidate for THR) only 17 underwent THR, with survival results of 66.5% at 48 months. In the other groups of patients (in which respectively 3, 2, 1 or no surgeons were in agreement that the patient was a candidate for THR) arthroplasty is not recorded. Hyaluronic Acid given by US guided injection seems to delay

						THR in the real context of actual overall management of symptomatic hip OA patients.
3	40	-	Knee osteoarthritis	4 ml mono-injection Hyalubrix 60	Evaluate efficacy and safety of Hyalubrix 60 in knee OA	Two groups of patients were included: 20 patients average age of 40 years, amateur marathon runners with mild osteoarthritis. The second group of 20 patients average age of 60 years, and moderate to severe osteoarthritis. The first group followed a course of one knee injection every three months; the second group followed a course of one injection every two months. Results showed, in the first group, improvements with respect to baseline in pain ($p<0.01$) and WOMAC scores ($p<0.01$). In the second group WOMAC scores improved from baseline 70 to 48; and Vas improved 60 to 36 mm.
4	168	Single site, investigator-initiated, open cohort study	Knee OA	Single ultrasound guided IA injection of Hyalone	Evaluate efficacy and safety	Pain significantly decreased after treatment. VAS pain decreased from the baseline mean value of 77.7 mm (SD 8.8 range:60-90) to mean value of 13.8 mm (SD 4.9, range:10-20) at week 24. The analysis of variance for repeated measures conducted on VAS, on each WOMAC subscale, on the total WOMAC score and on each KOOS subscale score showed a significant reduction in all scores at each study point (week 4, 12 and 24) ($p< 0.001$). Comparisons between week 4 and week 12 scores and week 12 and week 24 scores showed a significant and progressive improvement ($p<0.05$, Wilcoxon test) during the study. The present study suggests that a single IA injection of linear high MW HA in patients suffering from knee A is well tolerated and provides relief from pain. Benefit to knee function was confirmed by both the WOMAC and the KOOS scores. The patient's overall health status also improved as demonstrated by the high scores registered at the post-treatment KOOS Function in daily Living, quality of Life and Function in Sport and Recreation subscales.

12 Clinical data analysis

12.1 Performance

Ref 1

Evidences of the long term efficacy came out from Migliore's study. 120 patients were treated with double-dose, i.a. injections of Hyalubrix 60 one injection – 30 mg/2 ml followed by a second injection of 30 mg/2 ml. If required, intra-articular treatment could be repeated 6 months later according to the patient's level of pain. The hyaluronic acid was administered by means of the ultrasound-guided technique. These patients were clinically evaluated upon trial entry and after three and six months. The following parameters were considered: pain reduction, measured according to the visual analogue scale (VAS), Lequesne index and NSAID consumption, given as daily intake per month. The patients were also asked to provide an overall evaluation of the perception of their symptoms according to OMERACT criteria.

Results showed a significant reduction in pain according to the VAS (from 5.53 to 3.46 and 3.91 at three and six months respectively, with $p < 0.0001$ in both cases), and according to the Lequesne index (from 6.33 to 4.5 and 4.84 at 3 and 6 months respectively, with $p < 0.0001$ in both cases). NSAID consumption was reduced at 3 and 6 months (from 6.2 to 5.1 with $p = 0.228975$ at the 3rd month, reaching 2.5 at the 6th month, with statistical significance $p = 0.017177$). The overall perception of the symptoms was also improved (from 5.69 to 4.5 and 4.69 at 3 and 6 months respectively, with $p < 0.0001$ in both cases).

Ref 2

In this retrospective study a group of expert total hip replacement (THR) orthopedic surgeons evaluated all the patients involved in the cohort study from 2005 to 2007 to assess their suitability for undergoing THR. The orthopedists' recommendations for THR was compared with the actual rate of THR received by the patients during the cohort follow-up. The primary objective of this study was to appraise the frequency and timing of THR in patients suffering from hip OA treated with ultrasound-guided intra-articular injections of HyalOne (Hyalubrix 60 Italian brand). The secondary objective of the study was to identify possible indices of THR outcome relating to sex, age, radiological grading according to the

Kellgren-Lawrence (KL) classification, and clinical parameters. Each patient received a single 4 ml (60 mg) intra-articular injection of HyalOne® into the affected hip every 6 months. If clinically requested, it was possible to administer up to two additional injections, with a maximum of one injection per 3-month period, in any 1 year, as performed in standard clinical practice in our facility. Injections were performed every 6 months even in patients reporting an improvement in clinical parameters. Total number of patients were divided in three groups depending on number of injection received: Group A, 240 injections (mean of 3.87 injections for patient during the follow up study), Group B, 87 injections (mean of 4.14 injections for patient) and Group C, 522 injections (mean of 5.61 injections for patient. All intra-articular injections were performed using ultrasound-guidance to ensure accurate placement. All clinical parameters, observed during the 48 months of follow-up, demonstrated a statistically significant improvement after repeated injection of HA. Statistically significant differences were observed at all time points for all parameters ($p<0.05$). In this study 51 % of patients did not progress to THR in the 3 years after hyaluronic acid treatment. The authors also suggest that intra-articular hyaluronic acid can provide long-term pain relief even in patients eligible for THR. In this study, we found that 82 % of patients had not undergone THR during hyaluronic acid management in the whole cohort after 48 months; whereas in the group considered by orthopedists as eligible for THR, only 34 % underwent THR throughout the whole follow-up (48 months) and about 20 % in 2 years of follow-up. Taken together these results reveal that hyaluronic acid may be effective in reducing pain, in improving function, and consequently in delaying the clinical need for THR.

Ref 3

The experience of Dr. Minola assessed the safety and efficacy profile of Hyalubrix 60 in the osteoarthritic knee treatment. The aim of this study was to observe the effects of Hyalubrix 60 injection on young patients with sports habits and affected by knee osteoarthritis. Inclusion criteria were: radiographic evidence of symptomatic OA of the knee and dissatisfaction with prior attempts at non-operative management modalities. The WOMAC index and the 100 mm VAS scale were the outcomes instruments used to assess the response to treatment. Hyalubrix 60 was administered with the use of prefilled syringe. Two group of patients were included: a first group of 20 patients (mean age 40 years), who followed a course of one knee injection every 3 months; and a second group of 20 patients (mean age 60 years) who followed a course of one knee injection every 2 months.

All patients were seen after 12 months to evaluate the clinical outcome and the possible adverse events. From results, WOMAC scores improved in the first group from baseline from 42 to 18; the score on VAS improved from 35 to 16. In the second group, the WOMAC scores improved from the baseline 70 to 48; and on the VAS from 60 to 36.

Ref 4

The performance profile of Hyalone in reducing pain and improving knee function has been confirmed in Vetro A. et al publication. In this single-site open cohort study168 patients were enrolled and received an ultrasound guided injection at baseline visit. Before treatment patients reported intense pain: the mean VAS value was 78 mm (SD 8.8 range:60-90), the mean WOMAC pain score was 16.7 (SD 1.80, range:14-20) and the mean KOOS pain score was 23.6 (SD 11.66, range:5.56-41.68) as well as intense knee stiffness (mean WOMAC score of 6.7). Knee functionality was moderately compromised: the WOMAC total score presented a mean value of 79.8 (SD 8.08, range:64-96), the KOOS function in daily living (ADL) presented a mean score of 26.8 (SD range 11.76-38.24) and the KOOS sport recreation a mean score of 19.0 (SD9.40, range:5-35) The baseline mean VAS value significantly and progressively decreased at each study time point ($p<0.001$at the analysis of variance for repeated measures). All patients reported a reduction in pain at T1 and a further reduction at T2, while at T3 more than half of the treated patients (87 patients, 52%) reported an additional reduction in pain compared to T2. Pain perception at T3 compared to T2 was unchanged in the remaining 48% of patients. Patients reported an initial decrease in VAS of 36 mm that subsequently decreased by a further 19.9 mm at T2 and 6.4 mm at T3. During the study the WOMAC normalized pain score decreased from the mean value of 83.7 registered at T0 to a mean score of 8.7 at T3.

The stiffness score decreased from a mean value of 84.2 at T0 to a mean score of 14.8 at T3: the functionality score decreased from a mean value of 82.8 at T0 to a mean value of 5.7 at T3. Consequently the total WOMAC score also decreased from the T0 mean value of 83.1 to a T3 mean value of 7.1. The analysis of variance for repeated measures conducted on each WOMAC subscale and on the total WOMAC score showed a significant reduction in pain and stiffness and an increase in knee functionality at each study point after treatment. Mean baseline values of all KOOS subscales progressively increased at each study time point to reach the highest value at T3.

12.2 Safety

12.2.1 Data emerged from literature

Literature evidences confirm that HYALUBRIX 60 /HYALONE is safe and well tolerated as the all safety concerns emerged from clinical evidences were transient and associated to local effects already predicted and described in the 'Undesirable effects' section of the Instructions For Use (IFU).

Ref 1

In this study the ultrasound-guided intra-articular sodium hyaluronate injections resulted well tolerated. 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). However all were mild and transient, lasted 2–7 days, and resolved spontaneously or after the use of oral analgesics. Furthermore patients' daily activities were unaffected by these events.

Ref 2

In this study no serious systemic, infectious, or other severe adverse events were recorded. A mild transient pain, regressed without need of medication, was reported by 34 patients. No differences were observed in the occurrence of such events in the three groups.

Ref 3

In this study patients did not report any adverse events during the treatment apart from one patient who had a local reaction developed within 24 hours after injection.

Ref 4

In this study the treatment with intra-articular injection of HYALUBRIX 60/ HYALONE was well tolerated. No serious adverse events were reported by patients during the treatment. Only mild transient adverse events were reported in 5 patients. These device-related local AE consisted mostly of mild or moderate post injection pain and swelling which resolved spontaneously after a few days. Furthermore the patients daily activities were unaffected by these events.

12.2.2 Data emerged from Clinical Experience

Data collected from the web search did not show any important safety information for HYALUBRIX 60 /HYALONE and for the similar medical devices Orthovisc, Synvisc and Ostenil. Furthermore, while the use of Orthovisc has occasionally been associated with allergic/anaphylactic reactions and transient hypotensions, differently no ARs of 'allergic/anaphylactic reactions and transient hypotension' have been registered for HYALUBRIX 60 /HYALONE (Safety Surveillance HYALUBRIX 60/ HYALONE - Reference Period 01 August 2009 - 30 June 2016; HYALUBRIX 60/ HYALONE PMS EQD2 rev.0). This suggests that HYALUBRIX 60 /HYALONE results more safe and well tolerated and that no allergic reactions are related to its use.

13 Conclusions

Osteoarthritis (OA) is the most common, degenerative joint disorder affecting worldwide population and a major cause of disability in the elderly. According to the American College of Rheumatology (ACR), 70% of people aged over 70 years have an X-ray-confirmed diagnosis of osteoarthritis of the hip and knee. Italy does not differ very much from other international countries. Hip OA is often associated with a high mortality rate; hence 30-50% of patients are likely to need arthroplasty after 10 years of suffering from the disease. The problems related with hip and knee OA localization are significant, since these joints bear most of the body weight. A non-pharmacological approach that appears to solve the problem, at least for a limited timeframe, is replacement surgery. Although recent improvements in surgical technique as well as in prosthesis design have made replacement surgery a less risky procedure than it was years ago, it may still have potential – even important - consequences: among them, infections, thrombo-embolism, implant dislocation, and damaged nerves and vessels.

In addition, to the direct consequences of the surgical procedure, another relevant, influencing factor is the time and activities required to achieve complete functional recovery. There may be additional costs associated with rehabilitation, as well as other (social) costs, namely the missed workdays in the case of patients with an active career/lifestyle. Therefore substances that "lubricate" the damaged joint, such as intra-articularly injected hyaluronan have been considered as a good non-surgical option. Intra-articular viscosupplementation restores the viscoelastic properties of synovial fluid, and is a good alternative to NSAIDs and analgesics in terms of efficacy in controlling pain and improving joint function.

HYALUBRIX 60/ HYALONE is a sterile non-pyrogenic, viscoelastic solution manufactured with hyaluronic solution sodium salt, obtained by bacterial fermentation from a fraction of high molecular weight >1500 kDa. HYALUBRIX 60 /HYALONE restores the viscoelastic properties of knee and hip synovial fluid, and is a good alternative to NSAIDs and analgesics in terms of efficacy in controlling pain and inflammation, while maintaining a high safety profile. Clinical evidences confirm that the intra-articular injection of HYALUBRIX 60/ HYALONE act significantly reducing pain and improving mobility and quality of life in patients with OA. Furthermore preclinical results confirm that HYALUBRIX 60/ HYALONE is safe and well tolerated since it does not show any sensitizing or toxic effects. Furthermore implantation studies confirm that HYALUBRIX 60/ HYALONE does not have any local or systemic toxicity. In addition the ETO sterilization cycle for the sterilization of HYALUBRIX 60/ HYALONE syringes further guarantees the usage in microbiologically controlled environments such as surgery room thus reaching the possibility to use the product during post-operative or post-arthroscopy treatment. Moreover the mono-injection strategy is a HYALUBRIX 60/ HYALONE characteristic that exposes patients to a lower risk of administration-related side effects (e.g. pain at injection site, infection) and requires a lower number of patient visits to the clinic thus resulting in a money-saving opportunity for the patients.

Therefore the combination of evidences obtained from clinical data of similar products of HYALUBRIX 60/ HYALONE clearly support the conformity with Essential Requirements and the maintenance of the claimed characteristics and performances of HYALUBRIX 60/ HYALONE under the normal condition of use and the achievement of the intended clinical performance and safety. No new clinical investigation as per Annex X of Directive 93/42/EEC, has been performed (Post Marketing Clinical Follow Up_ HYALUBRIX 60/ HYALONE 2016).

Risk analysis and Risk/Benefit Balance

The viscosupplementation with HA is a reasonable treatment for patients with mild-to-moderate OA who have ongoing pain or are unable to tolerate conservative treatment or joint replacement. Intra-articular HA appears to have a slower onset of action than intra-articular steroids but the effects seem to last longer. Furthermore, viscosupplementation with HYALUBRIX 60/ HYALONE is a valuable technique for the management of painful OA of the hip and knee.

If the treatment is repeated within six months the viscosupplementation therapy is able to maintain a long term benefit in terms of pain relief and functional improvement and it can be an alternative for young candidates, patients with surgical contra-indications and patients in whom NSAID use is contraindicated. As stated above HYALUBRIX 60/ HYALONE differs from HYALUBRIX /INARTRAL, another IA hyaluronan medical device produced by Fidia, only for the quantity of HA solution contained in the syringes. Therefore the manufacturing data and post-marketing experience obtained with HYALUBRIX/ INARTRAL and its similar products have been considered to further assure the safety and performance of HYALUBRIX 60/ HYALONE.

Interestingly data collected until now on HYALUBRIX 60/ HYALONE reveal that there are no adverse effects that might represent a significant hazard for the treated population and no changes in the overall pattern of adverse effects have emerged. In fact between 01 August 2009 (first launch date) and 30 June 2016 (data Lock point for this document), a total of 5 safety complaints reporting 6 suspected Adverse Reactions (ARs) were received at Fidia Safety Surveillance Unit from post-marketing source. All 5 cases (6 ARs) were medically confirmed. All 5 cases (6 ARs) were deemed as being "non-serious". Of these 5 cases (6 ARs), 1 Case (2 ARs) was unlisted and 4 cases (4 ARs) were listed. It should be noted that a single case can contain either listed or unlisted ARs (table 3). The estimated number of patients who received the product, considering a unit for each patient is 467.095.

Altogether data collected in the period covered by this document revealed the lack of incidents and a low number of non-serious Adverse Reactions thus the incidence can be considered very low (0.0001%). Therefore the cumulative experience did not generate any safety concerns and demonstrate and confirm that HYALUBRIX 60/ HYALONE can be considered a safe and well tolerated therapy (Safety Surveillance HYALUBRIX 60/ HYALONE - Reference Period 01 August 2009 - 30 June 2016; HYALUBRIX 60/ HYALONE PMS EQD2 rev.0). Moreover, clinical and safety data collected on HYALUBRIX/ INARTRAL, another medical device produced by Fidia and marketed in several European countries which differs from HYALUBRIX 60/HYALONE only in volume contained in the syringes, confirm that this specific IA hyaluronan product is safe and well tolerated (Safety Surveillance HYALUBRIX 60/ HYALONE - Reference Period 01 August 2009 - 30 June 2016).

Based on that the extrapolated risk to humans, under normal clinical use, can be estimated as minimal or absent and comparable to that exhibited by other similar/equivalent devices already in use in the current medical practice. Furthermore, all risks, taken together, do not exceed the expected benefit to

the patient. Therefore the favorable risk-benefit ratio is confirmed and the documentation on the product HYALUBRIX 60 /HYALONE supplied by Fidia is to be considered adequate. In conclusion HYALUBRIX 60 /HYALONE satisfy essential requirements and the toxicological and regulatory requirements (HYALUBRIX 60/ HYALONE RMR EQD2 rev 9).

Lastly the review of the product labelling and instructions for use of HYALUBRIX 60/ HYALONE resulted consistent with the clinical data and post marketing evidences collected. Similar local, transient and occasional side effects (such as inflammatory reactions, local pain, swelling, heat and redness) described for HYALUBRIX 60/ HYALONE in the 'Undesirable Effects' section of the IFU are also reported in the IFU of Orthovisc, Synvisc and Ostenil.

Altogether data recorded in the period covered by this Clinical Evaluation Report and the cumulative experience confirm that HYALUBRIX 60/ HYALONE can be considered as a safe and well tolerated therapy. The analysis of the overall residual risk in front of the acceptability rating decided that no risk is in the unacceptable or in undesirable class. Therefore the risk is acceptable as none situation detected has been related to safety consequences and needs a product modification (HYALUBRIX 60/ HYALONE RMR EQD2 rev 9).

The lack of serious incidents, and the absence of serious adverse events occurred in this period reveal that the risk for the treated population to develop adverse effects is very low, thus being in line with the theoretical prediction of the Risk Management Plan and demonstrating the safety and the well tolerability of the product as well as justifying the human use of HYALUBRIX 60/ HYALONE.

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14 References

- BER_ HYALONE-HYALUBRIX60, October 2016.

- Safety Surveillance HYALUBRIX 60/ HYALONE - Reference Period 01 August 2009 - 30 June 2016;

- HYALUBRIX 60/ HYALONE PMS EQD2 rev.0.

- HYALUBRIX/ INARTRAL_ Post Marketing Surveillance period 2003-2016.

- HYALUBRIX 60/ HYALONE RMR EQD2 rev 9.

- Post Marketing Clinical Follow Up Plan_ HYALUBRIX 60/ HYALONE 2016

- Migliore A. et al. Intra-articular injection of hyaluronic acid (MW 1500 - 2000 KDa; HyalOne®) in symptomatic osteoarthritis of the hip: a prospective cohort study. Arch. Orthop. Trauma Surg, 2011.

- Migliore A. et al. Total Hip Replacement rate in a Cohort of Patients affected by Symptomatic Hip Osteoarthritis Following Intra-articular Sodium Hyaluronate (MW 1500 - 2000 KDa; HyalOne®) ORTOBRIX study. Clin. Rheumatol, 2012

- Minola R. et al. Use of Hyalubrix 60/Hyalone for the treatment of the knee. Data on file, 2011.

- Vetro A. et al. Pain Relief and functional recovery over a six-month period after intra-articular injection with sodium hyaluronate (MW 1500-2000KDA) in osteoarthritis of the knee. European journal of musculoskeletal diseases, 2014.

- A Migliore et al. Comparative, double-blind, controlled study of intra-articular hyaluronic acid (Hyalubrix®) injections versus local anesthetic in osteoarthritis of the hip. Arthritis Research & Therapy, 2009.

- F. Navarro et al. A 40-month multicentre, randomised placebo controlled study to assess the effi cacy and carryover effect of repeated intra-articular injections of hyaluronic acid in knee osteoarthritis: the AMELIA project. Ann Rheum Dis, 2011.

- K. Pavelka et al. 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.

- F Schieb et al. Intra-Articular Injections Of Hyaluronic Acid In The Treatment Of Arthropathies. Arthritis Rheuma 2003.

- C. Smiderle et al. Gait analysis of changes in clinical and biomechanical parameters in osteoarthritis knee patients after intraarticular infiltration with high molecular weight hyaluronic acid. Eur Med Phys 2007.

- C Foti et al. 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.

15 Annexes

15.1 Annex 1: Clinical Assessment Form

SEARCH AND WEIGHING OF REFERENCES FOR THE CLINICAL EVALUATION OF MEDICAL DEVICE

PRODUCT: _____

DATE |__|__|/|__|__|/|__|__| EVALUATOR _____

REFERENCE PERIOD |__|__|/|__|__| - |__|__|/|__|__|

KEY WORDS: _____ _____

_____

#	RELEVANCY	DESCRIPTION	YES/NO	EVALUATION	
Q1	Relevant paper	Does the paper carry on relevant data?	**YES**	**A1.** This is a clinical trial a) Controlled b) open-label **A2.** This is not a clinical trial a) In vitro/in vivo, ex vivo b) Review c) other **A3.** The content of the paper is not proper	|__| |__| |__|
			NO	**A1.** The content of the paper is no pertinent with the aim of the document a) The product is totally different from the device in question b) Different disorder c) Other	|__|

- If the paper is not a clinical trial it doesn't have to be considered in the literature analysis
- If the paper is a review, it has to be considered for the state of the art.
- Articles not in English were excluded unless the relevance of the articles requires a translation
- If the paper is a clinical trial please fill the table below using the score reported within "()"

  (1.5) – (1) – (0.5) – (0) = Score for the item
- If the considered paper is not from the device in question, the paper will be retained acceptable if the total score is > 12

#	RELEVANCY	DESCRIPTION	EVALUATION	SCORE
Q2	Proper Medical Device	Were the clinical data obtained from the device in question?	**B1.** From the device in question (1 YES - 0 NO)	|__|
			B2. From a similar medical device 1. clinical similarity a. same scope and clinical condition i. same intended use (1.5) ii. minor deviation (1) iii. major deviation (0.5) b. same body site i. Yes (1) ii. No (0) c. Same target patient i. Same target patient (1.5) ii. Minor deviation (1) iii. Major deviation (0.5) d. Same relevant ongoing i. Yes (1) ii. No (0) 2. Technical similarity a. Same applicative condition i. Yes (1)	|__|__|

			ii. No (0) b. Same design i. Yes (1) ii. No (0) c. Same tech. characteristics i. Contains all the ingredients (1.5) ii. Contains one or more ingredients (1) iii. It doesn't contain any ingredient (0.5) d. Same operating modes i. Same mechanism of action (1.5) ii. Minor deviation (1) iii. Major deviation (0.5) 3. Biological similarity a. Biocompatibility with the same human tissue i. Yes (1) ii. No (0)	
Q3	Target patients	Clinical data are generated from a clinical relevant representative target patients	**C1.** Applicable (1) **C2.** Partially applicable (0.5) **C3.** Not applicable (0)	|__|__|
Q4	Acceptable paper	The paper contains sufficient and pertinent data in so producing an objective evaluation	**D1.** Satisfactory data (1) **D2.** Minor deficiency (0.5) **D3.** Insufficient or preliminary information (0)	|__|__|
Q5	Journal quality	On which journal or information media the paper has been published	**E1.** Scientific paper; normative texts (1) **E2.** Specialist journal, internet (0.5) **E3.** Other (0)	|__|__|
Q6	Paper history	When it has been	**F1.** ≤ 5 years (1)	|__|__|

		published	**F2.** 5 years ≥ paper ≤10 years (0.5)	
			F3. ≥ 10 years or not known (0.5)	
Q7	Language	In which language it has been published	**G1.** English (1 YES - 0 NO)	
			G2. Italian (1 YES - 0 NO)	
			G3. Other languages (……) (0.5)	
TOTAL SCORE			|__|__|. |__|	

15.2 Annex 2: Literature search protocol

	EBSCO (# RESULTS)	PUB MED (# RESULTS)
Hyaluronan AND osteoarthritis AND synovial fluid	7	7
hyaluronic acid AND osteoarthritis AND synovial fluid	33	6
Hyalubrix 60 AND osteoarthritis AND synovial fluid	1	0
Hyalone AND osteoarthritis AND synovial fluid	1	0
Orthovisc AND osteoarthritis AND synovial fluid	0	0
Ostenil AND osteoarthritis AND synovial fluid	0	0
Synvisc AND osteoarthritis AND synovial fluid	1	3

Total number of results = 59 publications

15.3 Annex 3: Literature search report

PubMed
RCT state for Randomized Controlled Trial

Key words	Results	Screening
Hyaluronan AND osteoarthritis AND synovial fluid	7	1. Not considered because no pertinent with the aim of the document 2. Not considered because no pertinent with the aim of the document (Oral preparation Oralvisc) 3. Not considered because no pertinent with the aim of the document 4. Not considered because no pertinent with the aim of the document 5. Not considered because no pertinent with the aim of the document 6. Not considered because no pertinent with the aim of the document (celecoxib) 7. Not considered because no pertinent with the aim of the document
hyaluronic acid AND osteoarthritis AND synovial fluid	6	1. Not considered because no pertinent with the aim of the document (IL1) 2. Not considered because the product in question is different from Hyalubrix

		(Oralvisc-oral preparation) 3. Not considered because no pertinent with the aim of the document 4. Not considered because no pertinent with the aim of the document 5. Not considered because no pertinent with the aim of the document (glycoprotein metabolism) 6. Not considered because no pertinent with the aim of the document (celecoxib)
Hyalubrix 60 AND osteoarthritis AND synovial fluid	0	-
Hyalone AND osteoarthritis AND synovial fluid	0	-
Orthovisc AND osteoarthritis AND synovial fluid	0	-
Ostenil AND osteoarthritis AND synovial fluid	0	-
Synvisc AND osteoarthritis AND synovial fluid	3	1. Not considered because no pertinent with the aim of the document (different product analysed) 2. Not considered because no pertinent with the aim of the document 3. Not considered because no pertinent with the aim of

		the document

Ebsco
RCT state for Randomized Controlled Trial

Key words	Results	Screening
Hyaluronan AND osteoarthritis AND synovial fluid	7	1. Not considered because no pertinent with the aim of the document (proteoglycan effect) 2. Not considered because no pertinent with the aim of the document 3. Not considered because no pertinent with the aim of the document (proteoglycan and hyaluronan analysis content in synovial fluid) 4. Not considered because no pertinent with the aim of the document 5. Not considered because no pertinent with the aim of the document (Review) 6. Not considered because no pertinent with the aim of the document 7. Not considered because no pertinent with the aim of the document (IL1-Ra effect)
hyaluronic acid AND	33	1. Not considered because no

osteoarthritis AND synovial fluid		pertinent with the aim of the document (IL1) 2. Not considered because the product in question is different from Hyalubrix (Oralvisc-oral preparation) 3. Not considered because no pertinent with the aim of the document 4. Not considered because no pertinent with the aim of the document 5. Not considered because no pertinent with the aim of the document (glycoprotein metabolism) 6. Not considered because no pertinent with the aim of the document (biological marker) 7. Not considered because no pertinent with the aim of the document 8. Not considered because no pertinent with the aim of the document 9. Not considered because no pertinent with the aim of the document 10. Not considered because no pertinent with the aim of the document 11. Not considered because

		no pertinent with the aim of the document 12. Not considered because no pertinent with the aim of the document 13. Not considered because no pertinent with the aim of the document 14. Not considered because no pertinent with the aim of the document 15. Not considered because no pertinent with the aim of the document (review) 16. Not considered because no pertinent with the aim of the document 17. Not considered because no pertinent with the aim of the document 18. Not considered because no pertinent with the aim of the document (review) 19. Not considered because no pertinent with the aim of the document (nanoparticles) 20. Not considered because no pertinent with the aim of the document 21. Not considered because no pertinent with the aim of

		the document 22. Not considered because no pertinent with the aim of the document (different product) 23. Not considered because no pertinent with the aim of the document 24. Not considered because no pertinent with the aim of the document 25. Not considered because no pertinent with the aim of the document 26. Not considered because no pertinent with the aim of the document (Review) 27. Not considered because no pertinent with the aim of the document 28. Not considered because no pertinent with the aim of the document 29. Not considered because no pertinent with the aim of the document 30. Not considered because no pertinent with the aim of the document 31. Not considered because no pertinent with the aim of the document (it is not a

		clinical trial) 32. Not considered because no pertinent with the aim of the document 33. Not considered because no pertinent with the aim of the document (not clinical trial)
Hyalubrix 60 AND osteoarthritis AND synovial fluid	1	1. Considered Ref 2
Hyalone AND osteoarthritis AND synovial fluid	1	1 Considered Ref 2
Orthovisc AND osteoarthritis AND synovial fluid	0	-
Ostenil AND osteoarthritis AND synovial fluid	0	-
Synvisc AND osteoarthritis AND synovial fluid	1	1. Not considered because no pertinent with the aim of the document