HYALUBRIX /INARTRAL

CLINICAL EVALUATION REPORT:

CRITICAL ANALYSIS OF LITERATURE

DATE	DESCRIPTION OF REVISION
February 2001	First certification
October2010	Change HTL, additional supplier for HA
June 2011	Revision under G_MED remarks Change HTL, additional supplier for HA
October 2011	Renewal
April 2012	Change EtO sterilization
July 2012	Revision under G_MED remarks for Change EtO sterilization
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/ INARTRAL. HYALUBRIX and INARTRAL 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/ INARTRAL 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_ HYALUBRIX/INARTRAL 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/ INARTRAL.

Essential requirements

The scope of this document is the periodical update related to the confirmation of conformity of HYALUBRIX/ INARTRAL 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/ INARTRAL is a sterile, non pyrogenic, viscoelastic solution manufactured with hyaluronic acid sodium salt, obtained by bacterial fermentation from a fraction of high molecular weight (>1500 kDa). 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/ INARTRAL:

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/ INARTRAL is a class III medical device, in accordance with the rules 8 (Annex IX of EC Directive 93/42).

GMDN: 44757

3. Intended use

HYALUBRIX /INARTRAL is a temporary synovial fluid replacement for patients affected by degenerative or mechanical arthropathy, that causes an alteration of the functional performances of the synovial liquid, without active synovitis.

4. Dosage and administration

Inject HYALUBRIX /INARTRAL, using a suitable sterile needle (for example 18 or 20 G), in the affected joint at weekly intervals for 3 weeks. Subsequent injections may be performed, if necessary.
Product administration should be performed exclusively by qualified physicians. All the rules regarding the asepsis and the injection technique should be followed. Remove any joint effusion, if present, before injecting HYALUBRIX /INARTRAL. 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.

6. Warnings and Precautions

Although pre-clinical studies performed in experimental animals indicate that the product has no potential reproductive and developmental toxicity, HYALUBRIX /INARTRAL 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 /INARTRAL with other intra-articular products.

8. Product presentation

Box containing 1 pre-filled syringe

Box containing 3 pre-filled syringes

Each syringe is sealed in a blister sterilised by ethylene oxide and contains 30 mg hyaluronic acid sodium salt in 2 ml solution sterilised using steam.

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

The present document assesses a clinical perspective to current risk/benefit of HYALUBRIX /INARTRAL on the basis of the safety /performance data accumulated.

HYALUBRIX /INARTRAL is a viscous solution (30 mg/2 ml) of hyaluronic acid (HA) sodium salt obtained from bacterial fermentation having molecular weight >1500 kDa. The high concentration of 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. 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. 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. 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. Furthermore 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 (IA) pressure is raised during joint flexion.

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 /INARTRAL is a 1.5% solution of non-modified HA (15 mg/ml) obtained by biofermentation with molecular weight >1500 kDa. Thanks to its high molecular weight HYALUBRIX /INARTRAL 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 good residence time.

The safety profile of HYALUBRIX /INARTRAL has been confirmed by preclinical data obtained on the viscous solution HYALUBRIX60 /HYALONE. HYALUBRIX60 /HYALONE is a medical device produced and marketed by Fidia since many years which differs from HYALUBRIX /INARTRAL only for the dosage of hyaluronic acid sodium salt solution contained in the prefilled syringe and volume (HYALUBRIX/ INARTRAL 30mg/2mL whereas HYALUBRIX60/HYALONE 60mg/4mL). Therefore even if HYALUBRIX/INARTRAL is composed by half volume of HA solution, it is similar to HYALUBRIX60 /HYALONE for biological characteristics and composition, manufacturing process, anatomic site of administration and intended use (viscosupplementation by intra-articular injection). Based on that the biocompatibility of the product in the clinical use and the

safety results obtained on HYALUBRIX 60/HYALONE can be applied to HYALUBRIX/INARTRAL. Preclinical data collected on HYALUBRIX 60/HYALONE permits to confirm that HYALUBRIX /INARTRAL is non- toxic and with no sensitizing properties. Moreover, no systemic and local reactions nor mutagenic and clastogenic effects have been observed (BER_ HYALUBRIX_Gap Analysis_October 2016). HYALUBRIX /INARTRAL can be considered safe, well tolerated and the preclinical documentation is to be considered adequate to demonstrate the biocompatibility of HYALUBRIX /INARTRAL and to justify its clinical use.

Additionally collected human clinical trials results and post marketing surveillance data 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 /INARTRAL and justify the intra-articular use of the device.

Competitors

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

Table 1: Overview of HYALUBRIX /INARTRAL 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	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.

			acts as a lubricant and shock absorber for the joints. Synvisc is used to treat knee pain caused by osteoarthritis.		• Technical characteristics: Viscoelastic solution with similar principles of operation. • Biological characteristics: similar composition (HA based), temporary 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 /INARTRAL 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 /INARTRAL.

As mentioned above HYALUBRIX 60/ HYALONE is another medical device produced and commercialized by Fidia since many years. HYALUBRIX 60/ HYALONE and HYALUBRIX/ INARTRAL differ only for the amount of hyaluronic acid sodium salt solution contained in the prefilled syringes (60 mg/4ml in HYALUBRIX 60 /HYALONE and 30 mg/2ml in HYALUBRIX /INARTRAL). Furthermore although they are both used for the same clinical purpose (degenerative or mechanical arthropathy), HYALUBRIX/ INARTRAL is administered as a course of 3 injections once a week whereas HYALUBRIX60/ HYALONE (arthropathy of the hip and knee) is administered by single injection.

Considering that both HYALUBRIX /INARTRAL and HYALUBRIX 60 /HYALONE are constituted by the same type of HA (same viscoelastic characteristics and same molecular weight), the clinical evidences and results available on HYALUBRIX 60 /HYALONE have been evaluated and included in

this clinical evaluation report to further evaluate the performance and safety of HYALUBRIX /INARTRAL.

10. Clinical data appraisal

10.1 Data generated through Literature Search

Methods

HYALUBRIX/INARTRAL own data have been considered. Furthermore, citations emerged from previous versions of CERs have been taken in account to examine their possible inclusion or exclusion in the present consolidated Clinical Evaluation Report. A search from available literature data and from Fidia 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, Hyalubrix, Inartral, Orthovisc, Ostenil, Synvisc.

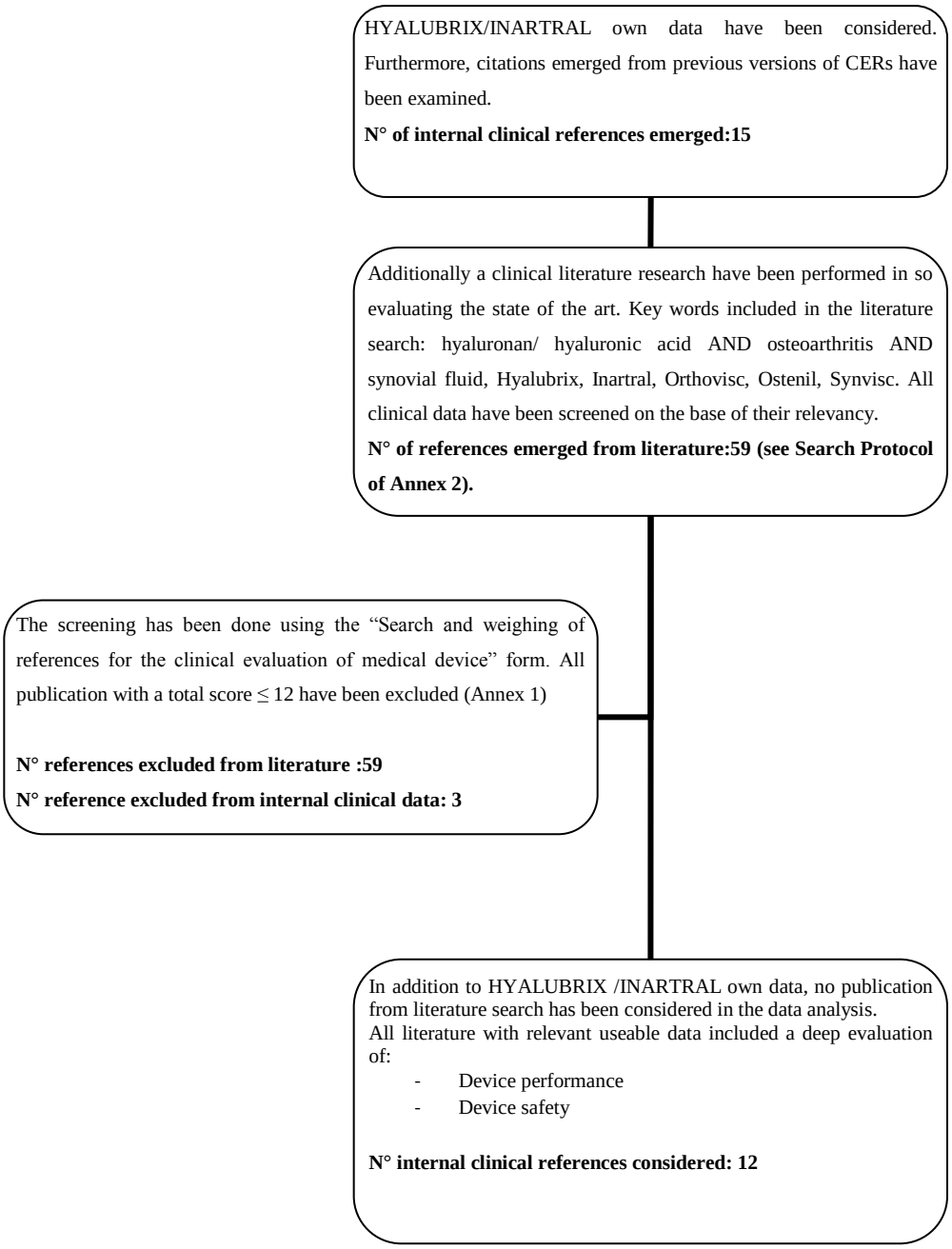
The various citations obtained were screened and only the publications containing relevant findings were considered. Suitable articles were evaluated and selected by assessment of type of the performed clinical study, study design, sample size of treated patients, the pathology treated and the statistical 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 search 15 studies emerged over the years however only 12 of them have been considered and analyzed from both efficacy and safety point of view (Ref 1-12, Table 2). All selected publications reached a score >12 in the assessment process (Annex 1). References 13-14 and 15 were excluded mainly because regarded data gained in devices different from what in question, with different technical characteristics or because papers contains no sufficient and no pertinent data (score ≤12).

Furthermore from literature database research 59 publications came out (see Search protocol and Search Report, Annex 2-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



The internal clinical articles available for HYALUBRIX/INARTRAL have been listed and summarized in the following Table 2. As previously explained only 12 of them (**Ref 1-12**) have been fully considered and examined to support the efficacy and safety of HYALUBRIX/INARTRAL.

Table 2: Relevant data considered from internal and literature review.

Ref	**Author**	**Title**	**Bibliography**	**Product**	**Considered/ Not Considered**
1	F. Schieb	Intra-Articular Injections Of Hyaluronic Acid In The Treatment Of Arthropathies.	Arthritis + Rheuma 2003;23 (6): 338-340	Hyalubrix	Considered Score:14,5
2	A.Migliore, U. Massafra, A. Capuano, E Mascheroni', M.L. Diaco, C. Padalino, A. Alimonti, F. lannessi, S. Tormenta	Comparison Between Hyalubrix® And Intra-Articular Mepivacaine In The Treatment Of Coxarthrosis.	Acta Biomedica 2006; 77(6): 11-12	Hyalubrix	Considered Score:13,5
3	A. Migliore, U. Massafra, F. Iannessi, A. Capuano, ML Diaco, E Mascheroni, A. Alimonti, G. Granata, C. Padalino, S. Tormenta	Efficacy And Safety Of Hyalubrix® Administration Into The Joint During Coxarthrosis: A Prospective Cohort Study.	Acta Biomedica 2006; 77(6): 13/14	Hyalubrix	Considered Score:13,5
4	F. Priano, M. Guelfi	Efficacy of intra-articular hyaluronic acid (Hyalubrix®) in arthroscopy.	Artroscopia 2007; 3(1)	Hyalubrix	Considered Score: 14,5
5	C. Smiderle, M. Scapin, M. Baldo, L. Ronconi, G. Marcolin, R. Villaminar	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	Considered Score:14,5
6	Marco Paoloni, Luca Di Sante, Mauro Dimaggio, Andrea Bernetti, Massimiliano Mangone, Sara Di Renzo, Valter Santilli	Kinematic and kinetic modifications in walking pattern of hip osteoarthritis patients induced by intra-articular injections of hyaluronic acid.	Clin Biomech. 2012 Epub	Hyalubrix	Considered Score:14,5
7	C. Foti , C. Cisari , S.	A prospective	Eur J Phys	Hyalubrix	Considered

	Carda , N. Giordan , A. Rocco , A. Frizziero , G. Della Bella	observational study of the clinical efficacy and safety of intra-articular sodium hyaluronate in synovial joints with osteoarthritis.	Rehabil Med 2011;47:1-9		Score:14,5
8	Ingegnoli et Al.	Power Doppler Sonography and Clinical Monitoring for Hyaluronic Acid Treatment of Rhizarthrosis: A Pilot Study.	J Hand Microsurg (July–December 2011) 3(2):51–54	Hyalubrix	Considered Score:13,5
9	Vetro et al.	Pain relief and functional recovery over a six month period after intra-articular injection with sodium hyaluronate (MW 1500-2000 KDA) in osteoarthritis of the knee.	European Journal of musculoskeletal diseases 2014	Hyalone	Considered Score:15,5
10	Migliore et al	Total hip replacement rate in a cohort of patients affected by symptomatic hip osteoarthritis following intra-articular sodium hyaluronate (MW 1,500–2,000 kDa) ORTOBRIX study.	Clin Rheumatol (2012) 31:1187–1196	Hyalone	Considered Score:13,5
11	Minola R.	Use of Hyalubrix 60/Hyalone for the treatment of the knee	Data on file, 2011	Hyalubrix 60	Considered Score:13
12	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:13,5
13	A. Migliore, M. Granata, S. Tormenta, B. Laganà, P. Piscitelli, E. Bizzi, U. Massafra, A. Alimonti, C. Maggi, R. De Chiara, F. Iannessi, A. Sanfilippo, R. Sotera, P. Scapato, S. Carducci, P. Persod, S. Denaro, M. Camminiti, M.G. Pagano, G.	Hip viscosupplementation under ultra-sound guidance riduces NSAID consumption in symptomatic hip osteoarthritis patients in a long follow-up. Data from italian registry.	European Review for Medical and Pharmacological Sciences 2011; 15: 25-34	High molecular weight hyaluronan	Not considered Score: 9.5

	Bagnato, G. Iolascon				
14	Bellamy, Campbell, Robinson, Gee, Bourne, Wells	Viscosupplementation for treatment of osteoarthritis of the knee.	The Cochrane Collaboration. Published by JohnWiley & Sons, Ltd. 2009	Hyaluronans	Not considered Score: 8.5
15	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	A 40-month multicentre, randomised placebo controlled study to assess the efficacy 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: 7

10.2 Data generated through Clinical Experience

Methods

To further confirm the safety profile Fidia performed additional web searches on Clinical Websites and/or Government database related to HYALUBRIX/ INARTRAL and to the 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/ INARTRAL is mainly marketed and in the databases of the international Health Authorities: FDA, EMA (Post Marketing Surveillance HYALUBRIX / INARTRAL- Reference Period: 1 January 2003 – 30 June 2016).

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 (Post Marketing Surveillance HYALUBRIX / INARTRAL- Reference Period: 1 January 2003 – 30 June 2016).

11 Clinical data results

Fidia considered the similar products and HYALUBRIX/ INARTRAL 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	1523	Observational study	Arthropaties treatment	Hyalubrix 3 injections	Efficacy and safety	In the sub-group of patients suffering from arthropathies of purely traumatic origin, the patients were generally younger, and with a shorter medical history as compared with those first observed. No significant differences were reported, however, between the different pathologies or frequency of injections. In any case, approximately 95.6% of patients reported a significant pain reduction. Efficacy and tolerability were evaluated as being positive both by the physician and patient, exactly as was the case for the others throughout the study. In this group, no negative results were reported. More than 91% of patients would willingly repeat the hyaluronic acid-based treatment in the future. It is therefore evident that it would be advisable to administer the preparation to patients suffering from arthropathies even for a short length of time and/or of traumatic origin.
2	30	Controlled, randomized, double-blind study	Coxarthrosis treatment	IA injections of Hyalubrix or mepivacaine	comparing the efficacy and tolerability of Hyalubrix® with that of mepivacaine	The preliminary results of this study would appear to indicate that, at the three months follow-up, ultrasound-guided intra-articular treatment with Hyalubrix® improves joint function and reduces the use of NSAIDs significantly, as compared with that reported for patients treated with the

						anesthetic. The results at six months concerning pain reduction, measured according to the VAS, are currently being evaluated. These results, although preliminary, are nonetheless of significant interest, also in the light of the rigorous study design, and are hugely supported by data already available in literature. Viscosupplementation with hyaluronic acid (Hyalubrix®) administered into the joint is confirmed, therefore, as a safe and effective method for the treatment of the symptoms of coxarthrosis.
3	151	Prospective cohort study	Coxarthrosis treatment	IA injections of Hyalubrix	pain reduction, NSAID consumption	At the three-month follow-up, a significant improvement in pain was observed, evaluated with both the VAS (from 5.63 to 3.74 with $p < 0.0001$) and the Lequesne index (from 6.64 to 4.78 with $p<0.0001$). NSAID consumption was also reduced, although during this phase, the change did not reach any statistical significance (from 5.50 to 4.37 with $p = 0.08$). The cohort evaluated at the six-month follow-up 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) (Fig. 2). 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).
4	100	Multicentre, randomized, open-controlled study	Knee arthroscopy treatment	IA injection of Hyalubrix	Pain on walking, at rest, during activity decrease	100 patients were enrolled for meniscectomy to a single knee. 51 patients were assigned to the treatment group with conventional therapy associated with Hyalubrix®, while 49 patients were assigned to the control group. The following populations were defined for the analysis of the results: ITT population: (100 patients: 51 treated group, 49 control group); the Protocol Population; Safety population (100 randomized and treated patients, coinciding with the ITT population). The enrolled population shows a prevalence of male patients (62%), which is distributed in a similar manner between those treated with Hyalubrix® and the controls. In 33% of patients, other concomitant pathologies were reported: considering the two groups separately, the percentage is 39% in the treated group and 29% in the control group. The median average of the two groups (95 days for the treated group and 113 for the control group) is not significantly different. The most frequently practiced procedure was selective, medial or lateral, meniscectomy, to the posterior horn or body. In 14% of cases, the procedure involved sub-total meniscus resection (24% in the treated group, 4% in the control group) and compromised cruciate ligament was reported in 29% of patients (24% in the treated group, 33% in the control group).
5	14	Gait analysis	Knee osteoarthritis	IA injection of Hyalubrix	the efficacy in knee OA	The efficacy of the infiltration treatment on pain reduction and personal performance improvement is shown by the

						reduction in the median values for the NR Scale (from 6.2 to 3.8), and the improvements in all the parameters measured with the Womac scale: pain (from 10.3 to 4.8); rigidity (from 4.5 to 2) and physical function (from 35.4 to 22.3). The statistical analysis of the gait analysis data allowed us to identify an improvement in the majority of the measured parameters, most of them in a statistically significant way (statistical significance was set at a p value < 0.05). These results demonstrate that patients treated intra-articularly with hyaluronic acid show improvement, based on subjective and clinical evaluation, and more importantly, according to statistically significant improvements in most Gait analysis parameters.
6	20	Prospective, open study	Hip OA	3 intra-articular injections of 2 ml of hyaluronic acid in the hip (1/week).	the clinical effects in terms of pain and function	Pain as measured with visual analog scale significantly dropped after this procedure (P<0.0001). A significant improvement was noted regarding stiffness (P=0.005) and disability (P=0.04), as measured by the Western Ontario and McMaster Universities osteoarthritis index. As regards gait analysis, patients at T3 walked with higher cadence (P=0.004) and stride length (P=0.02) compared to T0. Moreover, a significant increase for the pelvic tilt at heel contact (P=0.0004) and for hip flexion–extension moment at loading response sub-phases of gait cycle (P=0.02) was noted at T3. In line with current literature, our patients display clinical improvement 6 months after intraarticular injections of hyaluronic acid, accompanied by changes inwalking pattern,

						asmeasured by instrumental gait analysis. The kinematic and kinetic changes observed may be the consequence of the therapeutic effect of intra-articular injections of hyaluronic acid.
7	1266	Prospective, and observational study	Knee OA	Received IA injections of the study treatment (2 mL) once per week for 3 weeks.	Safety and efficacy of intra-articular (IA) sodium hyaluronate (MW 1500-2000	Data from 1266 participants were collected. The adverse event (AE) rate was 0.8% (95% CI, 0.4 to 1.5). Thirteen AEs were reported, 12 of which were mild or moderate in severity. Only one participant discontinued study treatment following an AE. No serious adverse events occurred. Coadministration of local anesthetic was required by up to 10% of patients. Statistically significant improvements in VAS, HAQ and EuroQoL were recorded in multiple joints (P<0.0001 for each). The study treatment was safe and well tolerated. The study treatment reduced pain, improved mobility, and increased QoL in participants with OA.
8	16	Prospective, pilot open-label study	Trapeziometacarpal (TMC) joint osteoarthritis	Three intraarticular injections of Hyalubrix.	Evaluate efficacy and safety on the OA of the thumb base	32 TMC joints of 16 patients with symptomatic thumb base OA were treated with three injections of high molecular weight HA at 1-week intervals. Before injection, at week 0, 1, 2, and 24 all patients underwent clinical and US examination. A significant clinical improvement was obtained by the decrease in visual analog scale for pain after 2 weeks of treatment (p= 0.0003) and this result is maintained at week 24 (p=0.009). The Dreiser's index also decreased after week 2 and remain stable after 6 months. Power Doppler signal significantly decreased after 2 weeks of treatment (p=0.02), even if this

						result was not maintained at week 24. No significant decrease in the synovial hypertrophy score was observed during the study. Our preliminary study suggests that US guided TMC injections by high molecular weight HA may be effective in decreasing local inflammation and pain.
9	168	Single site open cohort study	Knee OA	One ultrasound guided IA injection oh HyalOne	Evaluate the pain reduction and improvement on knee functionality.	168 patients with mild to moderate OA of the knee were enrolled to receive one ultrasound guided intraarticular injection of 4 ml Sodium Hyaluronate (Hyalone) and were followed up to 24 weeks. The primary efficacy oucome was the change from baseline to week 24 in patients pain perception using a 100 mm visual analogue scale (VAS). Additional outcomes included the WOMAC score and the KOOS assessed at 4,12, and 24 weeks. The patients enrolled sjowed a significant improvement from baseline in all symptomatic otcome measures. Pasin significantly decreased after treatment. KOOS and WOMAC score showed a significant reduction at each study point (week 4-12 and 24)The present study suggests that a single IA injection of linear high MW HA in patients suffering from knee OA is well tolerated and provides relief from pain.
10	176	Retrospective, open study in single cohort	Hip osteoarthritis	HyalOne	Evaluate efficacy and safety on the hip	This retrospective study in patients suffering from hip OA treated with ultrasound-guided intra-articular injections of HyalOne (Hyalubrix 60 Italian brand name) involving a group of THR expert orthopedic surgeons to appraise whether or not considered eligible for THR and the frequency and timing of THR (total hip replacement). At 24 months, 159 out of 76 (90 %) patients

						did not undergo to THR. At 48 months, 82 % (N0144) of the study population treated with intra-articular hyaluronic acid avoided 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 had undergone THR, with survival results of 82 % at 24 months. At 48 months, this percentage reduced to 66 % in this group. 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. Sodium hyaluronate (MW 1,500–2,000 kDa) given by ultrasound-guided injection seems to delay THR in the real context of actual overall management of symptomatic hip OA patients.
11	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.
12	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	This study investigated the long-term efficacy and tolerability of ultrasound-guided intra-articular sodium

					injection after 6 months	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.

12 Clinical data analysis

12.1 Performance

Ref 1

A six-week follow-up observational clinical trial conducted on 1523 patients in 515 centers can be considered. A diagnosis of degenerative arthropathy was the general indication for treatment with hyaluronic acid (90.5%), 81.3% of patients suffered from gonarthrosis. It was also possible to include 143 patients suffering from arthropathies of traumatic origin (9.5%); of these, 27 patients showed a combined degenerative/traumatic pathology. Disease duration varied greatly (from less than 1 year to more than 10 years). Only those suffering from an arthropathy of purely traumatic origin had, as could

be expected, a shorter onset of the pathology (often less than 1 year). Intensity of pain and mobility were evaluated according to a visual analogue scale, both at the start and end of treatment. At the end of the study, an overall tolerability evaluation was also made. During the study, most patients (83.2%) underwent one cycle of three injections of Hyalubrix®, thereby confirming previous findings that the high concentration of hyaluronic acid (30 mg/2 ml) contained in the preparation in question makes it possible to obtain good results with just 3 injections. In 217 patients (14.3%) showing the most serious conditions, with a longer history of the disease, 4 to 6 injections were administered into the affected joint. At the same time, for over 63% of patients who were taking NSAIDs or other oral painkillers, the dosage of the latter was significantly reduced, and approximately 14% of patients were able to suspend the aforementioned additional pharmacological treatments completely.
The final judgment of physicians and patients on treatment efficacy was as follows: 88% of physicians and 85.4% of patients judged the treatment to be ‘good' and 'very good', respectively.

Ref 2

In this clinical trial, Dr. A. Migliore's group evaluated the efficacy and safety of symptomatic treatment with Hyalubrix Vs local anesthetic (Mepivacaine) intra-articularly administered in terms of reducing pain, improving joint function, and decreasing NSAID use in patients diagnosed with coxarthrosis.
Thirty patients diagnosed with coxarthrosis were enrolled in the study, chosen according to specific inclusion/exclusion criteria: of these, 23 were included in the three months of follow-up.
Twelve patients were treated with two Hyalubrix® i.a. injections, at the double dose of 4 ml per treatment (30 mg/2ml x 2), administered into the joint, with a monthly interval between injections.
Eleven control subjects were treated with 2% mepivacaine (4 ml) administered in the same way as Hyalubrix. The injections were performed with the ultra-sound guided technique.
Treatment efficacy (at 3 months) was high for both groups, with an improvement in VAS ($p<0.001$), joint mobility ($p<0.001$) and a reduction in the consumption of NSAIDs ($p<0.06$), which was greater for Hyalubrix® than for mepivacaine.

Ref 3

In this study 151 patients were treated with double-dose, i.a. injections of Hyalubrix® (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 4

In this multicentre, randomized, open-controlled clinical study, carried out on 100 patients. In particular the recruited patient were divided into two treatment groups: 51 treated with Hyalubrix® (1 injection of 30 mg/2 ml) injected into the joint cavity after completion of the procedure, and 49 undergoing conventional postsurgical therapy, without the administration of Hyalubrix®.

Efficacy and tolerability of the investigational treatment was evaluated in terms of reduction of pain on walking, during activity, at rest and at night (using VAS scale); joint evaluation measured using category scales (absent, scarce, mild, moderate, severe); evaluation of the knee functional limitation measured by the Lysholm scale; overall opinion of patients and investigator; presence of side effects.

Pain reduction on walking, at rest, during activity and at pressure resulted to be statistically significant at 7, 30 and 60 days after treatment from baseline ($p<0,01$). Concerning the improvements of joint mobility reported as changes from baseline values, the difference between the two compared groups is statistically significant ($p=0.0369$) only at V2 (after 7days). The judgment given by both the doctor and patient generally show a more significant clinical improvement in patients belonging to the treated group. The difference between the two groups of patients is statistically significant from the first assessment, and is confirmed at subsequent assessments. The functional limitation of the knee,

measured by means of the Lysholm scoring scale differ in a statistically significant manner at baseline (p=0.0006), with the average values lower in the treated group than in the control group, the treated group recovers the initial disadvantage at V2 (after 7 days). At assessments V3 (after 30 days) and V4 (after 60 days), the treated group also shows an average functional capacity higher than that of the control group, again confirming the efficacy of the treatment in these patients.

In conclusion, the use of Hyalubrix® in arthroscopic meniscectomy is associated with a significantly better clinical outcome, both in terms of function and in relation to pain symptoms, as compared with the same procedure performed without this treatment. Three studies were carried out to evaluate efficacy, safety and benefit in terms of delay of THR surgery.

Ref 5

The goal of our research was to evaluate, in osteoarthritis of the knee patients, the efficacy of intra-articular high molecular weight hyaluronic acid (Hyalubrix - 30 mg/2 ml dose of sodium hyaluronate) for reducing pain and improving walking parameters, with the use of a sophisticated technique known as optoelectronic digital analysis of gait by analyzing both kinematics and kinetic parameters.

All participants signed a consensus form prior to the beginning of the treatment; 14 patients (6 males and 8 females) were chosen following very strict criteria including: age (at least 40 years old), and presence of grade 2 or 3 (according to the Kellegren and Lawrence scale) OA of one knee (14 knees) with pain greater than 4 on the Numerical Rating Scale (NRS). Criteria for exclusion included: concurrent presence of pathologies such as rheumatoid arthritis, gout, hip arthritis, compromised adjacent joints; presence of skin infections near the knee; use of corticosteroid in the last 3 months; simultaneous anticoagulant therapy; use of joint protective drugs; clotting anomalies; knee valgus; known adverse reactions to hyaluronic acid; presence of knee replacement or impending knee replacement surgery. The patients, after a complete verbal/questionnaire evaluation, clinical evaluation, anthropometric measurement evaluation (as prescribed by the Davis protocol), and an evaluation with the NRS and WOMAC scales, underwent the first round of gait analysis (t1). On the same day, after the instrumental analysis, the patients were given the first infiltration with hyaluronic acid. The protocol then prescribed one infiltration per week for three weeks. After 45 days from the first evaluation, the patients were assessed again with the NRS and WOMAC scales, and gait analysis.

The efficacy of the infiltration treatment on pain reduction and personal performance improvement is shown by the reduction in the median values for the NR Scale (from 6.2 to 3.8), and the improvements in all the parameters measured with the WOMAC scale: pain (from 10.3 to 4.8); rigidity (from 4.5 to 2) and physical function (from 35.4 to 22.3). The statistical analysis of the gait analysis data allowed us to identify an improvement in the majority of the measured parameters, most of them in a statistically significant way (statistical significance was set at a p value < 0.05).

Ref 6

Paoloni et al performed a prospective, open study in order to verify, in a group of 20 hip osteoarthritis patients (12 men, 8 women, mean age 60.5, range 47–73), the clinical effects of 3 intra-articular injections of 2 ml of hyaluronic acid in the hip (1/week) in terms of pain and function at 1 (T1), 3 (T2) and 6-month (T3) follow-ups, as well as changes in the kinematics and kinetics of gait at 6-month follow-up.

Pain as measured with visual analog scale significantly dropped after this procedure (P<0.0001). A significant improvement was noted regarding stiffness (P=0.005) and disability (P=0.04), as measured by the Western Ontario and McMaster Universities osteoarthritis index. As regards gait analysis, patients at T3 walked with higher cadence (P=0.004) and stride length (P=0.02) compared to T0. Moreover, a significant increase for the pelvic tilt at heel contact (P=0.0004) and for hip flexion–extension moment at loading response sub-phases of gait cycle (P=0.02) was noted at T3.

In line with current literature, our patients display clinical improvement 6 months after intraarticular injections of hyaluronic acid, accompanied by changes in walking pattern, as measured by instrumental gait analysis. The kinematic and kinetic changes observed may be the consequence of the therapeutic effect of intra-articular injections of hyaluronic acid.

Ref 7

This prospective, and observational study investigated the safety and efficacy of intra-articular (IA) sodium hyaluronate (MW 1500-2000KDa; Hyalubrix®) in the treatment of synovial joint OA. This study was carried out at 47 specialist centers for physiatrists, orthopedics and rheumatology in Italy; the enrolled population, 1266 outpatient, was predominantly female (66%, 840/1266), with a mean age of

66 years, and a mean weight of 74 kg. The Participants with OA received IA injections of the study treatment (2 mL) once per week for 3 weeks. The knee was the joint most commonly affected by OA (right knee 802/1266 [63%]; left knee 598/1266 [47%]), and the longest median duration of disease occurred in the carpal joint (right carpal joint 40 months; left carpal joint 60 months).

The primary endpoints were tolerability and details of usage of the IA sodium hyaluronate syringe device. Efficacy parameters included assessment of self-reported pain via the Visual Analogue Scale (VAS), and evaluation of motor function via the Health Assessment Questionnaire (HAQ). Quality of life (QoL) was assessed using the Euro QoL questionnaire (Clinical Trial Registration Number: ISRCTN 42690497). Results. Data from 1266 participants were collected. Statistically significant improvements in VAS, HAQ and EuroQoL were recorded in multiple joints (P<0.0001 for each).

The study treatment was safe and well tolerated; study treatment reduced pain, improved mobility, and increased QoL in participants with OA.

Ref 8

In this prospective pilot open label study 16 subjects affected by trapeziometacarpal (TMC) joint osteoarthritis (15 women and 1 man) with a median age of 62.46 years (range 43.5 to 79.4 years) were involved. US-guided injections were performed with a GE LOGIQ 9 unit (General Electric Medical Systems; Milwaukee, Wisconsin, USA) using a high-frequency 9–14 MHz linear array transducer. The setting for grey-scale US was 14 MHz and the pulse repetition frequency for the power Doppler signal (PDS) was set at 500 Hz.

All subjects during the same consultation, were referred to one physician who collected at baseline (week 0), after 2 and 24 weeks the following data: 1) VAS for pain; 2) hand function with Dreiser's index for the OA of the hand [14]; and 3) US examination assessing TMC joints for synovial hypertrophy and PDS, scored from 0 to 3 according to the preliminary scoring tool for hand OA. In our study, both hands of all the patients were treated with three US-guided intra-articular injections of Hyalubrix® at 1-week intervals.

A significant clinical improvement was obtained by the decrease in VAS pain after 2 weeks of Hyalubrix® treatment (p=0.0003) and this result was maintained at week 24 (p=0.009). In fact, at baseline, VAS pain was higher, median 68.8 mm (interquartile range 50.5–80.0 mm), than after 2 and 24 weeks (median 40 mm, 20– 68 mm and 55 mm, 45–70 mm respectively). The Dreiser's index also

decreased from 9.0 (5.5–11.5) at baseline to 8.0 (4.0–9.0) at week 2; after 6 months, the median of Dreiser's index remains stable at 8.0 (5.0–9.0), but these differences did not reach statistical significance.

Ref 9

In this single site open cohort study 168 patients with a mean age of 54-years, were enrolled. Patients received the injection at baseline and were followed up at 4(T1), 12 (T2) and 24 (T3) weeks after the first injection. Treatment with HyalOne resulted in a statistically significant improvement from baseline to week 24.

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. Patients reported an initial decrease in VAS of 37.6 m that subsequently decreased by a further 19.9 mm at T2 and 6.4 mm and 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 foam 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. Total WOMAC score showed a significant reduction in pain and stiffness and an increase in knee functionality at each study point. Mean baseline values of all KOOS subscales progressively increased at each study time point to reach the highest value at T3.

Ref 10

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 11

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 12

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 + 30 mg/2 ml – to be repeated, if required, 6 months later, at doses to be adjusted 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).

12.2 Safety

12.2.1 Data emerged from literature

Literature evidences confirm that HYALUBRIX/ INARTRAL is safe and well tolerated. The all local effects emerged from clinical evidences are temporary and already predicted and then reported in the IFU leaflet. Mainly the safety concerns are described as local pain, swelling, heat and redness that occur sporadically at the injection site and that are associated to local mild and transient symptoms fully described in the 'Undesirable effects' section of the IFU. The reported itching sensation can be considered as a symptoms of local inflammatory reaction.

Ref 1

The safety profile of this study was evaluated as positive. Of the 1523 patients treated, only 8 (0.5%) reported an adverse reaction, of which only one was considered of a serious nature. Specifically, six of these were local (reddening, itching or pain at the injection site), and may potentially be related to the product. The other two adverse reactions, including the most serious one, were not judged to be actually related to the treatment. Tolerability was judged as 'good' or 'very good' by 99,2% and 98,8% of physicians and patients. On the basis of these results concerning efficacy and tolerability, 89.6% of patients declared that they would willingly repeat the treatment in the future.

Ref 2

In this study the intra-articular treatment of patient affected by the osteoarthritis did not cause any significant local side effects at the injection site. Therefore viscosupplementation with hyaluronic acid (Hyalubrix) administered into the joint is confirmed as a safe and effective method for the treatment of the symptoms of osteoarthritis of the hip.

Ref 3

In this study the intra-articular treatment of patient affected by the osteoarthritis did not cause any systemic side effects. Therefore viscosupplementation with hyaluronic acid (Hyalubrix) administered into the joint is confirmed as a safe and effective method for the treatment of the symptoms of osteoarthritis of the hip.

Ref 4

In this study a total of 9 adverse events were described during this study, 4 of which were reported in the control group, and 5 in the treated group, with no significant difference between the two groups. Of these, none was classified by the investigator as serious, and all improved or recovered fully, with no consequences related to the study intervention.

Ref 5

In this study the intra-articular treatment of patient affected by the osteoarthritis did not cause serious systemic effects and no local side effects were reported in this clinical trial.

Ref 6

In this study the intra-articular treatment of patient affected by the osteoarthritis did not cause serious systemic effects and no local side effects were reported in this clinical trial.

Ref 7

In this study the adverse event (AE) rate was 0.8% (95% CI, 0.4 to 1.5). In total thirteen AEs were reported, 12 of which were mild or moderate in severity. Only one participant discontinued study treatment following an AE. No serious adverse events occurred.

Ref 8

In this study the intra-articular treatment of patient affected by trapeziometacarpal (TMC) joint osteoarthritis did not cause any adverse events.

Ref 9

During the study the treatment was well tolerated. Mild transient adverse events were reported in 5 patients and consisted on mild or moderate post injection pain and swelling which resolved spontaneously after a few days. Patients daily activities were unaffected by these events. No serious adverse events were reported by the patients during the treatment.

Ref 10

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 11

In this study no adverse events were reported by patients during the treatment apart from one patient who had a local reaction developed within 24 hours after injection.

Ref 12

In this study no systemic side effects were reported.

12.2.2 Data emerged from Clinical Experience

Data collected from the web search did not show any important safety information for HYALUBRIX/INARTRAL and for the similar medical devices Orthovisc, Synvisc and Ostenil. Furthermore whereas 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/INARTRAL (Post Marketing Surveillance HYALUBRIX / INARTRAL- Reference Period: 1 January 2003 – 30 June 2016). This suggests that HYALUBRIX/INARTRAL results more safe and well tolerated and that no allergic reactions are related to its use.

13 Conclusions

The high concentration of 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. 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. Therefore traumatic and degenerative joint disorders are characterized by an insufficient amount of hyaluronic acid and a loss of viscosity in synovial fluid, resulting in an impairment of joint function and in a painful symptomatology. Extensive data in the literature reveal that intra-articular administration of hyaluronic acid (viscosupplementation therapy) is capable to restore the viscoelastic properties of the synovial fluid with alleviation of pain and improvement of joint mobility. HYALUBRIX /INARTRAL is a 1,5% solution of non-modified HA obtained by bio fermentation with molecular weight >1500 kDa. Since rheological and mechanical properties of HYALUBRIX /INARTRAL are quite close to the ones characterizing the synovial fluid, it appears as an effective treatment for temporary synovial fluid replacement in patients affected by degenerative or mechanical arthropathy that causes an alteration of the functional performances of the synovial liquid. Furthermore clinical evidences and literature data gained up to now, date of this clinical evaluation report, confirm that HYALUBRIX /INARTRAL is safe and well tolerated. Accordingly preclinical results confirm that the HA-based product HYALUBRIX /INARTRAL is neither cytotoxic nor genotoxic. HYALUBRIX /INARTRAL does not have any sensitizing effects and implantation studies do not show any local or systemic toxicity. Moreover the preclinical and clinical data obtained on HYALUBRIX60 /HYALONE, a device constituted by the double volume of the same HA contained on HYALUBRIX /INARTRAL, further assure that the intra-articular injection of HYALUBRIX /INARTRAL results safe, well tolerated and no toxic. In addition the ETO sterilization cycle for the sterilization of HYALUBRIX /INARTRAL 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. The ETO sterilization doesn't influence the product characteristics, as attested by the check of the specifications after ETO sterilization cycle: the physical-chemical and viscoelatics characteristics of the product don't changed, so the there isn't any influence on the its shelf-life (HYALUBRIX/INARTRAL RMR EQ47/ rev 10, October 2016).

Altogether these results confirm the biocompatibility of HYALUBRIX /INARTRAL and justify the intra-articular of this device. In view of these observations the safety and performance profile of HYALUBRIX /INARTRAL as a temporary synovial fluid replacement for patients affected by degenerative or mechanical arthropathy is confirmed.

Therefore the combination of evidences obtained from clinical data of similar products and of HYALUBRIX /INARTRAL clearly support the conformity with Essential Requirements and the maintenance of the claimed characteristics and performances of HYALUBRIX /INARTRAL under the normal condition of use and the achievement of the intended clinical performance and safety (HYALUBRIX/INARTRAL RMR EQ47/ rev 10, October 2016). Based on that no new clinical investigation have been performed (Post Marketing Clinical Follow Up_ HYALUBRIX/INARTRAL 2016).

Risk analysis and Risk/Benefit Balance

The manufacturing data and post-marketing experience obtained with HYALUBRIX /INARTRAL and with similar products have been considered to assure the safety and performance of HYALUBRIX /INARTRAL.

Safety surveillance data from 01 January 2003 (first launch date) up to June 2016 confirm that HYALUBRIX /INARTRAL can be considered safe and well tolerated. A total of 324 case-reports reporting 530 suspected Adverse Reactions (ARs) were received at Fidia Safety Surveillance Unit from post-marketing source. It should be noted that from January 2005 to December 2005 an increased number of cases 203 were reported from the German market. Fidia decided for a temporary suspension of the product in this territory. In meantime Fidia performed the relevant investigations to identify the root cause of the problem and start the adequate corrective action to reduce the risk. The cause of these increased number of reporting was identified in a technical issue. The corrective measures were applied and the problem was solved. In September 2006 the product was reintroduced on the market. From this date up to 30 June 2016, ninety-five cases were registered however only two cases were considered incidents. Therefore data from post-marketing surveillance showed an incidence of 0,023% in 2003 and 0,096% in 2004. The reactions observed were mainly on local type in nature (injection site joint swelling, injection site joint inflammation, injection site joint pain, etc.). In 2005 has been detected a remarkable increasing of ARs. After the product was reintroduced on the market in 2006 till June 2016, the average incidence was reduced to 0.004%, revealing that the risk for the exposed population to develop adverse events is very low, thus demonstrating the effectiveness of the remedial actions implemented after the temporary suspension of the product from the German market in the 2005.

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. The frequency rate for each adverse event typology falls in the "very rare" category, i.e. an acceptable level of risk for patients and public health. The overall frequency of spontaneous reports, estimated from the sales data, does not indicate an increased incidence of any particular adverse event attributable to the product with the average incidence around 0.004% (Post Marketing Surveillance HYALUBRIX / INARTRAL- Reference Period: 1 January 2003 – 30 June 2016). Moreover, clinical and safety data collected on HYALUBRIX60 /HYALONE, another medical device produced by Fidia and marketed in several European countries which differs from HYALUBRIX /INARTRAL only in volume contained in the syringes, confirm that the IA hyaluronan products are safe and well tolerated.

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. No risk is in the undesirable or in intolerable class, as stated by the acceptability criteria for residual risk of the Risk Management Plan. Furthermore all risks, taken together, do not exceed the expected benefit to the patient so the favorable risk-benefit ratio is confirmed and the documentation on the product HYALUBRIX /INARTRAL supplied by Fidia is to be considered adequate. In conclusion HYALUBRIX /INARTRAL satisfies the essential requirements and the toxicological and regulatory requirements (HYALUBRIX/INARTRAL RMR EQ47/ rev 10, October 2016).

Lastly the review of the product labelling and instructions for use of HYALUBRIX /INARTRAL 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 /INARTRAL in the 'Undesirable Effects' section of the IFU are also reported in the IFU of Orthovisc, Synvisc and Ostenil. Additionally, no new relevant side effects emerged from clinical data analysis. Altogether data recorded in the period covered by this Clinical Evaluation Report and the cumulative experience confirm that HYALUBRIX /INARTRAL can be considered as safe and well tolerated therapy. 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 related to the device 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 /INARTRAL.

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15 Annexes

15.1 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 a) 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) b) 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) c) 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	**E1.** Scientific paper; normative texts (1) **E2.** Specialist journal, internet (0.5) **E3.** Other (0)	__|__|

		published		
Q6	Paper history	When it has been published	**F1.** ≤ 5 years (1)	
			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 AND osteoarthritis AND synovial fluid	1	1
Inartral AND osteoarthritis AND synovial fluid	0	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 AND osteoarthritis AND synovial fluid	1	1. Not considered because no pertinent with the aim of the document
Inartral 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 AND osteoarthritis AND synovial fluid	1	1. Not considered because no pertinent with the aim of the document (review)
Inartral 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	1	1. Not considered because no pertinent with the aim of the document