



FOCUSIAL

SODIUM HYALURONATE FOR INTRA-ARTICULAR USE LITERATURE REVIEW AND CLINICAL DATA

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PRESENTATION OF THE STUDY

This clinical and safety evaluation report is based on the recommendations of:

- Directive 93/42/EEC concerning Medical Devices as amended by Directive 2007/47/EC;
- MEDDEV 2.7.1 - Evaluation of clinical data: a guide for manufacturers and notified bodies;
- MEDDEV 2.12/1 - Guidelines on a Medical Devices Vigilance System;
- MEDDEV 2.12/2 - Post Market Clinical Follow-up studies.

1. PERSONS IN CHARGE OF THE CLINICAL EVALUATION

SYSTEM List of persons in charge:

- Andrea Ero Simonatti, Dr. in Medicine and Surgery, specialized in Stomatology.
- Corrado Bait, Dr. in Medicine and Surgery, specialized in Orthopaedics and Traumatology.

Validation of the selection:

Dr. Andrea Ero Simonatti is a surgeon specialized in implants, both intraosseous with titanium-based, that intradermal with hyaluronic acid-based gel. He worked in departments of Implantology, Orthodontics, Oral Surgery, and Maxillofacial Surgery.

Dr. Corrado Bait is a surgeon specialized in orthopaedics and traumatology. He works as physician at departments of Sports Traumatology, Arthroscopic Surgery, Orthopaedics and Traumatology of Developmental Age. He has many years of experience in the field of viscosupplementation with hyaluronic acid.

Conclusion:

The main responsible persons of this clinical evaluation report are suitably qualified for redacting the efficacy and security report.

2. ETHICAL STANDARDS

No unknown product will be used on humans; no unknown technology will be tried on humans; there is hence no risk about health and dignity.

All along the evaluation report, nevertheless, the ethical standards, as described in Helsinki declaration, date Oct 2008, will be respected.

The technology of injection that is used is based on a decades old technique of injection: intra-articular viscosupplementation with hyaluronic acid-based gels.

The technique used for injecting the product is the following one: a sterile syringe, not reusable, is filled with the sterile injectable product and injected through a needle in the intra-articular cavity.

The active components of the product are largely used in medicine and no report of toxicity has ever been done concerning these actives. Several devices are using a similar formula and are actually commercialized and certified as class III implantable Medical Devices.

Risk evaluation: speaking about an injectable product, the risk zero cannot exist but has to be kept extremely low, as low as possible and no harm should come from the actives their selves.

Given the large history of the viscosupplementation technique with injections of hyaluronic acid;
Given the use of non-reusable devices for injection;

Given the existence of multiple scientific publications, the existence of products being similar at the level of formulation and of indications;

Given the preclinical studies carried out on FOCUSIAL, that demonstrated the biocompatibility of this Medical Device;

Given the past clinical experience of the company with other class III injectable products;

We concluded to the possibility to assess the efficacy and the security of the products without conducting a typical clinical investigation on human cohorts. The life, health, dignity, integrity; the right to auto determination, intimacy and confidentiality of anybody will be threaten or damaged by this clinical evaluation.

No ethic committee is therefore needed.

Conclusions: Ethical standards are respected, no new technology is used, no specific risks have been pointed clinically or in the medical literature, many similar products co-exist on the market.

1) INTRODUCTION

1.1) joint injection

Over the last decades several intra-articular medical devices have been used to reduce pain and improve function in the joints.

The Joint injection of the knee 1.2.1, wrist 1.2.2, ankle 1.2.3, tmj 1.2.4, hip 1.2.5, is used for therapeutic or diagnostic reasons. In case of therapeutic use, Joint injections may be performed with different drugs such as corticosteroids, anesthetics and hyaluronic acid, which have been shown to provide pain relief in various circumstances. Recent studies are on going also on PRP and stem cells use for therapeutic treatments.

-The use of platelet-rich plasma (PRP) has expanded over the past years to not only just include the treatment of tendon and ligament injuries, but also in the treatment of cartilage injuries such as in knee OA.

PRP can be a useful treatment for knee OA but certainly additional studies are needed before conclusions regarding true efficacy. Further studies are also needed to determine the optimal composition of PRP (i.e., platelet concentration, leukocyte-rich or poor).

-Mesenchymal stromal cells [mesenchymal stem cells (MSCs) are multi potent cells that can be isolated from several human tissues. The immunomodulatory, reparative and anti-inflammatory properties of MSCs have been tested in a variety of animal models and appear to have potential clinical applications, which includes tissue repair.

-Intra-articular (IA) corticosteroid injections for knee OA appear to be an effective way to decrease pain in the short-term and should be used when signs of inflammation arise. A 2006 Cochrane review of the current literature found that IA corticosteroids were more effective than the placebo group for pain reduction and patient global assessment at 1 wk post-injection. “This review concluded that IA corticosteroid

injections appear to offer good short-term benefits with less evidence to support long term benefit”.

(Bellamy N, Campbell J, Robinson V, Gee T, Bourne R, Wells G. Intraarticular corticosteroid for treatment of osteoarthritis of the knee. *Cochrane Database Syst Rev.* 2006;2)

Bannuru et al. compared the efficacy of IA hyaluronic acid with corticosteroids for knee OA. While short-term analysis differed slightly from the Cochrane review, the results from baseline to 4 wk showed that IA corticosteroids appear to be relatively more effective for pain than IA hyaluronic acid. It similarly found that after 4 wk the IA hyaluronic acid continued to show superiority over IA corticosteroids further supporting the notion that IA corticosteroids should be implemented for reducing acute inflammation and relieving pain in the short-term, but it is not a good treatment option for long-term management of knee OA.

(Bannuru RR, Natov NS, Obadan IE, Price LL, Schmid CH, McAlindon TE. Therapeutic trajectory of hyaluronic acid versus corticosteroids in the treatment of knee osteoarthritis: a systematic review and meta-analysis. *Arthritis Rheum.* 2009;61:1704–1711.)

-Hyaluronic acid injections, often referred to as viscosupplementation, are marketed in different formulations that vary by molecular weights, concentration of hyaluronic acid, elasticity, viscosity.

The Viscosupplementation is a therapeutic technique used for the relief of pain in different joint. The intra-articular administration of preparations containing hyaluronic acid or hyaluronate is intended to restore the normal biological properties of hyaluronic acid normally found in synovial fluid. Viscosupplementation refers to the concept of synovial fluid replacement with intra-articular injections of hyaluronic acid (HA) for the relief of pain associated with osteoarthritis (OA). Viscosupplements, involving the intra-articular injection of HA, are classified as medical devices in the US under the regulation of the Food and Drug Administration. Since medical devices are regulated by different regulatory bodies across countries, it is relevant to assess the safety and efficacy profile of such products by country. Intra-articular viscosupplementation was approved by the Food and Drug Administration (FDA) in 1997. It is currently indicated only for the treatment of pain associated with knee OA.

1.2)

INDICATIONS

Osteoarthritis (OA) is the most common type of arthritis found in the United States' population. It is also the most common disease of joints in adults throughout the world. The knee is the most frequently affected of all joints.

Intra-articular hyaluronic acid viscosupplementation is gaining popularity as a treatment option in the nonoperative management of patients with osteoarthritis. Recent clinical studies have demonstrated that the anti-inflammatory, anabolic and chondroprotective actions of hyaluronic acid reduce pain and improve patient function. With evidence increasing in support of the efficacy of this treatment modality for patients with osteoarthritis, its potential use in additional patient populations and for other pathologies affecting the knee is being investigated. It is currently indicated only for the treatment of pain associated with knee OA, but OA can occur in several of the weight-bearing joints as foot, ankle or temporomandibular joint (TMJ).

Research:

key words: intra-articular sodium hyaluronate

1096 scientific references

345 scientific articles from 2010 (pub med); selected 14 concerning indications

References

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Legré-Boyer V1.

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Published online 2015 Feb 16. doi: 10.12998/wjcc.v3.i2.89 State-of-the-Art management of knee osteoarthritis

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Can viscosupplementation be used in the hip? An Italian perspective.

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Monseu AJ, Nazarene PS.

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Clin Rheumatol. 2012 Aug;31(8):1187-96. doi: 10.1007/s10067-012-1994-4. Epub 2012 Jun 8.

Diagnostic and therapeutic joint injections.

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Hyaluronic acid as a treatment for ankle osteoarthritis.

Sun SF, Chou YJ, Hsu CW, Chen WL.

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Hyaluronic acid viscosupplementation and osteoarthritis: current uses and future directions.

Strauss EJ, Hart JA, Miller MD, Altman RD, Rosen JE.

Viscosupplementation therapy for osteoarthritis.

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Sports Med Arthrosc. 2006 Sep;14(3):155-62. Review

[Research progress of viscosupplementation].

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Efficacy and safety of cross-linked hyaluronic acid single injection on osteoarthritis of the knee: a post-marketing Phase IV study.

Bashaireh K1, Naser Z2, Hawadya KA2, Sorour S2, Al-Khateeb RN3

J Arthroplasty. 2015 Mar;30(3):507-11. doi: 10.1016/j.arth.2013.10.019. Epub 2013 Nov 8.

Is intra-articular hyaluronic acid effective in treating osteoarthritis of the hip joint?

Lieberman JR1, Engstrom SM2, Solovyova O3, Au C4, Grady JJ5

Muscles Ligaments Tendons J. 2014 Jul 14;4(2):256-61. eCollection 2014.

Six-months pain relief and functional recovery after intra-articular injections with hyaluronic acid (mw 500-730 KDa) in trapeziometacarpal osteoarthritis.

Frizziero A1, Maffulli N2, Masiero S1, Frizziero L3

Orthopedics. 2014 Jan;37(1):48-55.

Can viscosupplementation be used in the hip? An Italian perspective.

Rivera F

1.2.1)

knee

There are several indications for diagnostic and therapeutic injection of the knee joint. Therapeutic knee injections are widely used to relief joint pain, and the most frequently injected drugs are HA, corticosteroids, and/or anesthetics. The ideal candidate for HA administration has yet to be defined, but nowadays it is widely accepted that HA should be used in patients with significantly symptomatic osteoarthritis, who have not responded adequately to standard treatments (pharmacological or non pharmacological) or are intolerant of these therapies (e.g., gastrointestinal problems related to anti-inflammatory medications, etc.).

“A systematic review of overlapping meta-analyses comparing treatment of knee osteoarthritis (OA) with intra-articular viscosupplementation (intra-articular hyaluronic acid [IA-HA]) versus oral non-steroidal anti-inflammatory drugs (NSAIDs), intra-articular corticosteroids (IA-corticosteroids), intra-articular platelet- rich plasma (IA-PRP), or intra-articular placebo (IA-placebo) determined which meta- analyses provide the best current evidence and identified potential causes of discordance.

This systematic review of overlapping meta-analyses, comparing IA-HA with other nonoperative treatment modalities for knee OA, shows that the current highest level of evidence suggests that IA-HA is a viable option for knee OA. Its use results in improvements of knee pain and function can persist for up to 26 weeks. IA-HA has a good safety profile, and its use should be considered in patients with early knee OA”.

Arthroscopy. 2015 May 18. pii: S0749-8063(15)00257-1. doi: 10.1016/j.arthro.2015.03.030. [Epub ahead of print]

Is Local Viscosupplementation Injection Clinically Superior to Other Therapies in the Treatment of Osteoarthritis of the Knee: A Systematic Review of Overlapping Meta-analyses.

Campbell KA1, Erickson BJ2, Saltzman BM2, Mascarenhas R3, Bach BR Jr2, Cole BJ2, Verma NN2.

A Cochrane review that included 40 trials comparing IA hyaluronic acid to placebo found that at the 5-13 wk post-injection period there was an improvement from baseline of 28%-54% for pain and 9%-32% for function for those receiving IA hyaluronic acid injections for knee OA. They did not find any of the different available hyaluronic acid products to be superior over another and there were very few adverse events reported in the studies. They concluded that viscosupplementation is an effective treatment for OA of the knee with benefits on pain, function, and patient global assessment. The authors also concluded that this review supports the use of the hyaluronic class of products in the treatment of knee OA and that these products provide not only statistically significant effects but also clinically important ones.

(Bellamy N, Campbell J, Robinson V, Gee T, Bourne R, Wells G. Viscosupplementation for the treatment of osteoarthritis of the knee. Cochrane Database Syst Rev. 2006;2

Lohmander et al. noticed that mainly “patients more than 60 years old and with severe symptoms obtained beneficial effects from the hyaluronan injections”. Patients who are not candidates for total knee replacement or who are unwilling to undergo surgery may also be candidates for viscosupplementation. Additionally, a total knee replacement in younger patients may be delayed with the use of HA. Therapeutic applications are represented by the viscosupplementation that is used for symptomatic osteoarthritis or for rhizarthrosis.

Viscosupplementation has demonstrated moderate but significant efficacy (20%) versus placebo in terms of pain and function, with a high rate of responders (60- 70%) in knee osteoarthritis. Clinical efficacy shows 1-4 weeks' later onset than corticosteroids, but is maintained for 6 or even 12 months.

Orthop Traumatol Surg Res. 2015 Feb;101(1 Suppl):S101-8. doi: 10.1016/j.otsr.2014.07.027. Epub 2015 Jan 14.

Viscosupplementation: techniques, indications, results.

Legré-Boyer V1

Viscosupplementation by hyaluronic acid (HA) injections is frequently used for local treatment of osteoarthritis (OA), due to ease of use and good tolerance.

The body of literature overall supports the use of IA hyaluronic acid injections for the treatment of knee OA and demonstrates it is a superior option for long-term management of knee OA compared to IA corticosteroids. Additionally, hyaluronic acid has an excellent safety profile making it a more suitable for being used for an extended period of time.

Research:

key word: intra-articular sodium hyaluronate 1096 reference

key word: intra-articular sodium hyaluronate knee OA, 247 references; last 5 ys 96 references; concerning our study 30 scientific references

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Waddell DD. The tolerability of viscosupplementation: low incidence and clinical management of local adverse events. *Curr Med Res Opin*. 2003;19:575–580.

Safety and efficacy of US-approved viscosupplements for knee osteoarthritis: a systematic review and meta-analysis of randomized, saline-controlled trials.

Strand V, McIntyre LF, Beach WR, Miller LE, Block JE.

J Pain Res. 2015 May 7;8:217-28. doi: 10.2147/JPR.S83076. eCollection 2015. Review.

1.2.2)

wrist

Intra-articular injection of HA is indicated for the treatment of osteoarthritis in non responsive conservative therapy or when patients are not surgical candidates.

A study investigates the effect of an intra- and postoperative intra-articular hyaluronan injection (HS) in patients undergoing wrist arthroscopy.

A total of 140 adults were included and prospectively randomised to one of 2 treatment groups. All patients presented wrist pain resistant to non-operative therapy. The HS administration (2 ml of 1% HS solution each) was performed directly at the end of arthroscopic procedure and a second time 3 weeks after surgery. The follow-up was 6 months. In both groups pain decreased and the function of the wrist joint improved. "While patients with additional HS injection had significantly better values in MMWS than patients without additional HS injection, no significant differences could be observed for DASH score, absolute grip strength and pain intensity. 12 and 24 weeks after surgery, therapeutic success was rated better in HS- group than in A-group. The highest clinical benefit was obtained for patients in the HS-group with marginal to moderate pathological findings".

[Effect of wrist arthroscopy with intraarticular hyaluronan substitution therapy: a randomised, controlled, prospective, non-blinded, single-centre, comparative trial].

Schütz A, Dobner P.

Handchir Mikrochir Plast Chir. 2013 Oct;45(5):277-84.

Another study, comparing intra-articular hyaluronic acid with corticoid injections for the treatment of rhizarthrosis, demonstrated that a single course of three SH injections (SH; Ostenil mini) is effective in relieving pain and improving joint function in patients with OA of the CMC joint of the thumb. Although in comparison

with triamcinolone its effects are achieved more slowly, the results indicate a superior long-lasting effect of hyaluronan at 6 months after end of treatment period.

Research

key words: sodium hyaluronate wrist

13 scientific articles; selected 5

References

[Effect of wrist arthroscopy with intraarticular hyaluronan substitution therapy: a randomised, controlled, prospective, non-blinded, single-centre, comparative trial].

Schütz A, Dobner P.

Handchir Mikrochir Plast Chir. 2013 Oct;45(5):277-84.

Diagnostic and therapeutic joint injections.

Masala S, Fiori R, Bartolucci DA, Mammucari M, Angelopoulos G, Massari F, Simonetti G.

Semin Intervent Radiol. 2010 Jun;27(2):160-71.

Injections for trapeziometacarpal osteoarthritis.

Wolf JM.

J Hand Surg Am. 2010 Jun;35(6):1007-9.

Intra-articular hyaluronic acid compared with corticoid injections for the treatment of rhizarthrosis.

Fuchs S, Mönikes R, Wohlmeiner A, Heyse T.

Osteoarthritis Cartilage. 2006 Jan;14(1):82-8.

Muscles Ligaments Tendons J. 2014 Jul 14;4(2):256-61. eCollection 2014.

Six-months pain relief and functional recovery after intra-articular injections with hyaluronic acid (mw 500-730 KDa) in trapeziometacarpal osteoarthritis.

Frizziero A1, Maffulli N2, Masiero S1, Frizziero L3.

1.2.3)

ankle

Ankle OA produces chronic disability that directly impacts the quality of life.

The potential for treating osteoarthritis of the ankle joint by viscosupplementation has been suggested in the literature. However no dosing studies have been published to date and dosing in the ankle joint remains an area for discussion. viscosupplementation could potentially provide an useful alternative in treating such patients with painful ankle OA.

Research:

key words: sodium hyaluronate ankle

32 scientific articles (last 5 ys) ; selected 5

References

Prognostic factors after intra-articular hyaluronic acid injection in ankle osteoarthritis.

Han SH, Park do Y, Kim TH.

Yonsei Med J. 2014 Jul;55(4):1080-6. doi: 10.3349/ymj.2014.55.4.1080.

Viscosupplementation of the ankle: a prospective study with an average follow-up of 45.5 months.

Lucas Y Hernandez J, Darcel V, Chauveaux D, Laffenêtre O.

Orthop Traumatol Surg Res. 2013 Sep;99(5):593-9. doi: 10.1016/j.otsr.2013.02.008. Epub 2013 Jul 8

Effectiveness of intra-articular hyaluronic acid for ankle osteoarthritis treatment: a systematic review and meta-analysis.

Chang KV, Hsiao MY, Chen WS, Wang TG, Chien KL.

Arch Phys Med Rehabil. 2013 May;94(5):951-60. doi: 10.1016/j.apmr.2012.10.030. Epub 2012 Nov 10

Hyaluronic acid for the treatment of osteoarthritis in all joints except the knee: what is the current evidence?

Colen S, Haverkamp D, Mulier M, van den Bekerom MP

Hyaluronic acid in ankle osteoarthritis: why evidence of efficacy is still lacking?

Abate M, Schiavone C, Salini V.

Clin Exp Rheumatol. 2012 Mar-Apr;30(2):277-81. Epub 2012 Apr 13.

1.2.4)

tmj

In some cases conservative treatment of internal derangements of the Temporomandibular Joint (TMJ) is considered low responsive. It is necessary to accomplish treatments that aim at reducing pain and improve function in patients who present arthrogenic temporomandibular disorders.

A recent study based on a systematic review of the literature, aimed to analyze the effectiveness of intra-articular injections with corticosteroids and sodium hyaluronate for treating internal derangements of the TMJ.

The research carried out in the following databases: MEDLINE, Cochrane, EMBASE, Pubmed, Lilacs, and BBO. Considered publications issued between 1966 and October 2010, focusing on randomized or quasi-randomized controlled clinical trials, single or double-blind. After analyzing the literature, it was found that intra-articular injection with corticosteroids and sodium hyaluronate seems to be an effective method for treating internal derangements of the TMJ. However further randomized controlled clinical trials, with representative samples and longer follow-up time, must be carried out in order to assess the real effectiveness of this technique.

Dental Press J Orthod. 2013 Sep-Oct;18(5):128-33.

Intra-articular injections with corticosteroids and sodium hyaluronate for treating temporomandibular joint disorders: a systematic review.

Machado E, Bonotto D, Cunali PA

Another recent study compared a group of patients treated with non-steroidal anti-inflammatory drugs to another group of patients underwent a cycle of 5 injections of HA into the TMJ. This study was to report the 1-year therapeutic outcome of intra-articular injections of high-molecular-weight hyaluronic acid (HA) without arthrocentesis in a group of 25 patients with osteoarthritis (OA) of the

temporomandibular joint (TMJ). Significant statistical differences for all clinical parameters were recorded 1 year after the end of treatment between the two groups. A cycle of 5 intra-articular injections of HA without arthrocentesis for patients with OA of the TMJ is considered successful at 1-year follow-up period.

Research:

KEY WORDS : SODIUM HYALURONATE TMJ

143 SCIENTIFIC ARTICLES FROM 2005; 41 SCIENTIFIC ARTICLES LAST 5 YEARS; SELECTED 10

References

Single- or multiple-session viscosupplementation protocols for temporomandibular joint degenerative disorders: a randomized clinical trial.

Guarda-Nardini L, Rossi A, Arboretti R, Bonnini S, Stellini E, Manfredini D.

J Oral Rehabil. 2015 Feb 19.

Effectiveness of treatment with viscosupplementation in temporomandibular joints with or without effusion.

Guarda-Nardini L, Rossi A, Ramonda R, Punzi L, Ferronato G, Manfredini D.

Int J Oral Maxillofac Surg. 2014 Oct;43(10):1218-23. doi: 10.1016/j.ijom.2014.05.001. Epub 2014 Jun

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Efficacy of hyaluronic acid injections in patients with osteoarthritis of the temporomandibular joint. A comparative study.

Triantafyllidou K, Venetis G, Bika O.

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WITHDRAWN: Hyaluronate for temporomandibular joint disorders.

Shi Z, Guo C, Awad M.

Cochrane Database Syst Rev. 2013

Internal derangement of temporomandibular joint: an evaluation of effect of corticosteroid injection compared with injection of sodium hyaluronate after arthrocentesis.

Giraddi GB, Siddaraju A, Kumar B, Singh C.

J Maxillofac Oral Surg. 2012 Sep;11(3):258-63. doi: 10.1007/s12663-011-0324-8. Epub 2011 Dec 28.

Evaluation of efficacy of arthrocentesis (with normal saline) with or without sodium hyaluronate in treatment of internal derangement of TMJ - A prospective randomized study in 20 patients.

Sharma A, Rana AS, Jain G, Kalra P, Gupta D, Sharma S.

J Oral Biol Craniofac Res. 2013 Sep-Dec;3(3):112-9. Epub 2013 Oc

[Hyaluronate sodium treatment for internal derangement of temporomandibular joint: a systematic review based on randomized controlled trials].

Li C, Zhang Y, Jia Y, Lü J, Li L, Shi ZD.

Hua Xi Kou Qiang Yi Xue Za Zhi. 2011 Oct;29(5):488-93.

Scientific evidence on the usefulness of intraarticular hyaluronic acid injection in the management of temporomandibular dysfunction.

Escoda-Francolí J, Vázquez-Delgado E, Gay-Escoda C.

Med Oral Patol Oral Cir Bucal. 2010 Jul 1;15(4):e644-8. Review

A comparative study on the impact of intra-articular injections of hyaluronic acid, tenoxicam and betametazon on the relief of temporomandibular joint disorder complaints.

Gencer ZK, Özkiriş M, Okur A, Korkmaz M, Saydam L.

J Craniomaxillofac Surg. 2014 Oct;42(7):1117-21. doi: 10.1016/j.jcms.2014.01.041.

1.2.5)

hip

The European League Against Rheumatology Committee agenda asks for research to investigate treatments able to slow down the progression of hip osteoarthritis (OA), to delay joint replacement and to determine the comparative effectiveness and cost- effectiveness of non-surgical and surgical treatment modalities as well as criteria relating to the indications for and timing of total hip replacement (THR).

Sodium hyaluronate given by ultrasound-guided injection seems to delay THR of symptomatic hip OA patients.

1.3)

CONCLUSIONS

The data of the international literature demonstrate how the use of intra-articular sodium hyaluronate is effective and universally accepted in the treatment of osteoarthritis of the knee.

As concern other joints, more data are needed to confirm its efficacy as an alternative to other treatments, due to the need to proceed in some of them (hip, wrist) under ultrasound guidance often limiting the operability.

However it should be noted that many published studies demonstrated that infiltration of sodium hyaluronate can bring benefit in the reduction of joint pain and improve mobility in other joints too, particularly in the long term with or without use of other therapeutic techniques.

2) FOCUSIAL

2.1) CLASSIFICATION

Sodium Hyaluronate for intra-articular use

Sterile class III Medical Device, in conformity with Directive 93/42/CEE as amended.

TECHNICAL DESCRIPTION

Medical device known as sodium hyaluronate with molecular weight of 1650 - 3000 kdalton for intra-articular use, sterile, belonging to Class III medical devices, according to Annex IX of Directive 93/42/EEC of 14/06/1993, implemented by the Legislative Decree of 24 / No 02/97 46 and subsequent amendments, in accordance with Rule No. 8: "All implantable devices and long-term invasive devices, surgical are in Class IIb unless they are intended to have a biological effect or to be wholly or mainly absorbed in which case they are in Class III".

The device consists of a sterile intra-articular gel of hyaluronic acid contained in a pre-filled syringe. FOCUSIAL is a medical device conforming to directive MDD 93/42/CEE, containing hyaluronic acid obtained by fermentation and chemically unmodified.

FOCUSIAL is a transparent, sterile, non-pyrogenic and viscoelastic solution supplied in syringe of 2/4ml.

FOCUSIAL - Sodium hyaluronate for intra- articular use COMPOSITION OF THE PRODUCT:

Component	Syringe of 2 ml (2%)
Sodium hyaluronate	40,0 mg
Nonpyrogenic sodium chloride	16,0 mg
Sodium phosphate monobasic x 2 H ₂ O	0,6 mg
Sodium phosphate dibasic x 12 H ₂ O	3,0 mg
WFI Water	q.s. for 2 ml
Vial Syringe	1
Envelope bag	1
Leaflet	1
Primary Label	1
Patient's Label	2
Cardboard box, lithographed	1

Hyaluronic acid is a natural polysaccharide present in numerous human tissues, especially synovial fluid, and acts on joints both as a cartilage and ligament lubricant and as a shock absorber.

Many studies have shown that the injection of hyaluronic acid into joints affected by osteoarthritis restores synovial fluid viscosity and elasticity, with a consequent reduction in pain and improvement in the joint's mobility.

FOCUSIAL acts only in the joint into which it is injected, without exercising any systemic action. The use of substances contained in this product is widely-known and documented by extensive literature. Studies also were performed to evaluate the tolerability of the product in accordance with the provisions of the UNI EN ISO 10993-1 "Biological evaluation of medical devices - Part 1: Evaluation and Testing."

2.2)

SIMILAR DEVICES: REVIEW

The different types of hyaluronic acid for intra-articular use in commerce differ according to their molecular weight, which varies from a few hundred Daltons (500- 700) up to reach 6 million Dalton (weight similar to hyaluronic acid present in a healthy joint) and beyond, thanks to the technology of cross-links.

FOCUSIAL can be classified as products based on sodium hyaluronate having a constant molecular weight between 2800 and 3000 kdalton.

There follows a list of medical devices currently on the market based on linear sodium hyaluronate with a constant molecular weight between 1300 and 3000 kdalton.

ARTHRUM H 2% (1 x 2ml)

LCA

Active substance:

Linear hyaluronic acid between 1.3 and 3.0 MDalton

Vials/Syringes per box: 1

Content per vial/syringe: 2 ml

ARTHRUM H 2% (3 x 2ml)

LCA

Active substance:

Linear hyaluronic acid between 1.3 and 3.0 MDalton

Vials/Syringes per box: 3

Content per vial/syringe: 2 ml

ARTHRUM 2,5% mono-injection

LCA

Active substance:

Linear hyaluronic acid between 1.3 and 3.0 MDalton

Vials/Syringes per box: 1

Content per vial/syringe: 3

ATHENAVIS 2000 (1 x 2 ml)

IBN Savio

Active substance:

Linear hyaluronic acid between 1.3 and 3.0 MDalton

Vials/Syringes per box: 1

Content per vial/syringe: 2 ml

ATHENAVIS 2000 (3 x 2 ml)

IBN Savio

Active substance:

Linear hyaluronic acid between 1.3 and 3.0

MDalton Vials/Syringes per box: 3

Content per vial/syringe: 2 ml

COX ARTHRUM

LCA

Active substance:

Linear hyaluronic acid between 1.3 and 3.0

MDalton Vials/Syringes per box: 1

Content per vial/syringe: 3 ml

CURAVISC (3 x 2 ml)

Curasan

Active substance:

Linear hyaluronic acid between 1.3 and 3.0

MDalton Vials/Syringes per box: 3

Content per vial/syringe: 2 ml

CURAVISC (1 x 2 ml)

Curasan

Active substance:

Linear hyaluronic acid between 1.3 and 3.0

MDalton Vials/Syringes per box: 1

Content per vial/syringe: 2 ml

EUFLEXXA (1 x 2 ml)

Ferring

Active substance:

Linear hyaluronic acid between 1.3 and 3.0 MDalton

Vials/Syringes per box: 1

Content per vial/syringe: 2 ml

EUFLEXXA (3 x 2 ml)

Ferring

Active substance:

Linear hyaluronic acid between 1.3 and 3.0 MDalton

Vials/Syringes per box: 3

Content per vial/syringe: 2 ml

FERMATHRON Plus

Biomet

Active substance:

Linear hyaluronic acid between 1.3 and 3.0 MDalton

Vials/Syringes per box: 1

Content per vial/syringe: 2 ml

HYALUBRIX (1 x 2 ml)

Fidia

Active substance:

Linear hyaluronic acid between 1.3 and 3.0 MDalton

Vials/Syringes per box: 1

Content per vial/syringe: 2 ml

HYALUBRIX (3 x 2 ml)

Fidia

Active substance:

Linear hyaluronic acid between 1.3 and 3.0 MDalton

Vials/Syringes per box: 3

Content per vial/syringe: 2 ml

HYALUBRIX 60

Fidia

Active substance:

Linear hyaluronic acid between 1.3 and 3.0 MDalton

Vials/Syringes per box: 1

Content per vial/syringe: 4 ml

INARTRAL

Fidia

Active substance:

Linear hyaluronic acid between 1.3 and 3.0 MDalton

Vials/Syringes per box: 3

Content per vial/syringe: 2 ml

ORTHOVISC (1 x 2 ml)

Vita Research

Active substance:

Linear hyaluronic acid between 1.3 and 3.0 MDalton

Vials/Syringes per box: 1

Content per vial/syringe: 2 ml

ORTHOVISC (3 x 2 ml)

Vita Research

Active substance:

Linear hyaluronic acid between 1.3 and 3.0 MDalton

Vials/Syringes per box: 3

Content per vial/syringe: 2 ml

ORTHOVISC MINI

Vita Research

Active substance:

Linear hyaluronic acid between 1.3 and 3.0 MDalton

Vials/Syringes per box: 1

Content per vial/syringe: 1 ml

RENEHAVIS

Athena Ph. Italia

Active substance:

Linear hyaluronic acid between 1.3 and 3.0 MDalton

Vials/Syringes per box: 1

Content per vial/syringe: 1.4 ml

SYALOSET (1 x 4 ml)

Lisapharma

Active substance:

Linear hyaluronic acid between 1.3 and 3.0 MDalton

Vials/Syringes per box: 1

Content per vial/syringe: 4 ml

SYNOCROM

Italchimici

Active substance:

Linear hyaluronic acid between 1.3 and 3.0 MDalton

Vials/Syringes per box: 1

Content per vial/syringe: 2 ml

SYNOLIS VA (1 x 2 ml)

Anteis

Active substance:

Linear hyaluronic acid between 1.3 and 3.0 MDalton

Vials/Syringes per box: 1

Content per vial/syringe: 2 ml

SYNOLIS VA (3 x 2 ml)

Anteis

Active substance:

Linear hyaluronic acid between 1.3 and 3.0 MDalton

Vials/Syringes per box: 3

Content per vial/syringe: 2 ml

VOLTAVISC (1 x 2 ml)

Novartis

Active substance:

Linear hyaluronic acid between 1.3 and 3.0 MDalton

Vials/Syringes per box: 1

Content per vial/syringe: 2 ml

VOLTAVISC (3 X 2 ML)

Novartis

Active substance:

Linear hyaluronic acid between 1.3 and 3.0 MDalton

Vials/Syringes per box: 3

Content per vial/syringe: 2 ml

PubMed reviews of scientific articles about products on the market

Key words:

ARTHRUM: 0 RESULTS ;

ATHENAVIS: 0 RESULTS ;

CURAVISC: 1 RESULTS

Clin Rheumatol. 2007 Nov;26(11):1977-9. Epub 2007 Apr 14. Acute pseudoseptic arthritis after viscosupplementation of the knee: a case report.

Tahiri L1, Benbouazza K, Amine B, Hajjaj-Hassouni N)

EUFLEXXA: 7 RESULTS

Intra-articular injections of hyaluronic acid in osteoarthritis of the subtalar joint: a pilot study.

Mei-Dan O, Carmont M, Laver L, Mann G, Maffulli N, Nyska M.

J Foot Ankle Surg. 2013 Mar-Apr;52(2):172-6. doi: 10.1053/j.jfas.2012.12.008. Epub 2013 Jan 17.

Safety and efficacy of retreatment with a bioengineered hyaluronate for painful osteoarthritis of the knee: results of the open-label Extension Study of the FLEXX Trial.

Altman RD, Rosen JE, Bloch DA, Hatoum HT.

Osteoarthritis Cartilage. 2011 Oct;19(10):1169-75. doi: 10.1016/j.joca.2011.07.001. Epub 2011 Jul 23.

Intra-articular hyaluronans: the treatment of knee pain in osteoarthritis.

Goldberg VM, Goldberg L.

J Pain Res. 2010 May 10;3:51-6.

High molecular weight hyaluronan for treatment of chronic shoulder pain associated with glenohumeral arthritis.

Weil AJ.

Med Devices (Auckl). 2011;4:99-105. doi: 10.2147/MDER.S22423. Epub 2011 Jul 26.

The effect of hyaluronan injections into human knees on the number of bone and cartilage wear particles captured by bio-ferrography.

Hakshur K, Benhar I, Bar-Ziv Y, Halperin N, Segal D, Eliaz N.

Acta Biomater. 2011 Feb;7(2):848-57. doi: 10.1016/j.actbio.2010.08.030. Epub 2010 Sep 6.

A double-blind, randomized, saline-controlled study of the efficacy and safety of EUFLEXXA for treatment of painful osteoarthritis of the knee, with an open-label safety extension (the FLEXX trial).

Altman RD, Rosen JE, Bloch DA, Hatoum HT, Korner P.

Semin Arthritis Rheum. 2009 Aug;39(1):1-9. doi: 10.1016/j.semarthrit.2009.04.001. Epub 2009 Jun 17.

Viscosupplementation for the treatment of osteoarthritis of the knee.

Bellamy N, Campbell J, Robinson V, Gee T, Bourne R, Wells G.

Cochrane Database Syst Rev. 2006 Apr 19;(2):CD005321. Review.

FERMATHRON: 4 RESULTS

No difference between intra-articular injection of hyaluronic Acid and placebo for mild to moderate knee osteoarthritis: a randomized, controlled, double-blind trial.

van der Weegen W, Wullems JA, Bos E, Noten H, van Drumpt RA.

J Arthroplasty. 2015 May;30(5):754-7. doi: 10.1016/j.arth.2014.12.012. Epub 2014 Dec 13.

Effect of subacromial sodium hyaluronate injection on rotator cuff disease: A double-blind placebo-controlled clinical trial.

Moghtaderi A, Sajadiyeh S, Khosrawi S, Dehghan F, Bateni V.

Adv Biomed Res. 2013 Nov 30;2:89. doi: 10.4103/2277-9175.122517. eCollection 2013.

Viscosupplementation for the treatment of osteoarthritis of the knee.

Bellamy N, Campbell J, Robinson V, Gee T, Bourne R, Wells G.

Cochrane Database Syst Rev. 2006 Apr 19;(2):CD005321. Review.

Viscosupplementation for the treatment of osteoarthritis of the knee.

Bellamy N, Campbell J, Robinson V, Gee T, Bourne R, Wells G.

Cochrane Database Syst Rev. 2005 Apr 18;(2):CD005321. Review. Update in: Cochrane Database Syst Rev. 2006;(2):CD005321.

HYALUBRIX: 5 RESULTS

Viscosupplementation with high molecular weight native hyaluronan. Focus on a 1500-2000 KDa fraction (Hyalubrix®).

Guidolin D, Franceschi F.

Eur Rev Med Pharmacol Sci. 2014;18(21):3326-38.

A randomized double-blind clinical trial on the treatment of knee osteoarthritis: the efficacy of polynucleotides compared to standard hyaluronan viscosupplementation.

Giarratana LS, Marelli BM, Crapanzano C, De Martinis SE, Gala L, Ferraro M, Marelli N, Albisetti W.

Knee. 2014 Jun;21(3):661-8. doi: 10.1016/j.knee.2014.02.010. Epub 2014 Feb 24.

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.

Migliore A, Bella A, Bisignani M, Calderaro M, De Amicis D, Logroscino G, Mariottini F, Moreschini O, Massafra U, Bizzi E, Laganà B, Piscitelli P, Tormenta S.

Clin Rheumatol. 2012 Aug;31(8):1187-96. doi: 10.1007/s10067-012-1994-4. Epub 2012 Jun 8.

A prospective observational study of the clinical efficacy and safety of intra-articular sodium hyaluronate in synovial joints with osteoarthritis.

Foti C, Cisari C, Carda S, Giordan N, Rocco A, Frizziero A, Della Bella G.

Eur J Phys Rehabil Med. 2011 Sep;47(3):407-15.

Comparative, double-blind, controlled study of intra-articular hyaluronic acid (Hyalubrix) injections versus local anesthetic in osteoarthritis of the hip.

Migliore A, Massafra U, Bizzi E, Vacca F, Martin-Martin S, Granata M, Alimonti A, Tormenta S.

Arthritis Res Ther. 2009;11(6):R183. doi: 10.1186/ar2875. Epub 2009 Dec

INARTRAL : 0 RESULTS

RENEHAVIS : 0 RESULTS

ORTOVISC : 21 RESULTS; 8 cited articles; 2 full text article

Intra-articular hyaluronans: the treatment of knee pain in osteoarthritis.

Goldberg VM, Goldberg L.

J Pain Res. 2010 May 10;3:51-6.

Intra-articular sodium hyaluronate injections in the osteoarthritic ankle joint: effects, safety and dose dependency.

Witteveen AG, Sierevelt IN, Blankevoort L, Kerkhoffs GM, van Dijk CN.

Foot Ankle Surg. 2010 Dec;16(4):159-63. doi: 10.1016/j.fas.2009.10.003. Epub 2009 Nov 8.

[Intra-articular sodium hyaluronate injections after arthroscopic debridement for osteoarthritis of the knee: a prospective, randomized, controlled study].

Heybeli N, Doral MN, Atay OA, Leblebicioğlu G, Uzümcügil A.

Acta Orthop Traumatol Turc. 2008 Aug-Oct;42(4):221-7. Turkish.

Arthroscopic debridement of the osteoarthritic knee combined with hyaluronic acid (Orthovisc) treatment: a case series and review of the literature.

Li X, Shah A, Franklin P, Merolli R, Bradley J, Busconi B.

J Orthop Surg Res. 2008 Sep 17;3:43. doi: 10.1186/1749-799X-3-43.

[The use of arthroscopic debridement and viscosupplementation in knee osteoarthritis].

Uluçay C, Altıntaş F, Uğutmen E, Beksaç B.

Acta Orthop Traumatol Turc. 2007 Nov-Dec;41(5):337-42. Turkish.

What is the evidence for viscosupplementation in the treatment of patients with hip osteoarthritis? Systematic review of the literature.

van den Bekerom MP, Lamme B, Sermon A, Mulier M.

Arch Orthop Trauma Surg. 2008 Aug;128(8):815-23. Epub 2007 Sep 15. Review.

Comparison of two different viscosupplements in knee osteoarthritis -- a pilot study.

Bayramoğlu M, Karataş M, Cetin N, Akman N, Sözü S, Dilek A.

Clin Rheumatol. 2003 May;22(2):118-22

Efficacy and safety of intraarticular sodium hyaluronate in knee osteoarthritis. ORTHOVISC Study Group.

Brandt KD, Block JA, Michalski JP, Moreland LW, Caldwell JR, Lavin PT.

Clin Orthop Relat Res. 2001 Apr;(385):130-43

SYALOSET : 0 RESULTS

SYNOCROM : 2 RESULTS

Viscosupplementation with hyaluronic acid in osteoarthritis treatment--our experiences

Stambuk B, Pasalić B.

Reumatizam. 2006;53(2):95-7. Croatian.

Viscosupplementation in the hip: evaluation of hyaluronic acid formulations.

van den Bekerom MP, Rys B, Mulier M.

Arch Orthop Trauma Surg. 2008 Mar;128(3):275-80. Epub 2007 Jun 16

SYNOLIS : 0 RESULTS

VOLTAVISC : 0 RESULTS

2.3)

Considerations of the authors

Among the most cited in the scientific literature we found 21 references regarding Orthovisc® and 7 references to Euflexxa.

The results indicate that sodium hyaluronate (Orthovisc®)

treatment is well tolerated and produces statistically and clinically significant improvement of symptoms in patients with mild to moderate knee osteoarthritis. Joint injection of intermediate sodium hyaluronate (Orthovisc®) has also been shown to persist for at least 6 months.

The efficacy and safety of sodium hyaluronate has been shown from many clinical studies.

An important systematic review to evaluate different sodium hyaluronate medical devices (Adant, Arthrum H, Artz (Artzal, Supartz), BioHy (Arthrease), Durolane, Fermathron, Go-On, Hyalgan, Hylan G-F 20 (Synvisc Hylan G-F 20), NRD-101, Orthovisc, Ostenil, Replasyn, SLM-10, Suplasyn, Synject and Zeel compositum) demonstrated that viscosupplementation is an effective treatment for OA of the knee with beneficial effects: on pain, function and patient global assessment.

Below is a complete review of the literature on the treatment of OA of the knee and a study more focused on reducing the pain associated with OA therapy with intra-articular injection of sodium hyaluronate.

The data on the efficacy and safety of treatment are shown in both studies.

To support the efficacy of sodium hyaluronate, it is included a recent presentation about the use in traumatic injuries of the knee (Dr. Bait).

In conclusion, we believe that the results of the literature of the last decades, the clinical use of sodium hyaluronate in various commercial formulations, has demonstrated safety and efficacy parameters suitable for use in the treatment of degenerative and traumatic injuries of the knee.

The use of sodium hyaluronate for intra-articular injection in other joints is currently the subject of numerous studies with promising results. Further investigations are deemed necessary anyway.

3) FOCUSIAL

3.1) CLINICAL SAFETY EVALUATION

The use of FOCUSIAL proved to be absolutely comparable and probably better to other formulations currently on the market for both as a result of its characteristics of practicality of use and clinical results. Numerous randomized clinical trials involving more than 1,000 patients have been conducted; mainly used at the joints of the knee, hip and shoulder, its molecular weight makes it particularly suitable in situations of arthritic degeneration of the joints; administration in multiple sessions per week (from 2 to 4 infiltration according to the location and the severity of the degenerative situation), did not show any reaction to allergic or intolerance to the product and has had positive effects in more than 90% of medium-term (5-6 months) cases.

The use of hyaluronic acid in this formulation allows to repeat the cycle of infiltration also two / three times a year with no risk of overdose or side effects. Therefore, it is recommended in all conditions of joint degeneration.

3.2) CLINICAL EFFICACY EVALUATION

The clinical efficacy of FOCUSIAL was also assessed using the Womac Scale; the study involved 21 patients with an age range varying from 52 to 84 years (mean 72), 14 knees, and also 5 hips, and 1 shoulder with results evaluated one month after administration of 2-4 vials. The subjective results are satisfactory in more than 88% of cases without history of hypersensitivity, with excellent tolerability by the subjects examine and an attenuation of the painful symptoms.

3.3) FINAL CONSIDERATION

Viscosupplementation is an effective treatment for OA of the knee and other joints with beneficial effects, especially on pain, function and patient global assessment.

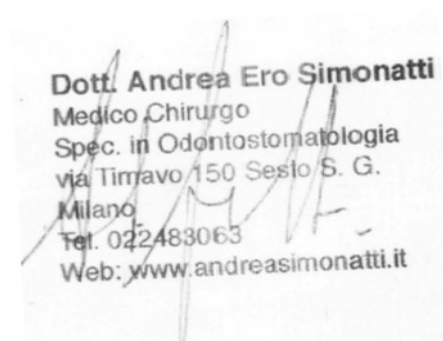
The results of the literature of the last decades and the clinical use of sodium hyaluronate, in various commercial formulations, has demonstrated safety and efficacy parameters suitable for use in the treatment of degenerative and traumatic injuries of the knee.

The use of FOCUSIAL proved to be absolutely comparable and probably better to other formulations currently on the market for both as a result of its characteristics of practicality of use and clinical results, therefore is really indicated in joint viscosupplementation for treatment of osteoarthritis.

Dr. Corrado Bait



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