OSTENIL® PLUS

SODIUM HYALURONATE 2% + MANNITOL

Flexible Treatment Scheme

TRB CHEMEDICA

OSTENIL® PLUS

Innovative patented formulation[1]

Intra-articular hyaluronic acid (HA) has an established place in the symptomatic treatment of osteoarthritis (OA).[2-4]

The aim of developing OSTENIL® PLUS was to allow a flexible treatment scheme with fewer injections and longer periods between injections, compared to standard treatment regimen in viscosupplementation.[5]

OSTENIL® PLUS results from the extensive experience of TRB Chemedica in the research, development and manufacture of HA products in the fields of Rheumatology/Orthopaedics and Ophthalmology.

OSTENIL® PLUS characteristics:

HA obtained from bacterial fermentation	Highly purified, natural, non-chemically modified product No avian proteins
HA 2% (40 mg/2 ml)	High concentration for prolonged activity
Molecular weight: 1-2 million Daltons	Optimal range for therapeutic benefits [6-8]
Mannitol 0.5% (10 mg/2 ml)	Antioxidant Protects HA from degradation by free radicals[9]
2 ml pre-filled syringe	Ready to use
Syringe equipped with a Luer-lok™ cap	Safe needle attachment
Terminal sterilisation by moist heat	Sterile syringe in the blister to facilitate aseptic use

Designed for optimal efficacy and safety

1. EP 0781547, 2002
2. Jordan KM et al. Ann Rheum Dis 2003; 62: 1145-55
3. Hochberg M et al. Arthritis Care Res 2012; 64 (4): 465-74
4. Zhang W et al. Osteoarthritis Cartilage 2010; 18: 476-99
5. Bellamy N et al. Cochrane Database Syst Rev 2006; 2: CD005321
6. Kikuchi T et al. Osteoarthritis Cartilage 1996; 4: 99-110
7. Gotoh S et al. Ann Rheum Dis 1993; 52: 817-22
8. Smith MM, Ghosh P. Rheumatol Int 1987; 7: 113-22

Mannitol-stabilised high dose hyaluronic acid for sustained effect

The novelty of OSTENIL® PLUS lies in the combination of high concentration HA + mannitol. The formulation offers the possibility of reducing the number of injections and increasing the intervals between injections.[10,11]

1. High concentration HA (2%)	OSTENIL® PLUS contains HA which increases synovial fluid viscoelasticity and restores joint homeostasis.
2. HA protection by mannitol	Mannitol acts as a free radical scavenger which protects HA from rapid depolymerisation.[9]
3. Prolonged symptomatic effect	A course of 1-3 injections of OSTENIL® PLUS provides rapid and prolonged relief of symptoms in knee and hip OA.[10,11]
4. Good tolerability and safety	Biocompatibility studies in animal models have shown that OSTENIL® PLUS is well tolerated.[12] Tolerability was also demonstrated to be very good in humans.[10,11] Natural fermentative HA is better tolerated than chemically modified HA of avian origin.[13]

9. Mendoza G et al. Carbohydr Res 2007; 342: 96-102
10. TRB Chemedica data on file
11. Borras-Verdera et al. Rev Esp Cir Ortop Traumatol 2012; 56(4): 274-80
12. TRB Chemedica data on file
13. Uebelhart D, Berz S. Osteoarthritis Cartilage 2003; 11 (Suppl A): P223

OSTENIL® PLUS

Protective role of mannitol

High concentration hyaluronic acid restores synovial balance

- HA injections increase the viscoelasticity of the synovial fluid, restoring its lubricating, shock-absorbing and filtering properties.[14,15]
- The protective HA coating is re-established over the inner surfaces of the joint.
- HA is a free radical scavenger.[16,17]
- HA reduces inflammation of the synovium.[18,19]
- HA masks the nociceptors in the joint, and thus alleviates pain.[7,20]

- Mannitol slows down the degradation of HA by reactive oxygen species (ROS).[9]

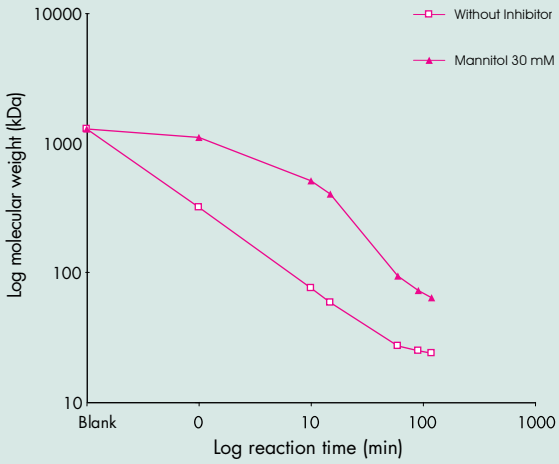


Figure 1: Inhibitory effect of 30 mM mannitol on HA degradation

14. Mensitieri M et al. J Mat Sci Mat Med 1995; 6: 130-7
15. Peyron JG. Osteoarthritis Cartilage 1993; 1: 85-7
16. Kvam BJ et al. Exp Cell Res 1995; 218: 79-86
17. Presti D, Scott JE. Cell Biochem Funct 1994; 12: 281-8
18. Frizziero L et al. Clin Exp Rheumatol 1998; 16: 441-9
19. Karatay S et al. Ann Clin Lab Sci 2004; 34: 330-5
20. Miyazaki K et al. Pharmacometrics 1984; 28: 1123-35

Mannitol stabilises HA chains against depolymerisation

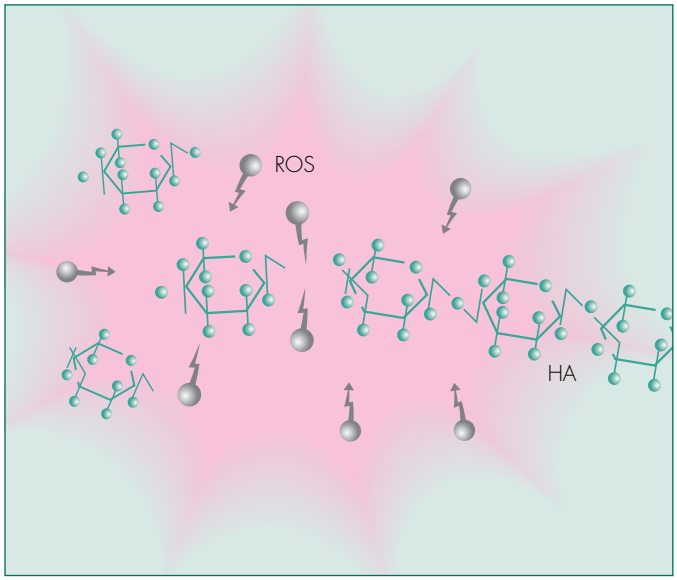


Figure 2a: ROS depolymerise long chain HA molecules, reducing chain length. The viscoelastic properties of the synovial fluid are thus reduced.

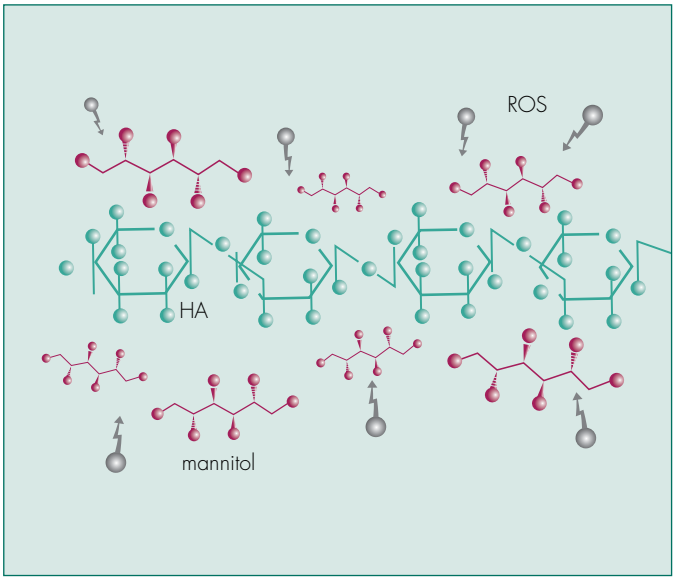


Figure 2b: Mannitol contained in OSTENIL® PLUS protects HA chains from depolymerisation triggered by ROS.

Unique combination of natural high dose HA (2%) + mannitol

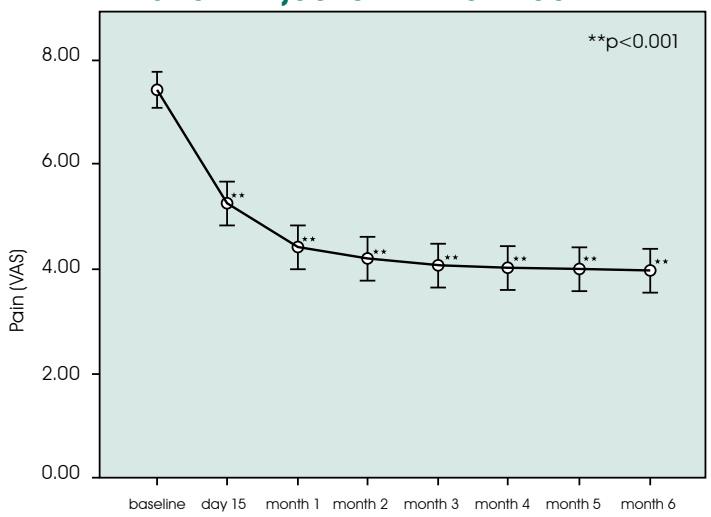
- Improved resistance to degradation
- Reduced number of injections (1-3)
- Longer intervals between injections

OSTENIL® PLUS

Rapid symptom relief in

OSTENIL® PLUS was tested in a prospective, open, multicentre study in 80 patients with symptomatic knee OA who received 1 injection of OSTENIL® PLUS.[11]

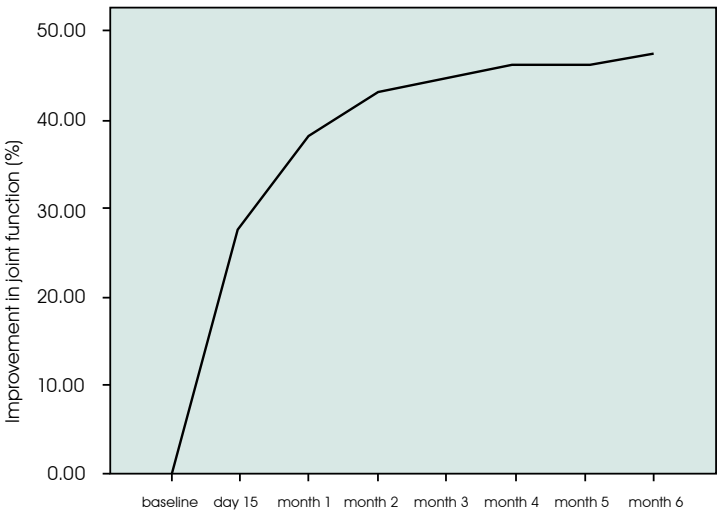
Pain relief over 6 months after 1 injection in the knee



The mean joint pain showed a statistically significant decrease from the first follow-up visit compared to baseline. The pain relief was maintained up to the final visit at 6 months after the injection.

Figure 3: After 1 injection of OSTENIL® PLUS, pain relief was significant and maintained for 6 months (end of study)

Long-lasting improvement in function after 1 injection in the knee



The improvement in function, calculated from the total WOMAC index values, was significant over the study period and reached 47.5% at 6 months.

Figure 4: After 1 injection of OSTENIL® PLUS, the improvement in function was rapid and maintained for 6 months (end of study)

A single injection of OSTENIL® PLUS reduces joint pain and improves function in patients with knee OA over a period of at least 6 months

osteoarthritis

Proven efficacy and safety of repeated injections

OSTENIL® PLUS was tested in a prospective, open, multicentre study in 38 patients with symptomatic knee OA who received 1 injection of OSTENIL® PLUS at 2 week intervals for a total of 3 injections.[10]

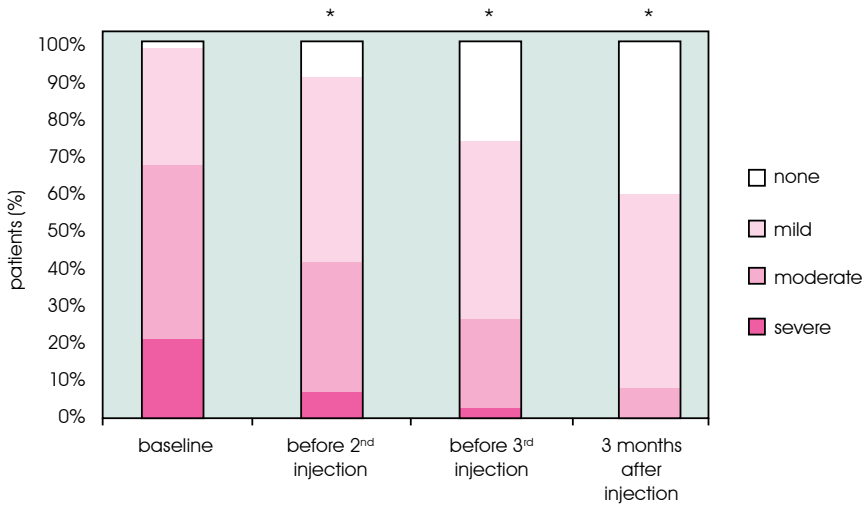


Figure 5: Patient rating for the intensity of pain on load in knee OA (*p=0.0001)

Pain on load had significantly improved after each injection (p=0.0001).

92% of patients had mild pain or no pain on load at the end of the study.

All patients judged the tolerability of OSTENIL® PLUS treatment as 'very good' (92.3% of patients) or 'good' (7.7% of patients).

No adverse events due to OSTENIL® PLUS were reported.[10]

OSTENIL® PLUS reduces pain and improves function in osteoarthritis [10,11]

- Flexible treatment scheme
- Effective treatment with 1-3 injections
- Symptom relief over 6 months after 1 injection
- Very good tolerability

printed in 10/12

INSTRUCTIONS FOR USE

OSTENIL® Plus

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

Composition:

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

Indications:

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

Contra-indications:

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

Interactions:

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

Side effects:

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

Directions for use:

Inject OSTENIL® Plus into the affected joint once a week for a total of 1–3 injections. Several joints may be treated at the same time. Repeat treatment cycles may be administered as required. In case of joint effusion it is advisable to reduce the effusion by aspiration, rest, application of an ice pack and/or intra-articular corticosteroid injection. Treatment with OSTENIL® Plus can be started two to three days later.

The content and the outer surface of the OSTENIL® Plus pre-filled syringe are sterile as long as the sterile pack is intact. Take the pre-filled syringe out of the sterile pack, unscrew the Luer lock cap from the syringe, attach a suitable needle (for example 18 to 25 G) and secure it by turning slightly. Remove any air bubble, if present, before injection.

Precautions:

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

Characteristics and mode of action:

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

Presentation:

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

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

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