Restoring Synovial Balance

Ostenil®

Sodium Hyaluronate

Designed for long-term relief in OA

Ostenil®
Sodium Hyaluronate

Ostenil®

Osteoarthritis is a degenerative joint disease that causes pain and loss of mobility. It is the most common rheumatic disease and is second only to cardiovascular disease in producing chronic disability.[1,2]

Osteoarthritis is not a passive 'wear and tear' phenomenon, as was believed until recently. It is an active disease with a complex underlying pathology.[2]

Ostenil® is a novel agent that has been developed specifically for the treatment of osteoarthritis. It is a solution of hyaluronan (sodium hyaluronate) and is administered intra-articularly as a course of three to five weekly injections.

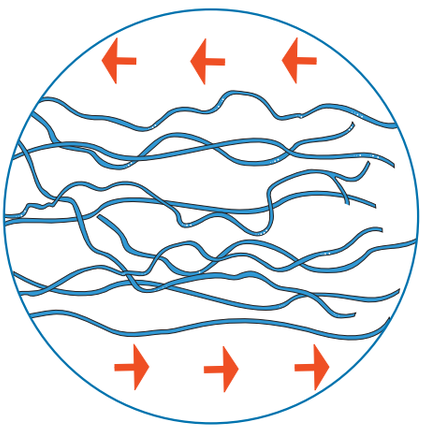
A novel treatment for osteoarthritis

The molecular weight of the hyaluronan in Ostenil® has been carefully selected to produce an optimal therapeutic profile.

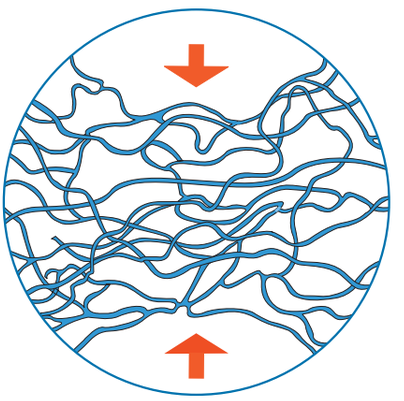
The beneficial effects of Ostenil® develop gradually during a course of injections and persist for several months. Following a course of five injections, symptomatic improvement can be expected to last for up to 12 months.[3–5]

Functions of hyaluronan in the healthy joint

Hyaluronan gives the synovial fluid its characteristic viscoelastic properties, enabling this fluid to act as a lubricant, a shock absorber and a filter controlling the movement of cells and large molecules within the joint.[6,7]



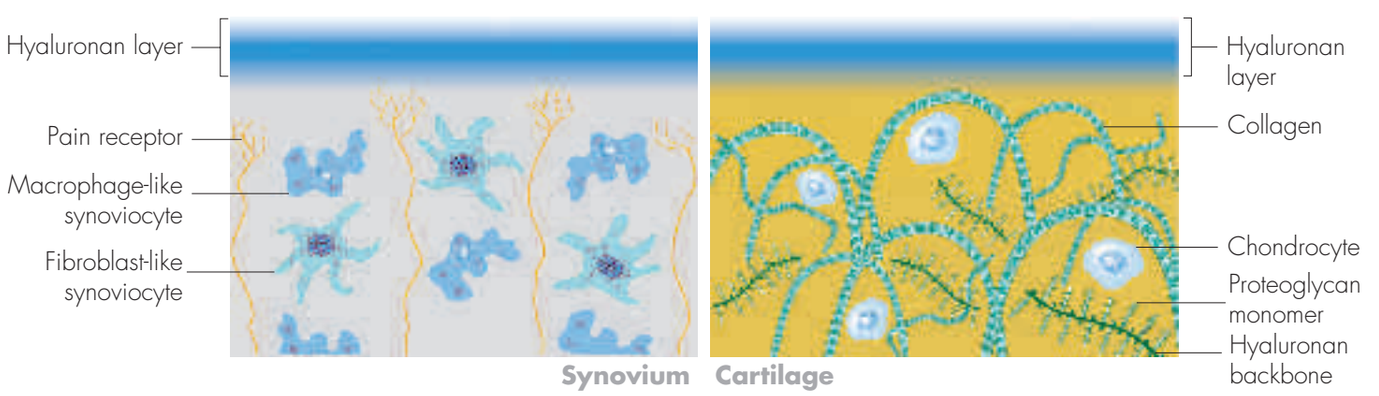
Under gradual shear stress, hyaluronan acts as a lubricant.



Under sudden loading, hyaluronan acts as a shock absorber.

Hyaluronan forms a coating over the entire inner surface of the joint.[8] This coating acts as a viscoelastic shield over the articular cartilage and synovium, protecting these structures from mechanical damage. In addition, it protects the cartilage and synovium from free radicals and other inflammatory factors.[9–11]

Hyaluronan also forms the backbone of the proteoglycan aggregates that are essential for the structural and functional integrity of the articular cartilage.[12,13]



Hyaluronan plays a vital role in the healthy synovial joint

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Loss of homeostasis in the osteoarthritic joint

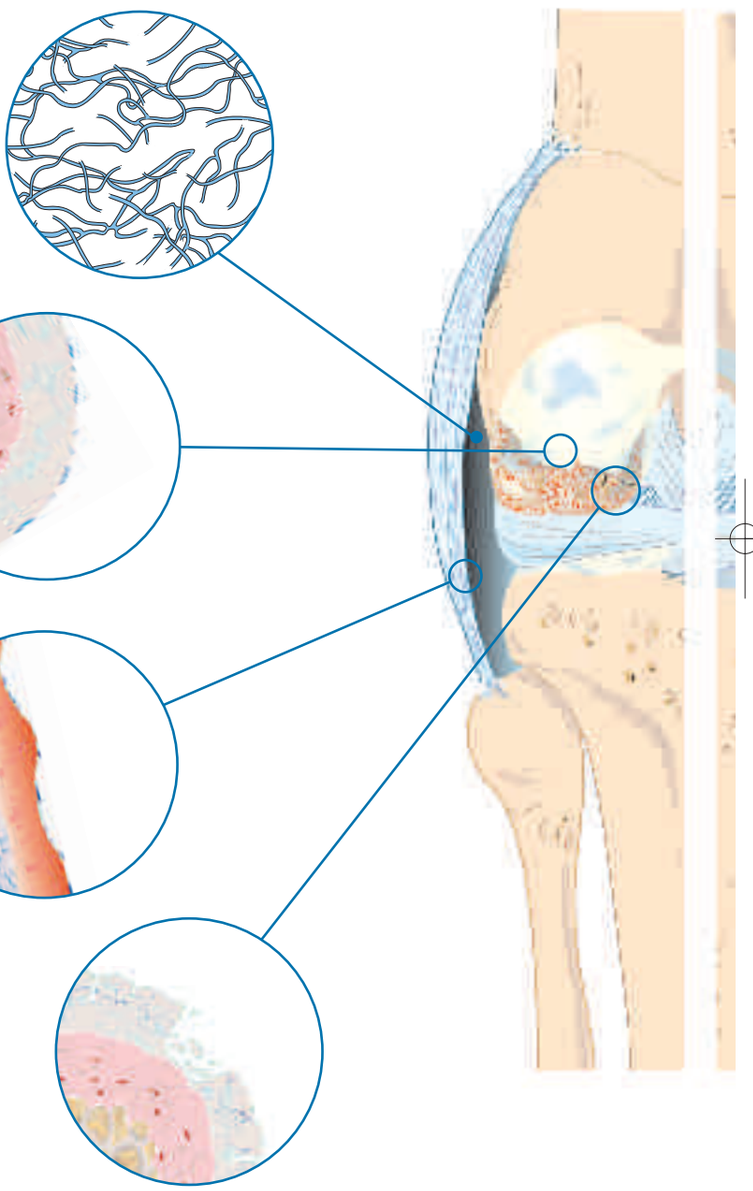
The healthy synovial joint is in a state of balance or homeostasis. The hyaluronan in the joint space is continuously replaced, but its concentration and molecular weight profile remain constant. In osteoarthritis, homeostasis is lost and the hyaluronan in the joint space becomes depolymerised and fragmented.[14]

The synovial fluid becomes less viscous and its lubricating, shock-absorbing and filtering abilities are reduced.[6]

The coating of hyaluronan over the surface of the joint breaks down, leaving the cartilage and synovium exposed to mechanical and inflammatory damage.[15]

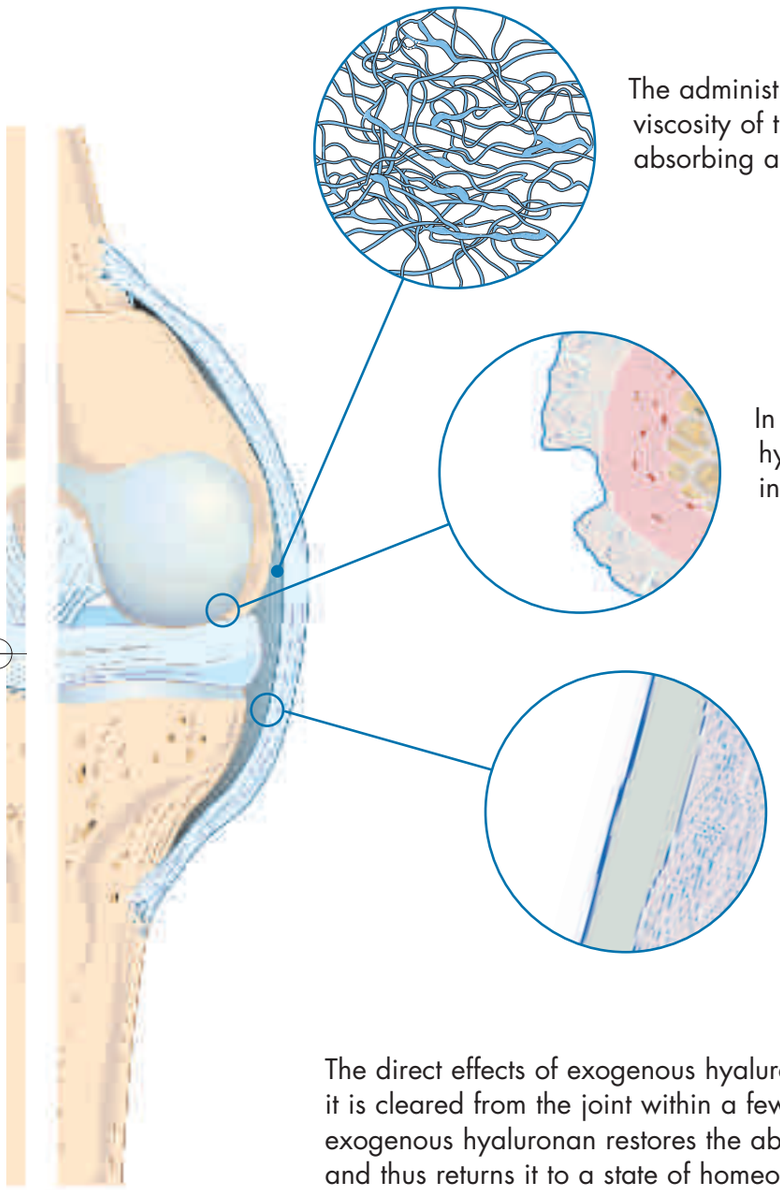
The synovium becomes inflamed. As a result, it grows more permeable to inflammatory molecules, which are therefore able to enter the joint in increased numbers.[15]

The articular cartilage is gradually destroyed.[16]



Osteoarthritis is accompanied by symptoms of pain, inflammation and reduced mobility

Exogenous hyaluronan restores synovial balance



The administration of exogenous hyaluronan increases the viscosity of the synovial fluid, restoring its lubricating, shock-absorbing and filtering properties.[7,14]

In addition, it re-establishes the protective coating of hyaluronan over the inner surface of the joint and increases the scavenging of free radicals.[9,11,17]

As a result of these changes, hyaluronan reduces inflammation of the synovium.[18–20] By masking the nociceptors, pain is also alleviated.[6,21,22]

The direct effects of exogenous hyaluronan cannot account for its long-term benefits, as it is cleared from the joint within a few days. It appears that, through its direct effects, exogenous hyaluronan restores the ability of the joint to produce its own hyaluronan and thus returns it to a state of homeostasis that persists for several months.[23]

Evidence exists suggesting that exogenous hyaluronan may slow the destruction of cartilage[8,24–26]

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Ostenil® mode of action

The efficacy of hyaluronan is related to its molecular weight. Ostenil® has a molecular weight that places it in the optimal range for therapeutic benefit, offering a favourable balance of biological activities (Figure 1).

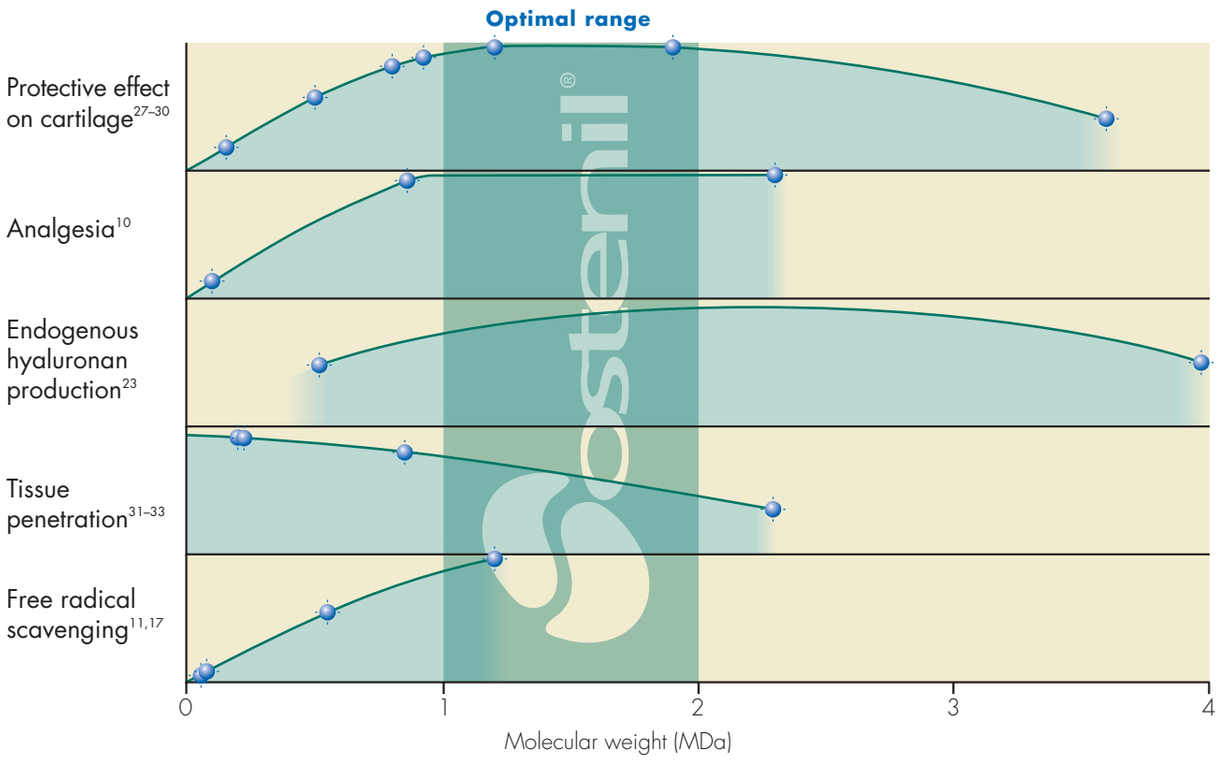

Figure 1. Biological activities of hyaluronan by molecular weight.

Ostenil® restores the viscoelastic properties of synovial fluid

With exogenous hyaluronan, the viscoelastic properties of synovial fluid are improved gradually during a course of injections (Figure 2). This augmentation of the synovial fluid properties is accompanied by a progressive improvement in symptoms.[4,7,14]

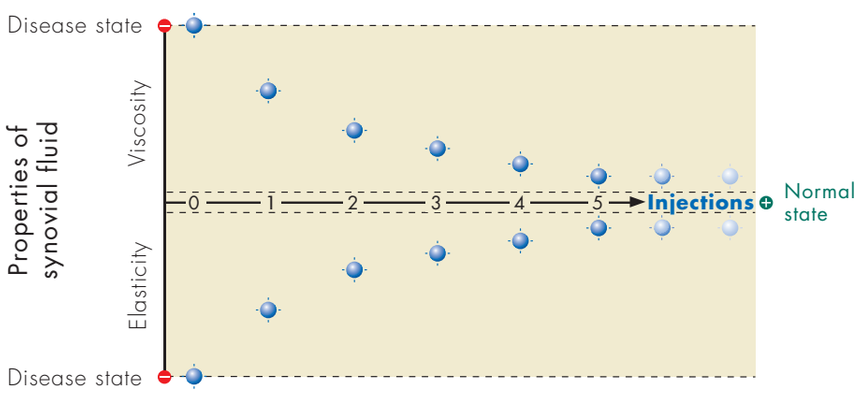

Figure 2. Improvement in the properties of synovial fluid with hyaluronan is accompanied by a progressive improvement in symptoms.

Ostenil® treatment regimen

A course of three to five injections of Ostenil® provides rapid and long-lasting relief from the symptoms of osteoarthritis (Figure 3).[4,34] Studies with hyaluronan have demonstrated the efficacy of this treatment regimen.

- A study of different dosing schedules of hyaluronan demonstrated that a minimum of three and up to five injections provide the maximal therapeutic response.[35]
- The therapeutic benefit of hyaluronan treatment is apparent after only 1 week, and increases over the course of injections.[36]
- A course of five injections with hyaluronan can provide up to 12 months of symptomatic relief.[4,5]

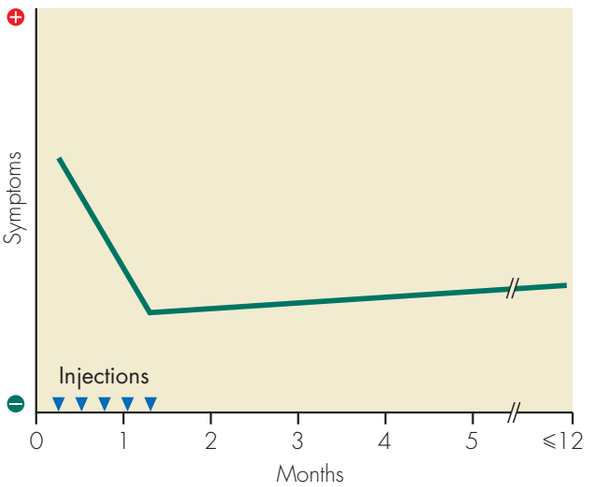

Figure 3. Symptomatic relief following treatment with intra-articular hyaluronan.

Synovial balance is restored after a treatment cycle of three to five injections of Ostenil® (Figure 4).

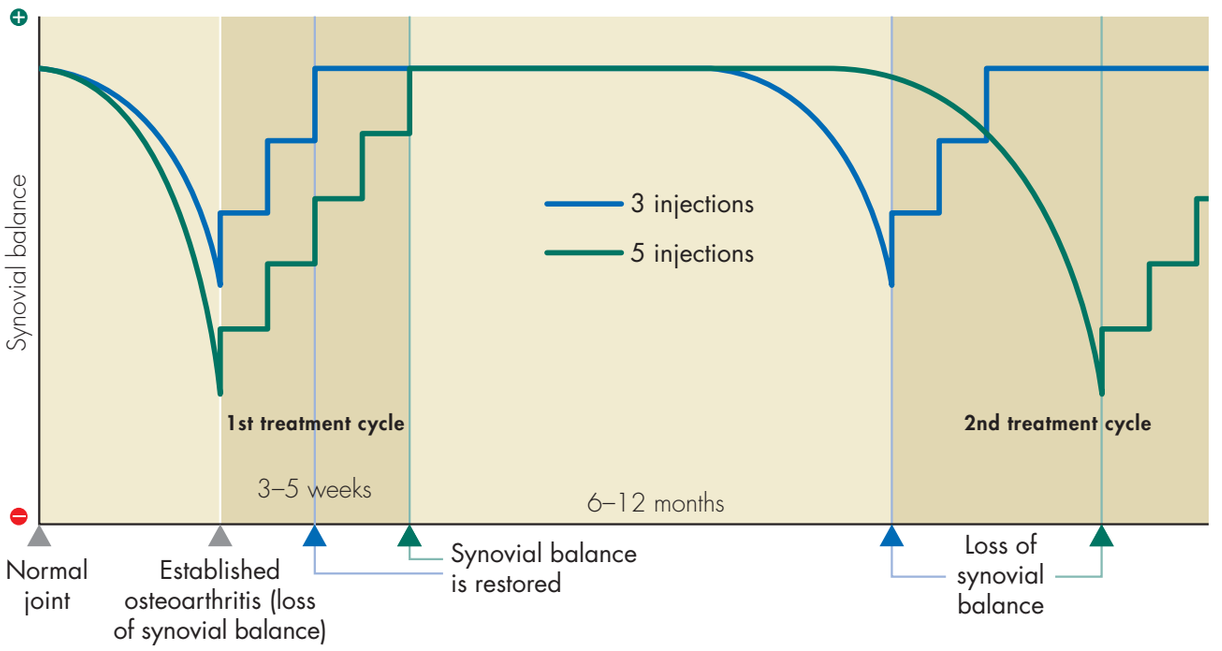

Figure 4. Restoring synovial balance.

A treatment cycle of three to five injections can restore synovial balance

Ostenil®
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Efficacy in relief of osteoarthritis of the knee

Hyaluronan has been shown to improve symptoms in patients with painful osteoarthritis of the knee.[1,37–39]

Efficacy after five injections

Pain relief – A course of five weekly injections of Ostenil® significantly reduces pain in affected joints.[4] Candidates for total knee replacement (n = 24) were treated with Ostenil®, with follow-up at 12 months*.[4] At week 4, pain in the affected joint had decreased significantly (p <0.05) compared with baseline. This beneficial effect was maintained during follow-up (Figure 5). Total knee replacement was deferred in 75% of patients.

* Follow-up between 3–12 months

Function improvement – Ostenil® improves quality of life and daily activities in patients with knee osteoarthritis.[3] In a study of 40 patients, treatment significantly improved function compared with baseline at week 4 after the start of therapy with Ostenil®. This beneficial effect was maintained during 6 months of follow-up (p <0.001; Figure 6).[3]

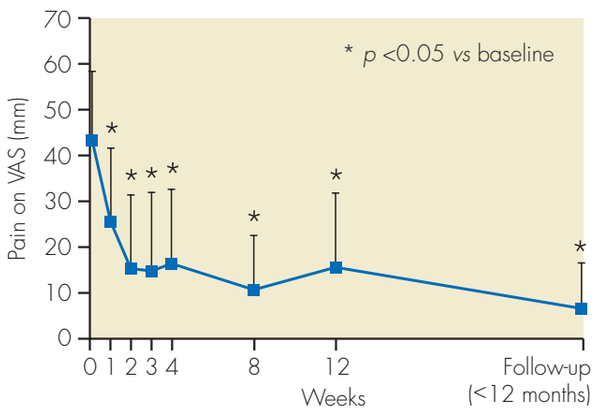

Figure 5. Pain on walking 20 m without support, measured on the 100 mm visual analogue scale (VAS).[4]

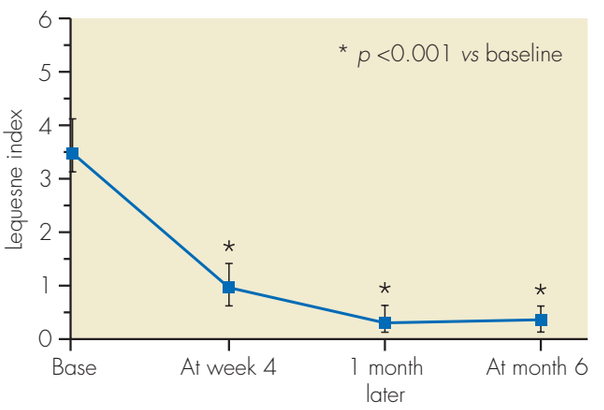

Figure 6. Lequesne index for patients with knee osteoarthritis treated with Ostenil®.[3]

Efficacy after three injections

Investigators' judgement of efficacy – Following a treatment regimen of three injections, investigator judgements favoured Ostenil® over a very high molecular weight cross-linked hyaluronan.[40]

A retrospective analysis of 225 patients with knee osteoarthritis, who received a course of three injections, compared investigators' assessments of the efficacy of Ostenil® with that of a very high molecular weight cross-linked hyaluronan.[40] Efficacy was significantly better (p = 0.03) in the Ostenil® group compared with the comparator group (Figure 7).

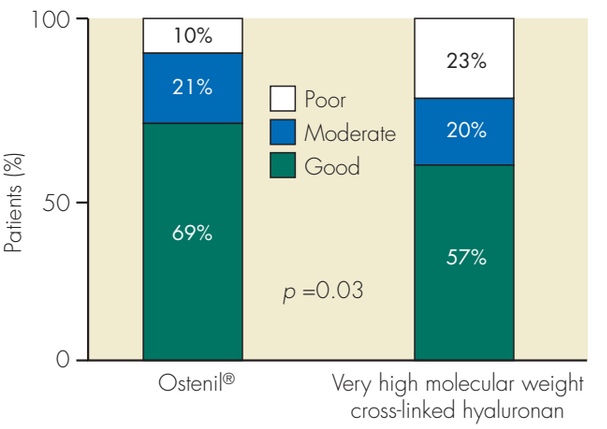

Figure 7. Investigator judgement of the efficacy of three injections of Ostenil® (n = 156) or very high molecular weight cross-linked hyaluronan (n = 69).[40]

Ostenil® for osteoarthritis of the hip and shoulder

Efficacy in hip osteoarthritis

Hyaluronan has demonstrated a beneficial effect on pain and function in patients with osteoarthritis of the hip.[41–43]

After five injections – Patients (n = 41) with severe osteoarthritis who were candidates for total hip replacement received five weekly injections of Ostenil®.[5] Following treatment, pain measured on the VAS (Figure 8) or the Harris hip score was significantly reduced compared with baseline (p <0.0005). This was maintained for up to 12 months (p <0.0005). Total hip replacement was deferred in 80% of patients.

After three injections – Ostenil® given as three injections is also effective in hip osteoarthritis. Among 25 patients with hip osteoarthritis who received Ostenil® for 3 weeks, mean pain on the VAS, the WOMAC index and the Lequesne index scores improved significantly compared with baseline (p <0.001 for each). Clinical improvement was maintained during 6 months of follow-up (Figure 9).[34]

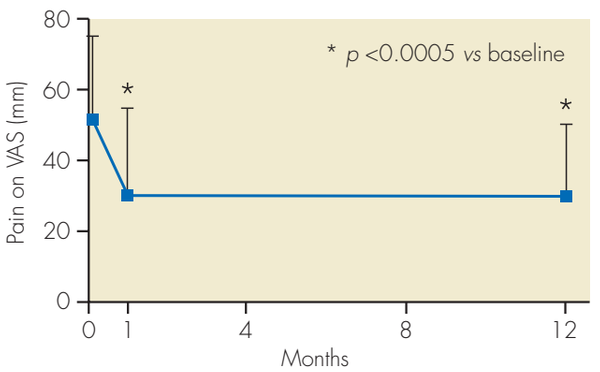

Figure 8. Pain on the 100 mm VAS following treatment with Ostenil®.[5]

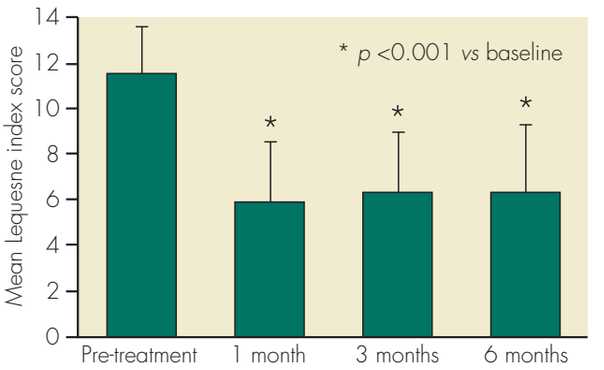

Figure 9. Improvement in function for patients receiving three injections with Ostenil® (n = 25).[34]

Efficacy in degenerative disorders of the shoulder

Clinical studies have shown hyaluronan to be an effective treatment for patients with degenerative or traumatic disorders of the shoulder.[44–47]

Among patients with advanced osteoarthritis of the shoulder who either refused or were considered medically unfit for shoulder replacement surgery, Ostenil® was associated with reduced pain and improved function (Figure 10).[48]

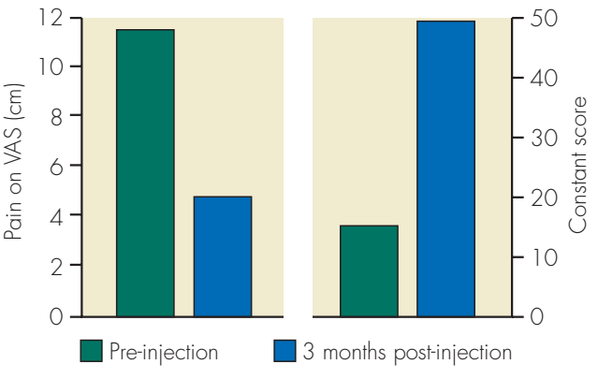

Figure 10. Pain on the 15 cm VAS and mean constant score (0–100) following treatment with Ostenil®.[48]

Significant and long-lasting improvement in pain and function are achieved in different joints after treatment with Ostenil®

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Ostenil® – designed for safety

Fermentation source

Ostenil® is produced by bacterial fermentation.

Hyaluronan from a bacterial source contains fewer impurities than hyaluronan isolated from animal origin. In particular, pro-inflammatory mediators are less likely to be present in bacterially derived hyaluronan preparations.[49]

Ostenil® is a highly purified product, containing no animal protein contamination; therefore, the allergenic potential of Ostenil® is negligible.

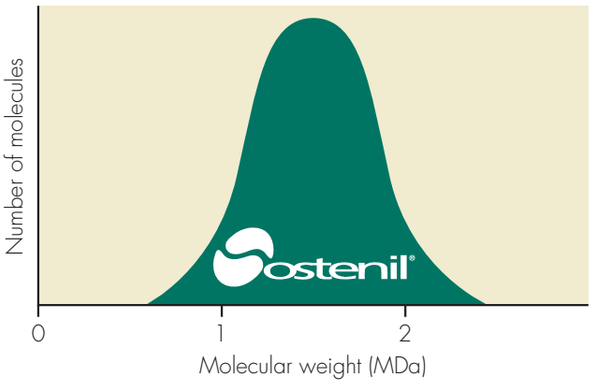


Figure 11. Molecular weight distribution for Ostenil®.

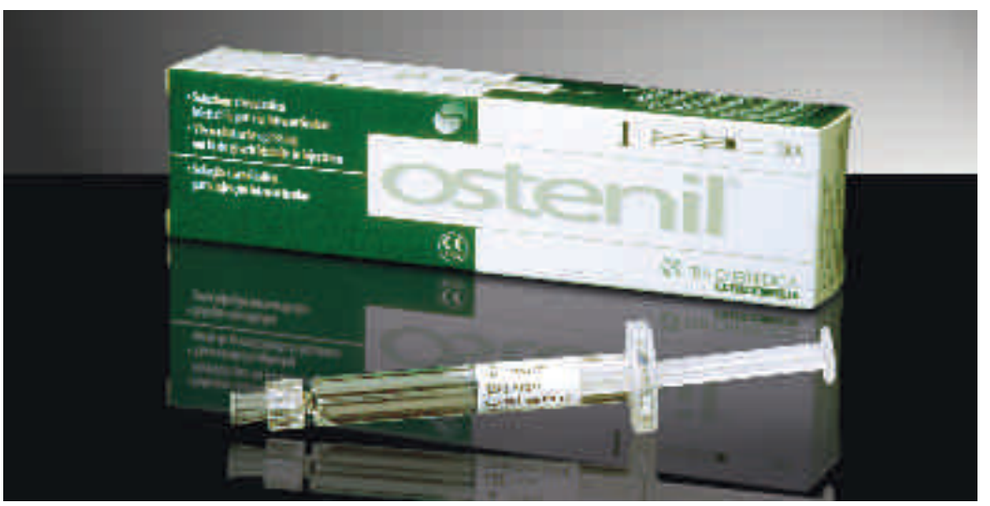
Molecular weight

The molecular weight distribution of Ostenil® is narrow and unimodal (Figure 11). This avoids both the potential inflammatory side-effects of low molecular weight hyaluronan[31,32] and the injection site pain that can be attributed to the viscosity of very high molecular weight cross-linked hyaluronan.[50]

Double sterilisation

Ostenil® is prepared using a double sterilisation technique. Following filtration of the bulk preparation, the syringes are filled and the blister-packed syringes are subjected to autoclaving (moist heat). Sterilisation by autoclave guarantees a high Sterility Assurance Level of 1:1,000,000 compared with 1:1000 for filtration alone.[51]

Ostenil® syringes are terminally sterilised – the device is sterile in the blister packaging in order to facilitate aseptic injection.



Ostenil® achieves optimum safety

Ostenil® is well tolerated

Clinical studies have shown that Ostenil® is well tolerated and has a low incidence of adverse effects.[3,50]

A retrospective study compared the tolerability of Ostenil® with that of a very high molecular weight cross-linked hyaluronan. The study highlighted the good tolerability associated with treatment – in 98% of 295 patients who received Ostenil®, tolerability was rated as 'good' (Figure 12).[40]

The incidence of adverse device reactions (ADRs) per injection was significantly lower in the Ostenil® group ($p \leq 0.02$; Figure 13).[40]

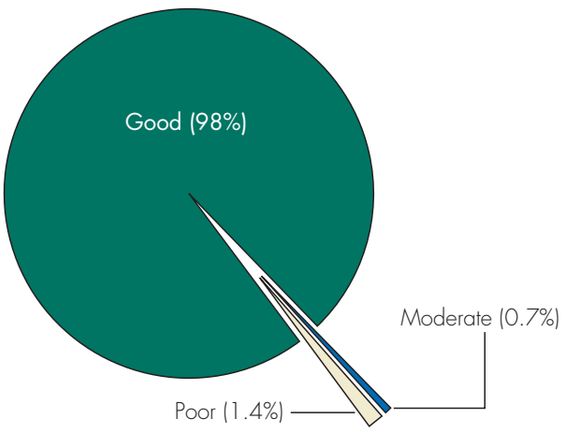


Figure 12. Assessment of tolerability following treatment with Ostenil®.[40]

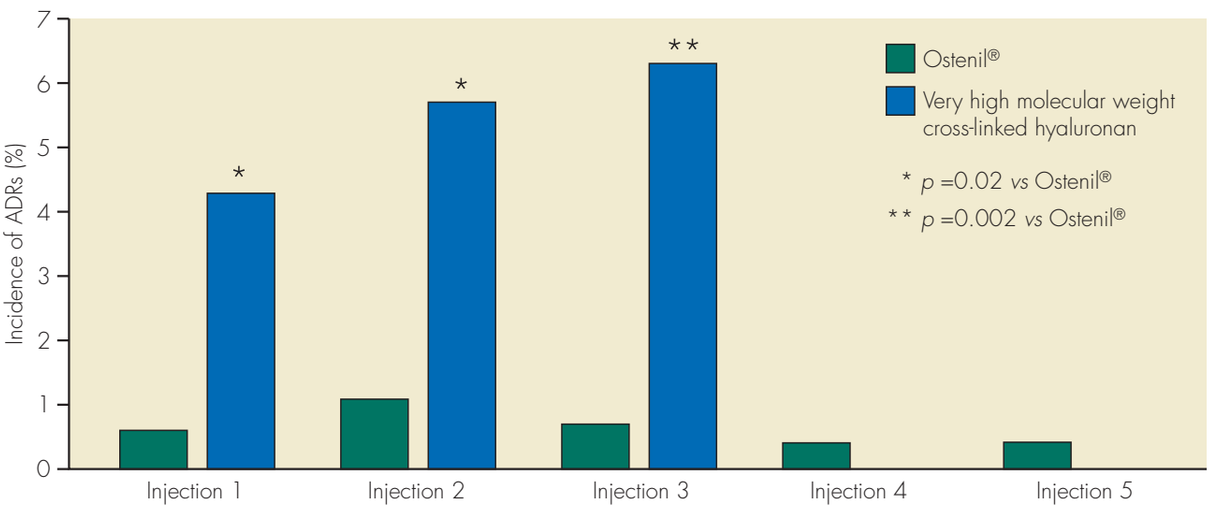


Figure 13. Incidence of ADRs per injection for Ostenil® compared with that for a very high molecular weight cross-linked hyaluronan.[40]

In addition, there was a lower incidence of inflammatory reactions in the Ostenil® group (swelling 1.1%, inflammation 0.2%) compared with the group receiving very high molecular weight cross-linked hyaluronan (swelling 6.5%, inflammation 8.7%).[40]

Ostenil®, which is of bacterial fermentation origin, is better tolerated than very high molecular weight cross-linked hyaluronan from an avian source.[40]

Ostenil® provides good tolerability and a low incidence of adverse reactions

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ostenil®

Sodium Hyaluronate

Designed for long-term relief in OA

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Prescribing information

OSTENIL® – Sodium hyaluronate 1.0%

Viscoelastic solution for injection into the joint cavity.

Sterile by moist heat.

Composition:
1 ml isotonic solution contains 10.0 mg sodium hyaluronate and sodium chloride, sodium monohydrogenphosphate, sodium dihydrogenphosphate, water for injection.

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

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

Precautions:
Caution should be exercised in patients with known hypersensitivity to drugs. The general precautions for intra-articular injections should be observed. OSTENIL® should be injected accurately into the joint cavity. 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® is not recommended in these cases. Do not use if the pre-filled syringe or sterile pack are damaged. Store at below 25°C! Do not use after the expiry date indicated on the box. Keep out of the reach of children.

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

Interactions with other products:
No information on the incompatibility of OSTENIL® with other solutions for intraarticular 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.

Dosage and administration:
Inject OSTENIL® into the affected joint once a week for a total of 3–5 injections. Several joints may be treated at the same time. Depending on the severity of the joint disease the beneficial effects of a treatment cycle of five intra-articular injections will last at least six months. 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® can be started two to three days later.

The contents and outer surface of the OSTENIL® pre-filled syringe are sterile as long as the sterile pack remains unbroken. Take the pre-filled syringe out of the sterile pack, remove the Luer lock cap from the syringe, attach a suitable cannula (for example 19 or 21 G) and secure it by turning slightly. Remove the air bubble from the syringe prior to injection.

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 a 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 with 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 of five intra-articular injections.

Presentation and package sizes:
One pre-filled syringe of 20 mg/2.0 ml of OSTENIL® in a sterile pack.
Three pre-filled syringes of 20 mg/2.0 ml of OSTENIL® in sterile packs.
Five pre-filled syringes of 20 mg/2.0 ml of OSTENIL® in sterile packs.

OSTENIL® is a medical device.

To be used under the direction of a physician.

Med IC3
Keele University Science Park,
Keele, Staffordshire, ST5 5NP

Tel: 0845 330 7556
Fax: 0845 330 7557
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