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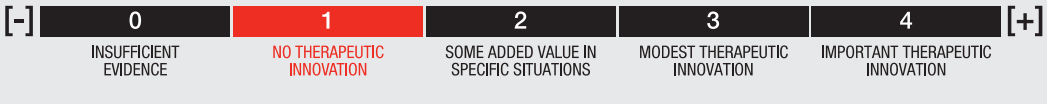
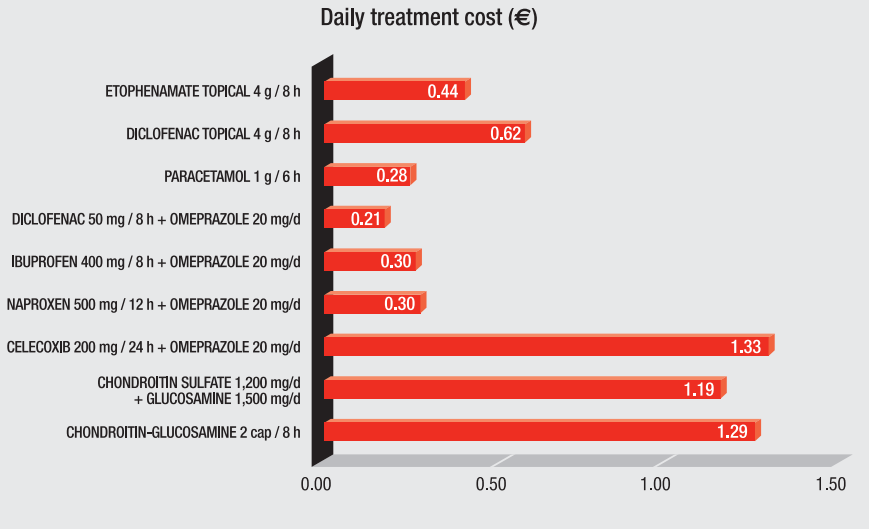
Chondroitin sulfate / Glucosamine (▲Droglican®) in osteoarthritis

Efficacy not demonstrated





A weakly supported indication

- The indication for the symptomatic management of knee osteoarthritis with moderate to severe pain is based on a small subgroup of patients in one clinical trial.
- None of its components has shown efficacy separately.
- Nor does the combination show superiority with regard to placebo in the symptomatic management of knee osteoarthritis.

Indications[1]

Symptomatic management of knee osteoarthritis in patients with moderate to severe pain in whom combined treatment with chondroitin sulfate and glucosamine is indicated.

Mechanisn of action and pharmacokinetics[1]

Chondroitin sulfate and glucosamine are components of cartilage. They promote the formation of new cartilage *in vitro* by stimulating the synthesis of collagen and proteoglycans.

The bioavailability of chondroitin sulfate oscillates between 15 and 24%. Of the absorbed fraction, 10% is found in chondroitin sulphate form and 90% in depolymerized forms of lower molecular weight, which suggests that there is a first pass effect. After the administration of oral chondroitin sulfate, the maximum concentration in blood is reached after 4 hours. At least 90% of the dose is metabolized mainly through lysosomal sulphatases. The elimination half-life runs between 5 and 15 hours. Elimination of chondroitin sulfate and the depolymerized forms occur mainly through the kidney.

The bioavialability of glucosamine is approximately 90%. It is excreted in urine 48 hours after oral administration, in a proportion of about 5% of the ingested dose. The main quantity of glucosamine administered orally is metabolized in tissues and eliminated as CO_2 in expired air. No pharmacokinetic studies have been carried out on the combination.

Posology and method of administration[1]

Two capsules 3 times a day (1,200 mg chondroitin sulfate daily and 1,500 mg glucosamine daily) for at least 6 months.

The qualification assigned to the drug was agreed by the Drug Assessment Committees of Andalusia, Basque Country, Catalonia Institute of Health, Aragon and Navarre. The current report is based on the available information and is susceptible to be updated according to the latest evidence. Let us remind the reader about the importance of notifying the Pharmacovigilance Centre when there are suspicions of adverse reactions to drugs.

The capsules can be taken before, during or after meals. It is recommmended that patients with gastric intolerance to drugs take chondrotin sulfate+glucosamine after meals.

Clinical efficacy

The efficacy of chondroitin/glucosamine compared to NSAIDs (celecoxib) was evaluated in the GAIT trial (*Glucosamine/Chondroitin Arthritis Intervention Trial*)[2] which included 1,583 patients under study for 6 months. The primary endpoint was "analgesic response" defined as a reduction of 20% in the WOMAC pain subscale. Paracetamol up to 4 mg daily was allowed as rescue medication. No statistically significant differences were found with placebo, or celecoxib in the whole of the patients. In the predefined group from the design of the trial, patients with moderate to severe pain at the onset (WOMAC score of 301-400) there were statistically significant differences with respect to placebo (79.2% vs 54.3%, p=0.002). However, it should be taken into account that this was a sub-analysis and the number of patients was small. The same invesigators qualified this analysis of the sub-group as exploratory.

In an open extension of the trial up to 24 months, there were no differences found vs placebo in the reducion of pain or in the global response. There was no separate information on the subgroups of patients with either moderate or severe pain[3].

Another small trial in 89 patients with mild to moderate pain was published.The study lasted one year. At the sixth month, a progressive intense exercise program was introduced. There were no differences found vs placebo with regard to function or pain measured WOMAC scale after 6 months and one year of treatment[4].

A systematic review was carried out on the efficacy of chondroitin sulfate, glucosamine or its combination that included trials with at least 100 patients. A network meta-analysis was performed with a Bayesian model. The primary endpoint was intensity of pain, where clinical relevance was defined as a difference of 0.9 cm in the visual analogue scale of 10 cm. Ten trials with 3,810 patients in total were included, of which only one (GAIT) offered data on the combined chondroitin/glucosamine treatment. No clinical relevant differences were found when comparing placebo to glucosamine or chondroitin sulfate or their combination. Nor did chondroitin, or glucosamine or their combination have any effect on narrowing the intraarticular space[5].

Safety

Chondrotin sulfate and glucosamine are components of cartilage and therefore, are part of the diet. There are no differences when compared to placebo with regard to treatment withdrawal due to adverse effects (OR=0.90; 0.43-1.85)[5].

Adverse reactions[1]

Frequent (1/100 to <1/10): cefalea, diarrhoea, nausea, dyspepsia, flatulence, constipation fatigue, abdomial pain.
Less frequent (1/1,000 to <1/100): skin eruptions, pruritus, blushing.
Rare (1/10,000 to <1/1,000): elevated liver enzymes, abnormal urinalysis, upper respiratory tract infections, urinary tract infections, gastro-oesophageal reflux, abdominal distension, muscle cramps, pain in one extremity.
Very rare (<1/10,000): oedema, liquid retention.
Unknown frequency: dizziness, vomiting, angio-oedema, urticaria.

Contraindications[1]

Hypersensitivity to the main active substances or any of the excipients. It should not be given to patients allergic to shellfish, as glucosamine is obtained from shellfish.

Warnings and precautions[1]

Glucosamine reduces the secretion of insulin and increases insulin resistance, probably due to an inhibitory effect of glucokinase in beta cells. The clinical relevance of this effect is unknown. In patients with glucose intolerance, it is recommended to monitor glycaemia, and when necessary evalute the need for insulin, before initiating and periodically during treatment.

Heart and/or kidney failure: in very rare occasions (<1/10,000) cases of oedema and/or liquid retention have been described. This phenomenon, could be attributed to the osmotic effect of chondroitin sulfate.

Use in special situations[1]

Children and adolescents: it has not been evaluated in children under 18 years.
Renal and/or liver impairment: no recommendations can be made as there are no studies available.

Interactions[1]

There is very limited data available on possible drug interactions with glucosamine. INR increase with concomitant use of cumarinic anticoagulants (warfarin and acenocoumarol) has been described. Patients should be closely monitored when initiating and during treatment.

Glucosamine can increase the absorption and serum concentrations of tetracyclins and reduce the absorption of penicilins and cloramphenicol.

Place in therapeutics

Management of osteoartritis starts with education of the patient with the objective of introducing an exercise program and control of overweight. The first step in pharmacological treatment is paracetamol and/or topical NSAIDs. In case no pain control is achieved, then oral NSAIDs, opioids, topical capsacin or intraarticular steroids can be administered. The NICE guidelines specifically do not recommend the use of chondroitin sulfate and glucosamine[7].

In patients with mild pain, chondroitin sulfate/glucosamine does not offer any clinically relevant benefit. With regard to moderate to severe pain, there are only scarce data supporting the use of chondroitin/glucosamine from a small subgroup of patients and from only one trial. Therefore, no conclusion can be made on any clinically significant benefit of its use.

Presentations

Droglican® (Bioibérica) 200 mg/250 mg 90 capsules (19.40 €)

References

A complete report on chondroitin sulfate - glucosamine can be found at: http://www.dtb.navarra.es

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