

DRUG UPDATE

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GLUCOSAMINE

Glucosamine, a component of cartilage, is sometimes advocated in the management of osteoarthritis and other arthritic conditions. A licensed preparation is available for mild to moderate knee osteoarthritis. Evidence for the efficacy of glucosamine is limited, and where benefits were demonstrated the size of the effect was generally small. In accordance with NICE guidance glucosamine is not recommended for osteoarthritis.

What is it?

Glucosamine is a natural component of articular cartilage.¹ Oral formulations are used in a variety of arthritic conditions, principally osteoarthritis (OA). Since the previous glucosamine Drug Update¹ important new evidence has been published,²⁻⁴ a licensed product has become available,⁵ and NICE has issued guidance on its use in OA.⁶ The licensed preparation (Alateris[®], glucosamine hydrochloride 625 mg tablets, Navamedic) is indicated for the relief of symptoms in mild to moderate knee OA.⁵

How effective is it?

A large randomised, double-blind, placebo controlled trial compared glucosamine alone (n = 317), chondroitin alone (n = 318), glucosamine plus chondroitin (n = 317), celecoxib (n = 318) or placebo (n = 313). The primary outcome was the proportion of patients reporting a $\geq 20\%$ decrease in pain score from baseline to 24 weeks. Patients were predominantly female (64%) and white (78%), with a mean age of 59 years, mean BMI > 30 kg/m², and a ten year history of OA and knee pain. There was no significant difference (p > 0.05) between placebo and any glucosamine or chondroitin treatment group with primary outcome rates for glucosamine, chondroitin, glucosamine plus chondroitin, celecoxib and placebo of 64%, 65%, 67%, 70%, and 60%, respectively.² Limitations of the study include; the high rate of placebo-response, that the patients had relatively mild knee pain at baseline, and that even the effects of celecoxib were smaller than those seen in other studies.

A randomised, placebo-controlled, double-blind trial, funded by a manufacturer of glucosamine products, compared glucosamine sulphate (n = 106) with paracetamol (n = 108) and placebo (n = 104). Patients were predominantly female (87%), with a mean age of 64 years, mean BMI > 27 kg/m², and a duration of knee OA > 6 years. The primary outcome was the change in a validated pain and function score (range 1 to 24) after six months. Scores decreased by 3.1 with glucosamine, 2.7 with paracetamol, and 1.9 with placebo (p = 0.032 for glucosamine vs. placebo). The p value for glucosamine vs. paracetamol was not stated.³

Most evidence for glucosamine in OA relates to the knee joint,⁷ however one randomised blinded study compared glucosamine sulphate (n = 111) with placebo (n = 111) in patients with hip OA. Patients were predominantly female (69%), with a mean age of 63 years, mean BMI > 27 kg/m²,

and $> 50\%$ had OA symptom duration of ≥ 3 years. The primary outcome measures were the change in pain and function scores, and joint space narrowing after two years. No statistically significant differences between placebo and treatment groups were observed.⁴ The product used in this study was a food supplement. Therefore the content, purity and dissolution of the preparation may not have been evaluated and approved by any competent regulatory authority. This emphasises the need for glucosamine products produced according to Good Manufacturing Practice.

A Cochrane review of the efficacy and safety of glucosamine in OA, published in 2008, included a meta-analysis of 20 randomised controlled trials (n = 2,570). The majority of the studies had an affiliation with a specific manufacturer of glucosamine. Analysis of all 20 studies identified a significant benefit for glucosamine on some, but not all, pain, function and stiffness scores. When analysis was restricted to the eight studies that did not use the Rotta brand of glucosamine, and to eight studies with adequate treatment allocation concealment, no significant differences were observed between glucosamine and control groups.⁷

What does NICE say?

NICE issued guidance for the care and management of OA in adults in 2008.⁶ Neither glucosamine nor chondroitin are recommended for the treatment of OA.^{6,8} However, patients may be advised on how to perform their own trial of therapy by evaluating their symptoms and reviewing the benefits after three months of taking glucosamine.⁸ NICE recommends exercise as first line treatment for OA combined with paracetamol or topical NSAIDs for pain relief.⁶

Rheumatoid arthritis

Although most evidence relating to the use of glucosamine is in OA, many unlicensed preparations are also marketed for rheumatoid arthritis. The evidence base for glucosamine in rheumatoid arthritis is scant with only one randomised placebo-controlled 12-week study identified (n = 51) that demonstrated ambiguous results with respect to several parameters. The study was confounded by differences in baseline medication use.⁹

How safe is it?

Glucosamine is generally considered to be safe.^{7,10} Reported adverse events are generally mild: gastrointestinal symptoms,

dermal symptoms, fatigue and headache were most common.⁵ People who are allergic to shellfish may react to naturally sourced glucosamine.⁵

Glucosamine may increase the INR value in patients stabilised on warfarin.¹¹ The mechanism of any interaction is unclear. Patients on warfarin therapy are advised not to take glucosamine.

Glucosamine has been associated with altered glucose metabolism in animals; raising concerns regarding the safety of glucosamine in diabetic patients. Any effect may not be clinically significant.¹⁰

The licensed preparation, Alateris[®], is formulated as the hydrochloride salt.⁵ There is a discrepancy in the evidence base for different salts of glucosamine, with the hydrochloride salt appearing less effective.^{2,7}

The sulfate component of glucosamine sulfate has been associated with a degree of pharmacological activity.^{7,12} It has

been postulated that the sulphate component is involved in the beneficial pharmacodynamic effects of glucosamine sulphate preparations, but this has not been proven.

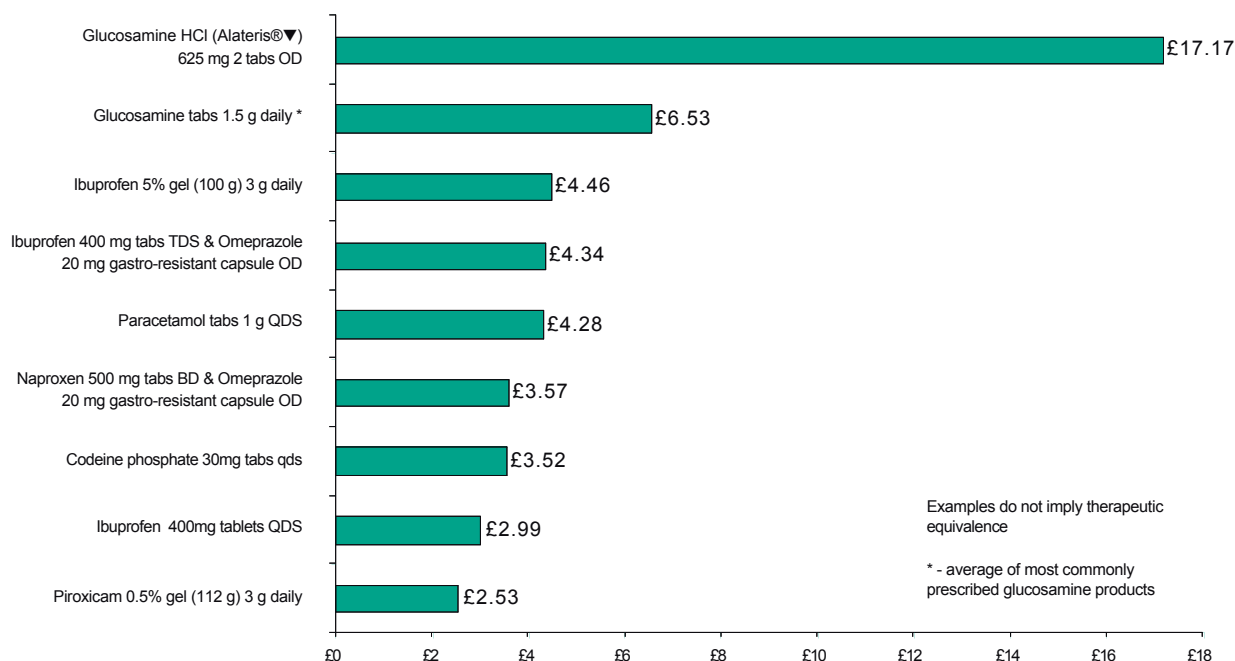
The potassium content per gram of glucosamine sulphate potassium chloride is ~130 mg (3.3 mmol), which may be clinically significant in some patient groups i.e. those with decreased renal function.

When should it be used?

Despite many years of clinical use and numerous studies, a clear benefit for glucosamine has yet to be demonstrated, with efficacy only slightly better than placebo in some studies.^{2,4,7-8} In line with NICE guidance neither glucosamine nor chondroitin are recommended for use in osteoarthritis.⁶ Patients who are currently maintained on glucosamine should have the efficacy of their treatment evaluated as part of regular, scheduled, medication reviews.

How much does it cost?

Cost of 28 days treatment (Drug Tariff and NHS dm+d, July 2008)



REFERENCES

1. Glucosamine Drug Update No. 43: Regional Drug and Therapeutic Centre; August 2005. www.nyrdtc.nhs.uk/docs/dud/DU_43_Glucosamine_a.pdf (G)
2. Clegg DO, Reda DJ, Harris CL et al. Glucosamine, chondroitin sulfate, and the two in combination for painful knee osteoarthritis. *N Engl J Med* 2006;354:795-808 (RCT)
3. Herrero-Beaumont G, Ivorra JA, Del Carmen Trabado M et al. Glucosamine sulfate in the treatment of knee osteoarthritis symptoms: a randomized, double-blind, placebo-controlled study using acetaminophen as a side comparator. *Arthritis Rheum* 2007;56:555-67. (RCT)
4. Rozendaal RM, Koes BW, van Osch GJ et al. Effect of glucosamine sulfate on hip osteoarthritis: a randomized trial. *Ann Intern Med* 2008;148:268-77. (RCT)
5. Ransom. Alateris[®] Summary of Product Characteristics 2007. www.williamransom.com/~william/uploads/File/Alateris%20SmPC.pdf
6. NICE. Osteoarthritis: The care and management of osteoarthritis in adults. Clinical Guideline 59 2008. www.nice.org.uk/guidance/index.jsp?action=byID&o=11926 (G)
7. Towheed TE, Maxwell L, Anastassiades TP et al. Glucosamine therapy for treating osteoarthritis. *Cochrane Database Syst Rev* 2008:CD002946 (MA)
8. The National Collaborating Centre for Chronic Conditions. Osteoarthritis: National clinical guideline for care and management in adults 2008. www.rcplondon.ac.uk/pubs/contents/d87b4537-b333-4b8a-a2d8-5e96b7f4b65a.pdf (G)
9. Nakamura H, Masuko K, Yudoh K, Kato T, Kamada T, Kawahara T. Effects of glucosamine administration on patients with rheumatoid arthritis. *Rheumatol Int* 2007;27:213-8 (RCT)
10. Anderson JW, Nicolosi RJ, Borzelleca JF. Glucosamine effects in humans: a review of effects on glucose metabolism, side effects, safety considerations and efficacy. *Food Chem Toxicol* 2005;43:187-201. (R)
11. MHRA. Current problems in Pharmacovigilance. May 2006;31. www.mhra.gov.uk/Publications/Safetyguidance/CurrentProblemsinPharmacovigilance/CON2023859
12. Hoffer LJ, Kaplan LN, Hamadeh MJ, Grigoriu AC, Baron M. Sulfate could mediate the therapeutic effect of glucosamine sulfate. *Metabolism* 2001;50:767-70. (RCT)

KEY RCT – randomised controlled trial, G – guideline, MA – meta-analysis, R – review

Regional Drug and Therapeutics Centre

Wolfson Unit, Claremont Place, Newcastle upon Tyne NE2 4HH

Tel: 0191 232 1525 Fax 0191 260 6192

E-mail: nyrdtc.di@ncl.ac.uk Website: www.nyrdtc.nhs.uk

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