Scottish Medicines Consortium

glucosamine (as hydrochloride), 625mg tablets (Alateris®)

No. (471/08)

William Ransom & Son plc

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The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

glucosamine (as hydrochloride) (Alateris®) is not recommended for use within NHS Scotland for relief of symptoms in mild to moderate osteoarthritis of the knee.

No direct clinical trial evidence of the efficacy and safety of this specific product is available. Randomised controlled trials of other formulations of glucosamine hydrochloride indicate little or no benefit over placebo in improving symptoms in patients with osteoarthritis of the knee.

In addition, the manufacturer did not present a sufficiently robust economic analysis to gain acceptance by SMC.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

Relief of symptoms in mild to moderate osteoarthritis of the knee. Glucosamine is not indicated for the treatment of acute painful symptoms. Relief of symptoms (especially pain relief) may not be experienced until after several weeks of treatment and in some cases even longer. If no relief of symptoms is experienced after 2-3 months, continued treatment with glucosamine should be re-evaluated.

Dosing information

Two tablets (1250 mg glucosamine) once daily.

Product availability date

1st October 2007

Summary of evidence on comparative efficacy

There are no curative or disease-modifying pharmacological treatments for osteoarthritis (OA). Glucosamine is an endogenous substance, a normal constituent of the polysaccharide chains of cartilage matrix and synovial fluid glucosaminoglycans. Its mechanism of action in humans is unknown. The product under review is the hydrochloride salt of glucosamine.

The European Medicines Agency (EMEA) granted Marketing Authorisation approval (MAA) for glucosamine (hydrochloride) based on a bibliographical application. Instead of investigating the medicinal product in clinical trials, evidence is taken from the published scientific literature.

No evidence was presented for the specific product under review. Evidence relating to various other formulations of glucosamine as hydrochloride or sulphate from many published studies was presented. Only the most relevant studies are included here.

Glucosamine hydrochloride studies

A multicentre, double blind, placebo- and celecoxib-controlled trial in the U.S.A. recruited patients ≥ 40 years of age with radiologically confirmed knee OA who had pain for at least six months and on the majority of days during the preceding month. Patients were in American Rheumatism Association functional class I, II, or III and had a Western Ontario and McMaster Universities Osteoarthritis (WOMAC) pain score of 125 to 400. The WOMAC index is a validated, disease specific questionnaire that addresses severity of joint pain (5 questions), stiffness (2 questions), and limitation of physical function (17 questions) and refers to the 48 hours before assessment. Seventy-eight % of patients had mild knee pain and the remainder had moderate to severe knee pain. Mean age was 59 years, mean body-mass index was 31.7 and 64% of patients were female.

A total of 1,583 patients were randomised, (with stratification according to centre and baseline WOMAC pain score), to 24 weeks treatment with one of the following: 500 mg glucosamine hydrochloride three times daily, 400 mg chondroitin sulphate three times daily, 500 mg glucosamine hydrochloride plus 400 mg chondroitin sulphate three times daily, 200 mg celecoxib daily, or placebo. Patients were evaluated at baseline, 4, 8, 16, and 24 weeks. The study was conducted under an investigational new drug application, and study drugs were subject to pharmaceutical regulation by the United States Food and Drug Administration. Paracetamol was allowed as rescue analgesia. Glucosamine hydrochloride was no better than placebo for any outcome including WOMAC pain, (primary outcome),

WOMAC stiffness, WOMAC function, patient's global assessment, physician's global assessment and consumption of rescue medication.

A double blind, placebo-controlled study in Canada, recruited patients who had primary knee OA, confirmed by radiological changes, with moderate or severe pain for at least 6 months. Patients were aged 40-85 years and able to walk without devices other than a cane. One hundred and eighteen patients were randomised equally to treatment with unlicensed glucosamine hydrochloride 500 mg capsules three times daily or placebo for eight weeks. Paracetamol was allowed for rescue analgesia. The primary outcome was change from baseline to week 8 in WOMAC pain subscale. There was no significant difference between treatment groups in WOMAC pain, stiffness, or function scores.

Glucosamine sulphate studies

Two double-blind, placebo controlled trials, in Belgium and the Czech Republic, recruited patients >50 years, (45 to 70 years in the Czech trial), with mild to moderate primary knee OA diagnosed according to the clinical and radiological criteria of the American College of Rheumatology. Four hundred and fourteen patients were randomised equally to once daily treatment with a licensed formulation of 1500 mg crystalline glucosamine sulphate, in sachets of powder for oral solution, or placebo, for 3 years. Rescue analgesia was paracetamol or nonsteroidal anti-inflammatory drugs (NSAIDs), (paracetamol only in the Czech trial). Fifty-one % of patients in the Belgian trial had not required OA treatment in the six months prior to enrolment.

The primary outcome of symptom modification was assessed by the 3-year % change in WOMAC total index. The Czech trial also used the Lequesne index, a validated, disease-specific questionnaire addressing knee pain (5 questions scored on a 0-2 scale with 0 indicating absent and 2 indicating severe), function limitation (4 questions, same scale), and maximum distance walked (1 question, scored on a 0-6 distance scale with 0 indicating ability to walk unlimited distance and 6 indicating ability to walk <100m). The worst possible score is 24 points. Analyses were in the intention to treat (ITT) populations.

In the Belgian trial symptoms worsened slightly in patients on placebo: 9.8%, 95% CI (-6.2 to 25.8) compared with the improvement observed after treatment with glucosamine sulphate: -11.7%, 95% CI (-20.3 to -3.2).

In the Czech trial glucosamine sulphate, compared with placebo, improved both Lequesne score: –1.7, (95% CI: -2.2 to –1.2) vs -0.82, (95% CI: -1.1 to –0.51), respectively and WOMAC total index: -8.0, (95% CI: -9.8 to –6.3) vs - 4.9, (95% CI: -6.5 to –3.2), respectively. There were significant improvements in WOMAC pain and physical function subscales with glucosamine sulphate compared with placebo in both trials, but the difference in the stiffness subscale was only significant in the Czech trial. There was no significant difference between treatment groups in consumption of rescue medication in either trial.

A six month randomised, double blind, placebo-controlled glucosamine sulphate discontinuation trial was conducted in 137 current users of glucosamine with knee OA who had experienced at least moderate improvement in knee pain after starting glucosamine. Study medication dosage was equivalent to the dosage of glucosamine sulphate taken prior to the study (maximum 1,500 mg/day). Follow up continued for 6 months or until disease flare, whichever occurred first. The primary outcome was the proportion of disease flares in the glucosamine sulphate and placebo groups using an intent-to-treat analysis. Secondary outcomes included time to disease flare; analgesic medication use; severity of disease flare; and change in pain, stiffness, function and quality of life in the glucosamine and placebo groups.

Disease flare was seen in 28 (42%) of 66 placebo patients and 32 (45%) of 71 glucosamine sulphate patients (a non-significant difference of -3%; (95% CI:-19 to 14); In a Cox regression analysis after adjustment for sex, study site, and OA radiographic severity, time to disease flare was not significantly different in the glucosamine compared with placebo group: hazard ratio of flare = 0.8; (95% CI: 0.5 to 1.4). At final study visit, there was no signficant difference between groups in the use of paracetamol or NSAID alone or combined. No differences were found in severity of disease flare or other secondary outcomes between placebo and glucosamine patients. Glucosamine was no better than placebo in the European Quality of Life (EQ-5D) questionnaire. There was no evidence of symptomatic benefit from continued use of glucosamine sulphate. Knee OA disease flare occurred as frequently, as quickly, and as severely in patients who were randomised to continue receiving glucosamine sulphate compared with those who received placebo.

A Cochrane systematic review of glucosamine therapy in OA evaluated 20 trials and 2,570 patients. It was published in 2005 and states: Although most of the randomised controlled trials (RCTs) show clear superiority of glucosamine over placebo in osteoarthritis, five RCTs failed to show that glucosamine was better than placebo. It is not entirely clear how to reconcile the negative results from these RCTs with the favourable results from the other RCTs. If only the best-designed studies are included, the benefit in pain and WOMAC function is no longer present. It is not known if glucosamine hydrochloride is as effective as glucosamine sulphate in the treatment of osteoarthritis.

Summary of evidence on comparative safety

The EMEA stated that safety in all the studies reviewed for the marketing authorisation application (MAA), covering thousands of patients, is reassuring and comparable to placebo. Pharmacovigilance reporting, mainly from Sweden and Spain did not indicate any new safety concerns. The large U.S. study described above, published after the MAA, demonstrated that glucosamine hydrochloride had a similar safety profile to placebo.

The most common adverse reactions associated with glucosamine treatment are nausea, abdominal pain, indigestion, constipation, and diarrhoea. In addition, headache, tiredness, rash, itching, and flushing have been reported. The reported adverse reactions are usually mild and transitory. Sporadic, spontaneous cases of hypercholesterolaemia have been reported, but causality has not been established.

Summary of clinical effectiveness issues

This product is the first licensed form of glucosamine in the U.K and is glucosamine hydrochloride. However, the efficacy and safety of this specific product have not been investigated in clinical trials. The evidence presented is from studies that used various other glucosamine formulations, including some of unknown quality, and different doses and dose frequencies. Most of the studies cited used glucosamine sulphate, not glucosamine hydrochloride. Bioequivalence of these products has not been proven, however the EMEA has stated that a comparative bioavailability study was not crucial for approval.

Although it is claimed that this product has no comparators, the indication of symptom relief in mild to moderate OA of the knee is common to glucosamine hydrochloride, (although it has the disadvantage not being effective until several weeks after initiating treatment) and to paracetamol and NSAIDs. Therefore these are valid comparators.

EMEA guidance on trials for medicinal products in OA states that for symptom modifying drugs, active-controlled studies with the most favourable comparator are necessary. Three-arm, placebo and active-controlled studies are recommended. . In the U.S. study described above, in which the glucosamine hydrochloride formulation was subject to pharmaceutical regulation by the USFDA, it was no better than placebo for any measured outcome while celecoxib was significantly better than placebo for the primary outcome and some secondary endpoints.

EMEA guidance also states that it might be possible to show that the beneficial effect is sustained long-term by means of a withdrawal study in which actively treated patients, at the end of the study period, are randomised to discontinue or continue double-blind treatment. The discontinuation trial described in the efficacy section is therefore considered to be of appropriate design.

Many factors may affect the evolution of osteoarthritis including age, sex, obesity, major joints injury, developmental abnormalities and familial osteoarthritis. These factors should be stratified at entry or adjusted at data analysis. This did not happen in many of the trials cited.

In the Belgian study more than half the patients had not required medication for osteoarthritis in the six months prior to enrolment. It is therefore unclear whether the patients in this trial are representative of the majority of patients referred to rheumatology clinics with osteoarthritis of the knee.

The company states that glucosamine hydrochloride is intended to be used in patients with knee pain who are unresponsive to paracetamol and intolerant to NSAIDs. No evidence has been provided to demonstrate efficacy of glucosamine products in this refractory patient group. The licensed indication does not niche this product.

The mean age of patients in the studies described above ranges from 59 to 66 years. It is not clear if this reflects the Scottish OA population.

Summary of comparative health economic evidence

The manufacturer presented cost-utility ratios for glucosamine compared to placebo for a proposed niche of patients with knee pain who are unresponsive to paracetamol and intolerant of NSAIDs. The analysis was taken directly from the NICE Clinical Guideline for the care and management of osteoarthritis in adults and was a simple piece of economic analysis. It looked only at the costs of glucosamine and one General Practitioner (GP) visit per year. Utility values were estimated by using a regression equation to translate WOMAC scores from the three clinical trials chosen to underpin the economic analysis into utility-based measures. The results suggested a base case cost per QALY ratio ranging from a low of £2,427 through to being dominated by placebo (i.e. more expensive and less effective) depending on the clinical trial data used in the analysis.

There were a number of significant weaknesses with the analysis:

- The cost per QALY ratios that were presented used costs and clinical evidence for glucosamine sulphate rather than glucosamine hydrochloride and as such the manufacturer did not technically present cost–effectiveness evidence for their product;
- The patient population of interest in the economic evaluation was not specifically addressed by the clinical evidence;
- The comparator was placebo but from the feedback from SMC experts, it is likely that other treatment options do exist for this niche of patients e.g. non-drug interventions, low potency opioid/paracetamol combination analgesics, or intra-articular steroid injections;

- The method used to derive utility values could not be properly checked as it is from an as yet unpublished piece of research and the resultant utility values used in the calculations were not presented;
- A weak sensitivity analysis which only examined the impact of adding one extra GP visit per year.

Given these weaknesses, the manufacturer did not present a sufficiently robust economic analysis to gain acceptance by SMC.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: guidelines and protocols

The National Institute for Health and Clinical Excellence (NICE) has just published a clinical guideline for the care and management of osteoarthritis in adults. In this document glucosamine products were evaluated as nutraceuticals. It concluded that the use of glucosamine products is not recommended for the treatment of osteoarthritis. The Guidelines Development Group felt that it would be beneficial to advise people who wanted to trial over-the-counter glucosamine that the only potential benefits identified in early research are purely related to a reduction of pain (to some people, and to only mild or modest degree) with glucosamine sulphate 1500 mg daily. They could also benefit from advice on how to perform their own trial of therapy, that is, to evaluate their pain before starting glucosamine and ensure they review the benefits of glucosamine after three months.

Additional information: previous SMC advice

After review of a full submission, the Scottish Medicines Consortium (SMC) issued advice on 7th March 2003 that etoricoxib (Arcoxia) is recommended for use within NHS Scotland. Its use should be in accordance with guidance issued by the National Institute for Clinical Excellence (NICE) for COX-2 selective NSAIDs in the treatment of OA & RA. Etoricoxib is effective in the symptomatic treatment of osteoarthritis (OA) and rheumatoid arthritis (RA). It is also effective in the treatment of acute gouty arthritis. It should be used for patients at high risk of gastro-intestinal adverse-effects to non-selective NSAIDs. In common with other COX-2 selective NSAIDs, etoricoxib is associated with less gastrointestinal adverse-effects than non-selective NSAIDs, but the relative risks of cardiovascular events in such patients are unclear. There is no evidence that etoricoxib has advantages or disadvantages compared with other COX-2 selective NSAIDs.

After review of an abbreviated submission, the Scottish Medicines Consortium (SMC) issued advice on 9th October 2006 that etoricoxib 60mg, 90mg and 120mg tablets (Arcoxia) are accepted for use in NHS Scotland for the symptomatic relief of osteoarthritis, rheumatoid arthritis and the pain and signs of inflammation associated with gouty arthritis, in patients for whom the use of etoricoxib is appropriate, taking account of current advice on the place in therapy of specific inhibitors of cyclo-oxygenase-2 (COX-2). The new tablet formulation is smaller than the existing formulation at the same cost per dose.

Additional information: comparators

The indication of symptom relief in mild to moderate OA of the knee is common to glucosamine hydrochloride, (although it has the disadvantage not being effective for several weeks after initiating treatment) and to paracetamol and NSAIDs. Therefore these are valid comparators.

Cost of relevant comparators

Drug	Dose regimen	Cost per year (£)
Glucosamine (as hydrochloride)	**Two 625mg tablets once daily.**	**223**
paracetamol	1g up to four times daily	28
NSAIDs		
celecoxib	200mg daily	261
ibuprofen	400 to 600mg three times daily	29 to 54
piroxicam	20mg daily	38
naproxen	250 to 500mg twice daily	19 to 23
diclofenac	25 to 50mg three times daily	16 to 23

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 27th February 2008.

Additional information: budget impact

The manufacturer estimated that the annual drug budget impact of using glucosamine hydrochloride in year one would be £158k in year one rising to £451k in year five. These figures were based on patient numbers of 715 in year one and 2044 in year five with all eligible patients being treated with glucosamine hydrochloride.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

This assessment is based on data submitted by the applicant company up to and including 18 April 2008.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database.

The undernoted references were supplied with the submission. Those shaded grey are additional to those supplied with the submission.

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(8):795-808.

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Reginster JY, Deroisy R, Rovati LC, et. al. Long-term effects of glucosamine sulphate on osteoarthritis progression: a randomised, placebo-controlled clinical trial. Lancet. 2001;357(9252):251-6.

Pavelka K, Gatterova J, Olejarova M, et. Al., Glucosamine sulfate use and delay of progression of knee osteoarthritis: a 3-year, randomized, placebo-controlled, double-blind study. Arch Intern Med. 2002;162(18):2113-23.

Cibere J, Kopec J, Thorne A, et al. Randomized, double-blind, placebo-controlled glucosamine discontinuation trial in knee osteoarthritis, Arthritis Care & Research, Issue:Volume 51(5) p 738-745, 2004

Cochrane Systematic Review: Towheed TE, Maxwell L, Anastassiades TP, et al Glucosamine therapy for treating osteoarthritis, 2005 http://www.thecochranelibrary.com

European Medicines Agency (EMEA) Points to consider on clinical evaluation of medicinal products used in the treatment of osteoarthritis CPMP/EWP/784/97: http://www.emea.europa.eu