Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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Resubmission

glucosamine sulphate 1,500mg powder for oral solution (Glusartel®)

SMC No. (647/10)

Rottapharm Madaus

08 July 2011

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 Scotland. The advice is summarised as follows:

ADVICE: following a resubmission

glucosamine sulphate (Glusartel®) is not recommended for use within NHS Scotland.

Indication under review: relief of symptoms in mild to moderate osteoarthritis of the knee.

In a placebo- and active-comparator study, glucosamine sulphate 1,500mg once daily was significantly better than placebo in the treatment of symptoms associated with osteoarthritis of the knee.

Overall the submitting company did not present a sufficiently robust clinical and 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.

Dosing Information

Glucosamine sulphate 1500mg (as sodium chloride) to be taken once daily. The entire contents of one sachet should be fully dissolved in at least 250ml of water before drinking. If no relief of symptoms is experienced after 2 to 3 months, continued treatment with glucosamine should be re-evaluated.

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

Product availability date

November 2009

Summary of evidence on comparative efficacy

The biosynthesis of glucosamine, an endogenous substance which helps to generate and maintain the thickness and elasticity of synovial fluid in joints and vertebrae, declines with age. Its precise mechanism of action in humans is unknown. Glucosamine, as the sulphate or hydrochloride salt, has been used widely in unlicensed over-the-counter preparations for the treatment of osteoarthritis (OA) and joint pain.

The submitting company has requested that the Scottish Medicines Consortium (SMC) considers the use of this product in a sub-population of the licensed indication, in patients where adequate symptom control has not been achieved with paracetamol and in patients who do not require or cannot tolerate non-steroidal anti-inflammatory drugs (NSAIDs).

One short-term active-comparator study and two three-year placebo-controlled studies have investigated glucosamine sulphate 1,500mg daily in OA. The randomised, placebo- and active-controlled, double-dummy comparator study was conducted in 318 patients with a diagnosis of primary symptomatic knee OA (in one or both knees) according to the clinical and radiographic criteria of the American College of Rheumatology. Enrolment of patients with a body mass index (BMI) > 30kg/m^2 was discouraged. After discontinuation of current symptomatic medication, patients were randomly assigned to glucosamine sulphate 1,500mg once daily, paracetamol 1g three times daily, or placebo, for six months. Ibuprofen 400mg was available as rescue analgesia and its use was recorded in a patient diary.

The primary outcome was the difference in the change from baseline in the Lequesne index after 6 months, in the intent to treat (ITT) population defined as all randomised patients with at least one efficacy assessment after randomisation. The Lequesne index is a disease specific index and consists of 10 questions: five on knee pain, four on knee function in activities of daily living and one on walking distance. A combined disease severity score was calculated, with the

maximum score being 24 and a score greater than 13 indicating extremely severe disease. At six months, mean (± standard deviation [SD]) changes in Lequesne scores were: -1.9 (95% confidence interval [CI]: -2.6 to -1.2), -2.7 (95% CI: -3.3 to -2.1) and -3.1 (95% CI: -3.8 to -2.3), for the placebo, paracetamol and glucosamine sulphate groups, respectively. The improvement was significant only for the comparison between glucosamine and placebo.

Secondary endpoints included the change in Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index (Likert version; normalised to a 0 to 100 scale). This index incorporated five questions on severity of knee pain, 17 on limitation of physical function and two on stiffness. The mean changes in WOMAC scores were -8.2 (95% CI: -11.3 to -5.1), -12.3 (95% CI: -14.9 to -9.7) and -12.9 (95% CI: -15.6 to -10.1) for the placebo, paracetamol and glucosamine sulphate groups, respectively. The improvement was significant only for the comparison between glucosamine and placebo. Rescue medication in all groups was used infrequently with a trend toward a lower number of days of rescue medication use in the glucosamine sulphate and paracetamol groups versus placebo (both 28 days versus 35 days). The number of patients who withdrew from the study was 34/104 (33%), 28/108, (26%) and 28/106 (26%) for the placebo, paracetamol and glucosamine sulphate groups, respectively.

Two three-year randomised placebo-controlled studies with similar designs were conducted in 212 and 202 patients to determine the effect of glucosamine sulphate 1,500mg once daily on joint structure and symptom changes. Rescue medication was permitted and included paracetamol or a NSAID in the first study, and paracetamol in the second study. Although attempts were made to carry out final examinations of patients after three years of treatment, this was not possible in all cases due to non-compliance and withdrawals. Therefore an ITT approach according to a worst-case scenario analysis was performed for those without a final three year assessment. These patients were assigned a poor outcome, corresponding to the final average change recorded in the per protocol completer population in the placebo group.

In the first study, outpatients aged over 50 years with primary knee OA and a BMI ≤ 30kg/m^2 were included. The combined primary outcome was a measure of joint-space narrowing in the signal joint and assessment of symptom modification using the WOMAC OA index (100mm visual analogue scale version with the total score corresponding to the sum of the 24 component item scores i.e. worst total score=2400mm). At baseline, the mean total WOMAC score was 940mm and 1030mm and the mean total joint-space width 5.39mm and 5.23mm for the placebo and glucosamine sulphate groups respectively. The number of patients who withdrew from the study were similar in the two groups (35/106 [33%] and 38/106 [36%] for the placebo and glucosamine sulphate groups respectively. Results for the primary endpoints are included in the table below.

In the second study, conducted in an outpatient centre, patients aged 45 to 70 years with primary knee OA, a Lequesne index score of between 4 and 12 and a BMI ≤27kg/m^2 were recruited. The combined primary outcome was a measure of joint-space narrowing in the signal joint and assessment of symptoms using the WOMAC knee OA index (Likert version; worst score=120) and Lequesne indices (worst score=24). At baseline, the mean total WOMAC score was 30.5 and 30.7, the Lequesne score 8.94 and 8.95 and the mean joint space width was 3.63mm and 3.89mm for the placebo and glucosamine sulphate groups, respectively. The numbers of patients who withdrew were 46/101 (46%) and 35/101 (35%) in the placebo and glucosamine groups, respectively. Results for the primary endpoint are included in the table below.

Table: Primary endpoints (joint-space narrowing and change in symptoms) for the placebo-controlled studies (ITT worst-case scenario population)

Study 1			
Outcome	Placebo (n=106)	Glucosamine sulphate (n=106)	Difference
Mean joint-space change after 3 years (95% CI), mm	-0.31 (-0.48 to -0.13)	-0.06 (-0.22 to +0.09)	0.24 (0.01 to 0.48)
% change in mean total WOMAC index score (95% CI)	+9.8% (-6.2% to +25.8%)	-11.7% (-20.3% to -3.2%)	21.6% (3.5% to 39.6%)
Study 2			
Outcome	Placebo (n=101)	Glucosamine sulphate (n=101)	Difference
Mean joint-space change after 3 years (95% CI), mm	-0.19 (-0.29 to -0.09)	+0.04 (-0.06 to +0.14)	0.23 (0.09 to 0.37)
Change in mean total WOMAC index score (95% CI)	-4.9 (-6.5 to -3.2)	-8.0 (-9.8 to -6.3)	3.1 (0.77 to 5.5)
Change in mean Lequesne index score (95% CI)	-0.82 (-1.1 to -0.51)	-1.7 (-2.2 to -1.2)	0.91 (0.34 to 1.5)

Glucosamine sulphate was significantly superior to placebo for all primary endpoints in both placebo controlled studies. In both studies there were no differences between groups in terms of requirement for rescue medication and there was no apparent relationship between use and change in joint structure or symptom outcomes.

Summary of evidence on comparative safety

In the comparative study, the numbers of adverse events (AE) reported were similar among the three groups; 89, 96 and 95 for the placebo, paracetamol and glucosamine sulphate groups, respectively, and the percentage of patients who withdrew due to AE were 8.6% (9/104), 11% (12/108) and 3.8% (4/106), respectively. Generally, AE were of minor clinical importance. Those that occurred more frequently in the glucosamine sulphate group than the paracetamol or placebo groups included dyspepsia (5 events versus 2 versus 4), gastroenteritis (4 versus 0 versus 2), back pain (7 versus 4 versus 5), neck pain (3 versus 2 versus 0) and fall injuries (5 versus 3 versus 2). In the first placebo-controlled study, AE rates were similar between groups and were generally transient and mild to moderate in severity. Withdrawal due to AE occurred in 17% (18/106) and 20% (21/106) of patients on placebo and glucosamine sulphate respectively and in about a half of cases were related to the gastrointestinal system (mainly abdominal pain and disturbed defaecation). Similar results were observed in the second placebo-controlled study. However, withdrawals due to AE were lower; 10% (10/101) and 7.9% (8/101) of patients on placebo and glucosamine sulphate, respectively.

Summary of clinical effectiveness issues

The submitting company has requested that SMC considers the use of this product in a sub-population of the licensed indication, in patients where adequate symptom control has not been achieved with paracetamol and in patients who do not require or cannot tolerate NSAIDs. No specific evidence has been provided to demonstrate efficacy of glucosamine sulphate in this refractory patient group and there are no studies comparing the product under review with the other licensed glucosamine product.

Unlike paracetamol and NSAIDs, glucosamine sulphate is not indicated for acute pain relief and treatment may take weeks or months to achieve relief of symptoms, especially pain.

There were concerns about the generalisability of the study results to the Scottish OA population eligible for treatment with glucosamine sulphate:

- studies excluded patients with a BMI ≥30kg/m^2 (27kg/m^2 for the third study); however 2008 Government figures estimated that 27% of the Scottish population was obese and this figure was predicted to continue rising.
- the proportion of female patients in the studies was between 76% to 87%.
- in the comparative study the dose of paracetamol was 3g daily, which reflected the maximum licensed dose in Europe but in the UK population the maximum dose of oral paracetamol is 4g/day.
- In the first placebo-controlled study, 51% of patients reported not requiring pharmacological treatment for their OA during the six months prior to study recruitment. Of the remaining patients 24% had received NSAIDs, 15% simple analgesics, 8% both NSAIDs and simple analgesics and 2% steroids. Patients recruited to this study may not be representative of the Scottish population likely to be treated according to the proposed positioning.

In the comparative study the effect size on the primary outcome measure for glucosamine compared with placebo was 0.32. The authors of the published study noted that a similar effect size has been observed with NSAIDs for short term pain relief in OA of the knee. However, effect sizes of 0.2 to 0.50 are considered small and therefore the clinical relevance of the study results is uncertain.

Follow-up of 275, patients, (approximately two thirds of the total recruited to the three-year placebo-controlled studies), was performed to retrospectively assess the incidence of total knee replacement.

The percentage of patients requiring total knee replacement was 6.3% (9/144) and 14.5% (19/131) in patients who had previously received glucosamine sulphate and placebo respectively; relative risk 0.43, (95% CI: 0.20 to 0.92).

According to experts consulted by SMC, many patients self medicate with glucosamine products bought in health food shops or over the counter in pharmacies.

Summary of comparative health economic evidence

The submitting company presented two economic analyses of glucosamine sulphate: a cost-minimisation analysis versus other glucosamine treatments; and a cost-utility analysis versus usual standard of care or placebo. Current standard of care was defined as involving GP visits, outpatients visits, inpatient care if needed, medicine consultations, complementary therapy and X-rays. For both analyses, the patient group of interest was defined as those patients requiring treatment for the relief of symptoms of mild to moderate OA of the knee where adequate symptom control has not been achieved with paracetamol and in patients who do not require or cannot tolerate NSAIDs. The choice of comparator was likely to be reasonable for the subgroup of patients proposed by the manufacturer, and prescribing data would support that there is some use of glucosamine in NHS Scotland. For both economic models a 50 year time horizon was adopted and the models included health states relating to mild/moderate OA, severe OA, and total knee replacement.

The clinical data to support the primary comparison with other glucosamine products was on the basis of assumed clinical equivalence rather than by use of a formal indirect comparison. In the case of the comparison to current standard of care data on patient flows through the health states of the model were taken from the two three- year clinical trials or the follow- up study examining rates of total knee replacement. Utility values were estimated either from mapping WOMAC scores from the study to EQ-5D or from literature values. Resource use and costs were estimated from standard NHS sources but it should be noted that the drug costs for other glucosamine treatments were estimated from Information Services Division (ISD) prescribing data rather than from using the (lower) list price of the alternative licensed glucosamine product.

For the primary comparison with other glucosamine products, the results indicated that glucosamine sulphate was the preferred treatment on cost-minimisation grounds. It was associated with a saving of £700 per patient over the duration of the model. This saving was entirely due to savings in the drug acquisition cost between the two treatments. Sensitivity analysis indicated that if the list price of the alternative licensed glucosamine treatment was used, then the results were cost-neutral.

For the comparison with standard of care/ placebo, the incremental cost per quality adjusted life year gained (QALY) was estimated as £12,402 on the basis of an incremental cost of £1,799 and an incremental QALY gain of 0.15. The QALY gains came from longer periods of time spent in the mild/moderate disease states in the model and the extra costs came from the drug acquisition costs of glucosamine, which were offset to some extent by savings in severe disease state costs and knee replacement costs. Sensitivity analysis indicated that the results for this scenario were most sensitive to the baseline utility score assumed for the mild to moderate disease state, with a cost per QALY of over £40,000 arising when the utility value was reduced by 20%.

Issues relating to the weaknesses associated with the clinical data used within the economic analysis have been raised in the clinical effectiveness section above, and these contribute to uncertainty within the economic analysis. A number of other key limitations should be noted.

- In the comparison with other glucosamine products, demonstration of equivalence with other glucosamine products using a formal indirect comparison was not provided.
- For both analyses, the evidence of effect for glucosamine sulphate is not specifically for

the patient group proposed by the manufacturer.

- For the comparison with other glucosamine products, glucosamine sulphate is only the preferred treatment on cost-minimisation grounds because the company has used ISD prescribing data to estimate the cost of alternative glucosamine treatments rather than using the list price of the other licensed treatment. If the list price of glucosamine hydrochloride had been used, the results would have been cost-neutral.
- Glucosamine was not assumed to be used in the severe OA state, but no further treatment or drug cost was added into the treatment pathway. This may not be realistic but probably does not bias the analysis in favour of glucosamine sulphate.

Given these issues, the economic case has not been demonstrated.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: guidelines and protocols

The National Institute of Health and Clinical Excellence published clinical guideline 59, "Osteoarthritis: the care and management of osteoarthritis in adults" in February 2008. A range of treatments are recommended for treatment of OA and include paracetamol, topical NSAIDs, topical capsaicin, oral NSAIDS (including cyclo-oxygenase [COX]-2 inhibitors), opioids and intra-articular corticosteroid injections. The guideline states that the use of glucosamine or chondroitin products is not recommended for the treatment of osteoarthritis.

Osteoarthritis Research Society International (OARSI) published "Recommendations for the management of hip and knee osteoarthritis, Part II: OARSI evidence-based, expert consensus guidelines" in 2008. The guideline notes the following in relation to glucosamine:

- Treatment with glucosamine and/or chondroitin sulphate may provide symptomatic benefit in patients with knee OA. If no response is apparent within 6 months treatment should be discontinued.
- In patients with symptomatic knee OA glucosamine sulphate and chondroitin sulphate may have structure-modifying effects while diacerein may have structure-modifying effects in patients with symptomatic OA of the hip.

An update to the guideline, published in 2010, noted that a cumulative meta-analysis of randomised controlled trials of glucosamine sulphate from 1981 to 2008 shows a progressive diminution of effect size.

Additional information: comparators

Paracetamol; NSAIDs; cyclo-oxygenase-2 (COX-2) inhibitors and glucosamine hydrochloride (note that SMC has not recommended glucosamine hydrochloride for use in NHS Scotland). Glucosamine, as the sulphate or hydrochloride salt, has been used widely in unlicensed, over-the-counter preparations for the treatment OA and joint pain.

Cost of relevant comparators

Drug	Dose Regimen	Cost per year (£)
Glucosamine sulphate (Glusartel®)	**1,500mg orally once daily**	**223**
Celecoxib	200mg orally once or twice daily	261 to 523
Glucosamine (as hydrochloride) (Alateris®)	1,250mg orally once daily	223
Etodolac	300mg orally twice daily .	93
Dihydrocodeine	30mg orally up to six times daily	up to 64
Tramadol	50 to 100mg orally up to four times daily	up to 63
Naproxen	250 to 500mg orally twice daily	34 to 45
Co codamol 8mg/500mg tablets	Two tablets orally up to four times daily	up to 43
Paracetamol	1g orally up to four times daily	up to 22
Diclofenac	25 to 50mg orally three times daily	16 to 18
Ibuprofen	400mg to 600mg orally three times daily	8.58 to 10

Doses are for general comparison and do not imply therapeutic equivalence. Costs from evadis on 04.05.11. NSAIDs in table are based on those most frequently prescribed in Scotland (ISD data). Costs of NSAIDs do not include gastric protection.

Additional information: budget impact

The submitting company estimated the population eligible for treatment to be 346 patients in year 1 rising to 365 patients in year 5. Based on an estimated uptake of 5% in year 1 and 25% in year 5, the impact on the medicines budget was estimated at £4K in year 1 and £20K in year 5. The net medicines budget impact was estimated at a saving of £1K and £6K in years 1 and 5 respectively. It should be noted that the net medicines budget impact figures assumed the cost of the alternative glucosamine product according to ISD prescribing data rather than the list price of the alternative licensed glucosamine product. Had the list price been used, there would have been a neutral net budget impact.

References

The undernoted references were supplied with the submission.

Herrero-Beaumont G, Ivorra JA, Del Carmen Trabado M, et al. Glucosamine sulphate 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.

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.

Pavelká K, Gatterová J, Olejarová M, et al. Glucosamine sulphate use and delay of progression of knee osteoarthritis: a 3-year, randomized, placebo-controlled, double-blind study. Arch Intern Med 2002;162: 2113-23.

This assessment is based on data submitted by the applicant company up to and including 17 June 2011.

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. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

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.