Glucosamine sulphate 1,500mg powder for oral solution (Glusartel®)
SMC No. (647/10)
Rottapharm Madaus

8 October 2010

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

**Indication under review**: relief of symptoms in mild to moderate osteoarthritis (OA) of the knee.

In an active-comparator study, glucosamine sulphate 1,500mg once daily was superior to placebo in the treatment of symptoms associated with osteoarthritis of the knee.

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
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 over-the-counter preparations for the treatment of osteoarthritis (OA) and joint pain. However the product under review, glucosamine sulphate (supplied as glucosamine sulphate sodium chloride [Glusartel®]), has only recently gained marketing authorisation.

The submitting company has requested that the Scottish Medicines Consortium considers the use of this product in a sub-population of the licensed indication, in patients where paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs) are the pain management modality of choice, but where these are not effective or other factors (e.g. liver function abnormalities, gastrointestinal and cardiovascular risk; long-term treatment) preclude their use.

One short-term active-comparator study and two three-year placebo-controlled studies have investigated glucosamine sulphate 1,500mg daily in OA. The comparator study was of randomised, placebo- and active-controlled, double-dummy design, and conducted in 13 rheumatology referral centres in Spain and Portugal. 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 were included. Enrolment of patients with a body mass index (BMI) > 30kg/m² was discouraged to avoid any bias introduced by this factor. Following a baseline period where current symptomatic medication was discontinued, patients were randomly assigned to glucosamine sulphate (sachet of powder for oral solution) 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 between groups 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

<table>
<thead>
<tr>
<th>Indication</th>
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<td>Relief of symptoms in mild to moderate osteoarthritis (OA) of the knee.</td>
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<table>
<thead>
<tr>
<th>Dosing Information</th>
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<tbody>
<tr>
<td>Glucosamine sulphate 1,500mg once daily.</td>
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| The entire contents of one sachet should be fully dissolved in at least 250ml of water (one glass) before drinking. If no relief of symptoms is experienced after 2 to 3 months, continued treatment with glucosamine should be re-evaluated. |

<table>
<thead>
<tr>
<th>Product availability date</th>
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<tr>
<td>November 2009</td>
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<tr>
<th>Summary of evidence on comparative efficacy</th>
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activities of daily living and one on walking distance. A combined disease severity score was calculated, with the maximum possible score being 24 and a score greater than 13 indicating extremely severe disease. The numbers of patients who withdrew from the study were 34/104 (33%), 28/108, (26%) and 28/106 (26%) for the placebo, paracetamol and glucosamine sulphate groups respectively. Mean (± standard deviation [SD]) Lequesne scores at baseline were 10.8 ± 2.6, 11.1 ± 2.7 and 11.0 ± 3.1 for the placebo, paracetamol and glucosamine sulphate groups respectively. At six months, the mean changes in score 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) respectively. The difference in mean scores between the glucosamine sulphate and placebo groups was significant (mean difference -1.2; 95% CI: -2.3 to -0.8). The difference in mean scores between the paracetamol and placebo groups was not significant (mean difference -0.8; 95% CI: -1.9 to 0.3).

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 (±SD) total WOMAC scores at baseline were 37.9 ± 14.3, 40.4 ± 14.8 and 38.3 ± 15.2 for the placebo, paracetamol and glucosamine sulphate groups respectively. 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) respectively. The difference in mean scores between the glucosamine sulphate and placebo groups was significant; however there was no significant difference between the paracetamol and placebo groups. The use of rescue medication in all groups was low and occurred an average of once in every five to six days. There was 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).

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 (sachet of powder for oral solution) once daily on joint structure and symptom changes. Rescue medication was permitted and included paracetamol or a NSAID from a predefined list in the first study, and paracetamol in the second study; use was recorded in the patient diary. 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, conducted in an outpatient clinic in Belgium, patients aged over 50 years with primary knee osteoarthritis of the medial femorotibial compartment and a BMI ≤ 30kg/m² 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 osteoarthritis index (100mm visual analogue scale version; 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 in the Czech Republic, patients aged 45 to 70 years with primary knee OA, a Lequesne index score of between 4 and 12 and a BMI ≤
were recruited. The combined primary outcome was a measure of joint-space narrowing in the signal joint and assessment of symptoms using the WOMAC osteoarthritis (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)

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

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 reported were similar between 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 adverse events were 8.6% (9/104), 11% (12/108) and 3.8% (4/106), respectively. Generally, adverse events 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). Abnormalities in transaminases and gamma
Glutamyl transferases were found in more patients on paracetamol (21) than glucosamine sulphate (2) or placebo (6) and resulted in study withdrawal for two patients (on paracetamol and placebo) who had elevated levels at baseline. During the study period serum glucose levels were practically unaltered in patients on paracetamol and glucosamine sulphate.

In the first placebo-controlled study adverse event rates were similar between groups and were generally transient and mild to moderate in severity. Withdrawal due to adverse events 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 (GI) system (mainly abdominal pain and disturbed defaecation). Similar results were observed in the second placebo-controlled study. However, withdrawals due to adverse events 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 the Scottish Medicines Consortium considers the use of this product in a sub-population of the licensed indication, in patients where paracetamol and NSAIDs are the pain management modality of choice, but where other factors (e.g. inadequate efficacy, liver function abnormalities, gastrointestinal and cardiovascular risk; long-term treatment) preclude their use. No specific evidence has been provided to demonstrate efficacy of glucosamine sulphate in this patient group.

There were concerns about the generalisability of the study results to the Scottish OA population eligible for treatment with glucosamine sulphate: all studies restricted inclusion or excluded patients with a BMI greater than 30kg/m\(^2\) (and 27kg/m\(^2\) for the third study); and the proportion of female patients in the studies was between 76% to 87%. In addition, 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 paracetamol is 4g/day.

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.

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 with no differences in use reported between groups. Patients recruited to this study may not be representative of the Scottish population likely to be treated according to the proposed positioning.

Follow-up of 274 patients 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.
Inconsistent findings have been reported in studies investigating different salts of glucosamine. However a health technology assessment of the effectiveness of glucosamine sulphate or hydrochloride and chondroitin sulphate in modifying the progression of OA of the knee, published in 2009, concluded that “There was evidence that glucosamine sulphate shows some clinical effectiveness in the treatment of OA of the knee.” However, it also noted that “the biological mechanism of glucosamine sulphate [and chondroitin] remains uncertain and, in particular, the proposal that the active substance may be sulphate should be explored further”.

**Summary of comparative health economic evidence**

The manufacturer presented a cost-utility analysis comparing glucosamine sulphate to paracetamol and placebo in patients with OA of the knee over a six month time horizon. The estimate of quality adjusted life years (QALYs) gained was taken from the short-term comparative study with these treatment arms and used a previously published algorithm to convert WOMAC scores measured in the clinical study into HUI (Health Utilities Index) and QALYs. The only costs considered were for prescribing of glucosamine sulphate or paracetamol, and it was assumed that ibuprofen was used as rescue medication. The clinical study was based in Spain and Portugal, and the manufacturer used Spanish costs for the medicines.

Compared to paracetamol, the manufacturer predicted a saving of £8.40 and a gain of 0.01 QALYs per patient over six months. Compared to placebo, glucosamine sulphate cost an additional £31.32; the QALY difference was not explicitly stated but appears to be 0.04. The only sensitivity analysis provided was a probabilistic analysis based on bootstrapping, which was reported to show a 79% chance that glucosamine dominated paracetamol.

Key weaknesses were as follows:

- Confusion over the role of the medicine and hence of the comparator – in the economic evaluation paracetamol was the comparator but in the budget impact estimate it was glucosamine-containing products. In the clinical effectiveness section of the submission the manufacturer proposes use in patients for whom paracetamol or NSAIDs are the treatment of choice but their use is precluded. The use of paracetamol as a comparator in the economics case does not reflect this positioning.
- Basing the analysis on a single study when other clinical evidence on both glucosamine sulphate and paracetamol is available.
- The medicines costs used were from Spain and seem very different to those in Scotland. In a revised analysis in response to questions from the SMC, the manufacturer predicted a saving of £144 for glucosamine sulphate compared to paracetamol using an estimated Scottish cost of £1.49 for 3g per day of paracetamol based on the unweighted average cost of ten different paracetamol preparations (including two parenteral preparations). This ignores the fact that the vast majority of prescribing will use the cheaper forms and the true NHS cost of 3g of paracetamol per day is likely to be around one-tenth of the figure used by the manufacturer.
- The QALY gain reported in a recent health technology assessment was much smaller than the figure suggested by the manufacturer's analysis, which may raise questions about validity of the utility estimates.
- The dose of paracetamol in the clinical study was relatively low.
- Around 20% of patients randomised in the study were excluded from the economic
evaluation because they had some missing data.

- The sensitivity analysis was limited and it was not possible to assess the impact of different medicines costs, nor was it possible to see what differences in inputs would change the conclusion.

As a result of these limitations the economic case made was not sufficiently robust 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 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, COX-2 inhibitors and glucosamine hydrochloride (note that SMC has not recommended glucosamine hydrochloride for use in NHS Scotland).
## Cost of relevant comparators

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose Regimen</th>
<th>Cost Per Year (£)</th>
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<tbody>
<tr>
<td>Glucosamine sulphate powder for oral solution (Glusartel®)</td>
<td>1,500mg orally once daily</td>
<td>223</td>
</tr>
<tr>
<td>Celecoxib</td>
<td>200mg orally, once or twice daily</td>
<td>261 to 523</td>
</tr>
<tr>
<td>Glucosamine hydrochloride tablets (Alateris®)</td>
<td>1,250mg orally once daily</td>
<td>223</td>
</tr>
<tr>
<td>Piroxicam</td>
<td>20mg orally once daily</td>
<td>128</td>
</tr>
<tr>
<td>Naproxen</td>
<td>250mg to 500mg twice daily</td>
<td>42 to 54</td>
</tr>
<tr>
<td>Paracetamol</td>
<td>1g orally up to four times daily</td>
<td>up to 53</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>400mg to 600mg orally three times daily</td>
<td>23 to 50</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>25mg to 50mg orally three times daily</td>
<td>18 to 21</td>
</tr>
</tbody>
</table>

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 3 August 2010. Costs of NSAIDs do not include gastric protection.

## Additional information: budget impact

The manufacturer assumed that all patients currently prescribed a glucosamine-containing product would switch to glucosamine sulphate with an associated saving in the medicines budget. The estimates of usage were based on English prescribing data and both the daily cost of glucosamine sulphate and its proposed positioning differed in the budget impact estimates from that in the economic evaluation. Given these issues, the budget impact savings estimated by the manufacturer are not reliable.
References

The undernoted references were supplied with the submission.

treatment of knee osteoarthritis symptoms: a randomized, double-blind, placebo-controlled

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

supplements in slowing or arresting progression of osteoarthritis of the knee: a systematic
review and economic evaluation. Health Technol Assess 2009;13 (52).

This assessment is based on data submitted by the applicant company up to and including 17
September 2010.

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.