Public Assessment Report

Glucosamine sulphate 1500 mg powder for oral solution

(Glucosamine sulphate sodium chloride)

PL 20416/0280

Crescent Pharma Limited
LAY SUMMARY
Glucosamine sulphate 1500 mg powder for oral solution (glucosamine sulphate sodium chloride)

This is a summary of the public assessment report (PAR) for Glucosamine sulphate 1500 mg powder for oral solution (PL 20416/0280). It explains how Glucosamine sulphate 1500 mg powder for oral solution was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use Glucosamine sulphate 1500 mg powder for oral solution.

Glucosamine sulphate 1500 mg powder for oral solution will be referred to as Glucosamine sulphate oral solution throughout this report.

For practical information about using Glucosamine sulphate oral solution, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What is Glucosamine sulphate oral solution and what is it used for?
Glucosamine sulphate oral solution is a medicine with ‘well-established use’. This means that the medicinal use of the active substance of Glucosamine sulphate oral solution has been well-established in the European Union (EU) for at least ten years, with recognised efficacy and an acceptable level of safety.

Glucosamine sulphate oral solution is used to relieve symptoms of mild to moderate osteoarthritis of the knee.

How does Glucosamine sulphate oral solution work?
Glucosamine sulphate oral solution contains the active substance glucosamine sulphate (as glucosamine sulphate sodium chloride), which belongs to a group of medicines called non-steroidal anti-inflammatory and anti-rheumatic agents. This active substance is a naturally occurring chemical within the body, where it is present within the joint connective tissue. The mechanism by which this active substance exerts anti-inflammatory and anti-rheumatic action in the human body is not fully understood.

How is Glucosamine sulphate oral solution used?
Glucosamine sulphate oral solution is taken by mouth. The powder from the sachet should be dissolved in a glass of water before drinking the solution.

The dose in adults, including the elderly, is 1 sachet (1500 mg) of glucosamine sulphate daily. Glucosamine is not used 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 the symptoms do not get better after 2-3 months, a doctor or pharmacist should be consulted as other treatments may need to be considered.

Glucosamine sulphate oral solution should not be used in children and adolescents below the age of 18 years.

Please read Section 3 of the PIL for detailed information on dosing recommendations, the route of administration, and the duration of treatment.

Glucosamine sulphate oral solution can only be obtained with a prescription.
What benefits of Glucosamine sulphate oral solution have been shown in studies?
As glucosamine sulphate sodium chloride is a well-known active substance, and its use in the relief of symptoms in mild to moderate osteoarthritis of the knee is well-established, the applicant presented data from the scientific literature. The literature provided confirmed the efficacy and safety of glucosamine sulphate sodium chloride for the proposed indication.

What are the possible side effects of Glucosamine sulphate oral solution?
Like all medicines, this medicine can cause side effects, although not everybody gets them.

For the full list of all side effects reported with Glucosamine sulphate oral solution, see section 4 of the package leaflet.

For the full list of restrictions, see the package leaflet.

Why is Glucosamine sulphate oral solution approved?
The MHRA decided that the benefits of Glucosamine sulphate oral solution are greater than its risks and recommended that it be approved for use.

What measures are being taken to ensure the safe and effective use of Glucosamine sulphate oral solution?
A risk management plan has been developed to ensure that Glucosamine sulphate oral solution is used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics (SmPC) and the patient information leaflet (PIL) for Glucosamine sulphate oral solution, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients and healthcare professionals will be monitored and reviewed continuously as well.

Other information about Glucosamine sulphate oral solution
The Marketing Authorisation for Glucosamine sulphate oral solution was granted in the UK on 01 March 2016.

The full PAR for Glucosamine sulphate oral solution follows this summary.

For more information about treatment with Glucosamine sulphate oral solution, read the PIL or contact your doctor or pharmacist.

This summary was last updated in March 2016.
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I Introduction

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the application for Glucosamine sulphate 1500 mg powder for oral solution (PL 20416/0280) is approvable. This is a prescription-only medicine (POM), indicated for the relief of symptoms in mild to moderate osteoarthritis of the knee.

This application was submitted under Article 10a of Directive 2001/83/EC, as amended, claiming to be an application for a product containing an active substance of well-established use. Therefore the evidence provided to demonstrate the safety and efficacy of this product is bibliographic in nature, which is appropriate for applications of this type.

This medicinal product contains the active ingredient glucosamine sulphate (as glucosamine sulphate sodium chloride). Glucosamine is a naturally occurring amino-monosaccharide within the human body, where it is synthesised from glucose and the amino acid glutamine. It is the normal constituent of the polysaccharide chains of cartilage matrix and synovial fluid glucosaminoglycans. In vitro and in vivo studies have shown glucosamine stimulates the synthesis of physiological glucosaminoglycans and proteoglycans by chondrocytes, and the synthesis of hyaluronic acid by synoviocytes. It has been demonstrated that supply of glucosamine to chondrocytes causes an increased anabolism and an inhibited catabolism, where adjustment upwards or downwards of the cells' mRNA apparently plays an important part. Furthermore, glucosamine is mildly anti-inflammatory, probably also due to an inhibition of the mRNA encoding the expression of various enzymes involved in inflammation. No animal experimental studies on the relation between dose and response are available. Furthermore, the mechanism of action of glucosamine sulfate relevant to symptom modification in human osteoarthritis is unknown.

No new non-clinical or clinical studies were performed for this application, which is acceptable given that this is a bibliographic application for a product containing an active ingredient of well-established use. The retrospective clinical and non-clinical bibliography adequately demonstrates the efficacy and safety, respectively, of the active ingredient in the proposed indication.

The Marketing Authorisation holder has provided adequate justification for not submitting an Environmental Risk Assessment (ERA).

A Risk Management Plan (RMP) and summary of the pharmacovigilance system have been provided with this application, and are satisfactory.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture and assembly of this product.

No new or unexpected safety concerns arose during the review of information provided by the Marketing Authorisation Holder and it was, therefore, judged that the benefits of taking Glucosamine sulphate 1500 mg powder for oral solution outweigh the risks and a Marketing Authorisation was granted.
II QUALITY ASPECTS

II.1 Introduction
This application is submitted according to Article 10a of Directive 2001/83/EC, as amended, claiming to be an application for a product containing an active substance of well-established use.

Glucosamine sulphate 1500 mg powder for oral solution is formulated as a white to slightly yellowish powder in single dose sachets.

Each Glucosamine sulphate 1500 mg powder for oral solution contains 1884 mg of glucosamine sulphate sodium chloride, which is equivalent to 1500 mg to glucosamine sulphate or 1178 mg glucosamine.

The excipients present are citric acid, anhydrous (E330), macrogol 4000, aspartame (E951) and sorbitol (E420).

All excipients comply with their respective European Pharmacopoeia monographs.

None of the excipients are sourced from animal or human origin.

The finished product is packaged in a sachet made of three layered material comprising white Kraft paper, aluminium and low density polyethylene. The pack sizes are 30, 60 or 90 sachets. Not all pack-sizes may be marketed.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components.

II.2 Drug Substance
**Glucosamine sulphate sodium chloride**

INN: Glucosamine sulphate sodium chloride

Chemical name: Bis(2-amino-2-deoxy-D-glucopyranose) sulphate bis (sodium chloride).D-Glucosamine Sulfate 2NaCl.

Structure:

![Glucosamine Structure](image)

Molecular formula: C_{12}H_{28}Cl_{2}N_{2}Na_{2}O_{14}S

Molecular weight: 573.3 g/mol

Appearance: white or almost white, crystalline powder

Solubility: Glucosamine sulphate sodium chloride is freely soluble in water, sparingly soluble in methanol and practically insoluble in acetone.

An Active Substance Master File (ASMF) has been provided by the active substance manufacturer, covering the manufacture and control of the active substance glucosamine sulphate (as glucosamine sulphate sodium chloride).
Synthesis of the drug substance from the designated starting materials has been adequately described, and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant certificates of analysis.

Appropriate proof-of-structure data have been supplied for the active pharmaceutical ingredient. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specification. This specification is in-line with the European Pharmacopoeia monograph for glucosamine sulphate sodium chloride.

Satisfactory Certificates of Analysis have been provided for all working standards. Batch analyses data are provided that comply with the proposed specification.

Suitable specifications have been provided for all packaging used to contain the active substance. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

II.3 Medicinal Product

Pharmaceutical development

The objective of the development programme was to formulate safe, efficacious, oral solution containing 1500 mg of glucosamine sulphate.

Manufacture of the product

A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results. Process validation data on commercial scale batches have been provided. The results are satisfactory.

Finished Product Specification

The finished product specification is acceptable. The test methods have been described and have been adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for all working standards used.

Stability of the product

Finished product stability studies were performed in accordance with current guidelines on batches of finished product in the packaging proposed for marketing. The data from these studies support a shelf-life of 3 years with no special temperature storage conditions.

Suitable post approval stability commitments have been provided.

II.4 Discussion on chemical, pharmaceutical and biological aspects

There are no objections to the approval of this application from a pharmaceutical point of view.
III  NON-CLINICAL ASPECTS

III.1 Introduction
The pharmacodynamics, pharmacokinetic and toxicological properties of glucosamine sulphate sodium chloride are well known. As this is a widely used, well-known active substance, no new non-clinical data have been supplied and none are required for applications of this type. The non-clinical overview has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier.

III.2 Pharmacokinetic
No new data have been submitted and none are required for applications of this type.

III.3 Pharmacodynamic
No new data have been submitted and none are required for applications of this type.

III.4 Toxicology
No new data have been submitted and none are required for applications of this type.

III.5 Environmental risk assessment (ERA)
Since this product is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.6 Discussion on the non-clinical aspects
No new non-clinical studies were conducted, which is acceptable given that this is a bibliographic application for a product containing active ingredients of well-established use.

There are no objections to the approval of this application from a non-clinical point of view.

IV  CLINICAL ASPECTS

IV.1 Introduction
As glucosamine sulphate sodium chloride is a well-known substance, no new clinical data have been submitted for this application. The applicant’s clinical overview on the clinical pharmacology, efficacy and safety of the product has been written by an appropriately qualified person and is adequate.

IV.2 Pharmacokinetics
The applicant has provided a summary of the known pharmacokinetics of glucosamine, based on literature data. Following oral administration, the oral bioavailability is estimated to be 26%. T<sub>max</sub> is around 8 hours and the elimination half-life is around 70 hours. After intravenous administration, the volume of distribution is 71 ml/kg. 34% is excreted in the urine (1.7% in faeces) and radioactivity was also excreted as [14C]-CO<sub>2</sub> in expired air. Steady state was reached by the second day of administration of a once daily 1500 mg dose of powder for oral solution.

A formal clinical pharmacology programme has not been conducted for glucosamine sulphate. The submitted literature data is sufficient to support this application. There is no data from formal interaction studies, or pharmacokinetics in special patient groups. This is adequately reflected in the summary of the product characteristics (SmPC).

IV.3 Pharmacodynamics
The mechanism of action relevant to symptom modification in human osteoarthritis is unknown.
The submitted literature data is sufficient to support this application.

IV.4 Clinical efficacy
The applicant has submitted bibliographic data from 23 studies and 3 meta-analyses in support of the proposed indication.

A summary of the bibliographic review is presented below.

In line with Guideline on clinical investigation of medicinal products used in the treatment of osteoarthritis (CPMP/EWP/784/97 Rev.1) maintenance of improvement should be evaluated after at least 3 months, when considering modification of symptoms. In addition, it is recommended that only one joint should be investigated as the target joint per study. Taking these factors into account, along with the relevance of the inclusion criteria and studied regimen to the proposed indication and posology, five studies are selected for a more detailed summary below.

Study 1
This was a randomised, placebo-controlled, double-blind trial to investigate the efficacy of glucosamine sulphate (GS) in osteoarthritis (OA) of the knee. 80 patients with OA of the knee were randomised to receive either 500 mg of GS three times a day (t.i.d) or placebo for 6 months. Patients were assessed four times during the study period at 0, 6, 12, and 24 weeks. The primary outcome measure was the visual analogue score (VAS) overall assessment of pain in the affected knee. The WOMAC osteoarthritis index was used to evaluate the functional activity and the McGill pain questionnaire assessed the effective and sensory components of pain. OARSI response criteria for relative and absolute reduction on pain and disability were used to classify the patients. Patients could be classified as responders in two ways: if their percentage reduction in global pain VAS was greater than 45% and there was a minimum absolute reduction of 20 mm, or if their percentage reduction in global pain VAS was less than 45% but greater than 15% and there was a minimum absolute reduction of 10 mm, and the WOMAC function score was greater than 30%.

There were no statistically significant differences in the primary outcome between groups at any time point during the study.

Study 2
This was a double-blind, randomised, placebo-controlled trial investigating the efficacy of GS in OA knee. One hundred and thirty-seven patients who had experienced at least moderate improvement in knee pain after starting to use GS were randomised to maximum 1500 mg GS (equivalent to the dose taken prior to start of study) or placebo daily for 6 months or until disease flare, whichever occurred first. The primary outcome was the proportion of disease flares in each treatment arm, using intent to treat (ITT) 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.

Disease flare was seen in 42% of placebo patients and 45% of glucosamine patients (P=0.76). In the Cox regression analysis, after adjustment for sex, study site and OA radiographic severity, time to disease flare was not significantly different in the GS compared with placebo group. No differences were found in severity of disease flare or other secondary outcomes between placebo and GS patients.

Study 3
The aim of this double-blind, randomised, placebo-controlled trial was to determine whether 3 years of treatment with glucosamine can modify the progression of joint structure and
symptom changes in knee OA. Using ACR criteria, 202 patients were randomised to receive either GS (1500 mg daily) or placebo. Changes in radiographic minimum joint space width (JSW) were measured in the medial compartment of the tibiofemoral joint, and symptoms were assessed using Lequesne’s ISK and WOMAC.

OA was of mild to moderate severity at enrolment, with average JSWs of slightly less than 4mm and a Lequesne’s ISK score of less than 9 points. Progressive joint space narrowing with GS was 0.04mm (95% CI, -0.06 to 0.14) compared to -0.19mm on placebo (95% CI, -0.29 to 0.09) after 3 years, with a significant difference between groups (P=0.001). Fewer patients treated with GS experienced predefined severe narrowing (>0.5mm): 5% vs. 14% (p=0.05). There were significant final differences in favour of GH for the Lequesne’s ISK score (GS -1.7; PL -0.82, P=0.002) and the WOMAC total index (GS -8.0; PL -4.9, P=0.01).

Study 4
This randomised, double-blind placebo-controlled study assessed the effects of GS on the long-term progression of knee OA joint structure changes and symptoms. 212 patients were recruited (ACR criteria) and received either 1500 mg GS daily or placebo for 3 years. Weight bearing, anteroposterior radiographs of each knee in full extension were taken at enrolment and after 1 and 3 years. Mean joint space width (JSW) of the medial compartment of the tibiofemoral joint was assessed by digital image analysis, whereas minimum JSW, i.e. at the narrowest point, was measured by visual inspection with a magnifying lens. OA symptoms were assessed by the WOMAC OA index.

The 106 patients on placebo had progressive joint space narrowing, with a mean joint space loss after 3 years of -0.31mm (95% CI -0.48 to -0.13). There was no significant loss of joint space in the 106 patients treated with GS: -0.06mm (-0.22 to 0.09). As assessed by change in WOMAC scores over the 3 years treatment duration, symptoms worsened slightly in patients on placebo (ITT analysis +9.8%) compared with the improvement after treatment with GS (ITT analysis -11.7%, p=0.02).

Study 5
This randomised double-blind active control study compared the efficacy of GS 500 mg t.i.d with ibuprofen 400 mg t.i.d over 3 months, in patients with temporomandibular joint (TMJ) arthritis. The primary outcome was TMJ pain with function (chewing, talking, yawning, laughing) using a modified VAS. 40 men and 5 women were randomised. 39 patients completed the study and were analysed. 15 (71%) of those on GS, and 11 (61%) of those on ibuprofen responded at day 90, as measured by a 20% improvement in the primary outcome measure. The difference was not statistically significant (p = 0.73).

Meta-analyses
A study evaluated the benefit of glucosamine for knee and/or hip osteoarthritis symptoms using systematic review and meta-analysis. Randomised double-blind placebo-controlled studies of at least 4 weeks duration were considered. The aggregated effect size was 0.44 (95% CI 0.24-0.64). The authors concluded that the trials demonstrate moderate to large effects, but quality issues and likely publication bias suggest that these effects are exaggerated. Nevertheless some degree of efficacy appears probable.

In addition a study reviewed all randomised controlled trials evaluating the effectiveness and toxicity of glucosamine in OA. They included placebo and active-controlled, single or double-blind trials. Collectively, the included trials provided evidence that glucosamine is safe and effective in osteoarthritis.
A literature study assessed structural and symptomatic efficacy of oral GS in knee osteoarthritis using meta-analysis. The authors concluded that there was highly significant efficacy for all outcomes including joint space narrowing and WOMAC.

The dossier includes literature reports of 5 studies conducted in line with the Guideline on clinical investigation of medicinal products used in the treatment of osteoarthritis (CPMP/EWP/784/97 Rev.1), i.e. of duration greater than 3 months, investigating one target joint, using relevant regimens. Four out of 5 studies investigate knee OA only. Only study 3 and 4 provided evidence of superiority of glucosamine relative to placebo. These were both 3 year placebo-controlled trials with appropriate inclusion criteria and relevant endpoints. Results are significant for the WOMAC scale, providing some evidence of efficacy for the relief of symptoms in mild to moderate osteoarthritis of the knee. The report of a study of TMJ OA (study 5) does not provide adequate evidence of efficacy, as there is insufficient information to conclude non-inferiority to ibuprofen. The meta-analyses also provided supportive evidence of efficacy.

In conclusion, the submitted literature studies provide evidence of efficacy to support an indication for the relief of symptoms in mild to moderate osteoarthritis of the knee, at a dose of 1500 mg daily.

IV.5 Clinical safety

The applicant has provided a review of the safety of glucosamine, based on the available literature.

The tolerability of glucosamine was evaluated in 1208 patients. 12% reported side effects, of which at least 1% reported epigastric pain/tenderness, heartburn, diarrhoea or nausea. The majority of side effects were mild in nature and all were reversible on cessation of treatment. According to a study review, of 1486 patients randomised, 48 (3.2%) reported an adverse reaction, and 7 patients withdrew due to an adverse reaction.

In the two large randomised controlled trials, the majority of patients experienced at least one adverse event. The frequency and pattern of adverse events was comparable to placebo. In another study, abdominal pain, diarrhoea, increased blood pressure and fatigue were the most commonly reported events in the glucosamine arm. A study also showed the most frequent events reported for the glucosamine arm involved the musculoskeletal and connective tissue disorders, the gastrointestinal disorders, hepatobiliary disorders and cardiac disorders.

A literature study reviewed clinical laboratory data from 13 studies, including more than 800 patients treated for an average of 40 weeks. None of the studies reported adverse effects in relation to clinical laboratory measurements.

Clinical pharmacodynamic studies do not indicate an effect of short-term glucosamine administration on glucose metabolism. In clinical trials, there is no evidence of an effect on fasting plasma glucose levels, insulin sensitivity or diabetic control. The 3 year study found no evidence of altered glucose homeostasis.

An interaction between glucosamine and warfarin has been identified from the World Health Organisation (WHO) and Food and Drug Administration (FDA) Medwatch databases, associating concomitant use of glucosamine or glucosamine-chondroitin sulphate and warfarin with altered coagulation manifested by increased International Normalised Ratio (INR), or increased bleeding or bruising. The survey found that in some cases, a decrease in the supplement dosage was followed by a return of the INR to the previous therapeutic range.
Similarly, a decrease in warfarin dosage was also followed by a decrease in INR in one patient who received long-term warfarin therapy. The authors of this database review paper concluded that patients treated with coumarin anticoagulants should therefore be monitored closely when initiating or ending glucosamine therapy.

Conclusion
The most common adverse effects (AEs) are gastrointestinal in nature. The neurological and cardiovascular AEs reported during longer-term studies are likely to reflect concomitant conditions in an elderly population, and occurred with similar frequency in the placebo groups. Section 4.4 of the SmPC contains a warning to monitor patients with impaired glucose tolerance. Section 4.5 of the SmPC includes a warning regarding the risk of interaction with coumarin anticoagulants. Based on the submitted data from the literature, glucosamine sulphate 1500 mg daily via the oral route has an acceptable safety profile.

IV.6 Risk Management Plan (RMP)
The MA holder has submitted an RMP, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Glucosamine sulphate 1500 mg powder for oral solution.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, is listed below:
<table>
<thead>
<tr>
<th>Safety concern</th>
<th>Routine risk minimisation measures</th>
<th>Additional risk minimisation measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interaction with coumarin anticoagulants (e.g. warfarin)</td>
<td>• Proposed text in the SmPC: Section 4.5: “Data on possible drug interactions with glucosamine is limited, but increased INR with coumarin anticoagulants (warfarin and acenocoumarol) has been reported. Patients treated with coumarin anticoagulants should therefore be monitored closely when initiating or ending glucosamine therapy.” • Prescription only medicine.</td>
<td>None proposed</td>
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<tr>
<td>Interaction with tetracyclines</td>
<td>• Proposed text in the SmPC: Section 4.5: “Concurrent treatment with glucosamine may increase the absorption and serum concentration of tetracyclines, but the clinical relevance of this interaction is probably limited.” • Prescription only medicine.</td>
<td>None proposed</td>
</tr>
<tr>
<td>Shellfish allergy</td>
<td>• Proposed text in the SmPC: Contraindication in section 4.3: “Glucosamine sulphate must not be given to patients who are allergic to shellfish, as the active ingredient is obtained from shellfish.”</td>
<td>None proposed</td>
</tr>
<tr>
<td>Safety concern</td>
<td>Routine risk minimisation measures</td>
<td>Additional risk minimisation measures</td>
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<td>Phenylketonuria</td>
<td>• Proposed text in the SmPC: Contraindication in section 4.3: “Glucosamine sulphate must not be given to patients who suffer from phenylketonuria, since it contains aspartame, a source of phenylalanine.”&lt;br&gt;• Prescription only medicine</td>
<td>None proposed</td>
</tr>
<tr>
<td>Use in patients with impaired glucose tolerance or diabetes</td>
<td>• Proposed text in the SmPC: Warning in section 4.4: “In patients with impaired glucose tolerance, monitoring of the blood glucose levels and, where relevant, insulin requirements are recommended before start of treatment and periodically during treatment.”&lt;br&gt;• Prescription only medicine</td>
<td>None proposed</td>
</tr>
<tr>
<td>Off-label use in children and adolescents less than 18 years of age</td>
<td>• Proposed text in the SmPC: Posology and method of administration in section 4.2: “Paediatric population: Glucosamine sulphate should not be used in children and adolescents below the age of 18 years (see 4.4).” Warning in section 4.4: “Glucosamine sulphate should not be used in children and adolescents under the age of 18 years since safety and efficacy have not been established.”&lt;br&gt;• Prescription only medicine</td>
<td>None proposed</td>
</tr>
<tr>
<td>Aggravation of asthma</td>
<td>• Proposed text in the SmPC: Warning in section 4.4: “A report on exacerbated asthma symptoms triggered after initiation of glucosamine therapy has been described (symptoms resolved after withdrawal of glucosamine). Asthmatic patients starting on glucosamine should therefore be aware of potential worsening of symptoms.”</td>
<td>None proposed</td>
</tr>
</tbody>
</table>
### Safety concern | Routine risk minimisation measures | Additional risk minimisation measures
---|---|---
Hypercholesterolemia | • Proposed text in the SmPC:
Listed in section 4.8: “Sporadic, spontaneous cases of hypercholesterolemia have been reported, but causality has not been established.”
• Prescription only medicine. | None proposed

Pregnancy | • Proposed text in the SmPC:
Section 4.6: “Pregnancy
There are no adequate data from the use of glucosamine in pregnant women. From animal studies only insufficient data are available. Glucosamine sulphate should not be used during pregnancy.”
• Prescription only medicine. | None proposed

Lactation | • Proposed text in the SmPC:
Section 4.6: “Breastfeeding
There are no data available on the excretion of glucosamine into human milk. The use of glucosamine during breastfeeding is therefore not recommended as there is no data on the safety for the newborn.”
• Prescription only medicine. | None proposed

Use in patients with impaired renal or liver function | • Proposed text in the SmPC:
Section 4.2: “Use in renal and liver impairment patients:
In patients with impaired renal and/or liver function no dose recommendations can be given, since no studies have been performed (see also section 4.4).”
• Prescription only medicine | None proposed

**IV.7 Discussion on the clinical aspects**
The grant of a Marketing Authorisation is recommended for this application.

**V User consultation**
The applicant has provided a bridging report. The proposed leaflet has been bridged to an approved leaflets Glusartel 1500 mg powder for oral solution (PL 18219/0010) for scientific content and Simvastatin 10 mg, 20 mg & 40 mg Tablets (PL 20416/0153, 0154 and 0155) for house style. This is satisfactory.
VI  Overall conclusion, benefit/risk assessment and recommendation
The quality of the product is acceptable, and no new non-clinical or clinical concerns have been identified. Extensive clinical experience with glucosamine sulphate sodium chloride is considered to have demonstrated the therapeutic value of the compounds. The benefit-risk assessment is, therefore, considered to be positive.
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPCs) and Patient Information Leaflets (PILs) for products granted Marketing Authorisations at a national level are available on the MHRA website.

The approved labelling for Glucosamine sulphate 1500 mg powder for oral solution is presented below:
Glucosamine sulphate 1500 mg powder for oral solution

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Table of content of the PAR update

Steps taken after the initial procedure with an influence on the Public Assessment Report (Type II variations, PSURs, commitments)

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