GLUSARTEL 1500MG POWDER FOR ORAL SOLUTION
PL 19053/0041

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GLUSARTEL 1500MG POWDER FOR ORAL SOLUTION
PL 19053/0041

LAY SUMMARY

On 26th October 2009, the MHRA granted Tenlec Pharma Limited a Marketing Authorisation (licence) for Glusartel 1500mg Powder for Oral Solution.

Glusartel 1500mg Powder for Oral Solution contains glucosamine sulphate (supplied as glucosamine sulphate sodium chloride).
Glucosamine sulphate belongs to a group of medicines called non-steroidal anti-inflammatory and anti-rheumatic agents.
Glusartel 1500mg Powder for Oral Solution is used to relieve symptoms of mild to moderate osteoarthritis of the knee.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits Glusartel 1500mg Powder for Oral Solution outweigh the risks; hence a Marketing Authorisation has been granted.
GLUSARTEL 1500MG POWDER FOR ORAL SOLUTION
PL 19053/0041

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted a marketing authorisation for the medicinal product Glusartel 1500mg Powder for Oral Solution (PL 19053/0041) to Tenlec Pharma Limited on 26th October 2009. This prescription only medicine is used for the relief of symptoms in mild to moderate osteoarthritis of the knee.

This application for Glusartel 1500mg Powder for Oral Solution is submitted as a bibliographic application according to Article 10.a of Directive 2001/83/EC.

The product contains the active substance glucosamine sulphate (supplied as glucosamine sulphate sodium chloride).

Glucosamine is formed in the body from glucose and is one of the principal substrates in the biosynthesis of numerous important sugar-based compounds such as glycosaminoglycans, which forms most of the cartilage tissue, proteoglycans, glycoproteins, and glycolipids. Glucosamine is structurally incorporated into bones, cartilage, tendons, and ligaments. It helps to generate and maintain the thickness and elasticity of synovial fluid in joints and vertebrae. The biosynthesis of glucosamine declines with age. For this reason it has been given in the treatment of degenerative rheumatic disorders such as osteoarthritis.
PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE

Glucosamine sulphate (supplied as glucosamine sulphate sodium chloride)

INN: Glucosamine sulphate (supplied as glucosamine sulphate sodium chloride)

Chemical name: 2-Amino-2-deoxy-D-glucose

Structure: Glucosamine sulphate sodium chloride is a stoichiometric mixture of glucosamine hydrochloride and anhydrous sodium sulphate in the molar ratio 2:1.

Physical form: Crystalline powder

Solubility: Soluble in water

Molecular formula: \( \text{C}_{12}\text{H}_{28}\text{N}_{2}\text{O}_{14}\text{SNa}_{2}\text{Cl}_{2} \)

Molecular weight: 573.31

Glucosamine sulphate sodium chloride is subject to in-house specifications. An Active Substance Master File (ASMF) has been provided covering the manufacture and control of the active substance 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.

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

An appropriate specification is provided for the active substance glucosamine sulphate sodium chloride. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification.

Satisfactory certificates of analysis have been provided for working standards used by the active substance manufacturer and finished product manufacturer.

The specifications and typical analytical test results are provided and are satisfactory.

Satisfactory specifications and certificates of analysis have been provided for all aspects of the container-closure system. A declaration has been provided that the primary packaging complies with current regulations concerning contact with foodstuff.

An appropriate retest period has been proposed based on stability data submitted for the active substance glucosamine sulphate sodium chloride.
DRUG PRODUCT
Other ingredients
Other ingredients consist of pharmaceutical excipients aspartame, sorbitol, citric acid anhydrous and macrogyl 4000. All excipients comply with their relevant European Pharmacopoeia monographs.

With the exception of chitin, none of the excipients used contain material of animal or human origin. Chitin is derived from crustacean shells and is not susceptible to TSE.

Product development
The applicant has provided a suitable product development section. Justifications for the use and amounts of each excipient have been provided and are valid.

Manufacture
A description and flow-chart of the manufacturing method has been provided.

In-process controls are satisfactory based on process validation data and controls on batches of the finished product. Process validation has been carried out on batches of finished product and the results appear satisfactory.

Finished product specification
The finished product specification is satisfactory. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis for all working standards used have been provided and are satisfactory.

Container-Closure System
The product is packaged in a sachet consisting of a three-layered material comprising paper, aluminium and polyethylene.

The product comes in pack sizes of 4 (sample pack), 30 and 90 sachets.

Stability
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 3 years for the product has been set with the storage precautions ‘Do not store above 30°C’ and ‘Store in original package’.

ADMINISTRATIVE
Expert Report
A pharmaceutical expert report has been written by a suitably qualified person and is satisfactory.

Summary of Product Characteristics (SPC)
This is pharmaceutically satisfactory.

Labelling
These are pharmaceutically satisfactory.
Patient Information Leaflet (PIL)
This is pharmaceutically satisfactory.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

MAA Form
This is pharmaceutically satisfactory.

Conclusion
It is recommended that a Marketing Authorisation is granted for this application.
PRECLINICAL ASSESSMENT

This application for Glusartel 1500mg Powder for Oral Solution was submitted as a bibliographic application according to Article 10.a of Directive 2001/83/EC.

1. INTRODUCTION

This is a Marketing Authorisation Application for Glusartel 1500mg powder for oral solution submitted by Tenlec Pharma Ltd through a national procedure. The legal basis for the application is Article 10a of Directive 2001/83/EC.

Glusartel 1500mg powder for oral solution (referred to hereafter as Glusartel) is indicated for the relief of symptoms in mild to moderate osteoarthritis of the knee. Glucosamine Sulphate, the active ingredient of Glusartel, is the sulphate salt of the natural amino-monosaccharide glucosamine which is physiologically present in the human body. In Glusartel, Glucosamine Sulphate is present as Glucosamine Sulphate Sodium Chloride (GSSC).

Glusartel is a powder for oral solution for a once-a-day administration. Each sachet contains Glucosamine Sulphate Sodium Chloride 1884 mg, equivalent to Glucosamine Sulphate 1500mg, or Glucosamine 1178mg. Several medicinal products containing glucosamine are currently authorised within and outside the EU as powder for oral solution, as well as other pharmaceutical forms, such as capsules, tablets and solution for injections.

This assessment report is based on the published non-clinical data submitted by the applicant.

2. GLP aspects

The information presented in the submission was obtained from the published literature and therefore it is not possible to ascertain the GLP status of the studies.

3. PHARMACOLOGY

Introduction

Glucosamine plays an important role in the biochemistry of the cartilage since it forms the polysaccharide chains of the main glycosaminoglycans of the synovial fluid and of the cartilage matrix. A number of in vitro and in vivo studies have been performed to determine the mode of action of GSSC. Table 1 summarizes the findings of the pharmacodynamic studies, on GSSC as they have been reported in several publications.
Table 1

<table>
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<th>Pharmacodynamic properties of Glucosamine</th>
<th>Principal findings</th>
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</thead>
<tbody>
<tr>
<td><strong>In vitro experiments</strong></td>
<td></td>
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</table>
| Anabolic effects                         | • Preferred and essential substrate for the synthesis of glycosaminoglycans and consequently of proteoglycans by the chondrocyte (Rodén L. 1956; Vidal y Plana R.R. et al. 1978)  
  • Stimulates cultured chondrocytes to synthesize proteoglycans (Bassler C. et al. 1992; Bassler C. et al. 1998)  
  • Increases gene expression of the proteoglycans aggrecan and perlecan in human chondrocytes (Jimenez S.A. and Dodge G.R. 1997) |
| Anti-catabolic effects                    | • Inhibits the action of catabolic enzymes such as stromelysin, collagenase, phospholipase A2 and aggrecanase (Piperno M. et al. 2000; Dodge G.R. et al. 1999)  
  • Promotes adhesion of chondrocytes to fibronectin (Piperno M. et al. 1998) |
### Pharmacodynamic properties of Glucosamine

<table>
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<th>Principal findings</th>
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<td><strong>In vitro experiments</strong> (cont.)</td>
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<td>Anti-catabolic effects (cont.)</td>
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<td>- Inhibits the generation of superoxide radicals (Setnikar I. et al. 1991a Setnikar I. et al. 1991b)</td>
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<td>- Inhibits the activity of lysosomal enzymes (Setnikar I. et al. 1991a Setnikar I. et al. 1991b)</td>
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<td><strong>In vivo experiments</strong></td>
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<td>Anti-inflammatory effects</td>
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<td>- Does not inhibit the synthesis of prostaglandins (Setnikar I. et al. 1991a Setnikar I. et al. 1991b)</td>
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<tr>
<td>- Increases PKC production (Piperno M. et al. 1998)</td>
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<td>- Prevents corticosteroid-induced cellular lesions (Raiss R. et al. 1985)</td>
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</table>

### Anabolic effects

**Early pharmacological studies** showed that exogenous glucosamine increases the incorporation of $^{35}$SO4 and of $^3$H-proline into the cartilage (Roden L. 1956; Vidal y Plana R.R. et al. 1978). Furthermore, in the presence of NSAIDs, which block proteoglycan synthesis, glucosamine significantly reduces this inhibition and restores cartilage uptake of $^3$H-proline and $^{35}$SO4 (Vidal y Plana R.R. et al. 1978).

Glucosamine enters the biosynthetic pathway of glycosaminoglycans, enhancing proteoglycans biosynthesis. This effect was also demonstrated in cultured human chondrocytes derived from osteoarthritic cartilage. GSSC added to the cultured medium stimulates chondrocytes to synthesize increased amounts of proteoglycans in a dose-dependent manner. The proteoglycans that are produced are comparable to physiological proteoglycans in terms of molecular size and ability to participate in complex formation with hyaluronic acid (Bassler C. et al. 1992; Bassler C. et al. 1998). This finding has been confirmed with different techniques (Piperno M. et al. 2000; Dodge G.R. et al. 1999) and by gene technology. In studies measuring gene expression of the key cartilage proteoglycans aggrecan and perlecan, GSSC induces a nearly two-fold increase in both aggrecan and perlecan mRNA (Jimenez S.A. and Dodge G.R. 1997).

**Anti-catabolic effects**

GSSC inhibits collagenase, one of the key enzymes in osteoarthritic cartilage destruction. GSSC was also able to inhibit phospholipase A2, an activator of collagenase, resulting in a complete suppression of collagenase activity (Piperno M. et al. 2000).

In studies measuring gene expression, GSSC caused a consistent decrease in levels of stromelysin mRNA. GSSC was also able to reduce the protein levels of the matrix metalloproteases (MMPs) 1 and 3 in human chondrocytes derived from cartilage taken from osteoarthritic knee joints (Dodge G.R. et al. 1999).
Additional *in vitro* experiments have shown that adhesion to fibronectin was substantially reduced in chondrocytes isolated from fibrillated cartilage compared to those isolated from macroscopically normal-appearing osteoarthritic cartilage. GSSC was able to reverse the osteoarthritis-induced reduction in adhesion to fibronectin and the enhancement of chondrocyte adhesion to fibronectin reached statistical significance (Piperno M. et al. 1998). The adhesion to fibronectin was suppressed by inhibitors of protein kinase C (PKC). GSSC significantly increased PKC production (Piperno M. et al. 1998). These data suggest that GSSC is able to modulate favourably important functions in osteoarthritic chondrocytes. GSSC has no effect on the inhibition of prostaglandin synthesis, but is able to inhibit lysosomal enzymes and the generation of superoxide radicals by macrophages (Setnikar I. et al. 1991a). By considering the efficacy vs. the safety ratio, the data from this study suggest that the use of GSSC is more favourable than the NSAID indomethacin.

**In vivo experiments**

*Anti-inflammatory effects*

The anti-inflammatory activity of GSSC was tested in experimental models of sub-acute inflammation, sub-acute mechanical arthritis, immunological reactive arthritis and generalized inflammation, e.g. adjuvant arthritis (Setnikar I. et al. 1991a; Setnikar I. et al. 1991b).

In in vivo experimental inflammatory models, GSSC is able to inhibit the proinflammatory effects of several agents e.g. carrageenin, dextran, formalin and acetic acid. By the contrary, GSSC exerts lesser effects than a NSAID, indomethacin, in the model of subacute granulomatous reactions induced in rats by sponge implantation or croton oil and in models of arthritis induced by kaolin or adjuvant (Setnikar I. et al. 1991b).

*Effects on cartilage metabolism*

The *in vivo* effects of GSSC on chondrocyte metabolism were studied using an ultrastructural chondrocyte test system. In this model, GSSC protects the chondrocytes by preserving their metabolic activity compared to chondrocytes with impaired functions induced by dexamethasone treatment (Raiss R. et al. 1985). The protective effect of GSSC was especially pronounced in the Golgi apparatus, where keratan and chondroitin are sulphated. Exogenous sulphate plays an important role when inorganic sulphate depletion occurs in serum, as is the situation for some NSAIDs and also corticosteroids used in the treatment of osteoarthritis. The effects of glucosamine and sulphate together improved cartilage metabolism and protected chondrocytes against the detrimental effects of dexamethasone.

**Secondary Pharmacodynamics**

The applicant states that published secondary pharmacodynamics studies on GSSC are not available.

**Safety Pharmacology**

No animal safety pharmacology studies have been retrieved from the literature, except for some publications on the effects of glucosamine on glucose metabolism. During continuous administration of GSSC for 3 years to patients with osteoarthritis of the knee (Reginster J.-Y. et al. 2001; Pavelka P. et al. 2002), no safety pharmacology effects of GSSC have been observed. Due to the sodium chloride load (approximately 400mg per dose), a warning for
subjects submitted to a low-salt diet has been introduced in section 4.4 “Special warnings and special precautions for use” of the SmPC of Glusartel 1500 mg powder for oral solution.

Since glucosamine is an aminomonosaccharide, theoretically it may alter glucose metabolism. In fact, a direct source of glucose or, alternatively, exogenous glucosamine may interfere with the hexosamine pathway leading to hyperglycaemia and insulin resistance. The possibility that glucosamine might alter glucose metabolism in humans has been raised following animal studies in which very large, supra-physiological amounts of glucosamine were intravenously infused into animals (Baron D et al 1995; Shankar R et al 1998). Under these conditions glucosamine tended to impair insulin secretion and/or insulin resistance in peripheral tissues. Other animal studies did not find any adverse effect on blood glucose (McNamara et al.1996; Kirker-Head C et al. 2001.), not even in models sensitive to insulin resistance (Echard B et al.2001). The influence of glucosamine on glucose metabolism in humans has been discussed in Clinical Overview. It has been extensively demonstrated that under recommended conditions of use, glucosamine is unlikely to affect glucose metabolism both in normoglycemic (Tannis et al 2004 and in diabetic subjects (Anderson JW et al 2005; Scroggie DA et al. 2003; Yu JG 2003).

Nevertheless, the applicant conservatively proposes a specific warning in section 4.4 “Special warnings and special precautions for use” of the SmPC of Glusartel 1500 mg powder for oral solution for patients with impaired glucose tolerance consisting in a closer monitoring of blood sugar levels at the beginning of treatment, but no restriction for use in these patients is recommended.

**Pharmacodynamic Drug interactions**

No specific drug interaction studies are available; however, due to its intrinsic physico-chemical and pharmacokinetic properties, GSSC is a compound with no potential for pharmacokinetic or other interactions with any other drug. Indeed, in vitro studies (see below) have shown that GSSC does not bind to plasma proteins, including human serum albumin, and cannot therefore displace drugs with an important binding to plasma proteins. Moreover, its metabolic fate as an endogenous compound entering the hexosamine pathway for the biosynthesis of glycosaminoglycans and proteoglycans, or its degradation through the Krebs cycle, in the absence of metabolism via the cytochrome P450 enzyme system, does not account for any possible metabolism-based drug interaction. Absorption or elimination interactions are also unlikely.

**4. PHARMACOKINETICS**

The absorption, distribution, metabolism and excretion (ADME) of glucosamine in the rat and dog are well known (Setnikar I. et al. 1984; Setnikar I. et al. 1986) and were extensively reviewed (Setnikar I. and Rovati L. C. 2001). The review summarizes the published results on the ADME of glucosamine found after administration of GSSC.

Glucosamine is 2-amino-deoxyglucose, with the molecular formula C₆H₁₃NO₅ and molecular weight 179.17. Glucosamine is very soluble in water, sparingly soluble in methanol or ethanol, practically insoluble in ether or chloroform. The pKa is 7.52 at 20°C and 6.91 at 37°C. In vitro, glucosamine does not bind with plasma proteins of man, dog or rat. For these physical properties, glucosamine freely diffuses through biological barriers. Active transport mechanisms of glucosamine are not known.

The ADME profile of glucosamine and GSSC in animals has not been completely elucidated.
due to insufficient specificity and sensitivity of the available assay methods of glucosamine in biological fluids at the time of the pharmacokinetic development of this substance. The limit of quantitation (LOQ) of the available chemical methods is 1-10 µmol/L and is not adequate for reliable ADME investigations after oral administration of glucosamine at therapeutic doses.

Recently, specific and sensitive bioanalytical methods for the determination of unchanged glucosamine in human plasma and urine have been developed (see Clinical Overview).

Most ADME investigations were carried out with $^{14}$C uniformly labelled G ($^{14}$C-G) diluted in GSSC, measuring the radioactivity originating from $^{14}$C-G. The method has a LOQ of between 1 and 10fM and is sufficiently sensitive for quantitative ADME measurements. The method is also able to trace the metabolites of glucosamine, which escape from the specific physical and chemical assays. The pharmacokinetic characteristics of GSSC were studied in rats and dogs. All experiments were performed on male and on female animals. No gender differences were found with regard to the investigated pharmacokinetic parameters.

**Single dose – intravenous administration**

**Rat**

After single i.v. administration to the rat of GSSC of 12.6 mg/kg GSSC traced with 20µCi/kg [$^{14}$C]-glucosamine, the radioactivity in plasma decreased rapidly during the first 30 minutes. In this phase, the plasma radioactivity is probably due to free glucosamine. During this phase, glucosamine was taken in large amounts by the liver; this suggests that the liver is the main organ responsible of the biotransformation of exogenous glucosamine. After 30 minutes, the radioactivity in plasma increased, reaching the peak at the second hour. Then it decreased very slowly, with a $t_\frac{1}{2}$ of 28 hours. In this phase the radioactivity probably originates from plasma proteins, to which the exogenous glucosamine is covalently bound or in which it or its fragments are incorporated. The radioactivity concentration in red cells was much smaller than that in plasma and evidenced a different kinetics. The radioactivity was rapidly incorporated in organs and tissues and retained there for a prolonged time. Notable was the incorporation into the cartilage.

The radioactivity excreted in the expired air as $^{14}$CO$_2$ amounted to half of the administered dose. It occurred mainly during the first 48 hours after administration and represents probably the fraction of G utilised as $-\text{NH}_2$ donor substrate and possibly as source of energy. Almost 40% of the radioactivity was excreted in the urine. The fecal radioactivity was only 2% and was probably due to contamination with urine.

**Dog**

During the first hour after single i.v. administration to the dog of 12.6 mg/kg GSSC traced with 250 μCi/kg [$^{14}$C]-glucosamine, the radioactivity in deproteinized plasma originates probably from unchanged [$^{14}$C]-glucosamine. Then the radioactivity in deproteinized plasma decreases to levels below the LOQ. At the same time the radioactivity appears and increases in the plasma globulins. The lag time of the globulin incorporation is 20 minutes, and the rate constant (ka) is 0.317/ h. *In vitro* glucosamine does not bind with plasma proteins and the globulin-incorporation of radioactivity occurs only after *in vivo* administration of GSSC. The electrophoretic pattern and the kinetics of the incorporation into globulins suggest that the radioactivity is chemically bound to plasma globulins, e.g. by covalent $-\text{O}$-bonds, to the polypeptide chains. It is not of physical nature, as for example, by hydrogen bonds with albumin of several drugs. It is probable that the transport of the i.v. administered
glucosamine to the peripheral tissues occurs largely through the O-linked glucosamine rather than through free unchanged glucosamine, because there is no consistent relationship between the radioactivity in deproteinized plasma with that in the peripheral tissues. Once arrived in the tissues, the O-linked glucosamine can be detached by enzymatic processes and locally utilized. The liver was the organ with the highest concentration of radioactivity. In fact, already after 2 hours, a large amount of radioactivity (45% of the administered dose) was found in the liver, at a concentration 68 times greater than in deproteinized plasma and 11 times greater than in plasma proteins. Significant amounts of radioactivity were found also in the kidneys, responsible for the excretion of free glucosamine. Remarkable is the presence of radioactivity already 2 hours after administration in the articular cartilage, in a concentration 13 times higher than that in deproteinized plasma and 2 times higher than that in plasma proteins. The radioactivity in the cartilage was detectable even 144 hours after administration, although in smaller concentrations than in plasma proteins. The ADME of glucosamine found in dog is consistent with that found after i.v administration of $^{14}$C-glucosamine to the rat.

**Single dose – oral administration**

**Rat**

After single oral administration to the rat of GSSC of 12.6 mg/kg GSSC traced with 20μCi/kg $[^{14}$C]-glucosamine, the radioactivity appeared in plasma already after 15 minutes and reached its peak 4 hours after administration. Then it declined with a $t\frac{1}{2}$ of 18 hours between hour 8 and 48 and of 46 hours after hour 48. The radioactivity disappeared rapidly from plasma. The same applies to tissues. A large amount of the administered radioactivity was observed in the expired $^{14}$CO$_2$ during the first 24-48 hours after administration, i.e. 61% in the first 6 hours. The urine and fecal excretion of radioactivity were small (6% and 5% of the administered dose, respectively) showing the good absorption of glucosamine from the gastrointestinal tract that occurs by simple diffusion. The recovery of radioactivity at 144 hours including the radioactivity found in organs and in the carcass was 98% of the administered dose. The pattern of tissue distribution was similar to that found after i.v. administration.

**Dog**

After single oral administration to the dog of 12.6 mg/kg GSSC traced with 250 µCi/kg $[^{14}$C]-glucosamine, in deproteinized plasma small amounts of radioactivity (4x1000 dpm/ml) appeared 15 min. after administration. The radioactivity increased to a maximum of 18.3 x 1000 dpm/ml at 75 minutes after administration. Then the radioactivity progressively decreased with a $t\frac{1}{2}$ of 4.6 hours. The AUC$_{0-144}$ measured with the trapezoid method was 724,000 h x 1000 dpm/ml. This radioactivity did not originate from free glucosamine, since glucosamine was always below the LOQ (5 µmol/L) and the chromatographic retention time was different from that of glucosamine. In plasma proteins the radioactivity appeared in quantifiable amounts after a lag time of 2 hours. The radioactivity increased to the $C_{max}$ of 141 x 1000 dpm/ml at 24 hours after administration, and disappeared then with a $t\frac{1}{2}$ of 63 hours. The AUC0-144 measured with the trapezoid method was 11,319 h x 1000 dpm/ml. The radioactivity in the electrophoretic strips of plasma sampled 4 and 24 hours after oral administration was spread in the globulin bands, with a peak associated with beta-globulins.

In the red cells the radioactivity reached quantifiable levels of 2.6x1000 dpm/ml 45 minutes after administration and then increased slowly up to 33.5x1000 dpm/ml 72 hours after administration. The radioactivity associated with the red cells is higher than that in deproteinized plasma but is much smaller than that incorporated into the plasma proteins.
The time course was similar to that observed for the plasma proteins. Initially, a large amount of radioactivity was found in the stomach and intestinal contents, which, however decreased rapidly and were very small 24 hours after administration. With regard to the organs, the liver had the highest concentration of radioactivity. Notable amounts of radioactivity were found also in the kidneys, responsible for the excretion of free glucosamine and for fragments of glucosamine. Remarkable is the presence, already 2 hours after administration, of radioactivity in the articular cartilage, in a concentration similar to that in deproteinized plasma. The radioactivity in the cartilage was still detectable 144 hours after administration. The urinary and fecal excretions were almost complete within the first 48 hours after administration. At hour 144, 22.3% of the administered dose was excreted by these routes (9.6% in urine and 12.7% in feces). This amount is 1.6 times smaller than that after i.v. administration. Notable amounts of radioactivity were found as $^{14}$CO$_2$ in expired air, but the experimental setup did not allow quantitative evaluations.

**Repeated dose – oral administration**

**Rat**

In a linearity pharmacokinetic study in the rat after oral administration three doses of GSSC were administered, i.e. 125.6 mg/kg (0.438 mmol/kg), 1256 mg/kg (4.381 mmol/kg) and 3392 mg/kg (11.831 mmol/kg), traced each with 20 µCi $^{14}$C-glucosamine. The three doses correspond approximately to 4.6, 46 and 125 times the daily therapeutic oral dose of GSSC. These very high doses were chosen to detect possible deviations from linear pharmacokinetics. In plasma the pharmacokinetics of radioactivity was linear, indicating that the absorption was not saturated at higher doses. At all doses there was a good recovery of the administered radioactivity (about 95%) in the expired air as $^{14}$CO$_2$, in the faeces and urine. This indicates that in the investigated dose range the disposition of radioactivity was not affected by the increase of doses. The pharmacokinetic of radioactivity was linear also in deproteinized plasma. The radioactivity originates mainly from unchanged glucosamine. The concentrations of radioactivity in liver, kidney and cartilage (of the femoral head) were dose proportional. The greatest concentration was found in the liver, probably reflecting the involvement of this organ in the elimination of glucosamine, mainly by biotransformation. In the kidneys the concentrations of radioactivity were always higher than in those in plasma. Notable was the concentration of radioactivity in the cartilage of the femoral head found already at 0.5 hours after dosing. From the 72 hours onward the radioactivity concentration in the cartilage was higher than that found in plasma indicating that it was incorporated in the macromolecules of the cartilage.

The ADME after oral administration of GSSC in rats repeated daily for 6 days was investigated and the single daily doses used were of 12.6 mg/kg GSSC traced with 20 µCi/kg $^{14}$C-glucosamine. The results confirm that in blood the radioactivity is mainly associated with the plasma proteins where it accumulates reaching the steady-state after the third administration. The t½ calculated from the Cmin accumulation ratio at steady state was 24 hours. The terminal t½ after the last administration was 79 hours, i.e. 2 times longer than the terminal t½ after the single administration.

No qualitative difference in tissue distribution of radioactivity was observed after repeated doses vs. that after single dose. The tissue/plasma radioactive concentration ratio of radioactivity remained similar to that after single dose. At 144 hours after the last administration, the concentration of radioactivity in tissues and organs was 3–5 fold larger than after single dose. In particular in the femoral cartilage it was approximately fourfold greater after repeated doses than after single dose. About 7% of the administered
radioactivity was excreted in the urine and the urinary excretion increased until the third dose. After discontinuation of treatment, the urinary excretion rapidly decreased to small amounts.

It is concluded from the reported results that the ADME features of glucosamine after oral administration of GSSC are the following:

• Glucosamine is practically completely absorbed, as shown by the scarce faecal excretion of radioactivity and by the large recovery of the administered radioactivity in the expired air and in the urine.

• The administered glucosamine is rapidly incorporated in the plasma globulins and in several tissues, including the articular cartilage, where it resides for a substantial time, with an elimination t1/2 of 2-3 days.

• Repeated oral administrations in rat have shown that the steady state in blood is reached after 3 days (peaks) and 4 days (AUCs). A potentially dangerous accumulation of glucosamine in blood or in tissues seems unlikely.

• Glucosamine is excreted mainly as CO2 in the expired air and as parent compound and metabolites in urine. Very scarce is the faecal excretion.

• The ADME profile of glucosamine in the rat and in the dog is very similar to that found in man (see Clinical Overview) showing that the two animal species can be validly used for safety studies.

5. TOXICOLOGY
The single oral administration of high doses of GSSC did not provoke acute neurological, somatic or gastrointestinal symptoms of toxicity. The LD50 observed after oral administration of GSSC was >10000mg/kg (corresponding to 8000mg/kg GS) in the rat and mouse and >7500 mg/kg (corresponding to 6000mg/kg GS) in the rabbit. Death followed sedation was probably due to electrolyte unbalance and osmotic dysquilibrium rather to specific toxicological effects (Setnikar I. et al. 1991a in Module 4, section 4.2.1, pages 59-63).

There is evidence, from the preclinical safety data of the Summary of Product Characteristics of a marketed medicinal product containing G (IPHA Electronic Medicines Compendium in Module 4, section 4.2.3, pages 1-5), that the following toxicological studies have been performed:

• subchronic toxicity studies of 4 weeks in the rabbit by the i. v. route up to 80 mg/kg, in the rat by the oral route up to 240 mg/kg, and in the dog by the i. v. route for 13 weeks up to 300 mg/kg;

• chronic toxicity studies of 52 weeks in the rat with oral doses up to 2700 mg/kg, and of 26 weeks in the dog with oral doses up to 2149 mg/kg;

• embryotoxicity studies in the rat and rabbit by the oral route up to 2500 mg/kg, and fertility studies in the rat by the oral route up to 2149 mg/kg;
• mutagenic potential studies in vitro up to concentration of 5000µg/ml and in vivo up to the oral dose of 1592 mg/kg in the rat and 7160 mg/kg in the mouse.

However, extensive experimental data and results on the above-mentioned studies are lacking. The doses used represent a very large multiple of the daily dose currently used in human therapy. The doses of the active ingredient are expressed in mg/kg of GS.

As reported in the preclinical safety data of the above mentioned Summary of Product Characteristics, the toxicological studies performed with glucosamine sulphate indicate the large safety margin of this drug substance. The maximum tested doses reported have shown no or minimal effects; these were reversible and there was no detectable target organ toxicity.

No published cancerogenesis data are available. However, no concerns on cancerogenesis potential should be arisen for the following reasons:
• Glucosamine is a biological constituent of endogenous compounds;
• according to the available toxicity information, the toxicity of glucosamine after single and repeated dosing studies was extremely low;
• no concerns of mutagenic potential have been reported for glucosamine.

The excipients used in the pharmaceutical form are of consolidate use in medicinal products and do not worsen the toxicity profile of glucosamine.

**6. ENVIRONMENTAL RISK ASSESSMENT**
Glusartel 1500 mg powder for oral solution contains 1884 mg of the active substance Glucosamine Sulphate Sodium Chloride, equivalent to 1500 mg Glucosamine Sulphate or 1178 mg of Glucosamine. The other ingredients are: Aspartame, Macrogol 4000, Citric Acid Anhydrous and Sorbitol.

Glucosamine Sulphate is a salt of the natural amino-monosaccharide Glucosamine which is physiologically present in the human body. Glucosamine derives from glucose and is used for the biosynthesis of proteoglycans, in particular of those of the articular cartilage.

The other ingredients of Glusartel 1500 mg powder for oral solution are of consolidated use in the pharmaceutical industry and comply with EP requirements.

There is no need for an ERA.

**7. SPC**
Section 5.3 is acceptable.

**8. OVERVIEW**
The overview has been written by a suitably qualified person and is satisfactory.

**9. OTHER CONCERNS**
None.
CLINICAL ASSESSMENT

CLINICAL PHARMACOLOGY
No bioequivalence studies have been performed and none are required for this application, as this is a bibliographic application and the active substance glucosamine sulphate, is a well-known, widely used substance.

EFFICACY
No new data has been provided, however a number of clinical studies from literature were discussed:

Study 1
Design: A double-blind, randomised (252 patients), placebo-controlled study using 1500 mg oral glucosamine sulphate or placebo during 4 weeks.
Inclusion: male and female subjects, with uni- or bilateral osteoarthritis of the knee with pain and limitation of motion and symptoms present for at least 6 months, index of severity at least 4 points measured using the Lequesne index.

Lequesne Index: This includes the measurement of pain (5 questions), walking distance (1 question), and activities of daily living (4 questions), with versions available for the hip and knee. Scores for each question are added together to provide a combined disease severity score. Scores of 1–4 are classified as mild osteoarthritis, 5–7 moderate, 8–10 severe, 11–13 very severe, and 14 as extremely severe osteoarthritis.

Results: Fifty-two percent of glucosamine treated patients responded to treatment (defined as an improvement in Lequesne’s index by 3 points) while 37% of placebo-treated patients exhibited such a response.

<table>
<thead>
<tr>
<th>Week</th>
<th>GA</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>10.6 ± 0.4 (4-22)</td>
<td>10.6 ± 0.4 (4-20)</td>
</tr>
<tr>
<td>1</td>
<td>10.0 ± 0.4 (0-26)</td>
<td>10.1 ± 0.4 (2-24)</td>
</tr>
<tr>
<td>2</td>
<td>8.8 ± 0.4 (0-21)</td>
<td>9.3 ± 0.4 (0-24)</td>
</tr>
<tr>
<td>3</td>
<td>7.9 ± 0.4 (0-20)</td>
<td>8.6 ± 0.4 (0-24)</td>
</tr>
<tr>
<td>4</td>
<td>7.4 ± 0.5 (0-21)</td>
<td>8.4 ± 0.4 (0-24)</td>
</tr>
</tbody>
</table>

Safety: glucosamine was well tolerated. Five patients with glucosamine and 8 patients with placebo withdrew from the study. Limited information regarding safety is available from the publication, most adverse events were mild.

<table>
<thead>
<tr>
<th>Condition</th>
<th>GA Adverse events</th>
<th>GA Withdrawals</th>
<th>Placebo Adverse events</th>
<th>Placebo Withdrawals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal disturbances</td>
<td>5</td>
<td>3</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Pruritus or skin reactions</td>
<td>1</td>
<td>0</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Headache</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Circulatory disturbances</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>8</td>
<td>5</td>
<td>13</td>
<td>8</td>
</tr>
</tbody>
</table>
Study 2

**Design:** A double blind, randomised, placebo-controlled study in osteoarthritis (212 patients) using oral glucosamine sulphate 1500 mg per day or placebo for 3 years.

**Inclusion criteria:** males and females over 50 years with primary osteoarthritis of the knee in the medial femoro/tibial compartment, diagnosed according to the clinical and radiological criteria and WOMAC scores. Mean duration of disease was 7.6 and 8.0 years in the glucosamine and placebo group respectively.

**Results:** 71 glucosamine treated and 68 placebo-treated completed the 3 yr. study period. Statistically significant differences were demonstrated for both the mean and minimum joint space narrowing after 3 yrs., but not after 1 yr of treatment (difference between treatment groups for joint space narrowing, mean: 0.24 mm (0.01-0.48); p=0.043 and minimum 0.33 (0.12-0.54); p= 0.003. ITT Similar data were obtained in a per-protocol analysis with p-values 0.038 and 0.002 for the mean and minimum measures respectively. During the placebo treatment there is a progressive narrowing of the joint space while virtually no change were seen during glucosamine treatment.

<table>
<thead>
<tr>
<th>Joint space narrowing</th>
<th>Placebo (n=106)</th>
<th>GA (n=106)</th>
<th>Difference between treatment groups</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (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>
<td>0.043</td>
</tr>
<tr>
<td>Minimum (mm)</td>
<td>-0.40 (-0.56 to -0.24)</td>
<td>-0.07 (-0.22 to 0.07)</td>
<td>0.33 (0.12 to 0.54)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

**Intention-to-treat analysis.**

The difference between groups in WOMAC index after 3 yrs of treatment was 21.6% (3.3-39.6) p=0.02 in favour of glucosamine (ITT). The per-protocol analysis gave a similar result, p=0.016, with a reduction of 24.3% in the glucosamine group.

Statistically significant improvements were also observed for the pain and function subscales (p=0.047 and p=0.02, respectively) in the ITT analysis of these secondary endpoints, while the stiffness subscale did not exhibit any significant differences between the groups.

**Change in total WOMAC index after 3 years of GA treatment versus placebo.**

<table>
<thead>
<tr>
<th>WOMAC total index</th>
<th>Placebo (n=106)</th>
<th>GA (n=106)</th>
<th>Difference between treatment groups</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>% change</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>
<td>0.020</td>
</tr>
</tbody>
</table>

**Safety.**

There were 18 withdrawals in the glucosamine group and 21 withdrawals in the placebo group due to adverse events. These events were judged to be unrelated to the study treatment and attributable to either pre-existing conditions or conditions commonly seen in the elderly population. There were no changes in laboratory tests, except for slight decrease in fasting blood glucose levels.

No changes in glucose homeostasis occurred.
Number of patients with adverse events with an incidence of ≥5% in the study.

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Placebo (n=106)</th>
<th>Placebo (n=106)</th>
<th>GA (n=106)</th>
<th>GA (n=106)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain</td>
<td>18</td>
<td>17</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>8</td>
<td>8</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>11</td>
<td>10</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>Increased blood pressure</td>
<td>15</td>
<td>14</td>
<td>15</td>
<td>14</td>
</tr>
<tr>
<td>Decreased blood pressure</td>
<td>8</td>
<td>8</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>7</td>
<td>7</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Fatigue</td>
<td>7</td>
<td>7</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>Headache</td>
<td>4</td>
<td>4</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Vertigo</td>
<td>3</td>
<td>3</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Neuritis</td>
<td>6</td>
<td>6</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Depressed mood</td>
<td>7</td>
<td>4</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Allergic episode</td>
<td>7</td>
<td>7</td>
<td>4</td>
<td>4</td>
</tr>
</tbody>
</table>

Seasonal/infective upper respiratory tract disorders were reported by 49% (placebo) and 51% (GA) and influenza-like symptoms by 23% (placebo) and 28% (GA).

The GUIDE and GAIT Studies
In the 2 most recent studies, the efficacy results are conflicting: positive in GUIDE study on glucosamine sulphate and negative in GAIT Study on glucosamine hydrochloride. It is to be noted that in GAIT study glucosamine hydrochloride was used and that this study was performed independently of the industry (this study was founded by the National Institutes of Health in United States). Moreover it was performed with a significant number of patients (more than 1500 patients distributed in 5 treatment groups) and was using so-called “pharmaceutical grade” glucosamine.

The placebo-controlled clinical study (GAIT study) available for glucosamine hydrochloride failed to show a statistically significant effect on symptoms of osteoarthritis of the knee.

The applicant has also submitted EULAR recommendations on knee osteoarthritis published in 2003. Part of the evidence for this paper was based on the earlier published papers for glucosamine and the conclusions of the 2001 Cochrane collaboration meta-analysis. The evidence has changed since these recommendations were published leading to the conclusions cited in the 2005 update to the review (see below).

Meta-analyses.
The clinical summary refers to three meta-analyses, McAlindon (2000), Towheed (2001) and Richy (2003). The McAlindon and Towheed meta-analyses conclude that glucosamine demonstrates efficacy versus placebo in the short term treatment of osteoarthritis, in addition they conclude that more long-term data is required. The Richy meta-analysis concluded that the results support the efficacy of glucosamine on joint space narrowing and WOMAC scores.

SAFETY
No new data has been provided, however studies from literature suggest that adverse events are, in general, mild.

In the referred studies there were fewer withdrawals due to adverse events compared with ibuprofen and the incidences of reported events are similar to those reported during placebo treatment. Gastrointestinal symptoms are the most frequently reported adverse events and varying skin reactions were also reported. Rare events reported in the literature are headache, fatigue, drowsiness, somnolence, vertigo, and depressed mood. Fewer adverse events have
generally been observed during glucosamine treatment than during ibuprofen treatment, primarily due to more frequent gastrointestinal side effects of ibuprofen.

Preclinical data have indicated that glucosamine might affect glucose homeostasis. With the use of euglycaemic hyperinsulinaemic clamps in rats, IV infusions of glucosamine at a rate of 0.1-6.5mg/kg/min during 2 hours, glucose uptake into the skeletal muscle was reduced. Control experiments with galactosamine and mannosamine infusions failed to affect glucose uptake. An effect of glucosamine on GLUT4 translocation was observed, and the authors concluded that glucosamine might induce insulin resistance.

To test whether glucosamine can affect insulin secretion and/or action, an IV glucose tolerance test followed by an euglycaemic insulin clamp during either saline or glucosamine infusion was performed in 10 healthy subjects. Glucosamine did not affect insulin levels or glucose-stimulated insulin secretion but increased fasting blood glucose levels. Furthermore, high glucosamine levels decreased insulin sensitivity. Taken together, glucosamine might exert some diabetogenic effects.

The risk is unknown in clinical practice with oral doses of 1500 mg/day, no cases of altered glucose tolerance or diabetes mellitus has been reported in the published literature. The only long-term study reported slight decreases in fasting blood glucose levels after 3 yrs of treatment, but no information regarding insulin levels was reported.

Until further evidence is available, caution should be exercised in patients with predisposing factors for diabetes mellitus and patients with existing diabetes mellitus should only be treated with careful monitoring of blood glucose and insulin requirements.

Glucosamine is contraindicated in patients with known shell-fish allergy as glucosamine is produced from chitin.

EXPERT REPORTS
The clinical expert report has been written by a suitably qualified person and is satisfactory.

PATIENT INFORMATION LEAFLET (PIL)
This is consistent with that for the reference product and is satisfactory.

LABELLING
These are satisfactory.

APPLICATION FORM (MAA)
This is satisfactory.

SUMMARY OF PRODUCT CHARACTERISTICS (SPC)
This is consistent with that for the reference product and is satisfactory.

DISCUSSION
In view of the outcome of the article 29(4) referral for Glucomed and associated trade names (INN: Glucosamine hydrochloride) with Navamedic ASA as marketing authorisation holder [EMEA/405628/2006 dated 13 December 2006], the benefits of Glusartel 1500mg Powder for Oral Solution outweigh the risks.
MEDICAL CONCLUSION
On the basis of the outcome of the article 29(4) referral for glucosamine it is considered that the grant of a marketing authorisation is recommended for the indication of the relief of symptoms in mild to moderate osteoarthritis of the knee.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The important quality characteristics of Glusartel 1500mg Powder for Oral Solution are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL
The pharmacology, pharmokinetics and toxicology of glucosamine sulphate are well-known. No new or unexpected safety concerns arise from this application.

EFFICACY
Glucosamine sulphate is a well-known drug and has been used for many years. No new or unexpected safety concerns arise from this application.

The SPC, PIL and labelling are satisfactory.

RISK BENEFIT ASSESSMENT
The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The data submitted supports the claim that the applicant’s product is of a well-known substance. Extensive clinical experience with glucosamine sulphate is considered to have demonstrated the therapeutic value of the compound. The benefit/risk for the indication of the relief of symptoms in mild to moderate osteoarthritis of the knee is, therefore, considered to be positive.
GLUSARTEL 1500MG POWDER FOR ORAL SOLUTION
PL 19053/0041

STEPS TAKEN FOR ASSESMENT

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>1</td>
<td>The MHRA received the marketing authorisation application on 5th February 2008.</td>
</tr>
<tr>
<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the application valid on 21st February 2008.</td>
</tr>
<tr>
<td>3</td>
<td>Following assessment of the application, the MHRA requested further information relating to the quality dossier on 6th November 2008. The MHRA requested further information relating to the clinical dossier on 31st March 2008.</td>
</tr>
<tr>
<td>4</td>
<td>The applicant responded to the MHRA’s requests, providing further information on 6th November 2008 for the quality and clinical section.</td>
</tr>
<tr>
<td>5</td>
<td>The application was determined on 26th October 2009.</td>
</tr>
</tbody>
</table>
GLUSARTEL 1500MG POWDER FOR ORAL SOLUTION
PL 19053/0041

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
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</tbody>
</table>
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Glusartel 1500 mg powder for oral solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each sachet contains: 1884 mg glucosamine sulphate sodium chloride, corresponding to 1500 mg glucosamine sulphate or 1178 mg glucosamine.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Powder for oral solution. White, crystalline, odourless powder contained in single-dose sachets.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS
Relief of symptoms in mild to moderate osteoarthritis of the knee.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION
1500 mg glucosamine sulphate (one sachet) to be taken once a day. The entire contents of one sachet should be fully dissolved in at least 250 ml of water (one glass) before drinking.
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 2-3 months, continued treatment with glucosamine should be re-evaluated.

Additional information on special populations
Children and Adolescents
Glusartel is not recommended for use in children and adolescents below the age of 18, due to lack of data on safety and efficacy.

Elderly
No specific studies have been performed in the elderly, but according to clinical experience dosage adjustment is not required when treating otherwise healthy, elderly patients.

Impaired renal and/or liver function
In patients with impaired renal and/or liver function no dose recommendations can be given, since no studies have been performed.

4.3 CONTRAINDICATIONS
Known hypersensitivity to glucosamine or to any of the excipients.
Glusartel must not be given to patients who are allergic to shellfish, as the active ingredient is obtained from shellfish.
Glusartel must not be given to patients who suffer from phenylketonuria, since it contains aspartame, a source of phenylalanine.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE
A doctor must be consulted to rule out the presence of joint diseases for which other treatment should be considered.
In patients with impaired glucose tolerance, monitoring of the blood glucose levels and, where relevant, insulin requirements is recommended before start of treatment and periodically during treatment.
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.
Patients with rare hereditary problems of fructose intolerance should not take this medicine.
One sachet contains 6.6 mmol (151 mg) sodium. To be taken into consideration by patients on a controlled sodium diet.
4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION
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. Concurrent treatment with glucosamine may increase the absorption and serum concentration of tetracyclines, but the clinical relevance of this interaction is probably limited. Due to limited documentation on potential drug interactions with glucosamine, one should generally be aware of altered response or concentration of concurrently used medicinal products.

4.6 PREGNANCY AND LACTATION

Pregnancy
There are no adequate data from the use of glucosamine in pregnant women. From animal studies only insufficient data are available. Glusartel should not be used during pregnancy.

Breast Feeding
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.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
No studies on the effects on the ability to drive and use machines have been performed. If dizziness or drowsiness is experienced car driving and the operating of machinery is not recommended.

4.8 UNDESIRABLE EFFECTS
The most common adverse reactions associated with treatment with glucosamine are nausea, abdominal pain, dyspepsia, diarrhoea and constipation. In addition, headache, somnolence, rash, pruritus and erythema have been reported.

<table>
<thead>
<tr>
<th>Organ System Class</th>
<th>Common from ≥1/100 to ≤1/10</th>
<th>Uncommon from ≥1/1,000 to ≤1/100</th>
<th>Rare from ≥1/10,000 to ≤1/1,000</th>
<th>Very rare ≤1/10,000</th>
<th>Unknown*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune system disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Allergic reaction</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Headache</td>
<td>Somnolence</td>
<td></td>
<td></td>
<td>Visual disturbances</td>
</tr>
<tr>
<td>Eye disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Diarrhoea</td>
<td>Constipation</td>
<td>Nausea</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Flatulence</td>
<td>Abdominal pain</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dyspepsia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Erythema</td>
<td>Pruritus</td>
<td>Rash</td>
<td></td>
<td>Hair loss</td>
</tr>
</tbody>
</table>

* frequency cannot be estimated by the available data
Sporadic, spontaneous cases of hypercholesterolemia have been reported, but causality has not been established.

4.9 OVERDOSE
No case of overdose has been reported.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES
Pharmacotherapeutic group: Other anti-inflammatory and anti-rheumatic agents, non-steroidal anti-inflammatory drugs. ATC code: M01AX05
Glucosamine is an endogenous substance, a 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 of hyaluronic acid by synoviocytes. The mechanism of action of glucosamine in humans is unknown. The period to onset of response cannot be assessed.

5.2 PHARMACOKINETIC PROPERTIES
Glucosamine is a relatively small molecule (molecular mass 179), which is easily dissolved in water and soluble in hydrophilic organic solvents. The available information on the pharmacokinetics of glucosamine is limited. The absolute bioavailability is unknown. The distribution volume is approximately 5 litres and the half-life after intravenous administration is approximately 2 hours. Approximately 38% of an intravenous dose is excreted in the urine as unchanged substance.

5.3 PRECLINICAL SAFETY DATA
D-glucosamine has low acute toxicity. Animal experimental data relating to toxicity during repeated administration, reproduction toxicity, mutagenicity and carcinogenicity is lacking for glucosamine. Results from in vitro studies and in vivo studies in animals have shown that glucosamine reduces insulin secretion and induces insulin resistance, probably via glucokinase inhibition in the beta cells. The clinical relevance is unknown.

6 PHARMACEUTICAL PARTICULARS
6.1 LIST OF EXCIPIENTS
Aspartame
Sorbitol
Citric acid anhydrous
Macrogol 4000

6.2 INCOMPATIBILITIES
Not applicable.

6.3 SHELF LIFE
3 years

6.4 SPECIAL PRECAUTIONS FOR STORAGE
Do not store above 30 °C.
Store in the original package.

6.5 NATURE AND CONTENTS OF CONTAINER
One sachet made of a three-layered material comprising paper, aluminium and polyethylene. Pack-sizes of 4 (sample pack), 30 and 90 sachets. Not all pack-sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Tenlec Pharma Ltd.
Hailsham, Sussex BN27 1PQ
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 19053/0041

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
26/10/2009

10 DATE OF REVISION OF THE TEXT
26/10/2009
2. Before you take Glusartel

Do not take Glusartel:
- if you are allergic (hypersensitive) to glucosamine or to any of the other ingredients (listed in section 6)
- if you are allergic (hypersensitive) to shellfish, as glucosamine is manufactured from shellfish
- if you suffer from phenylketonuria, as Glusartel contains aspartame, a source of phenylalanine.

Take special care with Glusartel
Tell your doctor or pharmacist:
- if you suffer from impaired glucose tolerance. More frequent controls of your blood glucose level may be necessary when starting the treatment with Glusartel
- if you have liver and/or kidney problems
- if you suffer from asthma. When starting on Glusartel, your asthma may get worse.

Important information about some of the ingredients of Glusartel
- This medicine contains sorbitol. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product
- One sachet contains 8.8 mmol (151 mg) sodium. If you have to follow a low-sodium diet, you should take this into account.

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Tell your doctor before taking Glusartel if you are taking any of the following:
- medicines to thin the blood (anticoagulants such as warfarin or acenocoumarol)
- tetracycline antibiotics.

Pregnancy and breast-feeding
Glusartel should not be used during pregnancy.
The use of Glusartel is not recommended during breast-feeding period.
Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
If you experience dizziness or drowsiness while taking Glusartel, you should not drive or operate machinery.

3. How to take Glusartel

Always take Glusartel exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Adults including the elderly
The dose is 1 sachet (1500 mg glucosamine sulphate) daily.
Dissolve the powder from the sachet in a glass of water (250 ml) and drink.
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 your symptoms do not get better after 2-3 months, consult your doctor or pharmacist, as you may need to consider other treatment.
Children and adolescents
Use of Glusartel is not recommended in children and adolescents below the age of 18.

If you take more Glusartel than you should
If you have taken more Glusartel than you should, you must consult your doctor or a hospital.

If you forget to take Glusartel
Take the dose as soon as you remember unless it is nearly time for your next dose. Do not take a double dose to make up for a forgotten dose.

If you stop taking Glusartel
Your symptoms may re-occur.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. Possible side effects
Like all medicines, Glusartel can cause side effects, although not everybody gets them.

Stop taking the solution and contact your doctor or go to the casualty department of your nearest hospital IMMEDIATELY if you have any of the following:
- swelling of the lips, face, tongue or throat
- difficulty swallowing or breathing
- skin rash or hives.

The symptoms above may mean that you are having a serious allergic reaction to this medicine.

The following side effects have been reported:

Common side effects (occurring in less than 1 in every 10 patients):
- stomach pain, indigestion, diarrhoea, constipation, nausea, flatulence
- headache, sleepiness or drowsiness.

Uncommon side effects (occurring in less than 1 in every 100 patients):
- rash, itching, patchy inflammation of the skin.

Other side effects:
Allergic reaction, visual disturbances, hair loss and hypercholesterolemia (increased cholesterol levels in blood) have also been reported occasionally.

If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. How to store Glusartel
Keep out of the reach and sight of children.
Do not use Glusartel after the expiry date which is stated on the carton/container or on sachets.
Do not store above 30°C.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. The measures will help to protect the environment.

6. Further Information
What Glusartel contains
The active substance is Glucosamine sulphate.
1 sachet contains 1884 mg glucosamine sulphate sodium chloride, corresponding to 1500 mg glucosamine sulphate or 1178 mg glucosamine.

The other ingredients are:
Aspartame, Sorbitol, Citric acid anhydrous, Macrogol 4000.

What Glusartel looks like and content of the pack
Glusartel is a white, crystalline, odourless powder contained in single-dose sachets.
Each carton contains 4 (medical samples), 30 or 90 sachets.
Not all pack sizes may be marketed.

Marketing Authorisation Holder
Tenlec Pharma Ltd.
Hailsham
East Sussex BN27 1PQ
United Kingdom

Manufacturer
Sigmar Italia S.p.A.
Via Sombreno, 11
24011 Almé - Italy

Leaflet approved:
GLUSARTEL ▼
1500 mg powder for oral solution
Glucosamine Sulphate

Powder for oral solution, single dose sachet

1 sachet contains:
Glucosamine Sulphate Sodium Chloride
1884 mg equivalent to Glucosamine Sulphate 1500 mg or Glucosamine 1178 mg.

Read the package leaflet before use.
Keep out of the reach and sight of children.
Do not store above 30°C.

Marketing Authorisation nr.: PL 19053/0041

Marketing Authorisation Holder:
Tenlec Pharma Ltd.
Hailsham, East Sussex BN27 1PQ
United Kingdom

Batch n°:  Expiry date:
1 sachet contains Glucosamine Sulphate, Sodium Chloride 1884 mg equivalent to Glucosamine Sulphate 1500 mg or Glucosamine 1178 mg. It contains aspartame (E951) and sorbitol (E420).

Please read the enclosed leaflet.

Oral use.

- Read the package leaflet before use.
- Take as directed by your doctor.
- Keep out of the reach and sight of children.
- Do not store above 30°C.
- The product should not be given to patients who are allergic to shellfish, as the active ingredient is obtained from shellfish.

POM
PL 19053/0041

Marketing Authorisation Holder:
Teslear Pharma Ltd.
Hailsham, East Sussex BN27 1PG
United Kingdom

BAR CODE
UKPAR Glusartel 1500mg Powder for Oral Solution

GLUSARTEL
1500 mg powder for oral solution
Glucosamine Sulphate

GLUSARTEL
1500 mg powder for oral solution
Glucosamine Sulphate

Powder for oral solution, single dose sachet

GLUSARTEL
90 sachets

1 sachet contains:
Glucosamine Sulphate Sodium Chloride 1804 mg equivalent to Glucosamine Sulphate 1500 mg or Glucosamine 1178 mg.
It contains aspartame (E951) and sorbitol (E420).
Please read the enclosed leaflet.

Oral use:
Read the package leaflet before use.
Take as directed by your doctor.
Keep out of the reach and sight of children.
Do not store above 30°C.
The product should not be given to patients who are allergic to shellfish, as the active ingredient is obtained from shellfish.

POM
PL 19053/0041
Marketing Authorisation Holder:
Tensile Pharma Ltd.
Halifax, East Sussex BN27 1PO
United Kingdom
GLUSARTEL
1500 mg powder for oral solution

Glucosamine Sulphate

Powder for oral solution, single dose sachet

4 sachets

Marketing Authorisation Holder:
Tenlec Pharma Ltd.
Hailsham, East Sussex BN27 1PQ
United Kingdom

4 sachets

GLUSARTEL
1500 mg powder for oral solution

GLUSARTEL
1500 mg powder for oral solution

FREE MEDICAL SAMPLE
NOT FOR SALE

PL 19053/0041