

Public Assessment Report

**Glucosamine sulfate 750 mg Film-coated Tablets
PL 36549/0001**

**Glucosamine sulfate 1500 mg Film-coated Tablets
PL 36549/0002**

CF Pharma Limited

LAY SUMMARY

Glucosamine sulfate 750 mg Film-coated Tablets
Glucosamine sulfate 1500 mg Film-coated Tablets
(glucosamine sulfate sodium chloride)

This is a summary of the public assessment report (PAR) for Glucosamine sulfate 750 mg and 1500 mg Film-coated Tablets (PL 36549/0001-0002). (Glucosamine sulfate 750 mg and 1500 mg Film-coated Tablets will be referred to as Glucosamine sulfate 750 mg and 1500 mg tablets throughout this report). It explains how Glucosamine sulfate 750 mg and 1500 mg tablets were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use Glucosamine sulfate 750 mg and 1500 mg tablets.

For practical information about using Glucosamine sulfate 750 mg and 1500 mg tablets, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What are Glucosamine sulfate 750 mg and 1500 mg tablets and what are they used for?

Glucosamine sulfate 750 mg and 1500 mg tablets are medicines with a 'well-established use'. This means that the medicinal use of the active substance of Glucosamine sulfate 750 mg and 1500 mg tablets has been well-established in the European Union (EU) for at least ten years, with recognised efficacy and an acceptable level of safety.

Glucosamine sulfate 750 mg and 1500 mg tablets are used for the relief of symptoms in mild to moderate osteoarthritis of the knee. Osteoarthritis is a type of joint degeneration that causes symptoms such as stiffness (after sleep or long rest) and pain at motion (e.g. when climbing the stairs or walking along uneven surfaces).

How do Glucosamine sulfate 750 mg and 1500 mg tablets work?

Glucosamine sulfate 750 mg and 1500 mg tablets contain the active substance glucosamine sulfate (as glucosamine sulfate sodium chloride), which belongs to a group of medicines called 'anti-inflammatory and anti-rheumatic agents, non-steroidal anti-inflammatory drugs'. 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 are Glucosamine sulfate 750mg and 1500 mg Film-coated Tablets used?

Glucosamine sulfate 750 mg and 1500 mg tablets should be swallowed whole with water. The dosage will depend on the strength of the tablet prescribed. If the patient has been prescribed Glucosamine sulfate 750 mg Film-coated Tablets, one tablet should be taken twice daily or two tablets should be taken once daily. If the patient has been prescribed Glucosamine sulfate 1500 mg Film-coated Tablets, one tablet should be taken once daily.

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

Glucosamine sulfate 750 mg and 1500 mg tablets can only be obtained with a prescription.

What benefits of Glucosamine sulfate 750 mg and 1500 mg tablets have been shown in studies?

As glucosamine sulfate is a well-known 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 sulfate in the relief of symptoms in mild to moderate osteoarthritis of the knee.

What are the possible side effects of Glucosamine sulfate 750 mg and 1500 mg tablets?
Like all medicines, this medicine can cause side effects, although not everybody gets them.

For information about side effects that may occur when using Glucosamine sulfate 750 mg and 1500 mg tablets, please refer to the PIL or the Summary of Product Characteristics (SmPC) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

Why are Glucosamine sulfate 750 mg and 1500 mg tablets approved?

It was considered that the benefits of Glucosamine sulfate 750 mg and 1500 mg tablets outweigh the risks, and the grant of these marketing authorisations was recommended.

What measures are being taken to ensure the safe and effective use of Glucosamine sulfate 750 mg and 1500 mg tablets?

A risk management plan has been developed to ensure that Glucosamine sulfate 750 mg and 1500 mg tablets are used as safely as possible. Based on this plan, safety information has been included in the SmPC and the PIL for Glucosamine sulfate 750 mg and 1500 mg tablets, 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 sulfate 750 mg and 1500 mg tablets

The marketing authorisations for Glucosamine sulfate 750 mg and 1500 mg tablets were granted in the UK on 30 October 2014.

The full PAR for Glucosamine sulfate 750 mg and 1500 mg tablets follows this summary.

For more information about treatment with Glucosamine sulfate 750 mg and 1500 mg tablets, read the PIL or contact your doctor or pharmacist.

This summary was last updated in December 2014.

TABLE OF CONTENTS

I	Introduction	Page 5
II	Quality aspects	Page 6
III	Non-clinical aspects	Page 8
IV	Clinical aspects	Page 9
V	User consultation	Page 14
VI	Overall conclusion, benefit/risk assessment and recommendation	Page 15
	Table of content of the PAR update	Page 26

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 applications for Glucosamine sulfate 750 mg and 1500 mg tablets (PL 36549/0001-0002) could be approved on 30 October 2014. These prescription-only medicines (POM) are indicated for relief of symptoms in mild to moderate osteoarthritis of the knee.

These marketing authorisations have been granted pursuant to Article 10a of Directive 2001/83/EC, as amended, claiming to be applications for products containing an active substance of well-established use. Therefore the evidence provided to demonstrate the safety and efficacy of these products is bibliographic in nature, which is appropriate for applications of this type.

The medicinal products contain the active ingredient glucosamine sulfate (as glucosamine sulfate 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 glycosaminoglycans 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 efficacy studies were performed for these applications, which is acceptable given that these are bibliographic applications for products 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 MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these product types at all sites responsible for the manufacture and assembly of these products.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the Community, the RMS has accepted copies of in-date manufacturing authorisations issued by the inspection services of an EU competent authority.

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

Glucosamine sulfate is a salt of a natural amino-monosaccharide, glucosamine, which is physiologically present in the human body. An Environmental Risk Assessment (ERA) is, therefore, not required.

II Quality aspects

II.1 Introduction

These applications are submitted according to Article 10a of Directive 2001/83/EC, as amended, claiming to be applications for products containing an active substance of well-established use.

Both Glucosamine sulfate 750 mg and 1500 mg tablets are formulated as off-white, oblong-shaped, film-coated tablets; the 750 mg strength tablet having dimensions of 8 x 19 mm, and the 1500 mg strength tablet having dimensions of 9.5 x 21 mm.

Each Glucosamine sulfate 750 mg Film-coated Tablet contains 942 mg of glucosamine sulfate sodium chloride, which is equivalent to 750 glucosamine sulfate.

Each Glucosamine sulfate 1500 mg Film-coated Tablet contains 1884 mg of glucosamine sulfate sodium chloride, which is equivalent to 1500 mg glucosamine sulfate.

The excipients present in the tablet are microcrystalline cellulose 101, microcrystalline cellulose 102, lactose monohydrate, pregelatinised maize starch, crospovidone, stearic acid and poly(vinyl) alcohol. The excipients present in the Opadry white film-coating are titanium dioxide (E171), talc (E553b), lecithin soya (E322) and Macrogol 3350.

Glucosamine sulfate 750 mg and 1500 mg tablets are each presented in either polyvinylidene-coated, polyvinylchloride/aluminium foil blisters or high-density polyethylene containers fitted with a tamper-evident, high-density polyethylene screw cap.

Glucosamine sulfate 750 mg Film-coated tablets are available in pack sizes 8, 10, 12, 14, 20, 28, 30, 56, 60, 112, 120, 168, 180, 336 and 360 film-coated tablets.

Glucosamine sulfate 1500 mg Film-coated tablets are available in pack sizes of 7, 10, 14, 20, 21, 28, 30, 56, 60, 84, 90, 168 and 180 film-coated tablets.

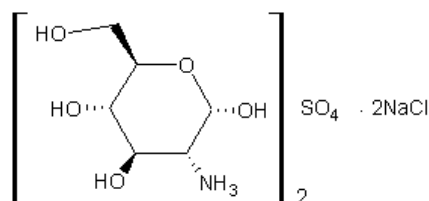
II.2 Drug Substance

Glucosamine sulfate sodium chloride

INN: No INN has been specifically assigned for glucosamine sulfate sodium chloride

Chemical name: Bis(D-Glucose, 2-amino-2-deoxy-), sulfate sodium chloride complex;
Bis(2-Amino-2-deoxy-β-D-glucopyranose) sulfate sodium chloride complex (-,-) ;
D-Glucosamine Sulfate 2NaCl.

Structure:



Molecular formula: $(\text{C}_6\text{H}_{14}\text{NO}_5)_2\text{SO}_4 \cdot 2\text{NaCl}$

Molecular weight: 573.3 g/mole

Appearance: white or almost white, crystalline powder
Solubility: freely soluble in water, sparingly soluble in methanol, 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 sulfate (as glucosamine sulfate 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 specifications. This specification is in-line with the European Pharmacopoeia monograph for glucosamine sulfate sodium chloride.

Satisfactory certificates of analysis have been provided for all working standards. Batch analysis data are provided and 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 was to develop tablets that meet the basic pharmaceutical requirements of a tablet and are suitable for a daily supplement of 1500 mg of Glucosamine sulfate.

All the excipients used in the manufacture of the proposed formulation, other than the film-coating, comply with their respective European Pharmacopoeial monographs. The Opadry white film-coating complies with a satisfactory in-house specification.

None of the excipients are sourced from animal or human origin, except for lactose monohydrate. A declaration has been provided by the supplier of lactose stating that the lactose used in the manufacture of lactose monohydrate is of animal origin and is derived from milk that has been collected from healthy animals in the same way as milk for human consumption. This satisfies the requirements of the Note for Guidance (NfG) on the reduction of transmission of spongiform encephalopathy (EMA/410/01 rev.3), which is acceptable.

No genetically modified organisms (GMO) have been used in the preparation of these products.

Manufacture of the products

Satisfactory batch formulae have been provided for the manufacture of both strengths of product, along with an appropriate account of the manufacturing process. Suitable in-process controls are in place to ensure the quality of the finished products.

The manufacturing process has been validated and has shown satisfactory results.

Finished Product Specifications

The finished product specifications are acceptable. Test methods have been described and have been adequately validated. Batch data have been provided and comply with the release specifications. Certificates of analysis have been provided for all working standards used.

Stability of the products

Stability studies were performed in accordance with current guidelines on batches of both strengths of finished product, in the packaging proposed for marketing. The data from these studies support a shelf-life of 3 years for both the blister packaging and the tablet container. Additionally, after first opening of the tablet container the medicinal product should be used within 6 months. The data also support special storage conditions for both strengths of "Store in the original package in order to protect from moisture" and "This medicinal product does not require any special temperature storage conditions".

Suitable post approval stability commitments have been provided.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The grant of these marketing authorisations is recommended.

III Non-clinical aspects

III.1 Introduction

The pharmacodynamic, pharmacokinetic and toxicological properties of glucosamine sulfate are well-known. Novel non-clinical information has not been provided on the basis that:

(i) the active ingredient, glucosamine, is a naturally occurring amino-monosaccharide compound in animals and human beings, where it is synthesised from glucose and the amino acid glutamine, and (ii) the retrospective clinical and non-clinical bibliography adequately demonstrates the efficacy and safety, respectively, of the active ingredient in the proposed indications. This justification is acceptable.

The company submitted a bibliographic review of the pharmacodynamics and pharmacokinetics of glucosamine sulphate, which is based on relevant references provided by searching the databases "MEDLINE" and "TOXNET" and the reference sections of reviews. No published animal experimental studies concerning long-term toxicity of glucosamine sulfate are available.

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. An addendum report written by a suitably qualified toxicologist is also included, which contains updated literature since the original non-clinical overview was originally submitted in 2003. This includes updated papers concerning the genotoxicity of glucosamine.

III.2 Pharmacology

Glucosamine is a naturally occurring compound in animals and human beings where it is included in the synthesis of glycosaminoglycan (GAG) which is a main part of all connective tissue. This also means that the compound is naturally present in animal food. Another consequence is that there is a coincidence between the normal biochemistry of glucosamine and its pharmacodynamics.

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' messenger Ribonucleic Acid (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.

III.3 Pharmacokinetics

No new pharmacokinetic data have been submitted and none are required for an application of this type.

A bibliographic review has summarised the absorption, distribution, metabolism and excretion of glucosamine sulfate in rats and dogs.

III.4 Toxicology

The toxicological assessment of the glucosamine sulfate is based on limited studies, but the presently available experimental studies and the clinical experience indicate that the compound is not toxic. There are no studies to investigate the teratogenicity, but the risk is assessed to be low. An overall assessment of the potential genotoxicity of glucosamine indicates that the risk, if any, is probably very low.

III.5 Ecotoxicity/environmental risk assessment (ERA)

Glucosamine sulfate is a salt of a natural amino-monosaccharide, glucosamine, which is physiologically present in the human body. An Environmental Risk Assessment (ERA) is, therefore, not required.

III.6 Discussion on the non-clinical aspects

Both the non-clinical overview and addendum report are acceptable.

From a non-clinical perspective the SmPCs are acceptable.

In conclusion, these applications are approvable from a non-clinical point of view.

IV Clinical aspects

IV.1 Introduction

Glucosamine sulfate is a well-known substance and the details of its pharmacokinetics are documented in various publicly accessible sources that the applicant has adequately summarised in the clinical overview. The applicant did not conduct any new research or provide any new data. This is acceptable.

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_{max} is around 8 hours and the elimination half-life is around 60 hours.

Pharmacokinetics are linear in the dose range 750 – 1500 mg. After intravenous administration, the volume of distribution is 71 ml/kg. After intravenous administration, 30% is excreted in the urine (< 1% in faeces) and 10-20% as CO₂ by the lungs.

A formal clinical pharmacology programme has not been conducted for glucosamine sulfate. The submitted literature data is sufficient to support these applications. There is no data from formal interaction studies, or pharmacokinetics in special patient groups. This is adequately reflected in the SmPC.

IV.3 Pharmacodynamics

The mechanism of action relevant to symptom modification in human osteoarthritis is unknown.

No studies have been performed to evaluate the relationship between dose and effect. The recommended dose of 1500 mg daily results in a plasma concentration of 100µmol/l in humans, which corresponds to the concentration at which a pronounced effect on proteoglycan synthesis is expected, based on *in vitro* data.

The submitted literature data is sufficient to support these applications.

IV.4 Clinical efficacy

The applicant has submitted bibliographic data from 22 studies, which included a total of 4304 osteoarthritis (OA) patients. A summary of the bibliographic review is presented below.

Randomised controlled studies vs. placebo

The applicant has identified 9 studies up until 2003 in which glucosamine sulfate was compared to placebo using a randomised double-blind design. In all but one, knee OA was investigated. These studies enrolled 1179 patients. The majority of studies included patients with mild or moderate knee OA (grade 3 or below using Kellgren and Lawrence's criteria). The majority of patients were women (60-90%), with mean age ranging 51-66 years. In most studies, glucosamine was given orally, 1500 mg daily. The treatment duration was 4-8 weeks in most studies. In 5 studies, the WOMAC or Lequesne indices were used to assess efficacy.

In 7 out of the 9 studies, a benefit was observed in 55-100% of patients in the glucosamine group, compared to 38-60% of those on the placebo group. In 2 studies, no benefit of glucosamine was observed, compared to placebo. However both studies investigated patients with severe arthritis.

In addition, one randomised double-blind study investigating glucosamine hydrochloride vs. placebo for knee OA was submitted. 58 patients were randomised to glucosamine and 60 to placebo (comprising 64% and 60% women respectively). The disease severity at baseline was not reported. Glucosamine 500 mg TID was compared to placebo over 8 weeks. There was a non-significant trend towards improved results in the active treatment group as measured by WOMAC score.

The results of a randomised, placebo-controlled, three arm, double-blind trial was also reported: 318 patients with moderate/severe knee OA were enrolled and randomised 1:1:1 to

receive oral glucosamine sulphate 1500 mg once daily, paracetamol 3g daily or placebo. The primary efficacy outcome measure was change in Lequesne index after 6 months. Secondary measures included WOMAC and OARSI scores. Glucosamine demonstrated a similar benefit to paracetamol and an improvement over placebo with regard to the Lequesne Score. Similar outcomes were observed for the WOMAC score.

Randomised controlled studies vs. active comparator

The applicant has identified 5 studies in which glucosamine was compared to an active comparator using a randomised, double-blind design. Nearly 500 patients were enrolled. The majority of patients were women (42-89%), with mean age ranging 57-75 years (except the TMJ study). The 3 studies investigating knee OA are the most relevant. However the disease severity at baseline was not reported. In the knee OA studies, glucosamine sulphate 500 mg TID was compared to ibuprofen 500 mg TID for 4-8 weeks. In one study the Lequesne index was used as an efficacy endpoint. The remaining studies used objective and subjective parameters such as pain, swelling and range of movement.

Two studies showed no significant difference between glucosamine and ibuprofen. One further study demonstrated increased benefit for glucosamine compared to ibuprofen.

Non-double-blind studies

The applicant has identified 8 studies including 2632 evaluable patients, in which the design was not double-blind. Of the 2 studies investigating only the knee joint, one compared intra-articular glucosamine sulphate with glycosaminoglycan polysulfate, and the other was single-arm.

Summary of applicant's bibliographic review

According to the 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 two long-term studies conducted against placebo, there was some evidence of superiority to placebo over 3 years as measured by WOMAC score / Lesquesne Index. In addition, a further study provided some evidence of efficacy at 6 months, which is comparable to paracetamol 3g/daily.

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

IV.5 Clinical safety

In all submitted literature, the frequencies of adverse events (AEs) were reported as low and comparable to placebo. In the active controlled studies, the frequencies of AEs were lower in the glucosamine groups compared to ibuprofen. The Applicant has provided a summary of AEs by SOC, from 10 studies ($n=687$) in which sufficient details were provided:

83 out of 303 listed side-effects were reported during a long-term study, including 21 out of 25 reported cardiovascular effects and 31 out of 51 reported neurological effects. There was no difference in frequency compared to placebo for the total AEs, and for the SOCs of gastrointestinal, neurological and cardiovascular effects, in this study.

A possible connection has been reported in one study between glucosamine sulphate and renal insufficiency in a 79 year old woman with knee OA and myasthenia gravis, who was also treated with cyclosporin and methylprednisolone.

In a separate study a probable case of asthma exacerbated by the use of a glucosamine-chondroitin sulphate supplement was reported in a patient with underlying intermittent asthma, who may have had a sea squirt allergy.

In non-clinical studies, parenteral administration of glucosamine has been associated with increased insulin resistance. A study in humans provided evidence of changes in glucose uptake by cells following glucosamine infusion in patients with hyperglycaemia, but not euglycaemia. There is no evidence of altered glucose metabolism following oral administration in humans, even long-term.

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.

Summary of applicant's bibliographic review

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 between warfarin and glucosamine. Based on the submitted data from the literature, glucosamine sulfate 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 sulfate 750 mg and 1500 mg tablets.

Summary table of safety concerns as approved in RMP

Summary of safety concerns	
Important identified risks	<ul style="list-style-type: none"> • Interaction with coumarin anticoagulants (e.g. warfarin) • Interaction with tetracyclines • Use in patients with impaired glucose tolerance or diabetes • Shellfish allergy • Soya or peanut or other ingredient allergies • Use in patients on a controlled sodium diet
Important potential risks	<ul style="list-style-type: none"> • Off-label use in children and adolescents less than 18 years of age • Worsening of asthma symptoms • Hypercholesterolemia
Missing information	<ul style="list-style-type: none"> • Safety data in pregnant women • Safety data with breast feeding • Use in patients with impaired renal or liver function

Summary of safety concerns and planned risk minimisation activities as approved in RMP

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Important Identified Risks		
Interaction with coumarin anticoagulants (e.g. warfarin)	Interactions stated in section 4.5 of the SmPC and section 2 of the PIL.	Not Applicable
Interactions with Tetracyclines	Interaction stated in section 4.5 of the SmPC and section 2 of the PIL.	Not Applicable
Use in patients with Impaired glucose tolerance or diabetes	Special warnings in section 4.4 of the SmPC and section 2 of the PIL. Interaction stated in section 4.5 of the SmPC. Adverse drug reactions listed in section 4.8 of the SmPC and section 4 of the PIL.	Not Applicable
Shellfish Allergy	Contraindication in section 4.3 of the SmPC and section 2 of the PIL.	Not Applicable
Soya or peanut or other ingredients allergies	Contraindication in section 4.3 of the SmPC and section 2 of the PIL.	Not Applicable
Use in patients on a controlled sodium diet	Special warning presented in section 4.4 and section 2 of the PIL.	Not Applicable
Important Potential Risks		
Off Label use in children and adolescents less than 18 years of age	Information regarding posology and limitation of knowledge in paediatric and	Not Applicable

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
	adolescents population presented in section 4.2.	
Worsening of asthma symptoms	Special warning presented in section 4.4 and section 2 of the PIL. Adverse drug reactions listed in section 4.8 of the SmPC and section 4 of the PIL.	Not Applicable
Hypercholesterolemia	Special warning presented in section 4.4 and section 2 of the PIL. Adverse drug reactions listed in section 4.8 of the SmPC and section 4 of the PIL.	Not Applicable
Missing Information		
Safety during pregnancy	Summary information relevant to pregnancy in section 4.6	Not Applicable
Safety during breast feeding	Summary information relevant to breast feeding in section 4.6	Not Applicable
Use in patients with impaired Renal and/or liver function	Information regarding The limitation of knowledge with patients with renal and liver function stated in section 4.2 of the SmPC and Section of 2 of the PIL.	Not Applicable

IV.7 Discussion on the clinical aspects

The grant of marketing authorisations is recommended for these applications.

V User consultation

A user consultation with target patient groups on the PIL has been performed on the basis of a bridging report making reference to Glucosamine 750mg Film-Coated Tablets (PL 40096/0002) and Glucosamine 1500mg Film-Coated Tablets (PL 40096/0003; IE/H/245/01-03/MR). The bridging report submitted by the applicant is acceptable.

VI Overall conclusion, benefit/risk assessment and recommendation

The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. These applications include an adequate review of published non-clinical and clinical data concerning the safety and efficacy of glucosamine sulfate. Glucosamine sulfate is a well-known active substance with established efficacy and tolerability. The proposed indication and posology wording is identical to that of glucosamine products previously approved and marketed in the UK. The benefit/risk assessment is, therefore, considered to be positive.

The summaries of product characteristics (SmPC), patient information leaflet (PIL) and labelling are satisfactory and in-line with current guidelines. In accordance with Directive 2012/84/EU, the current approved UK versions of the SmPCs and PILs for these products are available on the MHRA website.

The currently approved labels are listed below:

Glucosamine sulfate 750mg Film-coated Tablets

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND IMMEDIATE PACKAGING

LABELLING FOR CONTAINER CARTON AND CONTAINER

1. NAME OF THE MEDICINAL PRODUCT

Glucosamine sulfate 750mg Film-coated Tablets
Glucosamine sulfate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 942 mg glucosamine sulfate sodium chloride equivalent to 750 mg glucosamine sulfate or 589 mg glucosamine.

3. LIST OF EXCIPIENTS

Excipients: also contains sodium, soya lecithin and lactose monohydrate. See leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

8 Film-Coated Tablets
10 Film-Coated Tablets
12 Film-Coated Tablets
14 Film-Coated Tablets
20 Film-Coated Tablets
28 Film-Coated Tablets
30 Film-Coated Tablets
56 Film-Coated Tablets
60 Film-Coated Tablets
112 Film-Coated Tablets
120 Film-Coated Tablets
168 Film-Coated Tablets
180 Film-Coated Tablets
336 Film-Coated Tablets
360 Film-Coated Tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use. Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture.
Once opened the tablets should be used within 6 months.
Use by

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

CF Pharma Ltd., The Racecourse, Danesfort, Kilkenny, Ireland

12. MARKETING AUTHORISATION NUMBER(S)

PL 36549/0001

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

The tablets should be swallowed whole with water.

16. INFORMATION IN BRAILLE

Glucosamine sulfate 750mg tablets

17. OTHER PARTICULARS TO APPEAR ON THE OUTER PACKAGING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND IMMEDIATE PACKAGING

LABELLING FOR BLISTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Glucosamine sulfate 750mg Film-coated Tablets
Glucosamine sulfate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 942 mg glucosamine sulfate sodium chloride equivalent to 750 mg glucosamine sulfate or 589 mg glucosamine.

3. LIST OF EXCIPIENTS

Excipients: also contains sodium, soya lecithin and lactose monohydrate. See leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

8 Film-Coated Tablets
10 Film-Coated Tablets
12 Film-Coated Tablets
14 Film-Coated Tablets
20 Film-Coated Tablets
28 Film-Coated Tablets
30 Film-Coated Tablets
56 Film-Coated Tablets
60 Film-Coated Tablets
112 Film-Coated Tablets
120 Film-Coated Tablets
168 Film-Coated Tablets
180 Film-Coated Tablets
336 Film-Coated Tablets
360 Film-Coated Tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use. Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

CF Pharma Ltd., The Racecourse, Danesfort, Kilkenny, Ireland

12. MARKETING AUTHORISATION NUMBER(S)

PL 36549/0001

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

The tablets should be swallowed whole with water.

16. INFORMATION IN BRAILLE

Glucosamine sulfate 750mg tablets

17. OTHER

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

LABELLING FOR BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Glucosamine sulfate 750mg Film-coated Tablets

Glucosamine sulfate

2. NAME OF THE MARKETING AUTHORISATION HOLDER

CF Pharma Ltd

3. EXPIRY DATE

The batch number and expiry date are over printed on the blister strip.

4. BATCH NUMBER

The batch number and expiry date are over printed on the blister strip.

5. OTHER

< Calendar packs >

Glucosamine sulfate 1500 mg Film-coated Tablets

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND IMMEDIATE PACKAGING

LABELLING FOR CONTAINER CARTON AND CONTAINER

1. NAME OF THE MEDICINAL PRODUCT

Glucosamine sulfate 1500mg Film-coated Tablets
Glucosamine sulfate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 1884 mg glucosamine sulfate sodium chloride equivalent to 1500 mg glucosamine sulfate or 1178 mg glucosamine.

3. LIST OF EXCIPIENTS

Excipients: also contains sodium, soya lecithin and lactose monohydrate. See leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

7 Film-Coated Tablets
10 Film-Coated Tablets
14 Film-Coated Tablets
20 Film-Coated Tablets
21 Film-Coated Tablets
28 Film-Coated Tablets
30 Film-Coated Tablets
56 Film-Coated Tablets
60 Film-Coated Tablets
84 Film-Coated Tablets
90 Film-Coated Tablets
168 Film-Coated Tablets
180 Film-Coated Tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use. Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture.
Once opened the tablets should be used within 6 months.
Use by

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

CF Pharma Ltd., The Racecourse, Danesfort, Kilkenny, Ireland

12. MARKETING AUTHORISATION NUMBER(S)

PL 36549/0002

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

The tablets should be swallowed whole with water.

16. INFORMATION IN BRAILLE

Glucosamine sulfate 1500mg tablets

17. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND IMMEDIATE PACKAGING

LABELLING FOR BLISTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Glucosamine sulfate 1500mg Film-coated Tablets
Glucosamine sulfate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 1884 mg glucosamine sulfate sodium chloride equivalent to 1500 mg glucosamine sulfate or 1178 mg glucosamine.

3. LIST OF EXCIPIENTS

Excipients: also contains sodium, soya lecithin and lactose monohydrate. See leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

7 Film-Coated Tablets
10 Film-Coated Tablets
14 Film-Coated Tablets
20 Film-Coated Tablets
21 Film-Coated Tablets
28 Film-Coated Tablets
30 Film-Coated Tablets
56 Film-Coated Tablets
60 Film-Coated Tablets
84 Film-Coated Tablets
90 Film-Coated Tablets
168 Film-Coated Tablets
180 Film-Coated Tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use. Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

CF Pharma Ltd., The Racecourse, Danesfort, Kilkenny, Ireland

12. MARKETING AUTHORISATION NUMBER(S)

PL 36549/0002

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

The tablets should be swallowed whole with water.

16. INFORMATION IN BRAILLE

Glucosamine sulfate 1500mg tablets

17. OTHER

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

LABELLING FOR BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Glucosamine sulfate 1500mg Film-coated Tablets

Glucosamine sulfate

2. NAME OF THE MARKETING AUTHORISATION HOLDER

CF Pharma Ltd

3. EXPIRY DATE

The batch number and expiry date are over printed on the blister strip.

4. BATCH NUMBER

The batch number and expiry date are over printed on the blister strip.

5. OTHER

< Calendar packs >

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)

Date submitted	Application type	Scope	Outcome