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IRISH MEDICINES BOARD

PUBLIC ASSESSMENT REPORT FOR A
MEDICINAL PRODUCT FOR HUMAN USE

Scientific discussion

Doloritis 1500 mg Film-Coated Tablets
GLUCOSAMINE SULFATE (as GLUCOSAMINE SULFATE SODIUM CHLORIDE)
PA1780/001/001

The Public Assessment Report reflects the scientific conclusion reached by the Irish Medicines Board (IMB) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the IMB for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the IMB leading to the approval of the medicinal product for marketing in Ireland.

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the IMB has granted a marketing authorisation for Doloritis 1500 mg film-coated tablets from AHA Medical Services Ltd on 25th November 2013 for the management of chronic knee stiffness and pain after periods of immobility, and osteoarthritis as pre-diagnosed by a doctor.

This national authorisation has been granted in accordance with Article 10a of Directive 2001/83/EC "well-established use".

This product is authorised for sale through pharmacies only, but can be promoted to the general public.

The Summary of Product Characteristics for (SPC) for this medicinal product is available on the IMB's website at www.imb.ie

Name of the product	Doloritis
Name(s) of the active substance(s) (INN)	GLUCOSAMINE SULFATE SODIUM CHLORIDE
Pharmacotherapeutic classification (ATC code)	M01AX05
Pharmaceutical form and strength(s)	1500 mg Film-Coated Tablets
Marketing Authorisation Number(s) in Ireland (PA)	PA1780/001/001
Marketing Authorisation Holder	AHA Medical Services Ltd

II QUALITY ASPECTS

II.1. Introduction

This application is for Doloritis 1500 mg film-coated tablets.

II.2 Drug substance

The active substance is glucosamine sulfate sodium chloride an established active substance described in the European Pharmacopoeia, and is manufactured in accordance with the principles of Good Manufacturing Practice (GMP)

The active substance specification is considered adequate to control the quality and meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with this specification has been provided.

II.3 Medicinal product

P.1 Composition

Doloritis 1500 mg film-coated tablets are white to off white, oval shaped, bi-convex film-coated tablets with breakline on one side. The score line is only to facilitate breaking and ease of swallowing and not to divide into equal doses. Each film-coated tablet contains 1500 mg of glucosamine sulfate as glucosamine sulfate sodium chloride. The other ingredients are povidone K30, macrogol 4000, magnesium stearate and for the film coating hypromellose, titanium dioxide (E171), talc, propylene glycol and polysorbate 80.

P.2 Pharmaceutical Development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.

The manufacturing process has been validated according to relevant European/ICH guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients/*Ancillary Substances)*

All ingredients comply with Ph. Eur. specifications.

P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopoeial monograph for tablets, and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production site(s) have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material

The product is presented as a HDPE bottle with HDPE screw cap or Alu/PVC/PVdC blister packs. Pack sizes of 20,30, 60 and 90 tablets for the HDPE packaging and 2,4,10, 20, 30, 45,60, 90 and 180 tablets for the blisters are approved. Not all pack sizes may be marketed.

Evidence has been provided that both packaging type complies with Ph. Eur./EU legislation for use with foodstuffs requirements.

P.7 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines demonstrating the stability of the product for 3 years. This medicinal product does not require any special storage conditions. The HDPE bottle has an in-use shelf life of 6 months.

II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Doloritis 1500 mg film-coated tablets.

III NON-CLINICAL ASPECTS

III.1 Introduction

This active substance has been available on the European/Irish market for more than 10 years. Preclinical data have been superseded by clinical experience and therefore no additional preclinical data are required to support the application.

III.2 Pharmacology

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 glycosaminoglycans and proteoglycans by chondrocytes and of hyaluronic acid by synoviocytes. However, the exact mechanism of action of glucosamine is unknown.

III.3 Pharmacokinetics

Pre-clinical studies have shown that oral glucosamine is rapidly and almost completely absorbed and highly bioavailable (approximately 87% in one study). Glucosamine appears rapidly in the plasma (typically already detectable after 15 minutes), with a peak concentration after 2 to 4 hours. Within 3- 4 hours, the majority of glucosamine in the plasma is associated with plasma proteins. Studies with radio labelled glucosamine show that radioactivity rapidly accumulates in many organs and tissues, notably the liver and kidneys, but also cartilage tissue and bone. Faecal and urinary excretions of glucosamine are limited; excretion in urine varies between 3.5 % and 9 %, and excretion in faeces varies between 6 % and 20 %. Although differences depending on the animal species examined, the majority of radioactivity collected was eliminated via expired CO_2 in radio labelling studies.

III.4 Toxicology

D-glucosamine has low acute toxicity. Long-term studies (26-52 weeks) observed no clinical, laboratory or histopathological signs of toxicity at upper daily doses of 2150-2700 mg/kg glucosamine sulphate. Animal data relating to reproductive toxicity, mutagenicity, carcinogenicity or local tolerance is lacking for glucosamine.

III.5 Ecotoxicity/environmental risk assessment

The applicant has stated that as glucosamine is normally produced in the body and one of the active molecules in cartilage formation, the metabolites formed during metabolism of glucosamine are carbon dioxide and water which are considered non-toxic in a normal environment. Therefore, there is no requirement to carry out further studies on the environmental risk of DOLORITIS 1500mg film-coated tablets.
This is considerd acceptable.

III.6 Discussion on the non-clinical aspects

As the use of this medicinal product is well-established, additional non-clinical data are not required to support the application. Bibliographic references to demonstrate the non-clinical profile of the active substance have been provided by the applicant.

IV CLINICAL ASPECTS

Glucosamine is a well known active substance with well established efficacy and tolerability.

The use of this product is well-established, in accordance with Article 10a of Directive 2001/83/EC. The active substance has been in common use for over 10 years, and an appropriate body of evidence supporting the safafety and efficacy of the product has been gathered during the lifetime of the active substance in the indications applied for. As such, additional clinical studies are considered unnecessary to demonstrate the safety and efficacy of the substance, and bibliographic references only have been provided to support the application, which is appropriate for applications submitted under this legal basis. The references provided support the granting of a marketing authosiration.

The content of the SmPC approved during the national procedure is in accordance with that accepted for similarily authorised glucosamine-containing medicineal products.. The PSUR for gluucosamine was recently assessed as part of a PSUR-worksharing procedure, following which no changes were recommended to the product information.

No additional risk management procedures are required for this product outside those require for routine pharmacovigilance.

As this product is authorised in accordance with Article 10a, no PSURs are required to be routinely sublitted. Nonetheless, glucosamine is referred in the EURD list of active substances and has a PSUR frequency of 5 years therein. As such, the MAH for this product is required to keep their product information updated in line with evolving clinical knowledge

As part of this application, the applicant has applied for a change in the prescription status of the product. Currently, glucosamine sulfate, at the strength contained in this product , is subject to medical prescription which can be renewed (Schedule B of S.I. 540/2003, as amended). The applicant has requested that the prescription of this product be “Not subject to medical prescription”.

The applicant has provided a justification regarding this proposed change in prescription status, based on the criteria for the reclassification of medicinal products. This justification has been accepted by the Board. As such, the legal status of this product will be “Not subject to medical prescription”, but sale of this product will be restricted to pharmacies only.

The pharmacology of glucosamine has been described in previous sections.

V OVERALL CONCLUSIONS

Doloritis 1500 mg film-coated tablets is a well-establised medicinal product with a proven chemical-pharmaceutical quality and an established favourable efficacy and safety profile.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The applicant has provided an acceptable justification for the reclassification of this medical product to “not subject to medical prescription”

The IMB, on the basis of the bibliographic information submitted, considered that Doloritis demonstrated adequate evidence of efficacy for the approved indication(s) as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.