Public Assessment Report

Scientific discussion

Dolenio
Glucosamin

DK/H/1580/001/MR

This module reflects the scientific discussion for the approval of Dolenio. The procedure was finalised at 23 December 2009. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

This assessment report concerns Dolenio film-coated tablets containing 1884.60 mg glucosamine sulphate sodium chloride (corresponding to 1178 mg glucosamine), approved through Mutual Recognition Procedure on 23 December 2009 with Denmark acting as RMS. A national marketing authorisation in Denmark was granted on 20 September 2006.

The application is a bibliographical application and submitted in accordance with article 10a in Directive 2001/83/EC.

The indication is “relief of symptoms in mild to moderate osteoarthritis of the knee”.

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product prior to granting its National authorisation.

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 current GMP Certificates or satisfactory inspection summary reports, 'close-out letters' or 'exchange of information' issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

According to the Guidelines on Pharmacovigilance for medicinal products for human use, NTA vol. 9A all MAHs must have an appropriate system of pharmacovigilance in place. The RMS considers the Pharmacovigilance system as described by the applicant is sufficient.

II. QUALITY ASPECTS

II.1 Introduction

The finished product is a white to almost white, oblong, biconvex, film-coated tablet with a score-line on one side, to be marketed in HDPE containers in pack sizes of 30 and 90 tablets. Each tablet contains 1884.60 mg glucosamine sulphate sodium chloride corresponding to 1500 mg glucosamine sulphate corresponding to 1177.50 mg glucosamine.
The excipients are: povidone K30, macrogol 4000, magnesium stearate (core tablet), hypromellose, titanium dioxide (E171), talc, propylene glycol, polysorbate 80 (coating material).

II.2 Drug Substance

The product contains glucosamine sulphate sodium chloride as active substance which is not monographed in the Ph.Eur. (though appears in USP 26-NF 21). Full documentation on the drug substance is provided by the applicant. Synthesis, specifications and methods are all satisfactorily described.

The specification for glucosamine sulphate sodium chloride complies with general ICH for drug substance specifications and is aligned with the USP monograph. All necessary analysis methods and validations are provided. A retest period of 3 years with no particular storage precautions is accepted.

II.3 Medicinal Product

The product composition is adequately described. The development of the product has been satisfactorily performed and explained. The excipients used are common for manufacture of a film

coated tablet. The packaging materials are standard and shown suitable by the presented stability studies.

Product manufacture is standard and involves non aqueous granulation followed by compression. Batch sizes are 1,000,000 tablets. Satisfactory validation data are provided for 3 full scale manufacturing batches showing a well controlled process.

The finished product specification is standard for the pharmaceutical form and includes relevant physicochemical, ID, assay and purity tests. Separate release and shelf-life specifications are provided but limits are the same. Batch analysis data of 3 full scale batches (1,000,000 tablets) have been provided showing compliance with the release requirements.

Stability data are provided for 3 full scale batches stored in the proposed market packaging. No out of specification results were obtained. A shelf-life of 18 months with no special storage precautions is approved and supported by the presented stability data. Data are also provided for bulk packed tablets for which 6 months storage at 30°C is accepted.

III. NON-CLINICAL ASPECTS

Preclinical data have indicated that GA might affect glucose homeostasis. With the use of euglycaemic clamp technique in rodents, intravenous infusion of GA reduced glucose uptake into skeletal muscles.

IV. CLINICAL ASPECTS

GA, an amino-monosaccharide occurring naturally in the human body, is a water-soluble amino sugar, formed in the body from glucose. It 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. GA 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 GA declines with age. For this reason it has been given in the treatment of degenerative rheumatic disorders like OA.
After ingestion, GA in the form of a sulphate or hydrochloride salt is completely ionised in the acid environment of the stomach making free GA available for absorption in the small intestine. Thus irrespective of which GA salt that is ingested -sulphate and – hydrochloride would have similar bioavailability.
GA is not protein-bound but rather incorporates into plasma proteins, primarily globulins. Unbound GA is concentrated in the articular cartilage after systemic absorption.
Following absorption of an oral dose, first-pass metabolism results in approximately 26% bioavailability. GA is metabolised primarily in the liver and is excreted as carbon dioxide, water, and urea. The elimination half-life of GA incorporated in plasma proteins is 68 hours after oral doses. The highest concentrations are found in the liver, kidneys, and articular cartilage.
Although the mechanism of action of the symptom-modifying effects of GA is not well understood, it is thought to be related in part to increased synthesis of glycosaminoglycans in the condrocytes. In vitro experiments using condrocytes isolated from human osteoarthritis femoral heads, GA was shown to induce a significant and dose dependent increase in proteoglycan synthesis.

In clinical studies with i.v. GA infusion it has been shown that GA did not affect insulin levels or glucose- decreased insulin sensitivity.

Osteoarthritis (OA).
OA is a common joint disease particularly affecting people above 50 years with a predominance of women. OA is characterised by pain, morning stiffness, and gelling of the involved joint after immobility. Most cases of OA are classified as being primary and only a limited number are considered secondary following trauma or disease. Apart from the spine only one or a few joints are usually affected, mostly the knee, hip, and the proximal or distal interphalangeal fingerjoints. Patients

with OA have pain that typically worsens with weight bearing and activity and improves with rest. On physical examination they often have tenderness, bony enlargement, crepitus on motion and limitation on joint movement. Unlike rheumatoid arthritis and other inflammatory joint diseases, inflammation is rarely present in OA. In the Scandinavian countries OA is usually termed “osteoarthrosis” to make this distinction. Symptoms progress with age. Although the pathophysiology of OA is incompletely understood, biomechanical stress factors and biomechanical changes in the articular cartilage and synovial membrane as well as genetically predisposing factors are all likely to be important. OA is characterised by focal cartilage loss and accompanying reparative bone response. Typically radiographic features are joint-space narrowing, subchondrial osteosclerosis, marginal osteophyte formation and subchondrial cysts.
There is no cure for OA and current treatment is symptom modifying designed to reduce pain. Non-pharmacological approaches include patient education, weight-loss if overweight, exercise programmes physical therapy, bracing and footwear. Pharmacological treatment includes analgesics, NSAIDs, intra-articular steroids. Joint replacement surgery might be an alternative for severe cases when pharmacological methods fail.stimulated insulin secretion, but increased fasting blood glucose levels. Furthermore high GA levels

Clinical efficacy
The assessor agrees with the clinical expert that in the referred published studies there is an efficacy shown for symptomatic relief in patients with mild to moderate OA.

Clinical safety
The safety profile is favourable with mainly mild reactions and particularly from the gastrointestinal region. Some concerns are raised regarding patients with DM and the regulation of blood glucose homeostasis.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

From a quality, non-clinical and clinical point of view the benefit/risk is considered positive and Dolenio is recommended for approval.

The applicant has made the following commitments:

- The applicant commits to provide batch release certificates from the EU batch releaser on the first three commercialized batches when available.
- The applicant commits to provide process validation on the first three commercialized batches when available.
- The applicant commits to perform viral validation studies with human pathogenic enteric viruses. The applicant commits to produce the report before commercialisation.
- The applicant commits to demonstrate the absence of chloramphenicol. The report will be submitted along with the viral validation studies, which are to be performed before any commercialisation.
- The applicant commits to perform stability studies on the pack size of 30 tablets in the proposed process validation batches.
- The applicant commits to try to do a single crystal X-Ray structure analysis to elucidate the structure of the glucosamine sulphate sodium chloride salt.