CBG MEB

Public Assessment Report

Scientific discussion

Mesalazine Disphar 750 mg, gastro-resistant tablets

(mesalazine)

NL License RVG: 114896

Date: 14 June 2016

This module reflects the scientific discussion for the approval of Mesalazine Disphar 750 mg, gastro-resistant tablets. The marketing authorisation was granted on 9 July 2015. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
EC	Enteric-coated
EDQM	European Directorate for the Quality of Medicines
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Medicines Evaluation Board (MEB) of the Netherlands has granted a marketing authorisation for Mesalazine Disphar 750 mg, gastro-resistant tablets from Disphar International B.V.

The product is indicated for:

- treatment of mild to moderate ulcerative colitis, both in acute phase and for maintenance of remission
- treatment of Crohn's disease confined to the colon, both in acute phase and for maintenance of remission

A comprehensive description of the indications and posology is given in the SmPC.

This national procedure concerns a hybrid application, and a line extension to the registered products Mesalazine Disphar EC 250 and 500 mg gastro-resistant tablets (NL License RVG 27063 and 27064), which have been registered in the Netherlands by the same MAH since 10 September 2001. As indicated in the SmPC a maximal dose of 4.5 g/day divided over 3 to 4 doses can be administered. Thus the additional 750 mg strength would fit in the current dose regimen.

Mesalazine Disphar 750 mg was developed as a dose-proportional formulation to Mesalazine Disphar EC 250 and 500 mg. Dissolution profile comparison between the different gastro-resistant tablet strengths have been submitted to support the application. Furthermore, reference is made to pharmacokinetic studies submitted for the Mesalazine Disphar EC 500 mg gastro-resistant tablets, which were developed to be similar to Salofalk 500 mg gastro-resistant tablets.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Mesalazine Disphar 750 mg is a yellow ochre coloured oblong tablet with a smooth surface.

The excipients are: microcrystalline cellulose, silica colloidal anhydrous, povidone K 25/ K 90, crospovidone, magnesium stearate, hypromellose, macrogol 6000, methacrylic acid – methyl metacrylate copolymer, triethyl citrate, talc, titanium dioxide and yellow ferric oxide.

The product is packed in a transparent PVC/PVDC-Alu blister.

II.2 Drug Substance

The active substance is mesalazine, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is very slightly soluble in water, practically insoluble in ethanol. It dissolves in dilute solutions of alkali hydroxides and in dilute hydrochloric acid.

The CEP procedure is used for both manufacturers of the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Manufacturing process

CEPs have been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The drug substance specification is in line with the requirements of the Ph.Eur. and the additional requirements of the CEPs. The specification is acceptable in view of the route of synthesis and the various European guidelines. A limit for particle size is adopted for both suppliers. Sufficient batch analysis data have been provided.

Stability of drug substance
The active substance of both manufacturers is stable for 3 years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The choice of the packaging and manufacturing process are justified.
Due to the mechanism of action of mesalazine and the intended indication a gastro-resistant tablet was developed that does not disintegrate in the stomach, but from which the coating is dissolving after that the tablet has passed from the stomach to the duodenum, resulting in a release of active material from the jejunum
The product at issue is a line extension of the 500 mg product and is based on *in vitro* data only. The core tablets of the two strengths are dose proportional. Supportive dissolution data is provided. Dissolution of the 500 mg and 750 mg products in pH 6.8 after exposure to pH 1.2 and pH 4.5 is the same.
The provided data and justification on similarity of the 750 mg product to the 500 mg registered product are considered sufficient.

Manufacturing process
The product is manufactured via a wet granulation, compression of tablets, and coating with the different coating layers including a gastro-resistant layer. The manufacturing process has been adequately validated according to relevant European guidelines. As this is a modified-release preparation, the process at issue is to be regarded as non-standard. Process validation data on the product has been presented for three full-scale batches.

Control of excipients
The excipients comply with the Ph.Eur. or National Formulary (NF) requirements. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance, colour, and dimensions, average mass, identification, assay, impurities, dissolution, uniformity of dosage units, and microbial limits. The limits and test are the same for release and end of shelf-life. All limits are considered acceptable. The analytical methods have been adequately validated. Batch analytical data from the proposed production site have been provided on three full-scale batches, demonstrating compliance with the release specification.

Stability of drug product
Stability data has been provided on three batches stored at 30°C/75% RH (12 months) and 40°C/75% RH (6 months) of the 750 mg product. Supportive stability data on the 500 mg batches is presented as well for 2 pilot-scale batches and 4 full-scale batches up to 60 months at long term conditions (25°C/60% RH), intermediate conditions (30°C/75% RH, 12-16 months) and accelerated conditions (6 months). Stability studies are not fully performed in compliance with ICH guidance on stability testing as a higher humidity conditions (75% RH instead of 65% RH) is applied at the intermediate condition. This is acceptable. The tablets are packed in Alu/PVC/PVDC blisters.
The stability data of the 500 mg product stored at 25°C/60%RH for the period of 60 months and stored at 30°C/60%RH for 16 months show a slight increase in average mass, all other parameters remain stable and within specification. Although the long term stability conditions of the 500 mg product are not exactly the same as the stability conditions of the 750 mg product, the proposed shelf-life for the 750 mg product of 48 months is accepted as supportive data of the 500 mg product at intermediate conditions show similar results. The results of a photostability study show that the product is not

sensitive to light. The proposed storage conditions (store below 30°C in the original packaging in order to protect from moisture) is acceptable.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the MEB considers that Mesalazine Disphar 750 mg, gastro-resistant tablets has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Mesalazine Disphar intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a hybrid line extension to Mesalazine Disphar EC 250 and 500 mg gastro-resistant tablets, which are available on the market. Reference is made to the preclinical data obtained with mesalazine previously. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the MEB agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Mesalazine is a well-known active substance with established efficacy and tolerability.
A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the MEB agrees that no further clinical studies are required.

Mesalazine Disphar 750 mg is a higher strength formulation of the registered 250 and 500 mg EC gastro-resistant tablets. As indicated in the SmPC a maximal dose of 4.5 g/day divided over 3 to 4 doses can be administered. Thus the additional 750 mg EC strength would fit in the current dose regimen. Other mesalazine formulations up to a strength of 3 g are registered.

IV.2 Pharmacokinetics

Reference is made to pharmacokinetic studies submitted for Mesalazine Disphar 500 mg gastro-resistant tablets, which were developed to be similar to Salofalk 500 mg gastro-resistant tablets.

Biowaiver
The following general requirements as stated in the guidance for a biowaiver are fulfilled for Mesalazine Disphar 750 mg compared to Mesalazine Disphar EC 500 mg:

- the pharmaceutical products are manufactured by the same manufacturing process,
- the qualitative composition of the different strengths is the same,
- the composition of the strengths are quantitatively proportional (core tablet).

In addition, appropriate *in vitro* dissolution data of the 500 and 750 mg product should confirm the adequacy of waiving additional *in vivo* bioequivalence testing.

Dissolution of the 500 mg and 750 mg formulations in pH 6.8 after exposure to pH 1.2 and pH 4.5 is the same, *i.e*. the products are similar. A difference was observed in pH 7.2. However, this difference can be accepted as the delay in dissolution is not considered to be clinical meaningful.
The gastro-resistant coating is identical in composition and thickness for both the 500 mg and 750 mg tablets; it is to be expected that the tablets will behave similarly in respect to resistance to gastric acid and transit through the small intestines.

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, 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 Mesalazine Disphar.

- Summary table of safety concerns as approved in RMP

Important identified risks	Hypersensitivity reactions Kidney function disorders
Important potential risks	Aggravated bleeding tendency
Missing information	Exposure during pregnancy Exposure during breast feeding Exposure in children younger than 6 years old

The MEB agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with registered mesalazine formulations. No new clinical studies were conducted. Dissolution of the new 750 mg strength is considered similar to the dissolution of the registered 500 mg product. Risk management is adequately addressed.

V. USER CONSULTATION

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC.
The test consisted of a pilot test with 5 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. In both rounds of testing, all participants were able to find the information and answer the questions correctly. The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Mesalazine Disphar 750 mg, gastro-resistant tablets has a proven chemical-pharmaceutical quality and is an approvable line extension to Mesalazine Disphar 500 mg EC. Mesalazine Disphar is well-known and has an established favourable efficacy and safety profile.

In the Board meeting of 4 June 2015, the submitted *in vitro* data in support of the application were discussed. The observed delay in dissolution of the 750 mg compared to the 500 mg formulation at pH 7.2 was considered. The Board concluded that this difference is not expected to be clinically relevant. The gastro-resistant coating of the two strengths is identical, and the transit time through the small intestines will not be affected.

Overall, similarity of the 750 mg strength to Mesalazine Disphar 500 mg EC has been adequately demonstrated. The MEB has therefore granted a marketing authorization for Mesalazine Disphar 750 mg, gastro-resist tablets on 9 July 2015.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached