CBG MEB

Public Assessment Report

Scientific discussion

Pentasa Compact 4 g, prolonged-release granules

(mesalazine)

NL License RVG: 114015

Date: 30 March 2015

This module reflects the scientific discussion for the approval of Pentasa Compact 4 g, prolonged-release granules. The marketing authorisation was granted on 31 March 2014. For information on changes after this date please refer to the module 'Update'.

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 Pentasa Compact 4 g, prolonged-release granules from Ferring B.V.

The product is indicated for treatment of mild and moderate forms of ulcerative colitis and Crohn's disease, both in the acute phase and to prevent relapse of active disease.

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

Pentasa compact contains the active substance mesalazine, which is also known as 5-aminosalicylic acid (5-ASA). Mesalazine has *in vitro* and *in vivo* pharmacological effects that inhibit leucocyte chemotaxis, decrease cytokine and leucotriene production, and scavenge for free radicals. It is currently unknown which, if any, of these mechanisms play a predominant role in the clinical efficacy of mesalazine.

This national procedure concerns a line extension to already registered formulations of the same MAH: Pentasa Compact 1 and 2 g, prolonged-release granules (NL License RVG 18706 and 31379), which have been registered in the Netherlands since 1996 (1 g) and 2005 (2 g). The new 4 mg strength concerns identical granules as used for the 1 g and 2 g formulation.

The marketing authorisation has been granted pursuant to Article 8(3) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Pentasa Compact 4 g are whitish to pale brown rod shaped granules consisting of 4 g mesalazine, and the excipients povidone and ethylcellulose.

The granules are packed in tight polyester/aluminium/LD polyethylene sachets.

II.2 Drug Substance

The active substance is mesalazine, an established active substance which is described in the European Pharmacopoeia (Ph.Eur.). It is a white or light grey or light pink powder or crystals. The substance is very slightly soluble in water and practically insoluble in ethanol. It dissolves in dilute solutions of alkali hydroxides and in dilute hydrochloric acid.

The CEP procedure is used for 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
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and complies with the requirements of the Ph.Eur. Batch analytical data demonstrating compliance with this specification have been provided.

Stability of drug substance
The active substance is stable for 36 months 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.
Initially the 1 g Pentasa Compact prolonged-release granules were developed. A brief overview of the development has been provided. The 4 g sachet contains identical granules as used for the 1 g and 2 g products, filled into sachets of the same material. The granules are coated in order to control the release rate of the active ingredient mesalazine. The recommended posology for adults is individual dosage, up to 4 g mesalazine once daily or divided into 2-4 doses. Systemic exposure (AUC) and clinical efficacy and safety are considered equivalent. Therefore no comparative dissolution profiles have been submitted.

Manufacturing process
The manufacturing process consists of production of the granules, preparation of coated granules, filling of the sachets with the coated granules and assembling.
The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three production-scale batches. The product is manufactured using conventional manufacturing techniques.

Control of excipients
The excipients comply with the Ph.Eur. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance, identity, residual solvents, assay, related substances, microbiological test, uniformity of dosage units and dissolution. The specifications are in compliance with the already approved drug products and acceptable.
Batch analytical data from the proposed production site have been provided on three production-scale batches, demonstrating compliance with the release specification.

Stability of drug product
Since all relevant quality properties are identical for the three strengths, the proposed shelf life and storage conditions for the 4 g are similar to the other strengths. Based on stability data of Pentasa prolonged-release granules 1 g and 2 g, a shelf-life of 24 months, when stored in the original package was applied for.
The MEB raised a comment that the stability pattern for the 4 g strength could be different due to a different surface ratio between the granules and the sachet surface, which may possibly lead to a different pattern of moisture and/or oxygen uptake. Stability data in accordance with ICH were therefore submitted on three batches stored at long term, intermediate and accelerated conditions for 6 months. No trends or out-of-specification results were observed. The shelf-life of 24 months is therefore sufficiently confirmed for the 4 g strength.

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 Pentasa Compact 4 g prolonged-release granules have 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 the additional Pentasa Compact strength is intended as a substitute of the mesalazine available products, 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 line extension to Pentasa Compact 1 and 2 g, prolonged-release granules. No new preclinical data have been submitted. The MAH referred to the preclinical documentation included in the application for the initial registration. Therefore the application for the 4 g strength has not undergone additional preclinical assessment. This is acceptable for this type of application.
A non-clinical overview of the studies performed with regard to the pharmacology, pharmacokinetics and toxicology has been provided, which is based on non-clinical studies and supported by up-to-date and adequate scientific literature. Therefore, the MEB agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

Pentasa Compact 4 g prolonged-release granules is a line extension of the 1 and 2 g formulation. The active substance mesalazine is a well-known active substance with established efficacy and tolerability.
The 1 g, 2 g and 4 g are prolonged-release formulations intended for oral administration. The granules are coated in order to control the release rate of the active ingredient mesalazine. The 4 g granules are identical granules as used for the 1 g and 2 g formulation and filled into sachets of the same material as for the 1 g and 2 g formulation.

The high dose of up to 4 g once daily is the current recommended posology, as indicated in the SmPC. The systemic exposure (AUC) and clinical efficacy and safety are considered equivalent between strengths. Considering the above, the 4 g granules are acceptable. The MEB agrees that no further clinical studies are required.

IV.2 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 Pentasa Compact 4 g prolonged-release granules.

- Summary table of safety concerns as approved in RMP

Important identified risks	• Impairment of renal function • Impairment of hepatic function • Reversible myocarditis/pericarditis • Acute pancreatitis (AP) • Respiratory disorders • Blood dyscrasias
Important potential risks	Not applicable
Missing information	Not applicable

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

IV.3 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the Pentasa Compact 1 g and 2 g. As the composition of the 4 g granules is the same, no new clinical studies were required. Risk management is adequately addressed.

V. USER CONSULTATION

The package leaflet has not been evaluated via a user consultation study. The only difference with the currently approved text of the 1 and 2 g granules is the addition of the new strength. No further safety or medical information has been altered. The MEB agrees that further user testing is not necessary.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Pentasa Compact 4 g, prolonged-release granules has a proven chemical-pharmaceutical quality and is an approvable line extension to Pentasa Compact 1 g and 2 g, prolonged-release granules. Pentasa Compact is a well-known medicinal product with an established favourable efficacy and safety profile.

No bioequivalence study was needed, as the 4 g sachet contains identical granules as used for the 1 g and 2 g products.

The Board followed the advice of the assessors.

The MEB, on the basis of the data submitted, considered that efficacy and safety has been shown, and has therefore granted a marketing authorisation. Pentasa Compact 4 g, prolonged-release granules was authorised in the Netherlands on 31 March 2014.

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