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IRISH MEDICINES BOARD

PUBLIC ASSESSMENT REPORT FOR A MEDICINAL PRODUCT FOR HUMAN USE

Scientific discussion

Pentasa 1 g prolonged-release tablets
Mesalazine

PA1009/6/7

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 Pentasa 1 g prolonged-release tablets, from Ferring Ireland Ltd on 07th January 2011 for the treatment of Ulcerative Colitis and Crohn's disease.

This is an application for a line extension for a known active substance under an Article 8(3) application.

This is a prescription-only medicinal product.

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

Name of the product	Pentasa 1 g prolonged-release tablets
Name(s) of the active substance(s) (INN)	Mesalazine
Pharmacotherapeutic classification (ATC code)	A07EC02
Pharmaceutical form and strength(s)	1 gram
Marketing Authorisation Number(s) in Ireland (PA)	PA1009/6/7
Marketing Authorisation Holder	Ferring Ireland Ltd

II QUALITY ASPECTS

II.1. Introduction

This application is for Pentasa 1g Prolonged-release Tablets.

II.2 Drug substance

The active substance is mesalazine 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

Pentasa 1g Prolonged-release Tablets are White-grey to pale brown, speckled, oval tablet. Embossing on both sides: PENTASA

Composition of the medicinal product:

Active Substance:

Mesalazine 1 g

Excipients
Povidone

Ethylcellulose
Magnesium stearate
Talc
Microcrystalline cellulose

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

All ingredients comply with Ph. Eur..

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 double aluminium foil blisters.

Evidence has been provided that 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 when stored below 25°C in the original package.

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 Pentasa 1g Prolonged-release Tablets.

III NON-CLINICAL ASPECTS

III.1 Introduction

No new preclinical data have been submitted. The non-clinical documentation is cross-referenced to the approved documentation for PENTASA 500 mg tablets.As such, no pre-clinical assessment has been made on the application..

An environmental risk assessment is not considered necessary in the application as the introduction of PENTASA prolonged release tablet 1 g into the market is unlikely to change the environmental burden of mesalazine caused by products already available.

IV CLINICAL ASPECTS

IV.1 Introduction

Pentasa 1g is a line extension of a marketed modified release form (Pentasa 500mg tablet) and the release controlling excipients of the delivery system are proportionally identical as illustrated in the composition of the tablets.

The active ingredient is mesalazine 5 aminosalicyclic acid which belongs to the intestinal anti inflammatory agents. (A07 EC02) The tablets release mesalazine throughout the entire intestinal tract from the duodenum to the rectum at all ph levels.
The therapeutic activity of mesalazine is believed to depend on a local contact of the drug with the diseased area of the intestinal mucosa.

Recommended oral daily dose is up to 4 g of mesalazine.

This 1 g tablet has been developed as an alternative to the 500mg tablet or the 1g sachet in order to improve patient compliance.

The two strengths, the 500mg and the 1g contain prolonged release granules with the same qualitative composition and ratio between amounts of active substance and excipients.

No Clinical studies have been performed with the 1 g tablet which contain exactly the same prolonged release granules as the already registered 500mg strength and is to be used under the same dosing schedule

No bioequivalence studies have been performed with the 1g as the two 500mg are regarded as equivalent to 1g

The fast disintegration of the tablet to ethylcellulose coated granules in the stomach makes the two dosage forms prolonged release tablet and prolonged release granules (previously authorized) essentially interchangeable.

The tablets quickly disintegrate into the individual prolonged release granules upon contact with liquid and similar in vitro dissolution profiles have been shown for the two strengths

In vitro experiments comparing the tablets of the two strengths show that they quickly disintegrate into the individual prolonged release granules upon contact with liquid and display similar in vitro dissolution profiles at ph 1.2, 2.0 6.8 and 7.5.
The disintegration of pentasa 1g is immediate and rapid which renders the tablets to be completely disintegrated into prolonged release granules in less than 2 minutes.

From a clinical point of view a minor variation in disintegration time will have no impact on the effect since the disintegration will occur in the stomach,hence when emptied from the stomach the tablet will be completely disintegrated and the separate granules will be empted into the duodenum.

IV.2 Pharmacokinetics

No Pharmacokinetic studies have been performed with the 1g as the two 500mg are regarded as equivalent to 1g

IV.3 Pharmacodynamics

Mechanism of action, primary/secondary pharmacology, dose finding, genetic differences in PD response

IV.4 Clinical Efficacy

No new clinical data have been submitted. The clinical documentation is cross-referenced to the approved

documentation for Pentasa 500 mg tablets. The efficacy of Pentasa has been documented in the registration dossier for the 500mg tablet.

IV.5 Clinical Safety

Only minor changes to the safety info have taken place since the approval of the 500mg tablet and these have been addressed and included in the SPC for the 1 g tablet.

The Marketing Authorisation Holder submitted a set of documents describing the Pharmacovigilance System, including information on the availability of an EU Qualified Person for Pharmacovigilance (EU-QPPV) and the means for notification of adverse reaction reports in the EU or from a Third Country.

V OVERALL CONCLUSIONS

BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Pentasa 1g is a line extension of a marketed modified release form (Pentasa 500mg tablet) and the release controlling excipients of the delivery system are proportionally identical as illustrated in the composition of the tablets. The active ingredient is mesalazine 5 aminosalicyclic acid which belongs to the intestinal anti inflammatory agents. (A07 EC02) The therapeutic activity of mesalazine is believed to depend on a local contact of the drug with the diseased area of the intestinal mucosa.

The non clinical and clinical documentation is cross-referenced to the approved documentation for Pentasa 500 mg tablets.

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Pentasa 1 g prolonged-release tablets.

Based on the review of the data the IMB has granted a marketing authorisation for Pentasa 1 g prolonged-release tablets, from Ferring Ireland Ltd for the treatment of Ulcerative Colitis and Crohn’s disease.