Public Assessment Report
Scientific discussion

Azzavix 1000 mg Gastro-resistant Tablets
Mesalazine

ES/H/0587/002/DC

Applicant: Faes Farma, S.A.

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This module reflects the scientific discussion for the approval of **Azzavix 1000 mg Gastro-resistant Tablets**. The procedure was finalised on November 2020. 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 Member States have granted a marketing authorisation for Azzavix 1000 mg Gastro-resistant Tablets, from Faes Farma, S.A.

The product is indicated for the treatment of the acute phase of mild or moderate ulcerative colitis (UC), and the maintenance treatment of remission in UC (including patients unable to tolerate salazosulphapyridine, SASP) in adults.

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

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

II. QUALITY ASPECTS

II.1. Introduction

The finished product is presented as oblong tablets, with homogeneous gastro-resistant orange coloured coating, containing 1000 mg of mesalazine.

The maximum daily dose 4 g daily.

The product is available in PVC/PVDC-Aluminium blister.

II.2. Drug substance

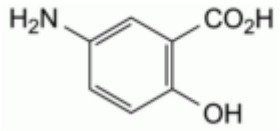
The active substance mesalazine is sourced by two suppliers, in both cases the quality is supported by CEPs.

General Information

Nomenclature:

INN:	Mesalazinum
Chemical name:	5-Amino-2-hydroxybenzoic acid.
CAS-No:	[89-57-6]

Structure:



Molecular formula: $C_7H_7NO_3$

Molecular weight: 153,1

General Properties:

Mesalazine is an almost white or light grey or light pink powder or crystals, very slightly soluble in water, practically insoluble in ethanol (96 per cent). It dissolves in dilute solutions of alkali hydroxides and in dilute hydrochloric acid.

Manufacture, process controls and characterization

As CEP procedure is used, information on manufacture, process controls and characterization of the active substance has been assessed by EDQM.

Specification, analytical procedures, batch analysis

Active substance specifications are in accordance with Ph. Eur. Monograph.

Container closure system

As CEPs procedures are used, information on packaging material of active substance has been assessed by EDQM.

Stability

Re-test periods are included in the CEPs. Stability studies have been assessed by EDQM

II.3. Medicinal Product

Description of the product

The product is oblong tablets, with homogeneous gastro-resistant orange coloured coating, containing 1000 mg of mesalazine. All the components of the product are included in the composition table. Excipients are listed specifying their common name, the quantity present, their function and a reference to a relevant standard.

The gastro-resistant tablets are packaged in PVC/PVDC-Aluminium blister.

Pharmaceutical Development

The development of the product has been described, the choice of excipients is justified and their functions explained.

The physicochemical characteristics of the active substance that may affect the pharmaceutical form are identified and their control strategy is justified.

The choice of dissolution method is considered appropriate. The information presented supports the proposed quality control dissolution method.

Manufacture of the product

The manufacturing process is fully described and in-process controls are appropriate considering the nature of the product and the manufacturing process. The industrial batch size is well-defined.

Sufficient validation data are provided.

Excipients

Excipients used are well known and of appropriate quality.

None of the excipients is of animal origin.

Product specification, analytical procedures, batch analysis

The finished product specifications are adequate to control the finished product. Provided description and validation data for the analytical methods are adequate. Batch analysis data have

been submitted and the results show that the finished product meets the proposed release specification.

Container closure system

The finished product is packaged in PVC/PVDC-Aluminium blister. The choice of the container closure system is justified considering the nature of the finished product. Compliance with the relevant requirements and/or regulations is confirmed.

Stability

Stability studies have been performed in accordance with current guidelines. The proposed protocol is considered adequate. The packaging material is the same as that intended for marketing. Proposed shelf-life and storage conditions are properly established.

Shelf-life: 3 years.

Storage conditions: This product does not require any special storage conditions.

III. NON-CLINICAL ASPECTS

III.1 Introduction

In accordance with article 8(3) 'Full-mixed application' of Directive 83/2001/EC, as amended, the Applicant has submitted scientific literature data to support the non-clinical package for the present MAA.

III.2 Critical evaluation of the Non-Clinical Overview

Pharmacodynamic, pharmacokinetic and toxicological properties of mesalazine are well known. As mesalazine is a widely used and well-known active substance, the Applicant has provided a non-clinical overview based on scientific literature which is considered appropriate.

III.3 Environmental Risk Assessment (ERA)

Mesalazine is not expected to pose a risk to the environment.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

Mesalazine 500 mg gastro-resistant tablets, is a modified formulation of Claversal 250 mg and Claversal 500 mg developed originally by Smith Kline in the 1980s and first time commercialized in 1988. Some years later, Smith Kline transferred the marketing authorization to different European companies around Europe, including FAES Farma. Within the transference of this marketing authorization, the Applicant received some reports of the original formulation of Claversal. These few reports are complemented with literature data obtained with different mesalazine-containing products.

Overall the pharmacokinetic properties of mesalazine were summarized by the Applicant taking into account the limited number of studies available at the time when the clinical development of the product was conducted and the information available in the public scientific literature. This brief information is considered acceptable for a product that has been in the market for more than 20 years.
Results from the submitted in vitro drug release study, particularly those from test series 2 indicate that the different enteric coated mesalazine formulations show similar in vitro release behavior and it is expected that the in vivo behavior will not be notably different. Therefore, it is likely that their in vivo release behavior with respect to both site and extent of drug release will not be essentially different. Consequently, it is reasonable to extrapolate the basic pharmacokinetic properties described in the literature for these similar products to the applied product.

IV.2 Pharmacodynamics

Mesalazine (5-ASA) is one of the two components of sulfasalazine (SASP), the other being sulfapyridine. While mesalazine is the active fraction, sulfapyridine is responsible for most adverse events associated with therapy with sulfasalazine.

Mesalazine mechanism of action in UC is unclear, but it appears to have a topical effect (Sonu *et al.*, 2010). The effectiveness of the drug is related to its mucosal concentration, and systemic dosages remain low after oral SASP and rectal 5-ASA administration. 5-ASA is believed to interact with damaged epithelium, be converted to acetylated-5-ASA (Ac-5-ASA, inactive acetylated form), and then absorbed and excreted into the urine or excreted into stool.

No new data on PD have been presented, which is considered acceptable based on the well-known – although not fully elucidated – mechanism of action of the compound mesalazine.

IV.3 Clinical efficacy

The Applicant has submitted these MAA of Mesalazine 1000 mg gastro-resistant tablets (ES/H/0587/002/DC & ES/H/0588/002/DC) as a line extension of the recently approved medicinal products Mesalazine 500 mg gastro-resistant tablets (ES/H/0587/001/DC & ES/H/0588/001/DC).

The intended indications of Mesalazine 1000 mg gastro-resistant tablets are the treatment of the acute phase of mild or moderate ulcerative colitis (UC), and the maintenance treatment of remission in UC (including patients unable to tolerate salazosulphapyridine, SASP) in adults

The intended indications and the proposed doses are the same as those approved for the above mentioned procedure of Mesalazine 500 mg gastro-resistant tablets and are in line with indications approved for other mesalazine-containing gastro-resistant tablets available in ES and other EU-MS.

The efficacy and safety of Mesalazine 1000 mg gastro-resistant tablets in the proposed indications and doses rely onare supported by own clinical data demonstrating the efficacy and safety of mesalazine, as well as on data described in the scientific literature.

The submitted efficacy documentation is the same as that submitted for the recently approved for Mesalazine 500 mg gastro-resistant tablets (ES/H/0587/001/DC & ES/H/0588/001/DC).

These studies include:

- Own studies using Claversal 250 mg gastro-resistant tablets.

- Studies published by other authors using mesalazine formulated with Eudragit L (Ardizzone *et al.*, 1995; Kruis *et al.*, 1998) or Eudragit L plus Eudragit S, (Raedler *et al.*, 2004).

- Two meta-analysis published by Wang *et al.* (Wang *et al.*, 2016a; Wang *et al.*, 2016b) in Cochrane database where they analyzed the efficacy and safety of multiple oral formulations of mesalazine.

The application contains an adequate review of own studies and published clinical data and these data support the efficacy of Mesalazine 1000 mg gastro-resistant tablets in the intended indications.

IV.4 Clinical safety

The characterization of the safety profile of Mesalazine 500 mg and 1000 mg gastro-resistant tablets relies on clinical data demonstrating the efficacy and safety of mesalazine owned by the Applicant and described in the scientific literature.

The submitted safety documentation is the same as the submitted documentation for the recently approved for Mesalazine 500 mg gastro-resistant tablets (ES/H/0587/001/DC & ES/H/0588/001/DC). Additionally the applicant has completed the safety documentation with the data provided in the studies CLEU-0218 BA-FAST and CLEU-0118 BA-FED designed to assess the comparative bioavailability of two gastro-resistant tablets formulations of Mesalazine (500 mg vs. 1g) after single dose administration of 1000 mg to healthy volunteers under fasting conditions and fed conditions, respectively.

Overall, melasazine shows few side effects with low clinical importance, except in certain rare cases. This is due to the fact that the 5-ASA deposited in the digestive tract is absorbed in small quantities, and that the molecules that carry it are inert substances with proven biological inactivity.

The safety profile of mesalazine is well-known. The clinical overview presented by the MAH adequately describes the safety profile of mesalazine oral formulations and does not appear to be differences between them from a safety point of view.

IV.5 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 Azzavix 1000 mg gastro-resistant tablets.

There are neither proposed additional pharmacovigilance activities nor proposed additional risk minimisation measures planned for Azzavix 1000 mg gastro-resistant tablets.

V. USER CONSULTATION

Directive 2001/83/EC as amended by Directive 2004/27/EC, requires that consultation with target patient groups are carried out to demonstrate the readability and usefulness of the package leaflet to patients. The study was conducted by Pharmalex Spain S.L. (Pharmalex) in 2020 in Spain. The package leaflet was tested using a preliminay phase with two subjects and subsequent two rounds of ten subjects each. The selection of the subjects is well defined and acceptable. The readability, comprehensive understanding of the text, traceability of information and applicability in the test were analyzed.

The results of the consultation can be accepted.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The present section supports the Marketing Authorization Application (MAA) for Mesalazine 1000 mg gastro-resistant tablets as formulated by Faes Farma, S.A. This medicinal product is intended for the treatment of the acute phase of mild or moderate ulcerative colitis (UC), and the maintenance treatment of remission in UC (including patients unable to tolerate salazosulphapyridine, SASP) in adults.

The clinical data described in the dossier consists on own data generated or acquired by the Applicant together with an update of bibliographic data. Therefore, the present MAA is submitted as a full mixed MAA in accordance with Article 8(3) of Directive 2001/83/EC.

Regarding Efficacy and safety data, Mesalazine 1.000 mg gastro-resistant tablets is intended for the treatment of the acute phase of mild or moderate ulcerative colitis (UC), and the maintenance treatment of remission in UC in adults. The indications and posology are the same as the approved for the recently approved procedures of Mesalazine 500 mg gastro-resistant tablets (ES/H/0587/001/DC & ES/H/0588/001/DC).

The application contains an adequate review of own studies and published clinical data.

Mesalazine 1000 mg gastro-resistant tablets has proven a chemical-pharmaceutical quality. The product has an adequate efficacy and safety profile which is considered widely established.

In conclusion, the benefit/risk relation is considered positive.