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Public Assessment Report

Scientific discussion

Mecolvix 1000 mg rectal foam (mesalazine)

ES/H/0588/004/DC

Date: 14/05/2025

This module reflects the scientific discussion for the approval of Mecolvix 1000 mg rectal foan. The procedure was finalised at 26/12/2024. 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 Mecolvix 1000 mg rectal foam, from FAES FARMA S.A.

The product is indicated for the treatment of the acute phase of mild or moderate distal ulcerative colitis and maintenance treatment of remission in distal ulcerative colitis.
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 white to brownish coloured foam for rectal administration.
It contains 1 g of mesalazine per 5 g of foam.
The maximum daily dose 2 g daily.
The product is packed in an aerosol container consisting in a single cylindrical aluminum piece, fitted with a 5 g dosing valve.

II.2 Drug Substance

The active substance Mesalazine is sourced by one supplier and the quality is supported by CEP.

General Information

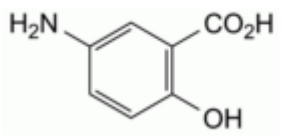
Nomenclature:

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 CEP procedure is used, information on packaging material of active substance has been assessed by EDQM.

Stability

Re-test period is included in the CEP. Stability studies have been assessed by EDQM

II.3 Medicinal Product

Description of the product

Mesalazine 1 g rectal foam is a white to brownish coloured foam for rectal administration. It contains 1 g of mesalazine per 5 g of foam. 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.

Mesalazine 1 g rectal foam is packed in an aerosol container consisting in a single cylindrical aluminum piece, fitted with a 5 g dosing valve.

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.

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 packed in an aerosol container consisting in a single cylindrical aluminum piece, fitted with a 5 g dosing valve. 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: Keep away from any source of heat, flame or ashes, including cigarettes. Protect from direct sunlight and do not destroy or burn, even when empty.

III. NON-CLINICAL ASPECTS

III.1 Introduction

As mesalazine is a well-established drug substance in the EU, the non-clinical components of the dossier have relied on an assessment of available data in the literature.

III.2 Pharmacology

Primary nonclinical pharmacological data collected, including both *in vitro* and *in vivo* studies, show that mesalazine has similar mechanisms of action in animal models of colitis as in humans.
The *in vitro* and *in vivo* secondary pharmacology studies performed in different animal models have explored the possible role of mesalazine as chemopreventive, in fibrotic diseases, in gastric mucosal injury and as an antihypertensive.
Safety pharmacological studies performed in mice, rats, and dogs, did not describe alterations related to mesalazine.

III.3 Pharmacokinetics

The pharmacokinetics of mesalazine and its metabolite, N-acetyl-5-aminosalicylic acid (N-ac-5-ASA) is well known. Nonclinical data include studies performed in mouse, rat, dog, rabbit and pig, after intra-rectal, intraduodenal, oral, or i.v. administration.
The main target organ for toxicity is the kidney; therefore, the use of mesalazine with other nephrotoxic drugs (e.g., nonsteroidal anti-inflammatory agents) may increase the risk of nephrotoxicity.

III.4 Toxicology

Single dose toxicity studies showed renal lesions in both the medulla and cortex at all doses of mesalazine tested. Nephrotoxicity and lesions of the gastrointestinal tract were observed in

repeat dose studies in rodent and non-rodent models. Repeated dose studies in rats, dogs and monkeys showed renal papillary necrosis, and ocular lesions in dogs. The no observed adverse effect level (NOAEL) were set as 80, 360 and 40 mg/kg/daily for rat, rabbit and dog respectively, and the maximum tolerated dose (MTD) was 120 and 1080 mg/kg/daily for rat and rabbit respectively.

Mesalazine does not induce any mutations *in vitro* or chromosomal aberrations *in vivo*; consequently, mesalazine is very unlike to exert genotoxic effects. No evidence of carcinogenic effects of mesalazine and no risks in the fertility and early embryonic development has been reported.

III.5 Ecotoxicity/environmental risk assessment (ERA)

An ERA phase I, Estimation of Exposure, in agreement with the "Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use" (EMEA/CHMP/SWP/4447/00 corr* 2), has been provided.

Since the PEC calculated using the refined Fpen is above the threshold set in the aforementioned guideline, a Phase II was performed.

Summary of main study results

Substance (INN/Invented Name): Mesalazine			
CAS-number (if available): 89-57-6			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	pH 4: -1.46 ± 0.004 pH 7: -2.37 ± 0.001 pH 9: -2.59 ± 0.003	Potential PBT N
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	-1.46 ± 0.004 (pH 4) -2.37 ± 0.001 (pH 7) -2.59 ± 0.003 (pH 9)	not B
Persistence	DT50 or ready biodegradability	ND	ND
Toxicity	NOEC	0.090 mg/L	not T
PBT-statement :	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC surface water, default or refined (e.g. prevalence, literature)	1.24	µg/L	> 0.01 threshold
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	OECD 106 …	K_{oc} = 105.8 and 47.4 mL/g	**KF,ocads [mL/g]** - Speyer 2.2 (Sandy loam): 3974/2726 - Speyer 2.3 (Sandy loam): 2991

					- Speyer 6S (Clay): 5277 - Tilburg (sludge): 72/66 -Aa en Maas (sludge): 32/29 **KF,ocdes [mL/g]** - Speyer 2.2 (Sandy loam): 12270 - Speyer 2.3 (Sandy loam): 12498 - Speyer 6S (Clay): 34508 - Tilburg (sludge): 167 -Aa en Maas (sludge): 70
Ready Biodegradability Test	OECD 301	60 % at the end of 10-day-window for pure substances			Readily biodegradable
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50, water}$ = $DT_{50, sediment}$ = $DT_{50, whole\ system}$ = % shifting to sediment =			Not required if readily biodegradable
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC	3850 (growth rate) 3850 (yield)	µg/L	Desmodesmus subspicatus
Daphnia sp. Reproduction Test	OECD 211	NOEC	2110 (Based on introduced parent animal) 2110 (Based on surviving parent animal) 4560 (Immobility)	µg/L	Daphnia magna

Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC	90 (hatchability) 90 (post hatch survival) ≥ 790 (wet weight) ≥ 790 (length)	µg/L	Danio rerio
Activated Sludge, Respiration Inhibition Test	OECD 209	EC	340000 (EC_{10}) 670000 (EC_{50})	µg/L	

Conclusions on studies:
Mesalazine is not a PBT substance. Considering the above data, mesalazine is not expected to pose a risk to the environment.

IV. CLINICAL ASPECTS

IV.1 Introduction

This Marketing Authorisation Application (MAA) is being submitted as a full mixed application in accordance with Article 8(3) of Directive 2001/83/EC. Accordingly, the clinical data related to mesalazine are derived from both the applicant's own studies and relevant published literature. The current formulation of Mesalazine 1000 mg rectal foam included in this MAA has the same qualitative and quantitative composition, as well as the same manufacturing process, as the product marketed by FAES Farma S.A. under the trade name Claversal. This formulation is identical to the one originally licensed from Smith Kline and used in the applicant's studies submitted with this application.

IV.2 Pharmacokinetics

For the present application the applicant has submitted one study (ACL-UK-014A) to characterize the relative bioavailability of Melcovix 1000 mg rectal foam compared to a liquid retention enema to bridge the efficacy and safety of the foam formulation compared to other with the same route of administration.
As the MAH of the present application is the licensee of GSK, the submitted study is from 1992 which was performed for the original marketing authorisation.
As the CSR is very old, only a small view of the study is presented here.

Bioequivalence study

Study ACL-UK-014A: this is a cross-over study to investigate the absorption kinetics of a 2 g -5ASA foam enema in comparison with a 1g 5ASA liquid retention enema (Pentasa) in healthy volunteers.

The results of this study demonstrated that the average maximum concentration and AUC following 2g of 5-ASA foam enema were approximately150% of those achieved with 1g of 5-ASA from a commercially available liquid retention enema. Furthermore, the plasma levels of 5-ASA and acetyl-5-ASA following foam enema administration were well within the ranges seen with several 5-ASA preparations including Asacol tablets.
Therefore, the study submitted by the applicant in terms of a relative bioavailability study comparing the foam enema vs a liquid retention enema is considered justified to cover the efficacy and safety of the present MAA from a pharmacokinetic point of view.

IV.3 Pharmacodynamics

Mesalazine has an anti-inflammatory effect in the gastrointestinal tract but its precise mechanisms of action in UC is unclear. It appears to involve several actions acting locally rather than systemically. The effectiveness of the drug is related to its mucosal concentration, and systemic dosages remain low after rectal mesalazine administration. Mesalazine is believed to interact with damaged epithelium, be converted to inactive N-acetylated-5-ASA (Ac-5-ASA), and then absorbed and excreted into the urine or excreted into stools (Sonu et al., 2010; Mesalamine AHFS Drug Information, 2023).

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.4 Clinical efficacy

The intended indications of Mesalazine 1000 mg/dose rectal foam are the treatment of the acute phase of mild or moderate distal ulcerative colitis and maintenance treatment of remission in distal ulcerative colitis. The dose and duration of the treatment should be established by the prescriber, considering the extent and severity of the disease and the patient's adherence to the treatment. In general, the recommended dose is 1 - 2 applications per day.

The present MAA is being submitted as a full mixed MAA in accordance with Article 8(3) of Directive 2001/83/EC and therefore, the clinical mesalazine-related data derives from own data and from relevant published data identified from the literature. The current formulation of Mesalazine 1000 mg rectal foam covered in the present MAA has the same quantitative and qualitative composition and the same manufacturing process as the product commercialized by FAES Farma S.A. with the tradename Claversal and it is identical to the formulation initially licenced from Smith Kline, which has been used in the Applicant’s studies included in this application.

Therefore, the proposed indications and doses for Mesalazine 1000 mg/dose rectal foam in the present MAA rely on own clinical data demonstrating the efficacy of mesalazine, as well as on data described in the scientific literature

The submitted efficacy documentation includes:

- One study owned by the Applicant using Mesalazine 1000 mg/dose rectal foam (Study ASA-IT-21).

- Monographs, scientific publications and literature review including studies using mesalazine in different rectal pharmaceutical forms (rectal foam, enema and suppositories).

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

IV.5 Clinical safety

The characterization of the safety profile of Mesalazine 1000 mg rectal foam 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 includes 13 studies to support the safety section (4 own studies and 9 clinical trials from the literature) in which patients received between 1-4 g/day of mesalazine rectal formulations. Overall, mesalazine rectal formulations show few side effects, mild in nature, mainly gastrointestinal disorders such as abdominal pain or distention, nausea and anal discomfort or irritation. The results obtained in the Applicant's studies are in line with the AEs reported in the studies from the literature.

The safety information, including results from clinical studies and data from post-marketing vigilance, adequately supports the safety of mesalazine 1000 mg rectal foam in the treatment of adult patients with acute episodes of mild to moderate UC with rectal involvement. It also supports the safety of mesalazine 1000 mg/dose rectal foam in the maintenance of remission. The observations supports a good safety profile of mesalzine 1000 mg rectal foam.

IV.6 Risk Management Plan

The MAH has submitted a risk management plan (version 1.6, 17 July 2024) , 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 Mecolvix 1000 mg rectal foam.

There are neither proposed additional pharmacovigilance activities nor proposed additional risk minimisation measures planned for Mecolvix 1000 mg rectal foam.

V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to "Claversal rectal foam" approved through a national procedure in Spain. The rationale is that the medicinal product is essentially the same, and layout and style of writing are the same in both package leaflets. The bridging report submitted by the Applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Based on the review of the data on quality, safety and efficacy, the RMS considers that the application for Mecolvix 1000 mg rectal foam is approvable.