LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Mesalazin ESPL
(mesalazine)

SE/H/2039/01/DC
2019-1473

This module reflects the scientific discussion for the approval of Mesalazin ESPL. The procedure was finalised on 2020-12-17. For information on changes after this date please refer to the module 'Update'.

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.lakemedelsverket.se E-mail: registrator@lakemedelsverket.se

I. INTRODUCTION

The application for Mesalazin ESPL, 1g, suppository, is a hybrid application made according to Article 10(3) of Directive 2001/83/EC. The applicant, ESPL Regulatory Consulting Limited, applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and AT, CZ, DE, DK, EE, EL, ES, FI, FR, IE, IS, LT, LV, NL and NO as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Salofalk, 500mg, entero depot granules authorised in Germany since 2001, with Dr. Falk Pharma GmbH as marketing authorisation holder.

The reference product used in the comparative pharmacokinetic study is Salofalk 1g Suppositorien from Germany with Dr. Falk Pharma GmbH as marketing authorisation holder.

For approved indications, see the Summary of Product Characteristics.

For recommendations to the marketing authorisation not falling under Article 21a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a or 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

III.1 Discussion on the non-clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to preclinical data, no further such data have been submitted or are considered necessary.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

To support the marketing authorisation application the applicant has conducted one comparative pharmacokinetic study of Mesalazin ESPL (mesalazine) with the reference product Salofalk.

According to Guideline on equivalence studies for the demonstration of therapeutic equivalence for locally applied, locally acting products in the gastrointestinal tract (CPMP/EWP/239/95 Rev.1 Corr.1*), in those cases where systemic bioavailability is observed, a PK bioequivalence study is required in order to address systemic safety, unless otherwise justified. In such cases plasma levels could also be used as a surrogate of equivalence in efficacy for products acting locally in the rectum and the colon (e.g. enemas) if the drug is absorbed from the sites of action. As mesalazine is a suppository with systemic bioavailability, a single-dose bioequivalence study is adequate.

Study TP0801

Methods

This was a single-dose, two-way crossover study conducted in 88 healthy volunteers, comparing Mesalazin ESPL (mesalazine), 1 g, suppository with Salofalk, 1 g, suppository. Blood samples for concentration analysis were collected pre-dose and up to 48 hours post-dose. Urine samples were collected pre-dose and up to 48 hours post-dose. Plasma concentrations of mesalazine were determined with an LC-MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for $AUC_{0\text{-}tlast}$ and C_{max}. The study was conducted between 2019-01-15 and 2019-05-29.

Results

The results from the pharmacokinetic and statistical analysis are presented in the table below.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, tmax median, range) for mesalazine in plasma, n=87.

Treatment	$AUC_{0\text{-}tlast}$ ng*h/ml	C_{max} ng/ml	t_{max} h
Test 1	**3460 ± 2420**	**227 ± 93.8**	**4.50 (2.50-48.0)**
Test 2	**4080 ± 2680**	**259 ± 131**	**5.00 (1.50-36.0)**
Reference 1	**3710 ± 2170**	**237 ± 125**	**4.00 (1.50-48.0)**
Reference 2	**3760 ± 2600**	**245 ± 110**	**4.50 (1.50-36.0)**
***Ratio (90% CI)**	**96.08 (85.23-108.30)**	**97.91 (89.84-106.70)**	**-**

$AUC_{0\text{-}t}$	area under the plasma concentration-time curve from time zero to t hours
C_{max}	maximum plasma concentration
t_{max}	time for maximum plasma concentration

**calculated based on ln-transformed data*

Discussion and overall conclusion
The bioequivalence study and its statistical evaluation were in accordance with accepted standards for bioequivalence testing, as stated in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr).

The applicant performed pharmacokinetic analysis on mesalazine and the main metabolite Ac-5-ASA (Acetylated 5-aminosalicylic acid) both in plasma and in urine.

According to the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1/Corr), in principle, evaluation of bioequivalence should be based upon measured concentrations of the parent compound. According to same guideline, the use of urinary excretion data as a surrogate for plasma concentration may be acceptable. As data for mesalazine in plasma is presented, the urinary data is considered as supportive data.

For $AUC_{0\text{-tlast}}$ and C_{max} values for mesalazine in plasma the 90 % confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00 %.

According to Guideline on equivalence studies for the demonstration of therapeutic equivalence for locally applied, locally acting products in the gastrointestinal tract (CPMP/EWP/239/95 Rev.1 Corr.1*), excipient composition should be critically reviewed since excipients may affect tolerability, systemic absorption, local residence time, *in vivo* solubility or *in vivo* stability of the active substance. The applied product has the same pharmaceutical form and the same qualitative and quantitative composition in drug substance. Thus, there are no concerns regarding the excipients in the applied product.

Based on the submitted bioequivalence study, Mesalazin ESPL (mesalazine) can be considered bioequivalent with Salofalk.

IV.2 Discussion on the clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to clinical efficacy/safety data, no further such data have been submitted or are considered necessary.

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 Mesalazin ESPL.

Safety specification
The safety concerns of mesalazine are currently published on the CMDh website and are based on the RMP of the medicinal product Salofalk 1g gastro-resistant tablets (Version 1.2 dated 17.03.2017). However, the applicant considers it necessary to update the safety concerns, in line with GVP Module V (EMA/838713/2011 Rev 2).

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	Safety in pregnancy and lactation

Pharmacovigilance Plan
Routine pharmacovigilance is suggested, and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

However, concerning the missing information on safety in pregnancy and lactation there are routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:
Specific adverse reaction follow-up questionnaires for Pregnancy, Lactation / Pattern of Use forms:

Use during pregnancy and lactation
A Pregnancy Outcome Questionnaire is used to obtain structured information on all cases of drug use during pregnancy and lactation, inter alia: General information about the mother including obstetrics and detailed information about the live born infant or foetus.

Patterns of use:
To capture information about special patterns of use, including off-label use (which indication), overdose, misuse or abuse, occupational exposure, use during pregnancy or while breastfeeding, lack of efficacy, medication error, unexpected therapeutic benefit, drug-drug interaction, a Pattern of Use Form is used to obtain structured information on the cases.

Risk minimisation measures
Routine risk minimisation is suggested, and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of the RMP
The submitted Risk Management Plan, version 1.1 signed 29 January 2020 is considered acceptable.
The removal of safety concerns currently published on the CMDh website is justified as the GVP Module V (EMA/838713/2011 Rev 2 states that concerns that only require routine pharmacovigilance activities and routine risk management measures should not be listed in the summary of safety concerns. For the missing information on safety in pregnancy and lactation a questionnaire will provide more information and hence it can be left in the summary of safety concerns.
Part 1 of the RMP should be updated with the agreed indication at the first regulatory opportunity.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of an RMP coincide, they can be submitted at the same time, but via different procedures.

V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PL) has been performed on the basis of a bridging report making reference to

* (content) the product Mezavant 1200 mg, gastro-resistant, prolonged release tablets, assessed and accepted in NL/H/0732/001/DC.
* (layout) the product Pentasa Slow Release Tablets, assessed and accepted by MHRA for the approval of
PL 03194/0108.

The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the product, Mesalazin ESPL, is found adequate. There are no objections to approval of Mesalazin ESPL from a non-clinical and clinical point of view. Bioequivalence between the test and reference product has been adequately demonstrated. The product information is acceptable.
The benefit/risk ratio is considered positive and Mesalazin ESPL, 1g, suppository is recommended for approval.

List of recommendations not falling under Article 21a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

The decentralised procedure for Mesalazin ESPL, 1g, suppository was positively finalised on 2020-12-17.

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Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.lakemedelsverket.se E-mail: registrator@lakemedelsverket.se