Medicines Evaluation Board

Public Assessment Report
Scientific discussion

Mesalazine Ipca 500 mg and 1000 mg prolonged-release tablets (mesalazine)

NL/H/6150/001-002/DC

Date: 6 August 2026

This module reflects the scientific discussion for the approval of Mesalazine Ipca 500 mg and 1000 mg prolonged-release tablets. The procedure was finalised on 27 February 2026. For information on changes after this date, please refer to section 'steps taken after finalisation' at the end of this PAR.

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List of abbreviations

AE	Adverse Event
AI	Acceptable Intake
ANOVA	Analysis of Variance
BCS	Biopharmaceutics Classification System (-based biowaiver)
BE	Bioequivalence
CBG /MEB	College ter Beoordeling van Geneesmiddelen / The Medicines Evaluation Board
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State(s)
DCP	Decentralised Procedure
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
ERP	European Reference Product
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation (of Technical Requirements for Pharmaceuticals for Human Use)
LALA	Locally applied, locally acting products
MAH	Marketing Authorisation Holder
PAR	Public Assessment Report
PD	Pharmacodynamics
Ph.Eur.	European Pharmacopoeia
PK	Pharmacokinetics
PL	Package Leaflet
PSURs	Periodic safety update reports
QC	Quality control
RH	Relative Humidity
RMP	Risk Management Plan
RMS	Reference Member State
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy
USP/NF	United States Pharmacopoeia/National Formulary

Note: *Not all abbreviations may apply for this PAR.*

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Mesalazine Ipca 500 mg and 1000 mg prolonged-release tablets, from IPCA Produtos Farmaceuticos Unipessoal Lda.

The products are indicated to treat mild to moderate forms of ulcerative colitis and Crohn's disease, both in the acute phase and to prevent recurrences.

A comprehensive description of the up-to-date indications and posology is given in the SmPC.

II. EXECUTIVE SUMMARY

II.1. Rationale for the product

The marketing authorisation was applied for pursuant to Article 10(3) Hybrid medicinal product application of Directive 2001/83/EC.

In this decentralised procedure the reference medicinal product is Pentasa 1000 mg, tabletten met verlengde afgifte, which has been authorised in the Netherlands via procedure RVG 14797 by Ferring B.V. since 12 October 1990.

This medicinal product is a locally applied and a local acting (LALA) product. To demonstrate therapeutic equivalence with the reference medicinal product, the MAH has submitted two bioequivalence studies (one under fasted conditions and one under fed conditions) with the 1000 mg strength and has requested a biowaiver for the 500 mg strength. See Section V. Clinical aspects.

This application has been assessed with The Netherlands as Reference Member State (RMS) and Germany and Spain as concerned Member States (CMS).

II.2. About the product

Mesalazine (INN), also known as mesalamine (USAN), 5-aminosalicylic acid, or 5-ASA is an amino salicylate. This drug substance has been used for more than 30 years for the treatment of inflammatory bowel disease including ulcerative colitis and Crohn’s disease. The present application concerns 500 and 1000 mg mesalazine prolonged-release tablets. The therapeutic effect of mesalazine is considered to be due to a topical anti-inflammatory effect on the colonic mucosal cells through mechanisms that have not yet been fully clarified. Mesalazine has been shown to inhibit LTB4-stimulated migration of intestinal macrophages by restricting migration of macrophages to inflamed areas. The production of pro-inflammatory leukotrienes in macrophages of the intestinal wall is thereby inhibited. Mesalazine has been shown to activate PPAR-γ receptors which counteract nuclear activation of intestinal inflammatory responses.

Pharmaco-therapeutic group (ATC Code): A07EC02
Dispensing status: Prescription Only

II.3. General comments on compliance with GMP, GLP, GCP and agreed ethical principles.

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, 'close-out letters' or 'exchange of information' issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

GMP active substance
Regarding the statement on GMP for the active substance a statement/declaration is provided from the manufacturer(s) responsible for manufacture of the medicinal product and batch release situated in the EU

GCP
Based on the data and documents submitted, the RMS has been assured that the studies were conducted and reported in compliance with GCP: a GCP statement and audit certificate(s) were provided; monitoring report(s) and recent inspection(s) by competent authorities identified no concerns relevant to the study; and, where conducted outside the EU, compliance with the ethical requirements of EU legislation (Directive 2001/20/EC or Regulation EU No. 536/2014, as relevant) was confirmed.

III. QUALITY ASPECTS

III.1. Introduction

Mesalazine Ipca 500 mg and 1000 mg are prolonged-release tablets. Each prolonged-release tablet contains 500 mg or 1000 mg mesalazine as active substance. The pharmaceutical form of the different strengths can be distinguished by their colour, size and debossing and are as follows:

Mesalazine Ipca 500 mg are off white to pale brown coloured, speckled, round tablets (diameter 13.6 mm and thickness 4.6 mm), debossed with "E" and "24" across the score line on one side and plain on the other side.

Mesalazine Ipca1000 mg are off white to pale brown coloured, speckled, oval tablets (dimensions 21.4 × 11.8 mm and thickness 7.8 mm), debossed with "CC77"on one side and plain on other side.

The break line is only to facilitate breaking so that swallowing is easier and not to divide into equal doses.

The excipients are:
Povidone K25 (E1201), ethylcellulose, acetone, magnesium stearate (E470b), cellulose, microcrystalline (E460), crospovidone (E1202), silica, colloidal anhydrous (E551), isopropyl alcohol and purified water.

The tablet content of the two strengths are dose proportional.

The prolonged-release tablets are packed in plain aluminium foil, aluminium/aluminium (Alu Alu) blisters or high-density polyethylene (HDPE) bottles with screw cap.

III.2. Active Substance

The structure of the active substance has been adequately proven and its physico-chemical properties are sufficiently described. The active substance is mesalazine, an established active substance described in the European Pharmacopoeia (Ph.Eur.) The active substance is almost white or light grey or light pink powder or crystals and is very slightly soluble in water and practically insoluble in ethanol (96%). It dissolves in diluted solutions of alkali hydroxides and in 1N hydrochloric acid.

Mesalazine exhibits polymorphism, for this product, a polymorphic form is consistently produced and demonstrated with XRPD (X-ray powder diffraction) test results.

Manufacturing process
The manufacture of the active substance has been adequately described. The used starting materials, solvents and reagents are considered acceptable. Adequate tests and acceptable specifications have been adopted for these.

Quality control of the active substance
The active substance specification includes relevant tests and the limits for impurities and degradation products have been justified in accordance with the applicable ICH Guidelines for impurities in new Drug Substances. The analytical methods applied are suitably described and non-compendial methods have adequately been validated. The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. with additional requirements for impurities and particle size distribution. Batch analytical data demonstrating compliance with this specification have been provided.

Stability of the active substance
Based on the data submitted, the stability for the active substance was confirmed for 60 months when stored under the stated conditions. This is acceptable.

III.3. Medicinal Product

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of the excipients is justified, and their functions explained. The development of the product has been described and is based on the characterisation of the medicinal reference product Pentasa 500 mg and 1000 mg Retard tabletten. The same drug substance as used in the reference product is selected for the current product. Pharmaceutical development concentrated mainly on process

development, i.e. optimisation of the prolonged-release coating and process conditions. The choices of the packaging and manufacturing process are justified.

Therapeutic equivalence for Mesalazine Ipca 500 mg and 1000 mg with the reference product was demonstrated by an bioequivalence study on the higher strength. The requested biowaiver of strength for the 500 mg strength is acceptable. Compatibility studies have shown that the drug substance is stable with the selected excipients and no significant degradation is observed. This is acceptable. Alcohol-induced dose dumping have been performed for with the 1000 mg strength. It could be observed that the percentage of drug substance release is similar both in buffer (pH 7.5) and acid medium (pH 1.2) for the test and reference product + 0% alcohol, + 5% and + 20 % (v/v) alcohol. There is no increase in percentage of drug substance release in the acid or buffer medium with 20% alcohol compared to 0% alcohol in the test product. Hence, alcohol-induced dose dumping can be excluded for the proposed drug products.

Manufacturing process

The manufacturing process is a non-standard production process. It has been sufficiently described and critical steps identified. The manufacturing process has been validated according to relevant European/ICH guidelines.

Process validation data on the product have been presented for three production scale batches of each strength in accordance with the relevant European guidelines.

Control of excipients

The excipients comply with the current version of the Ph.Eur. monograph. With additional in-house specifications for functional related characteristics (FRC's). These specifications are acceptable.

Quality control of the medicinal product

The medicinal product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for description, average weight, uniformity of weight, identification, dissolution, assay, uniformity of dosage units, related substances, impurities. residual solvents, disintegration and microbial quality. The release and shelf-life tests and limits are identical for all test parameters. Limits in the specification have been justified and are considered appropriate for the adequate quality control of the product.

An adequate risk evaluation report on nitrosamines has been submitted. No risk for the presence of nitrosamines in the medicinal product was identified. This justifies the absence of any further testing for nitrosamine impurity in the active substance and medicinal product.

Satisfactory validation data for the non-compendial analytical methods have been provided. Batch analytical data for three production scaled batches from the proposed production site(s) have been provided, demonstrating compliance with the specification.

Stability of the medicinal product

Stability data on the product filled in blisters have been provided for three commercial scaled batches of each strength stored at 25°C/ 60% RH (18 months for the 500 mg strength and 24 months for the 1000 mg strength) and 40°C/75% RH (6 months for the 500 mg and 1000 mg strengths). Furthermore, stability data on the product filled in HDPE bottles have been provided for six commercial scaled batches of each strength stored at 25°C/ 60% RH (18 months for the 500 mg strength and 24 months for the 1000 mg strength) and 40°C/75% RH (6 months for the 500 mg and 1000 mg strengths). The stability was tested in accordance with applicable European guidelines. Photostability studies were performed in accordance with ICH

recommendations. The results showed that the product is stable when exposed to light. Based on the data submitted, a shelf life of 2 years was granted. The labelled storage conditions are: "This medicinal product does not require any special storage conditions."

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.

III.4. Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the Member States consider that Mesalazine Ipca 500 mg and 1000 mg have a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and medicinal product.

IV. NON-CLINICAL ASPECTS

IV.1. Introduction

Pharmacodynamic, pharmacokinetic and toxicological properties of mesalazine are well known. As mesalazine is widely used and well established in the clinic, no further non-clinical studies are required. Overview based on literature review is appropriate.

IV.2. Pharmacology

Mesalazine (5-ASA) is an anti-inflammatory drug structurally related to the salicylates. Its mode of action is uncertain, but may be due, at least in part, to its ability to inhibit local prostaglandin and leukotriene synthesis in the gastrointestinal mucosa *(Ham & Moss, 2012; Nakashima & Preuss, 2023)*. This drug substance has been used for more than 30 years in the clinic for the treatment of inflammatory bowel disease including ulcerative colitis and Crohn's disease. No new non-clinical pharmacology studies have been submitted with the present application. Since this is a hybrid application and the posology and indications for the new product are identical to those of the reference product, there is no need for any additional non-clinical studies.

IV.3. Pharmacokinetics

Experimental data indicates that while oral administration of 5-ASA results in rapid and extensive absorption from the small intestine, only partial absorption occurs in the terminal ileum/colon *(Bilyard et al.,1990; Clerici et al., 1994; Doggwiler et al., 2023; Jin et al., 2016; Yokoe et al., 2003; Wei et al., 2010)*. Acetylation of 5-ASA to N-acetyl-5-ASA occurs in various segments of the intestine and in the liver, suggestive of gastrointestinal and hepatic first-pass metabolism *(Bilyard et al.,1990; Yokoe et al., 2003; Bilyard et al.,1990; Zhou et al., 1999)*. Absorbed 5-ASA is distributed widely and excreted in the urine, primarily in the acetylated form. *(Jin et al., 2016; Yokoe et al., 2003; Zhou et al., 1999; Clerici et al., 1994, Gutiérrez-Sánchez et al., 2021)*. No new non-clinical pharmacokinetic studies have been submitted with the present application. Since this is a hybrid application and the posology and indications for

the new product are identical to those of the reference product there is no need for any additional non-clinical studies.

IV.4. Toxicology

Previously conducted toxicology studies show that 5-ASA has low acute toxicity in rats and dogs. The main findings in repeat-dose toxicity studies were gastrointestinal toxicity, renal toxicity, and mucoid conjunctivitis *(Gutiérrez-Sánchez et al., 2021; Proctasa Mesalazine Delayed-Release Tablets: Product Monograph, 2023)*. Ophthalmic effects have not been seen in the clinic and seem to be dog-specific. 5-ASA was not genotoxic in a standard package of in vitro and in vivo studies *(CDER, Mesalazine, 2008)*. There was no evidence of carcinogenic potential in two rodent (mouse, rat) carcinogenicity studies *(CDER, Mesalazine, 2008; Proctasa Mesalazine Delayed-Release Tablets: Product Monograph, 2023; Product Monograph of Mesalazine, Takeda Canada Inc, 2021)*. 5-ASA did not affect fertility and general reproductive performance of rats. (SmPC of Pentasa 1 g prolonged-release tables, 2023; Proctasa Mesalazine Delayed-Release Tablets: Product Monograph, 2023). An embryo-foetal toxicity study in rats demonstrated maternal toxicity but showed no evidence of a teratogenic effect at the highest dose of 480 mg/kg/day. A similar study in rabbits demonstrated transient reductions in food intake but no teratogenic effect at the highest dose of 480 mg/kg/day (CDER, Mesalazine, 2008). A peri- and post-natal study in rats, with drug-related toxicity in dams treated at the 2 highest dose levels (360 and 480 mg/kg/day), produced no evidence of an effect on foetuses and pups, other than a slight and transient body weight depression in pups, which was possibly related to maternal toxicity *(Proctasa Mesalazine Delayed-Release Tablets: Product Monograph, 2023).*

No new toxicology studies have been submitted. Since this is a hybrid application and the posology and indications for the new product are identical to those of the reference product there is no need for any additional non-clinical studies.

IV.5. Ecotoxicity/environmental risk assessment (ERA)

At the time of the approval of this application, before 1 September 2024, the revised ERA guideline (EMEA/CHMP/SWP/4447/00 Rev. 1- Corr.*) was not yet applicable. Then the conclusion for this medicinal product was: since Mesalazine Ipca 500 mg and 1000 mg are intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment was therefore not deemed necessary.

IV.6. Discussion on the non-clinical aspects

The submitted non-clinical overview to support the pharmacology, pharmacokinetics and toxicology of Mesalazine Ipca 500 mg and 1000 mg is adequate. Since mesalazine is a well-known substance, the submitted non-clinical overview to support the pharmacology, pharmacokinetics and toxicology of Mesalazine Ipca 500 mg and 1000 mg is adequate and is of sufficient high quality in view of the present European regulatory requirements.

V. CLINICAL ASPECTS

V.1. Introduction

Mesalazine is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The Member States agreed that no further clinical studies are required, besides the two bioequivalence studies discussed below. The bioequivalence studies are in accordance with the EMA/CHMP/EWP/280/96 Rev1, Guideline on the Pharmacokinetic and Clinical Evaluation of Modified Release Dosage Forms Guidelines and CPMP/EWP/239/95 Rev. 1, Corr.1* Guideline on equivalence studies for the demonstration of therapeutic equivalence for locally applied, locally acting products in the gastrointestinal tract.

V.2. Pharmacokinetics

To support the application, the MAH has submitted two bioequivalence studies (one study under fed and one under fasting conditions) comparing the pharmacokinetic profiles of the test product Mesalazine Ipca 1000 mg prolonged-release tablets, from IPCA Produtos Farmaceuticos Unipessoal Lda. and the reference medicinal product PENTASA (mesalazine) prolonged-release tablets 1000 mg, Ferring B.V., Germany. A biowaiver was requested for the lower strength 500 mg. The formula and manufacturing process of the bioequivalence batch was identical to the formula proposed for marketing.

Biowaiver
According to the EMA bioequivalence guideline, the following general requirements must be met where a waiver for additional strength is claimed:

a. the pharmaceutical products are manufactured by the same manufacturing process,
b. the qualitative composition of the different strengths is the same,
c. the composition of the strengths are quantitatively proportional, i.e. the ratio between the amount of each excipient to the amount of active substance(s) is the same for all strengths (for immediate release products coating components, capsule shell, colour agents and flavours are not required to follow this rule),
d. appropriate *in vitro* dissolution data should confirm the adequacy of waiving additional *in vivo* bioequivalence testing.

The MAH performed dissolution studies at pH 1.2, 4.5 and 6.8 with the 500 mg validation batches and the 1000 mg biobatch. The calculated f_2-values were ≥ 50. An f_2 value between 50 and 100 suggests that the two dissolution profiles are similar. However, due to high RSD% values on the first timepoint, the MAH was requested to reprocessed data using bootstrap analysis in line with the with ICH M9 and the EMA Guideline on the Investigation of Bioequivalence. The bootstrap analysis of the similarity factor f_2 was performed using a validated statistical program to estimate the 90% confidence intervals of f_2. For each dissolution medium, dissolution profiles were resampled using 5,000 samples with replacement, and f_2 values were calculated for each bootstrap replicate. Dissolution similarity was interpreted as demonstrated when the lower bound of the 90% bootstrap confidence interval exceeded 50. The applied methodology is acceptable.

The lower bound of the 90% bootstrap confidence interval for f_2 exceeds 50 in the tested pH values 1.2, 4.5, and 7.5 phosphate buffer, which confirms dissolution similarity under these conditions. However, the lower bound of the 90% bootstrap confidence interval was below 50 for pH 6.8 phosphate buffer. As recommended, the MAH performed an additional dissolution

study and bootstrap analysis to evaluate the dissolution similarity between two tablets of the lower strength 500 mg and one tablet of the higher strength 1000. The lower bound of the 90% bootstrap confidence interval for f_2 exceeds 50 in pH 6.8 phosphate buffer, which confirms dissolution similarity between two tablets of the lower strength and one tablet of the higher strength under these conditions.

Based on this outcome, the comparable dissolution of the 1000 mg biobatch and the 500 mg batch is considered demonstrated. As the conditions for the biowaiver criteria are met, a biowaiver for the lower 500 mg strength has been granted. Furthermore, comparative *in-vitro* dissolution data between the test and reference products are not provided since the reference product was not available. However, given that bioequivalence has been demonstrated *in vivo* for the highest strength, and that dissolution similarity between the reference and test products of the 1000 mg strength has been shown, at 100 RPM, *the in-vivo* data are considered to prevail from a pharmacokinetic standpoint.

Bioequivalence studies

Study C1B01823: single dose study under fasting conditions

Design
A single-dose, randomised, open label, two-treatment, four-period, two-sequence, fully replicate, crossover, balanced, oral bioequivalence study was carried out under fasted conditions in 130 healthy male subjects, aged 18-44 years. Each subject received a single dose (1000 mg) of one of the two mesalazine formulations. The tablet was orally administered with about 240 mL water after a overnight fasting period of at least eight hours. The subjects were divided in two groups. There were four dosing periods, separated by a washout period of 10 to 15 days.

The plasma concentration time curve was used to assess the rate and extent of absorption. Blood samples were collected pre-dose and at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, 10, 11, 12, 13, 14, 16, 24, 36 and 48 hours after administration of the products.

Results
From the 130 subjects, two subjects were discontinued from the study, because they did not reported during check in at period 1. Fifteen subjects were discontinued from a period but completed at least two periods of which one period with the reference product and one with the test product. Reasons for withdrawal from a period were: 3 subjects due to adverse events (skin abrasion (1), vomiting (1) and increased blood creatinine (1)), 6 subjects due to protocol violation (positive for drug of abuse), 2 subjects due to housing deviations, 1 subject due to personal reasons and 5 subjects did not report for the next period. A total of 128 subjects completed the study and were included in the statistics for bioequivalence evaluation. The pharmacokinetic results are shown in table 1.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of mesalazine, 1000 mg under fasted conditions.

Treatment N=128	AUC_{0-4} ng/ml/h	AUC_{4-t} ng/ml/h	AUC_{0-t} ng/ml/h	$AUC_{0-t\ last}$ ng/ml/h	$AUC_{0-\infty}$ ng/ml/h	C_{max} ng/ml	t_{max} h
Test	1684.0 ± 956.0	1503.5 ± 939.3	3158.8 ± 1455.1	3187.5 ± 1464.4	3295.5 ± 1464.6	1082.0 ± 727.7	2.0 (0.5-7.0)
Reference	1367.0 ± 753.3	1471.7 ± 1085.4	2800.8 ± 1426.6	2838.7 ± 1444.3	2963.7 ± 1469.4	914.6 ± 705.7	2.5 (0.5-7.5)
***Ratio (90% CI) CV%**	125.6 (117.7-134.0) 45.6	103.8 (96.71-111.5) 50.4		113.9 (108.3-119.8) 34.7	113.1 (107.6-118.9) 34.6	120.7 (113.0-128.8) 46.1	

$AUC_{0-\infty}$	Area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t}	Area under the plasma concentration-time curve from time zero to the last measurable plasma concentration / to t = 44 hours
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval
*	Back-transformed from ln-transformed least-squares mean values

Study C1B01824: single dose study under fed conditions

Design

A single-dose, randomised, open label, two-treatment, four-period, two-sequence, fully replicate, crossover, balanced, oral bioequivalence study was carried out under fasted conditions in 150 healthy male subjects, aged 18-44 years. Each subject received a single dose (1000 mg) of one of the two mesalazine formulations. The tablet was orally administered with about 240 mL water after a overnight fasting period of at least eight hours. 30 minutes prior to scheduled dosing time, the subjects consumed within 30 minutes a standardised high fat, high calorie breakfast (with a total of 956 calories). The subjects were divided in three groups There were four dosing periods, separated by a washout period of 8 to 20 days.

The plasma concentration time curve was used to assess the rate and extent of absorption. Blood samples were collected pre-dose and at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, 10, 11, 12, 13, 14, 16, 24, 36 and 48 hours after administration of the products.

Results

From the 150 subjects, one subject was discontinued from the study, due to an adverse event (headache). Fifteen subjects were discontinued from a period but completed at least two periods of which one period with the reference product and one with the test product. Reasons for withdrawal from a period were: 2 subjects due to adverse events (skin abrasion (1) and diarrhoea) (1), 4 subjects due to protocol violation (positive for drug of abuse) and 8 subjects did not report for the next period. A total of 144 subjects completed the study and were included in the statistics for bioequivalence evaluation. The pharmacokinetic results are shown in table 2.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of mesalazine, 1000 mg under fed conditions.

Treatment N=144	AUC_{0-5} ng/ml/h	AUC_{5-t} ng/ml/h	AUC_{0-t} ng/ml/h	$AUC_{0-t\ last}$ ng/ml/h	$AUC_{0-\infty}$ ng/ml/h	C_{max} ng/ml	t_{max} h
Test	1925.3 ± 1351.0	2435.2 ± 1474.5	4367.1 ± 2247.2	4360.5 ± 2245.8	4463.2 ± 2221.5	1581.5 ± 1070.1	4.5 (1.5-14.0)
Reference	2138.9 ± 1954.3	2656.0 ± 1797.3	4804.9 ± 3015.6	4794.8 ± 3013.2	4873.8 ± 2996.9	1835.0 ± 1411.1	4.5 (1.5-13.0)
***Ratio (90% CI) CV%**	101.2 (93.1-110.1) 65.8	94.5 (88.9-100.4) 45.4		94.0 (88.8- 99.5) 42.8	95.0 (89.8-100.5) 41.9	88.8 (82.2- 96.0) 60.6	

$AUC_{0-\infty}$	Area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t}	Area under the plasma concentration-time curve from time zero to the last measurable plasma concentration / to t = 48 hours
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval
*	Back-transformed from ln-transformed least-squares mean values

The bioequivalence studies under fed and fasting conditions were considered necessary as according to the SmPC, the product should be administered with some water or yogurt and in case of stomach complaints, the tablets can be taken during or just after a meal. The design of both studies were considered acceptable.

Bioanalytical/statistical methods
The bioanalytical method has been adequately validated according to current guidelines (ICH Guideline M10 on bioanalytical method validation) and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Conclusion on bioequivalence studies:
C_{max}, AUC_{0-5}, AUC_{5-t}, $AUC_{0-tlast}$, and $AUC_{0-\infty}$ of the Test and Reference products are contained within the (widened) acceptance ranges. In the ANOVA model no significant period effect was observed. Cmax was not observed in the first sampling point in any case. Based on the submitted bioequivalence studies Mesalazine Ipca 1000 mg is considered bioequivalent with Pentasa 1000 mg under fasted and fed conditions.

As a biowaiver has been granted, the results of studies C1B01823 and C1B01824 with the 1000 mg formulation can be extrapolated to the lower strength of 500 mg, in accordance with the conditions in the applicable guidelines (EMA/CHMP/EWP/280/96 Rev1 and CPMP/EWP/239/95 Rev. 1, Corr.1*).

V.3. Pharmacodynamics/ Clinical efficacy and Clinical safety

For this hybrid application no new studies on pharmacodynamics, clinical efficacy or clinical safety have been submitted. Instead an overview based on literature have been submitted. This is acceptable.

The therapeutic effect of mesalazine is considered to be due to a topical anti-inflammatory effect on the colonic mucosal cells through mechanisms that have not yet been fully clarified.

Studies in adults have evidenced the therapeutic efficacy of mesalazine in the treatment of mild to moderate ulcerative colitis and Crohn's disease. The MAH has provided detailed information on efficacy studies in the Clinical Overview.

Safety profile of mesalazine is well established in published literature. In clinical studies the mesalazine is well tolerated. The common AEs related to mesalazine administration are reported ascolitis (including ulcerative colitis), abdominal pain, headache, diarrhea, and nausea. The MAH has provided detailed information on adverse events in the Clinical Overview.

V.4. Summary Pharmacovigilance system

The MAH has submitted a signed Summary of the MAH's and/or Proposed Future MAH's Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module, the RMS considers the Summary acceptable.

V.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 to Mesalazine Ipca 500 mg and 1000 mg prolonged-release tablets. At the time of approval, the accepted version of the RMP was version 0.1 with sign-off date 9 August 2024.

Table 3. Summary table of safety concerns as approved in the RMP

Important identified risks	None
Important potential risks	None
Missing information	None

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

V.6. Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the reference medicinal product PENTASA prolonged-release tablets 1000 mg. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This current medicinal product can be

used instead of the medicinal reference product. The clinical aspects of this product are approvable.

VI. USER CONSULTATION

The package leaflet (PL) has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PL was English.

The test consisted of: a pilot test with 4 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VII. POST-APPROVAL COMMITMENTS (PAC's)

Post-approval commitments: not applicable.

VIII. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Mesalazine Ipca 500 mg and 1000 mg prolonged-release tablets have a proven chemical-pharmaceutical quality and hybrid forms of Pentasa 1000 mg prolonged-release tablets. Pentasa is a well-known medicinal product with an established favourable efficacy and safety profile.

For the 1000 mg strength, bioequivalence has been shown between the test and reference medicinal products, in line with the requirements of European guidance documents.

Therapeutic equivalence with the reference medicinal product has been shown by the comparison of the dosage form, qualitative and quantitative composition and the results of *in vitro* studies on the relevant quality attributes. A biowaiver has been granted.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between Member States was reached during a written procedure. The Member States, based on the data submitted, considered that essential similarity has been demonstrated for Mesalazine Ipca 500 mg and 1000 mg prolonged-release tablets with the reference medicinal product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 27 February 2026.

IX. RECOMMENDATIONS AND CONDITIONS FOR MARKETING AUTHORISATION AND PRODUCT INFORMATION

IX.1. List of recommendations not falling under Article 21a/22 of Directive 2001/83/EC

N.A.

IX.2. List of conditions pursuant to Article 21a or specific obligations pursuant to Article 22 of Directive 2001/83/EC

N.A

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STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
N.A.	N.A.	N.A.	N.A.	N.A.	N.A.