COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Famotidine Prolepha 20 mg and 40 mg, film-coated tablets (famotidine)

NL License RVG: 129840-1

Date: 14 June 2024

This module reflects the scientific discussion for the approval of Famotidine Prolepha 20 mg and 40 mg, film-coated tablets. The procedure was finalised on 7 June 2023. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
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
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
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
RMS	Reference Member State
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Medicines Evaluation Board (MEB) of the Netherlands has granted a marketing authorisation for Famotidine Prolepha 20 mg and 40 mg, film-coated tablets, from Prolepha Research B.V.

The product is indicated for the treatment of the following conditions that require a reduction in gastric acid secretion:

- duodenal ulcers (ulcera duodeni) and benign stomach ulcers (ulcera ventriculi)
- Zollinger-Ellison syndrome
- mild to moderate reflux oesophagitis

And only for the 20 mg strength:

- the prevention (prophylactic treatment) of recurrent duodenal ulcers.

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

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC, which concerns a generic application.

In this national procedure, essential similarity is proven between the new product and the innovator product Pepcid 10 mg film-coated tablets which has been registered in Spain (MA (EU) Number 62090) by Johnson & Johnson S.A. since 1 May 1998.

II. QUALITY ASPECTS

II.1 Introduction

Famotidine are film-coated tablets and contains as active substance famotidine 20 mg or 40 mg. The two strengths of the tablets can be distinguished by their colour and size and are as follows:

Famotidine 20 mg is presented as hexagonal, biconvex, brown film-coated tablet. The dimensions of the tablets are 7 mm from tip to tip and 6.2 mm from edge to edge.

Famotidine 40 mg is presented as circular, biconvex, pink film-coated tablet with a break line on one side. The dimension of the tablets is 8 mm.

The excipients are:
Tablet core - pregelatinised starch, microcrystalline cellulose (E460), talc (E553b), magnesium stearate (E470b), iron oxide red (E172).
Tablet Coat – hypromellose (E464), macrogol and titanium dioxide (E171),

- Only for the 20 mg tablet: talc (E553b), and iron oxide yellow/red/black (E172).
- Only for the 40 mg tablet: indigo carmine aluminium lake (E132), quinoline yellow aluminium lake (E104), azorubine aluminium lake (E122).

The two tablet strengths are dose proportional.

The coated tablets are packed in comprised polyvinyl chloride (PVC) aluminium blisters strips. The blisters are packed in a cardboard box.

II.2 Drug Substance

The active substance is famotidine, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a white or yellowish-white crystalline powder and is very slightly soluble in water. Famotidine crystallises in two different polymorphic forms, the metastable polymorph B and the stable polymorph A. According to the MAH the polymorphic form is not critical for the drug product. Famotidine is achiral.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The active substance specification is as stated in the CEP with additional requirements for particle size distribution. The specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. Batch analytical data demonstrating compliance with this specification have been provided for six batches (four from Site I and two from Site II).

Stability of drug substance
The active substance is stable for 5 years when stored under the stated conditions. Assessment thereof was part of granting the CEP (and has been granted by the EDQM).

II.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 excipients is justified and their functions explained. Comparative impurity profiles between the reference product and the test product have been provided showing that the impurity profiles of both products are similar. The 40 mg strength has a break line on one side; it has been shown that this break line can be used to divide the tablets into equal halves.

A bioequivalence study (BE) was performed with the 40 mg strength, produced by the proposed commercial manufacturing process, and the reference product. *In vitro* dissolution tests complementary to the bioequivalence studies were performed at pH 1.2 HCl 0.1N, pH 4.5 acetate buffer, pH 6.8 phosphate buffer and pH 4.5 QC medium. The dissolution profiles of the test (1 tablet of 40 mg) and the reference product (4x tablets of 10 mg) are similar, all with more than 85% dissolution within 15 minutes. A biowaiver was requested for the 20 mg strength, see details in section IV.2. The pharmaceutical development of the product has been adequately performed.

Manufacturing process

The product is manufactured using conventional manufacturing techniques. The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for seven commercial scale batches (four 20 mg and three 40 mg) in accordance with the relevant European guidelines.

Control of excipients

Excipients pregelatinised starch, microcrystalline cellulose, talc and magnesium stearate comply with Ph. Eur. requirements. Iron oxide complies with the USP, and for the coating blends in-house specifications have been set. These specifications are acceptable.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, uniformity of dosage units, identity, assay, related substances and total impurities, dissolution, residual solvent and microbiological quality. The release and shelf-life specifications are identical. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. An adequate nitrosamines risk evaluation report has been provided. No risk for presence of nitrosamines in the drug product was identified.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from seven production scaled batches (four 20 mg and three 40 mg) from the proposed production sites have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product has been provided for four full scale batches of the 20 mg strength and three full scale batches of the 40 mg strength. The batches were stored at 25°C/ 60% RH (36 months for one batch of both strengths, 24 months for one batch of the 40 mg strength and 3 batches of the 20 mg strength and 18 months for one batch of the 40 mg strength) and 40°C/ 75%RH (all 6 months). The stability was tested in accordance with applicable European guidelines. For one batch of the 40 mg strength an out-of-specification (OOS) result is observed for assay, based on this result the MAH proposed to store the 40 mg tablets below 25°C. Other tested parameters were within the limits with no significant variations. Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light. On basis of the data submitted, a shelf life was granted of 3 years. For the 20 mg strength, no specific storage conditions

needed to be included in the SmPC or on the label. For the 40 mg strength, the labelled storage conditions are 'Store below 25°C'.

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.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the MEB considers that Famotidine Prolepha has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Famotidine Prolepha is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Pepcid 10 mg film-coated tablets which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the MEB agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Famotidine is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The MEB agreed

that no further clinical studies are required, besides the bioequivalence study discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Famotidine Prolepha 40 mg, film-coated tablets (Prolepha Research B.V.) was compared with the pharmacokinetic profile of the reference product Pepcid 10 mg tablets Pepcid 10 mg film-coated tablets (Johnson & Johnson S.A., Spain).

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution study results and composition. The formula and preparation of the bioequivalence batch was identical to the formula proposed for marketing. The batches are acceptable. For the 20 mg strength, a biowaiver was requested.

Biowaiver

The following general requirements must be met where a waiver for additional strength is claimed, according to the EMA Bioequivalence guideline CPMP/EWP/QWP/1401/98 Rev. 1/ Corr):

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 is 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 dissolution profiles of the 20 mg and 40 mg strengths (12 units of each strength per test) were studied at pH 1.2 HCl 0.1N, pH 4.5 acetate buffer and pH 6.8 phosphate buffer. Dissolution similarity at the three tested pHs between the 20 mg and 40 mg has been demonstrated, more than 85% of the active is released within 15 minutes. With these results, the requirements for the biowaiver for the additional strength have been met.

Bioequivalence studies

Design

A single-dose, open label, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 46 healthy male subjects, aged 18-44 years. Each subject received a single dose (Test 1X 40 mg or Reference 4x 10 mg) of one of the two famotidine formulations. The tablets were orally administered with 240 mL water after overnight fasting for at least 10 hours before the scheduled start time of dosing and 4 hours after dosing. Except for the water given for dosing, drinking water was not allowed from 1 hour before dosing until 1 hour post-dose. There were two dosing periods, separated by a washout period of two days.

Famotidine was analysed in plasma. Blood samples were collected pre-dose and at 0.5, 1.0, 1.3, 1.7, 2.0, 2.3, 2.7, 3.0, 3.3, 3.7, 4.0, 4.5, 5.0, 6.0, 8.0, 10, 12, 16 and 24 hours after administration of the products.

Famotidine may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of Famotidine. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

Analytical/statistical methods
The analytical method has been adequately validated 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.

Results
In the protocol, it was specified that 2 additional subjects may be enrolled to handle any dropout/withdrawal before the period I-dosing. A total of 46 + 2 subjects were enrolled in the study. The two additional subjects were checked out from the facility after the completion of the period I-dosing. No subjects were withdrawn during the study, the 46 subjects completed the study and were included in the pharmacokinetic analyses.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of famotidine, 40 mg under fasted conditions.

Treatment N=46	**AUC_{0-t} (ng.h/mL)**	**$AUC_{0-\infty}$ (ng.h/mL)**	**C_{max} (ng/mL)**	**t_{max} (h)**
Test	1067 ± 279	1102 ± 292	155± 43	2.0 (1.0 – 4.5)
Reference	1079± 336	1113 ± 354	162 ± 52	2.0 (1.0 – 5.0)
***Ratio (90% CI)**	1.00 (0.93 – 1.07)	1.00 (0.93 – 1.07)	0.97 (0.89 – 1.05)	-

$AUC_{0-\infty}$	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 = 24 hours
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**ln-transformed values*

Conclusion on bioequivalence study:
The 90% confidence intervals calculated for AUC0-t, AUC0-∞ and Cmax are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study, Famotidine Prolepha is considered bioequivalent with Pepcid 10 mg film-coated tablets under fasted conditions. Furthermore, the results of study with the 40 mg formulation can be

extrapolated to strength 20 mg, according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

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 Famotidine Prolepha.

Table 2. Summary table of safety concerns as approved in RMP

Important identified risks	• Hypersensitivity reactions • Impaired ability to drive and use machines
Important potential risks	• Potential for delayed diagnosis and/or treatment of other more serious medical conditions due to temporary relief of symptoms
Missing information	• Use in children

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

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Pepcid. 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 generic medicinal product can be used instead of the reference product.

V. 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 four participants, followed by two rounds with ten 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.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Famotidine Prolepha 20 mg and 40 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Pepcid 10 mg film-coated tablets. Pepcid is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The Board followed the advice of the assessors.

The MEB, on the basis of the data submitted, considered that essential similarity has been demonstrated for Famotidine Prolepha with the reference product, and have therefore granted a marketing authorisation. The national procedure was finalised with a positive outcome on 7 June 2023.

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
1037876	Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of human medicinal products intended to implement the outcome of a procedure concerning PSUR or PASS, or the outcome of the assessment done by the competent authority under Articles 45 or 46 of Regulation 1901/2006SmPCSmPC: - Implementation of wording agreed by the competent authority.	Yes	22-9-2023	Approved	N.A.