COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

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

NL/H/5960/001-002/DC

Date: 2 July 2026

This module reflects the scientific discussion for the approval of Famotidine Aurobindo 20 mg and 40 mg, film-coated tablets. The procedure was finalised on 5 June 2025. 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 Member States have granted a marketing authorisation for Famotidine Aurobindo 20 mg and 40 mg, film-coated tablets, from Aurobindo Pharma B.V.

The product is indicated in adults for:

- Prevention of recurrent duodenal ulcers (only for 20 mg)
- Duodenal ulcer
- Benign gastric ulcer
- Zollinger-Ellison-syndrome
- Symptomatic treatment of mild reflux oesophagitis (only for 20 mg)
- Treatment of mild to moderate reflux oesophagitis (only for 40 mg)

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

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC, which concerns a hybrid application.

In this decentralised procedure, therapeutic equivalence is proven between the new product and a European Reference Product (ERP), Pepcid 10 mg film-coated tablets, which has been registered in Spain via a procedure (MA (EU) Number 62090) by Johnson & Johnson S.A. since 1 May 1998.
The justification to use this product is based on information received from Spain.
Famotidine Aurobindo is shown to be therapeutically equivalent to the reference medicinal product Pepcid of Spain. The pharmaceutical strength and therapeutic indications of Famotidine Aurobindo are different from Pepcid.

The concerned member state (CMS) involved in this procedure was Germany.

II. QUALITY ASPECTS

II.1 Introduction

Famotidine Aurobindo 20 mg and 40 mg are film-coated tablets. The film-coated tablets are white coloured and oblong shaped. The two strengths of the film-coated tablets can be distinguished by size and debossing as follows:

Famotidine Aurobindo 20 mg
Approximately 8.1 x 4mm, film coated tablets debossed with '20' on one side and plain on the other side. Each tablet contains as active substance 20 mg of famotidine.

Famotidine Aurobindo 40 mg
Approximately 10.1 x 6.1mm, film coated tablets debossed with '40' on one side and a breakline on other side. The tablets can be divided into equal doses. Each tablet contains as active substance 40 mg of famotidine.

The excipients are:
Tablet core – microcrystalline cellulose (grade 101 & 102), maize starch, sodium starch glycolate (type A), hypromellose 2910 (5mPas) (E464), and magnesium stearate.
Tablet coating – hypromellose 2910 (15mPas) (E464), hydroxypropylcellulose (6-10mPas) (E463), calcium carbonate (E170), talc (E553b), and carnauba wax (E903).

The two tablet strengths are dose proportional.

The film-coated tablets are packed in white opaque polyvinyl chloride – Aluminium (PVC-Alu) foil blister packs.

II.2 Drug Substance

The active substance is famotidine, an established active substance described in the European Pharmacopoeia (Ph.Eur.). Famotidine is a crystalline powder and is very slightly soluble in water. Famotidine is achiral. For this product, polymorphic form B is consistently produced.

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 considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. as well as additional requirements for the residual solvents, a specific intermediate, polymorph control, particle size, and microbiological quality. Batch analytical data demonstrating compliance with this specification have been provided for two full scaled batches.

Stability of drug substance
Stability data on the active substance have been provided for three full scaled batches in accordance with applicable European guidelines demonstrating the stability of the active substance. Based on the data submitted, a retest period could be granted of 48 months when stored under the stated conditions.

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 dissolution testing at 3 pHs has been successfully performed in support of the bioequivalence study and the biowaiver of strength for the 20 mg strength. The choices for packaging and manufacturing process are justified. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing process has been validated according to relevant European/ICH guidelines. The process consists of sifting, mixing, wet granulation, wet milling, drying, sifting, mixing, blending, lubrication, tablet compression and coating. Process validation data on the product have been presented for two full scaled batches per strength in accordance with the relevant European guidelines. The product is manufactured using conventional manufacturing techniques. Process validation for full-scale batches will be performed post authorisation.

Control of excipients
The excipients comply with Ph. Eur. requirements, except for the coating mixture which is controlled according to an in-house specification. 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 description, identification, dissolution, related substances, assay, uniformity of dosage units, water, average mass, microbial contamination and subdivision of tablets for the 40 mg strength. 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 two full scaled batches per strength from the production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided from two minimum size production batches per strength stored at 25°C/60% RH (24 months) and 40°C/75% RH (6 months) in accordance with applicable European guidelines. Photostability studies showed that the product is stable when exposed to light. On basis of the data submitted, a shelf life was granted of 24 months. Through a variation procedure, an updated shelf life was granted of 36 months (see 'steps taken after finalisation' at the end of this PAR).
No specific storage conditions needed to be included in the SmPC or on the label.

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 member states consider that Famotidine Aurobindo 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)

At the time of submission of this application, before 1 September 2024, the revised ERA guideline (EMEA/CHMP/SWP/4447/00 Rev. 1- Corr.*) was not yet applicable. At the time of approval the conclusion for this medicinal product was:
Since Famotidine Aurobindo is intended for hybrid substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment was therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a hybrid formulation of Pepcid 10 mg which is available on the European market. Reference was made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which was 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 member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Since the indications for Famotidine Aurobindo 20 mg and 40 mg differ from the indications of the reference product Pepcid 10 mg, the MAH refers to the published scientific literature to demonstrate clinical efficacy and safety of famotidine. A clinical overview has been provided.
To demonstrate clinical efficacy of famotidine 20 mg and 40 mg in the indications the MAH refers to the published literature. Various studies are cited, where the experimental drugs were innovator products (Pepcid, Pepcid AC, Pepcid Akut, Pepcidac, Pepcidin, Pepcidina, Pepcidine, Pepcidin M, Pepdin, Pepdine, Pepdul, Peptan, Gastridin, Motiax, Mylanta, Tamin, Amfamox, Efficid, Gaster, MK-208, YM-11170, etc.), or the study sponsor or manufacturer were the innovator companies (Yamanouchi, J&J, Johnson, Janssen, JNTL, Merck, MSD, MSDRL, JJMCP, McNeil, etc.) for the studies (Alcala-Santaella et al., 1989; Barbara et al., 1985; Berlin et al., 1991; Brazer et al., 1989; Decktor et al., 1998; Feldman, 1996; Gitlin et al., 1987; Gottlieb et al., 1995; Howard et al., 1985; Howard et al., 1985; Humphries et al., 1991; Kawano et al., 2002; Laskin et al., 1993; McCallum et al., 1985; Miner et al., 2007; Miwa et al., 1984; Paoluzi et al., 1985; Robinson et al., 1991; Rodrigo et al., 1989; Simon et al., 1993; Simon et al., 1994; Simon et al., 1995a; Simon et al., 1995b; Taha et al., 2009).

According to the clinical overview, the innovators of the 10 mg famotidine reference medicinal product (Merck or Johnson & Johnson–Merck Consumer Pharmaceuticals Co. joint venture) were the sponsor or manufacturer of all the submitted publications for all applied indications. The 10 mg famotidine reference medicinal product used in the bioequivalence study was used in some of the publications, in other publications 20 mg or 40 mg strengths were used. Although in several publications the dose strengths of respective famotidine medicinal products were different or may differ from the 10 mg famotidine reference medicinal product, the clinical effects of equipotent famotidine dosing of different famotidine dose strength of the same pharmaceutical company will be the same. Hence, the clinical effects of the 10 mg famotidine reference medicinal product can be extrapolated from the known indication in which the 10 mg famotidine reference medicinal product has been used (symptomatic treatment of mild reflux oesophagitis) to the other applied indications. This also applies to the famotidine 20 and 40 mg film-coated tablets in this marketing authorisation application, since

the MAH demonstrated that these tablets are bioequivalent to the 10 mg famotidine reference medicinal product Pepcid 10 mg film-coated tablets.

In conclusion, the MAH appropriately justified for all applied indications that the clinical effects of Famotidine Aurobindo 20 mg and 40 mg, film-coated tablets are similar to the famotidine medicinal products that were used in the submitted publications from literature. Hence, bridging between the Famotidine Aurobindo 20 mg and 40 mg, film-coated tablets and famotidine medicinal products that were used in publications from literature has been demonstrated appropriately.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Famotidine Aurobindo 40 mg, film-coated tablets (Aurobindo Pharma B.V., the Netherlands) was compared with the pharmacokinetic profile of the reference product Pepcid 10 mg film-coated tablets (Johnson and 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 for marketing.

Biowaiver

The following general requirements are met where a waiver for the additional 20 mg strength is claimed, according to the EMA Bioequivalence guideline:

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 formulation of Famotidine Aurobindo 20 mg, film-coated tablets was compared with Famotidine Aurobindo 40 mg, film coated tablets. Both formulations have a similar composition and had a dissolution of >85% after 15 minutes in 0.1 N HCl, pH 4.5 acetate buffer and pH 6.8 phosphate buffer at standard conditions. The calculated f_2 similarity factor values were within criteria (>50%). An f_2 value between 50 and 100% suggests that the two dissolution profiles are similar.
In earlier studies dose proportionality was reported for oral dosing of 5 mg to 40 mg famotidine.
The biowaiver request for Famotidine Aurobindo 20 mg is considered acceptable.

Bioequivalence study 144-21

Design

A balanced, open label, single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 40 healthy subjects,

aged 22-44 years. Each subject received a single dose (40 mg) of one of the two famotidine formulations (either 1 tablet of 40 mg of the test product, or 4 tablets of 10 mg of the reference product). The tablet was orally administered with 240 mL water after an overnight fast of at least 10 hours. There were two dosing periods, separated by a washout period of 8 days.

Blood samples were collected pre-dose and at 0.33, 0.67, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.50, 4, 5, 6, 8, 10, 12, 16, 20 and 24 hours after administration of the products.

The design of the study is acceptable.

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
All 40 subjects were eligible for pharmacokinetic analysis.

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

Treatment N=40	**AUC_{0-t} (ng.h/mL)**	**$AUC_{0-\infty}$ (ng.h/mL)**	**C_{max} (ng/mL)**	**t_{max} (h)**
Test	791 ± 28	821 ± 28	120 ± 30	2.17 (1.00 – 4.00)
Reference	778 ± 27	807 ± 27	118 ± 30	2.00 (1.00 – 6.00)
***Ratio (90% CI)**	1.02 (0.94 – 1.09)	-	1.01 (0.93 – 1.10)	-

$AUC_{0-\infty}$	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 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 AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Famotidine Aurobindo 40 mg is considered bioequivalent with Pepcid 10 mg.

The results of study 144-21 with 40 mg formulation can be extrapolated to the other 20 mg strength, 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 Pharmacodynamics

The MAH provided an overview of the published literature to demonstrate the pharmacodynamics of famotidine. As famotidine is a widely used, well-known active substance, the applicant has not performed additional studies. Bridging between the famotidine medicinal products in literature and the proposed Famotidine Aurobindo 20 mg and 40 mg film-coated tablets has been demonstrated appropriately.

IV.4 Clinical efficacy

Since the indications for Famotidine Aurobindo differ from the indications of the reference product, the MAH refers to the published literature to demonstrate clinical efficacy of famotidine in each of the proposed indications. In total 24 studies are cited, where the experimental drugs were innovator products, or the study sponsor or manufacturer were the innovator companies.

As famotidine is a widely used, well-known active substance, the MAH has not performed additional studies.
No search strategy or method of selection of publications is reported. Therefore it is not clear whether the literature overview is comprehensive. However, the provided literature sufficiently supports the efficacy of famotidine in the proposed indications.

Several placebo-controlled, active-controlled and non-controlled clinical studies have evaluated the efficacy of famotidine in the proposed indications. Famotidine was found to be superior to placebo in the prevention of recurrent duodenal ulcers, treatment of duodenal ulcer, benign gastric ulcer, and treatment of mild to moderate reflux oesophagitis. Active-controlled studies support the efficacy of famotidine in the indications mentioned above, as well as in Zollinger-Ellison syndrome.

Regarding the therapeutic indications, as stated in the SmPC guideline, it should be specified in which age groups the product is indicated, e.g. ‘X is indicated in adults’. Currently, no age groups are specified in the therapeutic indications. A contra-indication for use in children is included based on a lack of information about the safety and efficacy of famotidine in children. However, according to the current SmPC guideline, lack of information should not lead to a contra-indication unless a safety issue can be predicted. Upon request, MAH did not indicate that there are any particular safety concerns of famotidine for children. Therefore, use of famotidine in the pediatric population should not be contra-indicated.
SmPC sections 4.1, 4.2, 4.3 and 4.4 should be amended with regard to the paediatric population and other special populations, in accordance with the current SmPC guideline

(2009) and EMA guidance on the wording of a therapeutic indication (EMA/CHMP/483022/2019).

IV.5 Clinical safety

The MAH proviuded an overview of the published literature to demonstrate clinical safety of famotidine 20 mg and 40 mg. As famotidine is a widely used, well-known active substance, the applicant has not performed additional studies.

Overall, famotidine is well tolerated and the safety profile is in accordance with other H2-receptor antagonists. At a later stage, the MAH appropriately demonstrated that the clinical safety of the famotidine medicinal products in literature can be extrapolated to the proposed Famotidine Aurobindo 20 mg and 40 mg film-coated tablets.

The safety-related sections of the proposed SmPC did initially not fully reflect the information provided in the clinical overview. Later, the MAHadjusted SmPC sections 4.4 (monitoring of blood count and liver function in case of long term treatment with high dosage, abrupt withdrawal after symptom relief in case of longstanding ulcer disease) and 4.7 (impact of famotidine on the ability to drive and use machines) appropriately in this respect.

IV.6 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 Aurobindo. At the time of approval, the most recent version of the RMP was version 1.2 dated 9 April 2025.

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

IV.7 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Pepcid 10 mg. The MAH demonstrated through a bioequivalence study and a biowaiver that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product.
Risk management is adequately addressed. This hybrid medicinal product can be used instead of the reference product. The clinical aspects of this product are approvable.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Famotidine Prolepha 20 mg and 40 mg film-coated tablets (National RVG 129840 and 129841) for key messages and to Metoprolol Aurobindo 50 mg and 100 mg film-coated tablets (SE/H/120l/001-002/DC) for both design and layout. The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Famotidine Aurobindo 20 mg and 40 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are a hybrid form 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.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Famotidine Aurobindo with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 5 June 2025.

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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
NL/H/5960/001-2/IB/001/G	Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes	Yes	3 August 2025	Approved	N/A
NL/H/5960/001-2/IB/002	Change in the shelf-life or storage conditions of the finished product - Extension of the shelf life of the finished product - As packaged for sale (supported by real time data)	Yes	15 September 2025	Approved	N/A