COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

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

NL/H/6144/001-002/DC

Date: 6 July 2026

This module reflects the scientific discussion for the approval of Famotidine Centrafarm 20 mg and 40 mg, film-coated tablets. The procedure was finalised on 10 October 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
BE	Bioequivalence
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 Centrafarm 20 mg and 40 mg, film-coated tablets, from Centrafarm B.V.

The product is indicated in adults for:

- duodenal ulcer
- benign gastric ulcer
- Zollinger-Ellison-Syndrome
- prevention of recurrent duodenal ulcers (only for 20 mg)
- 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.

This application has been assessed with The Netherlands as Reference Member State (RMS) and Austria, France, Germany, Ireland, Italy, Malta and Spain as concerned member states (CMS).

The reference medicinal product used in the RMS (NL) and the CMS's, with the exception of Spain, is the European Reference product (ERP) Pepcid AC 10 mg, film-coated tablets, which was registered by JNTL Consumer Health Limited, Ireland (formally a division of Johnson & Johnson) since September 1996. This product is indicated in patients aged 16 years and above for relief of heartburn, indigestion (dyspepsia) and excess acid and for the prevention of these symptoms when associated with meals including nocturnal symptoms.

For the CMS Spain, the reference product used is the ERP Pepcid 10 mg comprimidos recubiertos, which has been authorised in Spain (MA EU-Number 62090) since 1 May 1998. The current MAH is JNTL Consumer Health Spain S.L (Spain), (formally a division of Johnson & Johnson). This product is indicated in patients aged 16 years and above for the relief and symptomatic treatment of heartburn.

Both reference products belong to the same global marketing authorisation (GMA). The current product differs from the reference products in pharmaceutical strength and in the proposed indications. A bioequivalence study was conducted between the current product and the reference Pepcid 10 mg comprimidos recubiertos (Spain). No other new studies were performed to investigate the clinical and non-clinical aspects of the product. To support this application the MAH has been submitted an overview based on the literature with the justification for bridging between their product and the product used in the literature, as no reference products are available for the 20 mg and 40 mg strengths.

II. QUALITY ASPECTS

II.1 Introduction

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

Famotidine 20 mg is presented as yellow coloured, round, biconvex film-coated tablets debossed with "2V" on one side and plain on the other side, with a diameter of approximately 6 mm.

Famotidine 40 mg is presented as brown coloured, round, biconvex film-coated tablets debossed with "4V" on one side and plain on the other side, with a diameter of approximately 8 mm.

The excipients are:
Tablet core - microcrystalline cellulose (E460 (i)), pregelatinised starch, talc (E553b), silica colloidal anhydrous (E551) and magnesium stearate (E470b).

Tablet coat - polyvinyl alcohol-partially hydrolysed (E1203), talc (E553b), titanium dioxide (E171), macrogol, lecithin (soya) (E322), iron oxide yellow (E172) (in the 20 mg and 40 mg strength) and iron oxide red (E172) (in the 40 mg strength).

The two tablet strengths are dose proportional.

The film-coated tablets are packed in oriented polyamide/aluminium//polyvinyl chloride (oPA/Alu/PVC//Alu) or polyvinyl chloride/ aluminium (PVC/Alu) blisters.

II.2 Drug Substance

The active substance is famotidine, an established substance described in the Pharmacopoeia (Ph.Eur.). Famotidine is a white or yellowish-white crystalline powder or crystals, very slightly soluble in water. Famotidine exhibits polymorphism. Polymorphism in the drug substance is controlled by the drug product manufacturer. 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 considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. and the CEP, with additional requirements for particle size distribution. Polymorphism is controlled using the same method applied by the drug substance manufacturer. Residual solvents are controlled in line with the CEP and the specification applied by the drug substance manufacturer. Potential mutagenic impurity is adequately controlled in line with the applicable ICH guidelines. The specification is acceptable in view of the route of synthesis and the various European guidelines.

Batch analytical data demonstrating compliance with this specification have been provided for two batches per manufacturing site.

Stability of drug substance

The active substance is stable for 60 months 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 development of the product has been described, the choice of excipients is justified and their functions are explained. Formulation development and optimisation have been adequately described. The comparative dissolution experiments complementary to the bioequivalence study have been performed in line the conditions described with the EMA guideline on bioequivalence. *In vitro* dissolution studies complementary to the bioequivalence (BE) study has been conducted using the same test and reference batches used in the BE study. Similarity in dissolution properties was demonstrated without the need to calculate f_2 factors at 0.1N HCl (QC media) and pH 4.5 acetate buffer. The MAH concluded that similarity of the dissolution profiles was also demonstrated at pH 6.8 based on f_2 calculations is also agreed. *In vitro* dissolution tests in support of the biowaiver of strengths for the 20 mg have been submitted. The biowaiver of strength is acceptable from a quality point of view, see details in section IV.2.

The development of the *in vitro* dissolution method is adequately described. The proposed dissolution method has been justified and its discriminatory power has been sufficiently demonstrated.

Manufacturing process

The choice of excipients is justified and their functions explained. The manufacturing process consists of the following main steps: sifting of raw materials, granulation, drying, sift and milling, wet mixing, drying, pre-lubrifaction and lubrification blending, tablet compression,

film coating and packaging. The product is manufactured using conventional manufacturing techniques.

The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three production batches of each strength manufactured at the proposed minimum commercial scale. This is considered sufficient in view of the manufacturing process and taking into account the percentage in size of the minimum commercial batch compared to the maximum batches size.

Control of excipients

The excipients comply with Ph. Eur. requirements where applicable, or with other relevant compendial requirements. In-house requirements are applied to the coating materials. 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, identity, identification of colour, average mass, loss on drying, dissolution, assay, uniformity of dosage units, related substances and microbiological quality. The release and shelf-life specifications are identical with the exception of the limits for related substances and loss on drying. 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 have been submitted for three batches of each strength, manufactured at commercial scale at the proposed production site, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product has been provided on three production scale batch of each strength packaged in both types (oPA/Alu/PVC//Alu) or (PVC/Alu) of blisters proposed for marketing. The batches were stored at 25°C/60% RH (24 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guidelines. The data presented confirm compliance with specification. No significant changes were observed under accelerated storage conditions. Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light. Based on the data submitted, a shelf life was granted of 30 months. 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 Centrafarm 20 mg and 40 mg are film-coated tablets have 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 Pharmacology, pharmacokinetics and toxicology

The sought-after indications were already approved for other Famotidine 20 mg and 40 mg tablets on the market. Because the indications of Famotidine Centrafarm differ from the reference medicinal products Pepcid 10 mg, a more in-depth assessment on the primary pharmacology has been performed. The provided non-clinical pharmacodynamic literature supports partly the use of famotidine for the indications listed by the MAH. H_2-receptor inhibition has been shown in several *in vitro* studies. *In vivo* data from rats and dogs demonstrated the efficacy of famotidine in the prevention, reduction and healing of gastric and duodenal ulcers. In most studies famotidine was at least as good (or better) than other frequently used pharmaceuticals for the same indications, such as cimetidine and ranitidine. Since the symptoms of Zollinger-Ellison syndrome are caused by increased gastric acid secretion, the provided literature on gastric- and duodenal ulcers also supports this indication. *In vitro* and *in vivo* data from rats demonstrated the efficacy of famotidine in inhibiting reflux esophagitis (Bisson et al., 1993) (Gladziwa et al., 1993; Langtry et al., 1989; Laskin et al., 1993).

III.2 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 Centrafarm 20 mg and 40 mg are 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.3 Discussion on the non-clinical aspects

Pharmacodynamic, pharmacokinetic and toxicological properties of famotidine are well-known. As famotidine is a widely used, well-known active substance, the MAH has not provided additional non-clinical studies, and further studies are not required. The non-clinical overview provided based on literature review is thus appropriate.

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 member states agreed that no further clinical studies are required, besides one bioequivalence study, which is discussed below. Additionally, a biowaiver of strength was requested.

IV.2 Pharmacokinetics

Pharmacokinetics overview

Famotidine kinetics are linear (SmPC Epci AC, Ireland). Oral bioavailability is approximately 40 %. Peak plasma concentrations, which are respectively 50 to 60 µg/L and approximately 78 µg/L after administration of 20 mg and 40 mg, are achieved 1-3.5 hours after administration (Campoli-Richards et al., 1986). Repeated administration does not lead to an accumulation of the active ingredient (Famotidine Tablets, USP product monograph).

The apparent volume of distribution of famotidine after intravenous administration was reported to be 1.14 to 1.42 L/kg, however, the volume of distribution following oral administration nor the distribution of famotidine into human tissues and fluids have been described. Following oral administration of famotidine 20 mg to 5 healthy volunteers the mean proportion of drug which was plasma bound was 21.8% at 2 hours after administration, 19.3% at 3 hours, and 15.1% at 4 hours (Campoli-Richards et al., 1986; Echizen et al., 1991).

Famotidine is excreted in the urine and faeces. Mean urinary recovery of unchanged famotidine was from 25 to 30% of orally administered doses. The elimination half-life in the plasma is approximately 2.5 to 4 hours (Echizen et al., 1991).

Famotidine S-oxide is the only known metabolite of the drug in humans. After intravenous administration of famotidine, about 2 to 8% of the dose was recovered in urine as famotidine S-oxide in humans. The biological activity of famotidine S-oxide, if any, is currently unknown (Campoli-Richards et al., 1986; Echizen et al., 1991).

The maintenance dosage of famotidine for patients with renal insufficiency should be reduced according to the individual CL_{cr} (Creatinine Clearance) (Therapeutic Goods Administration (TGA) Australia) because the elimination half-life and area under the plasma concentration-time curve were significantly increased.

No relevant drug interactions have been identified (Locniskar et al., 1986).

Bioequivalence

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Famotidine Centrafarm 40 mg, film-coated tablets (Centrafarm B.V., the Netherlands)

was compared with the pharmacokinetic profile of the reference product Pepcid 10 mg comprimidos recubiertos (JNTL Consumer Health Spain S.L, 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.

Biowaiver of strengths

The following requirements for granting the biowaiver for the 20 mg famotidine film-coated tablets based on the bioequivalence study with the highest strength of 40 mg have been met:

- the strengths have been manufactured by the same process and manufacturer
- the pharmacokinetics can be considered dose linear
- the compositions are qualitatively similar and dose proportional.
- Comparative dissolution experiments in three dissolution media (pH 1.2, 4.5 and 6.8) with the lower strength were performed. The paddle method with an agitation speed of 50 rpm and a volume of 900 mL were used, which complies with the bioequivalence Guideline.

At pH 1.2 and 4.5, the dissolution profiles showed a dissolution percentage above 85% within 15 min for all strengths and were considered similar.
At pH 6.8, the calculated f_2-values met the acceptance criteria of 50-100, and thus, the dissolution profiles of the two strengths were considered similar.

All RSD (residual standard deviation) values were found to be less than 20% for the first time point and less than 10% for all subsequent time points, complying with the Bioequivalence Guideline. According to the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **) the additional strength of famotidine film-coated tablets meets the general bio-waiver acceptance criteria. Therefore the biowaiver for the strength 20 mg was granted.

Bioequivalence study 111-22

Design

An open label, balanced, randomised, two-treatment, two-sequence, two-period, single-dose, crossover, oral bioequivalence study was carried out under fasted conditions in 47 healthy, adult human participants (38 male and 9 female), aged 21-44 years. Each subject received a single dose (40 mg) of one of the two famotidine formulations (reference (4 tablets x 10 mg) or tests (1 tablet x 40 mg). The tablet was orally administered with 240 mL water after overnight fasting for at least 10 hours. There were two dosing periods, separated by a washout period of three days.

Blood samples were collected pre-dose and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2., 2.25, 2.5, 2.75, 3, 3.25, 3.5, 4, 6, 9, 12, 15, 18, 24 hours after administration of the products.

The design of the study is acceptable.

According to the SmPC of the product, food has no influence on the absorption of famotidine. The medicinal product may be taken without reference to food intake. 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
A total of 50 participants were dosed. Four participants were withdrawn from the study due to mild or moderate adverse events (period I: one participant due to vomiting. Period II, one participant due to vomiting and two due to vomiting and fever. One participant dropped out with consent). 47 participants completed the study and were included in the pharmacokinetic and statistical analysis.

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

Treatment N=47	AUC_{0-t} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	C_{max} (ng/mL)	t_{max} (h)
Test	1287 ± 443	1332 ± 462	198.7 ± 66.3	2.00 (0.75-4.00)
Reference	1270 ± 475	1314 ± 500	187.9 ± 61.7	2.25 (0.75-4.00)
***Ratio (90% CI)**	102.3 (95.8-109.2)	102.4 (96.0-109.2)	105.7 (98.7-113.1)	---

$AUC_{0-\infty}$	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 = 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 80 – 125%. Based on the submitted bioequivalence study Famotidine Centrafarm 40 mg is considered bioequivalent with Pepcid coated tablets 10 mg.

A biowaivers of strengths for the 20 mg strength was granted based on the submitted dissolution data of the 20 mg and 40 mg strengths. The results of study 111-22 with the 40 mg formulation can be extrapolated to the lower strength product of 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 Pharmacodynamics

No new pharmacodynamic studies were performed by the MAH. Pharmacodynamic data are derived from the published literature. This is acceptable. The submitted documentation describes the general pharmacodynamic effects of famotidine appropriately.

Famotidine is a competitive inhibitor of H_2 receptor. Famotidine inhibits basal and stimulated gastric acid secretion in a dose-dependent manner after oral administration of 5 to 40 mg. Maximal effect is achieved by the 40 mg dose (Chremos, 1986). Upon oral administration, the onset of the antisecretory effect of famotidine occurs within one hour (Bisson et al., 1993). Duration of inhibition of secretion by famotidine doses of 20 and 40 mg is 10 to 12 hours (Chremos, 1986). The pharmacodynamic effects of famotidine increase at increasing famotidine dosages. Hence, there is a positive dose-response relationship (Laskin et al., 1993).

The submitted documentation supports the inhibitory pharmacodynamic effect of 5-40 mg famotidine on the gastric acid secretion in healthy volunteers. In patients with gastroesophageal reflux disease, famotidine 20 and 40 mg twice daily reduce the intraoesophageal acid exposure into the normal range as measured by 24 hour intraoesophageal pH monitoring. These data support the primary pharmacodynamic effects of famotidine 20 and 40 mg twice daily for gastroesophageal reflux disease i.e. symptomatic reflux oesophagitis (Shaqran et al., 2023). The evaluated dosage is the proposed recommended dosage of famotidine for the proposed reflux oesophagitis indications of famotidine. This is acceptable.

Inhibitory pharmacodynamic effects of famotidine on the gastric secretion were also observed in patients with a duodenal ulcer (Langtry et al., 1989).

The MAH did not specifically discuss the pharmacodynamic effects of famotidine with respect to the prevention of recurrent duodenal ulcers, benign gastric ulcer, and Zollinger-Ellison-Syndrome. However, the pharmacodynamic effects of famotidine are the same as for reflux oesophagitis. Therefore, the general inhibitory effects of famotidine on the gastric secretion also apply to the conditions for which no data on the pharmacodynamic effects of famotidine have been submitted. Indications similar to those of Famotidine Centrafarm have been accepted for other nationally or decentralised authorised famotidine medicinal products (e.g. Famotidine CF 20 mg and 40 mg (respectively NL/H/5592/001 and NL/H/5592/002)). For aforementioned reasons, no further substantiation is requested on the pharmacodynamic effects of famotidine for all applied indications.

No secondary pharmacological effects of famotidine have been reported for famotidine doses up to 40 mg twice daily.

No clinically important pharmacodynamic interactions between famotidine and other drugs or substances have been recorded.
In conclusion, the submitted documentation describes the general pharmacodynamic effects of famotidine appropriately. This is acceptable.

IV.4 Clinical efficacy

Famotidine Centrafarm film-coated tablets in dose strengths of 20 and 40 mg are proposed for different indications with different posologies as described in Tabel 2. No clinical studies were conducted to evaluate the clinical efficacy of famotidine 20 and 40 mg tablets with respect to the proposed indications. Instead, an overview based on literature was submitted.

Table 3. Famotidine Glenmark 10 mg, 20 mg and 40 mg film-coated tablets indications and posologies per strength

Indications	Posology	
	20 mg	**40 mg**
Duodenal ulcers and ventricle ulcers	40 mg once daily before going to sleep for 4-8 weeks. Depending on the presence or absence of ulcer healing upon endoscopy this period can respectively be shortened (exact duration not specified) or extended (maximum treatment period 12 weeks).	40 mg once daily before going to sleep for 4-8 weeks. Depending on the presence or absence of ulcer healing upon endoscopy this period can respectively be shortened (exact duration not specified) or extended (maximum treatment period 12 weeks).
Benign gastric ulcers	40 mg once daily at night for 4-8 weeks, unless earlier healing is revealed by endoscopy	40 mg once daily at night for 4-8 weeks, unless earlier healing is revealed by endoscopy
Prophylactic treatment of relapses duodenal ulcers	20 mg once daily in the evening up to 12 months duration	N/A
Zollinger-Ellison-Syndrome	start: 20 mg every 6 hours, up to 800 mg per day as long as clinically necessary	start: 20 mg every 6 hours, up to 800 mg per day as long as clinically necessary
Symptomatic treatment of mild to moderate reflux oesophagitis	20-40 mg twice daily for 6-12 weeks	40 mg twice daily for 6-12 weeks

Dose-response studies

- Wesdorp et al., (1993) evaluated the clinical effects of 20 mg (n= 238) and 40 mg (n= 236) famotidine twice a day in a double-blind, randomised multicentre study in 474 symptomatic patients with erosive ulcerative reflux esophagitis. Relief of symptoms was significant in all patients after 6 and 12 weeks and not different in both treatment groups. Overall endoscopic healing was better in the famotidine 40 mg twice a day group compared with 20 mg twice a day at week 6 (58% versus 43%; $p < 0.05$) and at week 12 (76% versus 67%; $p < 0.05$). Extending treatment to 24 weeks with 40 mg of

famotidine twice a day in those patients who were not healed after 12 weeks was not more effective. The differences in efficacy of these two doses were more pronounced with increasing severity of oesophagitis.

- Taha et al., (1996) evaluated the efficacy of two doses of famotidine (20 mg and 40 mg, each given orally twice daily), compared with placebo, in preventing peptic ulcers in 285 patients without peptic ulcers who were receiving long-term NSAID therapy for rheumatoid arthritis or osteoarthritis. The study results support the efficacy of famotidine for the prevention of gastric and duodenal ulcers during NSAID treatment.

Main studies supporting the proposed indications and posologies

Active duodenal ulcer (40 mg famotidine once daily before going to sleep for 4-8 weeks)

- Gitlin et al. (1987) compared the efficacy and safety of famotidine in a multicentre, double-blind, randomised, placebo-controlled study in 384 patients with acute duodenal ulcer disease. The patients received either famotidine or a placebo for 8 weeks. The patients receiving famotidine were treated with one of three dose regimens, 40 mg at bedtime, 20 mg or 40 mg twice daily. At week 4, the endoscopic healing rate was 70%, 75%, 67%, and 31% for the famotidine 40 mg at bed time, 40 mg twice daily 20 mg twice daily, and placebo groups, respectively. The 8-week healing rates for the same respective groups were 83%, 82%, 82%, and 45%. Ulcer pain and antacid consumption occurred less often in the famotidine groups. The clinical and laboratory safety profile of the famotidine groups was similar to that of the placebo group.
- Okada et al. (1992) conducted a randomised controlled study comparing once-a-day morning and once-a-day bedtime administration of 40 mg famotidine in treating duodenal ulcers in 99 Japanese patients. Eighty-two patients fulfilled the evaluation criteria (38 in the morning group and 44 in the bedtime group). The healing rates were 66% after 3 weeks and 95% after 6 weeks in the morning group, and 57% after 3 weeks and 80% after 6 weeks in the bedtime group. The differences were insignificant between the two groups. It is agreed with the authors that the efficacy of once-a-day morning and bedtime administration of 40 mg famotidine in treating duodenal ulcers are comparable.
- Rohner & Gugler (1986) conducted a study with 100 patients treated with a single nocturnal dose of famotidine 40 mg. After four weeks treatment the healing rates were 94%.

Prevention of recurrent duodenal ulcers (20 mg once daily in the evening up to 12 months duration)

- Taha et al. (2009) conducted a study with patients receiving low-dose aspirin for vascular protection without ulcers or erosive oesophagitis on endoscopy at baseline were randomised to receive famotidine 20 mg twice daily (n=204) or placebo twice

daily (n=200). The primary endpoint was the development of new ulcers in the stomach or duodenum or erosive oesophagitis at 12 weeks after randomisation. The occurrence of gastric ulcers (3.4 vs. 15.0%; odds ratio [OR] 0.20, 95% CI 0.09-0.47; p=0.0002), duodenal ulcers (0.5 vs. 8.5%; OR 0.05, 0.01-0.40; p=0.0045), and erosive oesophagitis (4.4 vs.19.0%; OR 0.20, 0.09-0.42; p<0.0001) was lower among famotidine-treated patients as compared to placebo-treated patients.

- Baglioni et al., 1985 conducted a double-blind multicentre study. In this study ulcer recurrence tended to be lower at a famotidine dosage of 20 mg as compared to placebo once a day at bedtime during a treatment period of 6 months (22% vs. 55%).

Benign gastric ulcer (40 mg once daily before going to sleep for 4-8 weeks)

- Lyon (1986) described a worldwide study in 14 countries on four continents (eight European, three South American, two North American, and one African) with 336 patients with gastric ulcers, comparing famotidine (40 mg at bedtime) with placebo. Famotidine was more effective than placebo in treating gastric ulcers regarding the relief of pain and complete endoscopic healing. According to the authors, short-term oral famotidine, at a dose of 40 mg daily, was well tolerated.
- Dammann et al. (1985) conducted a double-blind multicentre study treating gastric ulcers. Famotidine 40 mg was found to be statistically significantly superior to placebo. The recommended dosage for famotidine was 40 mg once a day at bedtime for 4 to 8 weeks.

Zollinger-Ellison-Syndrome (20 mg every 6 hours, up to 800 mg per day as long as clinically necessary)

- Howard et al. (1985) compared famotidine with cimetidine and ranitidine in 9 patients with Zollinger-Ellison syndrome. The mean minimum daily requirement of famotidine to control gastric acid hypersecretion was 0.24 g (range 0.08-0.48 g) compared with 2.1 g (range 0.6-3.6 g) for ranitidine and 7.8 g (range 1.2-13.2 g) for cimetidine.
- Vinayek et al. (1986) compared famotidine with ranitidine and cimetidine in its ability to control gastric acid hypersecretion in 33 patients with gastric hypersecretory states (32 patients with Zollinger- Ellison syndrome and one patient with idiopathic hypersecretion). The mean daily maintenance dose with famotidine was 0.33 g per day (range, 0.05 to 0.8 g). Gastric acid hypersecretion was controlled in seven patients with less frequent dosing with famotidine than with cimetidine or ranitidine.

Symptomatic treatment of mild reflux oesophagitis (20 mg)/ Treatment of mild to moderate reflux oesophagitis (40 mg) (20 mg or 40 mg twice daily for 6-12 weeks)

- Referred is to the section on dose-response above. The additionally submitted publications on the clinical efficacy of famotidine for (symptomatic) treatment for reflux oesophagitis support the clinical efficacy of famotidine 20 mg twice daily (Wada

et al., 2005) and famotidine 40 mg once daily (Kim et al., 2015).

Yamao et al. (2006) provides some support for the use of 20 mg famotidine per day for the treatment of NSAID-associated gastric mucosal lesions using upper gastrointestinal endoscopy.

Conclusion on clinical efficacy
Based on the submitted bioequivalence study, Famotidine Centrafarm 40 mg film-coated tablets are considered bioequivalent with 4 tablets Pepcid 10 mg from JNTL Consumer Health (Spain) (see section IV.2). In addition, based on an acceptable biowaiver, this can be extrapolated to the 20 mg strength. The submitted literature for each applied indication includes publications on studies in which medicinal products of 20 mg and/or 40 mg famotidine were evaluated. The clinical effects with respect to the applied indications of Famotidine Centrafarm 20 mg and 40 mg are similar to those of the famotidine medicinal products used in the literature.

Based on this, it is considered that the results of the clinical effects obtained with the medicinal products used in the literature, can be applied to Famotidine Centrafarm 20 mg and 40 mg film-coated tablets in their respective indication.

Overall, the publications support the clinical efficacy of the recommended famotidine dosages for each indication.

IV.5 Clinical safety

No clinical studies were conducted to evaluate the clinical safety of famotidine 20 and 40 mg tablets with respect to the proposed indications. Instead, an overview based on literature was submitted.

Safety per indication

Multiple indications

- Howden & Tytgat (1996) conducted a systematic review on famotidine in duodenal or gastric ulcer, gastroesophageal reflux disease (GERD), Zollinger- Ellison syndrome (ZES), anastomotic ulcer, or dyspepsia famotidine was well tolerated during long-term use. In general, no dose-related differences in the incidence of clinical or laboratory adverse events were apparent among famotidine treated patients in the included studies (27 studies, 7483 patients). The profile of adverse events in patients receiving maintenance therapy with famotidine during investigational studies was comparable to that seen in acute therapy studies. Famotidine was found generally well tolerated in patients with cardiovascular, renal, or hepatic dysfunction or with Zollinger-Ellison syndrome who have tolerated doses up to 800 mg daily.
- Saigenji et al. (1987) described a post marketing survey of famotidine usage (phase IV survey) tracked 6346 patients at 602 locations from August 1985 to April 1986. The patients included 4618 cases of peptic ulcer, 106 cases of reflux esophagitis, 1006 cases of upper gastrointestinal tract bleeding, 343 cases of bleeding and ulcer prophylaxis,

and 273 cases of gastritis and other diseases. Side effects occurred in only 0.43% of patients, and abnormalities in laboratory test results were observed in <1% of patients. Gastrointestinal side effects, especially constipation, occurred most frequently. Most side effects were mild.

- Miwa & Miyoshi (1987) conducted a multicentre, double-blind, comparative study was conducted to determine the effects of famotidine, a new H2-receptor antagonist, for treating erosions and/or mucosal haemorrhages, patients received one of three oral doses (5, 10, or 20 mg) of famotidine twice daily for 2 weeks. After 2 weeks of treatment, 88.5% and 91.7% of the patients in the 10- and 20-mg dosage groups, respectively, did not have evidence of erosions or haemorrhages, compared with 73% of patients in the 5-mg group. No adverse reactions occurred during treatment

Duodenal ulcer

- Dobrilla et al. (1987) conducted a multicentre, double-blind, randomised, controlled study in 234 duodenal ulcer patients to compare the efficacy and safety of the H2-receptor antagonists famotidine and ranitidine in the treatment of duodenal ulcer. Patients received 40 mg famotidine (119 patients) or 300 mg ranitidine (115 patients) once daily at bedtime for 4 weeks. If ulcer lesions persisted, treatment was extended to 6 weeks. The incidence of untoward effects was low in both treatment groups. Abnormal results in laboratory tests were observed in one famotidine-treated patient, a chronic alcoholic receiving famotidine, who withdrew from the study because of a slight elevation in serum transaminase levels.
- Bianch Porro et al. (1987) studied the efficacy and safety of famotidine in 1031 patients by 68 investigators in 19 countries in a worldwide dose-ranging multicentre comparative study. Three doses of famotidine (40 mg at bedtime, 20 mg twice daily, 40 mg twice daily) were compared to ranitidine 150 mg twice daily. The occurrence and type of adverse clinical experiences reported was similar for each of the four treatment groups. The most common adverse experiences were headache and diarrhoea.
- Rodrigo et al., 1989 evaluated the efficacy and safety of famotidine (40 mg at night) in 119 patients by four investigators in four Spanish hospitals in a randomised double-blind comparative study with cimetidine (800 mg at night). Antacid tablets were allowed as additional treatment, if needed for pain relief. There were no significant differences between the groups in baseline characteristics, including duodenal ulcer size. The intake of antacids, as well as the clinical and laboratory safety profile were similar for both groups.

Prevention of recurrent duodenal ulcers

- Porro et al. (1991) conducted a 24-week, double-blind, randomised study at 13 centres to compared the efficacy and safety of 20 mg famotidine nocte and 150 mg ranitidine at bedtime for the prevention of duodenal ulcer recurrence. All participants had been

successfully treated for an acute duodenal ulcer with 40 mg famotidine nocte. No laboratory abnormalities related to the study-drugs were noted and only two drug related (possibly or probably) adverse experiences were reported, both in the famotidine group. The tolerability for long-term therapy was comparable for the evaluated famotidine and ranitidine treatment.

Benign gastric ulcer

- Paoluzi et al. (1985) evaluated the efficacy and safety of famotidine in promoting the healing of active gastric ulcer when compared to placebo. Of the 71 patients who took part in this multicentre double-blind study in Italy, 37 were administered famotidine 40 mg once daily and 34 placebo. Treatment duration was for up to 8 weeks. Both treatments were well tolerated, and no alterations in laboratory tests were observed.

Zollinger-Ellison syndrome

- Howard et al. (1985) concluded that no haematological, biochemical, or clinical toxicity was observed upon famotidine treatment for Zollinger-Ellison syndrome. Long-term treatment with famotidine was not associated with any hematologic or biochemical toxicity or clinical side effects.
- Howden & Tytgat (1996) evaluated the tolerability and safety of famotidine. Patients suffering from Zollinger-Ellison syndrome tolerate famotidine doses up to 800 mg daily without significant adverse.

Mild reflux oesophagitis

- Robinson et al. (1991) compared the safety profile and efficacy of famotidine oral dosing regimens, 40 mg nocte and 20 mg twice daily with placebo during a 6-week treatment period for the relief of symptoms in patients suffering from frequent heartburn found to have endoscopically normal oesophageal mucosa or mild non-erosive oesophagitis. No statistically significant differences between famotidine and placebo in the number of patients who experienced clinical adverse experiences were noted and no serious adverse events attributable to famotidine occurred. Based upon these findings, patients with gastro-oesophageal reflux symptoms experience good relief of their complaints with twice daily famotidine in standard doses.
- Simon et al. (1994) conducted a multicentre, randomised, double-blind, placebo-controlled, parallel group study to determine the effects of two twice daily oral famotidine regimens on symptom relief and healing of erosive oesophagitis in patients with gastro-oesophageal reflux disease. 318 patients were enrolled: 66 received placebo, 125 received famotidine 20 mg twice daily, and 127 received famotidine 40 mg twice daily. The treatment duration was 6-12 weeks. There were no significant differences among treatment groups in the incidence of clinical or laboratory adverse events. It was concluded that famotidine 40 mg twice daily was a better regimen than

famotidine 20 mg twice daily or placebo and well tolerated.

According to the proposed SmPC, common (≥ 1/100 to < 1/10) adverse drug reactions of famotidine concern headache, dizziness, constipation and diarrhoea. Uncommon (≥ 1/1 000 to < 1/100) adverse drug reactions of famotidine concern dry mouth, nausea, vomiting, gastrointestinal complaints, flatulence, loss of appetite, rash, pruritis, and fatigue.

Renal impairment
Halstenson et al. (1987) and Inotsume et al. (1989) concluded that dose reduction or prolongation of the famotidine dosing interval is needed in case of impaired renal function. The daily dosage of famotidine should be reduced to 50% in patients with impaired renal function in whom creatinine clearance is less than 30 ml/min.

Hepatic impairment
No dose adjustment of famotidine is necessary in case of hepatic impairment.

Overdosing
There is no experience to date with overdosage. Famotidine overdosing may however occur. In the event of famotidine overdosage, treatment should be symptomatic and supportive. Unabsorbed material should be removed from the gastrointestinal tract, the patient should be monitored, and supportive therapy should be employed.

Conclusion on clinical safety
According to the proposed SmPC, common (≥ 1/100 to < 1/10) adverse drug reactions of famotidine concern headache, dizziness, constipation and diarrhoea. Uncommon (≥ 1/1 000 to < 1/100) adverse drug reactions of famotidine concern dry mouth, nausea, vomiting, gastrointestinal complaints, flatulence, loss of appetite, rash, pruritis, and fatigue.

The publications support the clinical safety of the recommended famotidine dosages. Overall, famotidine treatment was well tolerated in the studies of the literature. Furthermore, the submitted study data show that famotidine doses up to 800 mg daily as proposed in the SmPC are well-tolerated in patients suffering from Zollinger-Ellison syndrome.

The MAH demonstrated that the medicinal product applied for is similar to the products described in the literature. Therefore, it is concluded that the safety results for famotidine reported in the literature can be applied to Famotidine Centrafarm 20 mg and 40 mg film-coated tablets.

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 Centrafarm 20 mg and 40 mg. At the time of approval, the most recent version of the RMP was version 0.4 dated 17 September 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 AC 10 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. Furthermore,

Famotidine 20 mg and 40 mg are used in the proposed indications for decades within the European Union. The indications for Famotidine Centrafarm 20 mg and 40 mg film-coated tablets are supported by publications from literature. The MAH demonstrated that the medicinal product applied for is similar to the product(s) described in the literature. Therefore, it is concluded that the clinical efficacy and safety results for famotidine reported in the literature can be applied to the proposed Famotidine Centrafarm 20 mg and 40 mg film-coated tablets.

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

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 3 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.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Famotidine Centrafarm 20 mg and 40 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are hybrid forms of Pepcid AC 10 mg, film coated tablets. Pepcid

AC 10 mg 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 bioequivalence has been demonstrated for Famotidine Centrafarm 20 mg and 40 mg with the reference products, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 10 October 2025.

LITERATURE REFERENCES

1. Bisson, C., St.-Laurent, M., Michaud, J. T., & LeBel, M. (1993). Pharmacokinetics and pharmacodynamics of ranitidine and famotidine in healthy elderly subjects: a double-blind, placebo-controlled comparison. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy, 13(1), 3-9.
2. Baglioni, A., Barbara, L., Bianchi-Porro, G., Blasi, A., Canelli, B., Cheli, R., ... & Hentschel, E. (1985). Famotidine versus placebo in prevention of the recurrence of duodenal ulcer disease. A multicenter study in Germany, Austria and Italy. Zeitschrift fur Gastroenterologie, 23(12), 665-669.
3. Bianch Porro, G., Dicenta, C., Cook, T., & Humphries, T. J. (1987). Review of an extensive worldwide study of a new H2-receptor antagonist, famotidine, as compared to ranitidine in the treatment of acute duodenal ulcer. Journal of Clinical Gastroenterology, 9, 14-18.
4. Campoli-Richards, D. M., & Clissold, S. P. (1986). Famotidine: pharmacodynamic and pharmacokinetic properties and a preliminary review of its therapeutic use in peptic ulcer disease and Zollinger-Ellison syndrome. Drugs, 32(3), 197-221.
5. Chremos, A. N. (1986). Pharmacodynamics of famotidine in humans. The American Journal of Medicine, 81(4), 3-7.
6. Dammann, H. G., Walter, T. A., Hentschel, E., Muller, P., & Simon, B. (1987). Famotidine: proven once-a-day treatment for gastric ulcer. Scandinavian Journal of Gastroenterology, 22(sup134), 29-33.
7. Dobrilla, G., Pretis, G. D., Piazzi, L., Boero, A., Camarri, E., Crespi, M., ... & Tittobello, A. (1987). Comparison of once-daily bedtime administration of famotidine and ranitidine in the short-term treatment of duodenal ulcer a multicenter, double-blind, controlled study. *Scandinavian Journal of Gastroenterology*, *22*(sup134), 21-28.
8. Echizen, H., & Ishizaki, T. (1991). Clinical pharmacokinetics of famotidine. Clinical pharmacokinetics, 21(3), 178-194.
9. Famotidine Tablets, USP product monograph. https://pdf.hres.ca/dpd_pm/00014548.PDF, accessed on 17 Oct 23.
10. Gitlin, N., McCullough, A. J., Smith, J. L., Mantell, G., Berman, R., & Multicenter Famotidine Cooperative Study Group. (1987). A multicenter, double-blind, randomized, placebo-controlled comparison of nocturnal and twice-a-day famotidine in the treatment of active duodenal ulcer disease. Gastroenterology, 92(1), 48-53.
11. Gladziwa, U., Wagner, S., Dakshinamurty, K. V., Desoky, E. E., Dreuw, B., & Klotz, U. (1993). Pharmacokinetics and pharmacodynamics of famotidine in patients with reflux oesophagitis. European journal of clinical pharmacology, 44(4), 357-360.
12. Halstenson, C. E., Abraham, P. A., Opsahl, J. A., Chremos, A. N., Keane, W. F., & Matzke, G. R. (1987). Disposition of famotidine in renal insufficiency. *The Journal of Clinical Pharmacology*, *27*(10), 782-787.
13. Howard, J. M., Chremos, A. N., Collen, M. J., McArthur, K. E., Cherner, J. A., Maton, P. N., ... & Jensen, R. T. (1985). Famotidine, a new, potent, long-acting histamine H2-receptor antagonist: comparison with cimetidine and ranitidine in the treatment of Zollinger-Ellison syndrome. Gastroenterology, 88(4), 1026-1033.
14. Howden, C. W., & Tytgat, G. N. (1996). The tolerability and safety profile of famotidine. Clinical therapeutics, 18(1), 36-54

15. Inotsume, N., Nishimura, M., Fujiyama, S., Sagara, K., Sato, T., Imai, Y., ... & Nakano, M. (1989). Pharmacokinetics of famotidine in elderly patients with and without renal insufficiency and in healthy young volunteers. *European journal of clinical pharmacology*, *36*(5), 517-520.
16. Kim, E. H., Lee, Y. C., Chang, Y. W., Park, J. J., Chun, H. J., Jung, H. Y., ... & Lee, S. W. (2015). Efficacy of lafutidine versus famotidine in patients with reflux esophagitis: a multi-center, randomized, double-blind, non-inferiority phase III trial. *Digestive diseases and sciences*, *60*(6), 1724-1732.
17. Langtry, H. D., Grant, S. M., & Goa, K. L. (1989). Famotidine: an updated review of its pharmacodynamic and pharmacokinetic properties, and therapeutic use in peptic ulcer disease and other allied diseases. Drugs, 38(4), 551-590.
18. Laskin, O. L., Patterson, P. M., Shingo, S., Lasseter, K. C., & Shamblen, E. C. (1993). Pharmacodynamics and Dose-Response Relationship of Famotidine: A Double-Blind Randomized Placebo-Controlled Trial. The Journal of Clinical Pharmacology, 33(7), 636-639.
19. Locniskar, A., Greenblatt, D. J., Harmatz, J. S., Zinny, M. A., & Shader, R. I. (1986). Interaction of diazepam with famotidine and cimetidine, two H2-receptor antagonists. The Journal of Clinical Pharmacology, 26(4), 299-303.
20. Lyon, D. T. (1986). Efficacy and safety of famotidine in the management of benign gastric ulcers. The American Journal of Medicine, 81(4), 33-41.
21. Miwa, T., & Miyoshi, A. (1987). Famotidine in the treatment of gastritis. *Scandinavian Journal of Gastroenterology*, *22*(sup134), 46-50.
22. Okada, M., Arita, M., Iida, M., Yao, T., Sakurai, T., Hoshiko, K., ... & Sakamoto, K. (1992). A comparative study of once-a-day morning and once-a-day bedtime administration of 40 mg famotidine in treating duodenal ulcers. *Gastroenterologia Japonica*, *27*(2), 179-186.
23. Paoluzi, P., Torsoli, A., Bianchi Porro, G., Lazzaroni, M., Barbara, L., Corinaldesi, R., ... & Matarazzo, P. F. (1985). Famotidine (MK-208) in the Treatment of Gastric Ulcer Results of a Multicenter Double-Blind Controlled Study. *Digestion*, *32*(Suppl. 1), 38-44.
24. Porro, G. B., Lazzaroni, M., Barbara, L., Corinaldesi, R., Blasi, A., Mangiameli, A., ... & CALACRO, A. (1991). A controlled study of 20 mg famotidine nocte vs. 150 mg ranitidine nocte for the prevention of duodenal ulcer relapse. *Alimentary pharmacology & therapeutics*, *5*(2), 181-189.
25. Rohner, H. G., & Gugler, R. (1986). Treatment of active duodenal ulcers with famotidine: A double-blind comparison with ranitidine. *The American Journal of Medicine*, *81*(4), 13-16.
26. Robinson, M., Decktor, D. L., Stone, R. C., Pevelery, M., Barden, P., Moyer, R., ... & Berlin, R. D. (1991). Famotidine (20 mg) bd relieves gastrooesophageal reflux symptoms in patients without erosive oesophagitis. *Alimentary pharmacology & therapeutics*, *5*(6), 631-643.
27. Rodrigo, L., Viver, J., Conchillo, F., Barrio, E., Forné, M., Zozaya, J. M., ... & Ruiz-Capellán, R. (1989). A multicenter, randomized, double-blind study comparing famotidine with cimetidine in the treatment of active duodenal ulcer disease. Digestion, 42(2), 86-92.
28. Saigenji, K., Fukutomi, H., & Nakazawa, S. (1987). Famotidine: Postmarketing clinical experience. *Scandinavian Journal of Gastroenterology*, *22*(sup134), 34-40.
29. Shaqran, T. M., Ismaeel, M. M., Alnuaman, A. A., Al Ahmad, F. A., Albalawi, G. A., Almubarak, J. N., AlHarbi, R. S., Alaqidi, R. S., AlAli, Y. A., Alfawaz, K. S., & Daghriri, A. A. (2023). Epidemiology, Causes, and Management of Gastro-esophageal Reflux Disease: A Systematic Review. Cureus, 15(10), e47420.
30. Simon, T. J., Berenson, M. M., Berlin, R. G., Snapinn, S., & Cagliola, A. (1994). Randomized, placebo-controlled comparison of famotidine 20 mg bd or 40 mg bd in patients with erosive

oesophagitis. *Alimentary pharmacology & therapeutics*, *8*(1), 71-79

31. Summary of Product characteristics, PEPCID AC, Johnson & Johnson (Ireland) Limited.
32. Taha AS, Hudson N, Hawkey CJ, Swannell AJ, Trye PN, Cottrell J, Mann SG, Simon TJ, Sturrock RD, Russell RI. Famotidine for the prevention of gastric and duodenal ulcers caused by nonsteroidal antiinflammatory drugs. N Engl J Med. 1996 May 30;334(22):1435-9.
33. Taha, A. S., McCloskey, C., Prasad, R., & Bezlyak, V. (2009). Famotidine for the prevention of peptic ulcers and oesophagitis in patients taking low-dose aspirin (FAMOUS): a phase III, randomised, double-blind, placebo-controlled trial. The Lancet, 374(9684), 119-125.
34. Therapeutic Goods Administration (TGA), Australia : https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2023 PI-02238-1, accessed on 10 Oct 23.
35. Texter EC Jr, Navab F, Mantell G, Berman R. Maintenance therapy of duodenal ulcer with famotidine. A multicenter United States study. Am J Med. 1986 Oct 24;81(4B):25-32. doi: 10.1016/0002-9343(86)90597-8. PMID: 2877571.
36. Vinayek, R., Howard, J. M., Maton, P. N., Wank, S. A., Slaff, J. I., Gardner, J. D., & Jensen, R. T. (1986). Famotidine in the therapy of gastric hypersecretory states. *The American journal of medicine*, *81*(4), 49-59.
37. Wada, T., Sasaki, M., Kataoka, H., Tanida, S., Itoh, K., Ogasawara, N., ... & Itoh, M. (2005). Efficacy of famotidine and omeprazole in healing symptoms of non-erosive gastro-oesophageal reflux disease: randomized-controlled study of gastro-oesophageal reflux disease. Alimentary Pharmacology & Therapeutics, 21, 2-9.
38. Wesdorp, I. C. E., Dekker, W., & Festen, H. P. M. (1993). Efficacy of famotidine 20 mg twice a day versus 40 mg twice a day in the treatment of erosive or ulcerative reflux esophagitis. Digestive diseases and sciences, 38(12), 2287-2293.
39. .Yamao, J. I., Kikuchi, E., Matsumoto, M., Nakayama, M., Ann, T., Kojima, H., ... & Fukui, H. (2006). Assessing the efficacy of famotidine and rebamipide in the treatment of gastric mucosal lesions in patients receiving long-term NSAID therapy (FORCE—famotidine or rebamipide in comparison by endoscopy). *Journal of gastroenterology*, *41*(12), 1178-1185.

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.