COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Esomeprazol Cipla 10 mg, gastro-resistant granules for oral suspension in sachet (esomeprazole magnesium dihydrate)

NL/H/5465/001/DC

Date: 24 March 2025

This module reflects the scientific discussion for the approval of Esomeprazol Cipla 10 mg, gastro-resistant granules for oral suspension in sachet. The procedure was finalised on 7 July 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
CRS	Certified Reference Standards
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
GERD	Gastroesophageal reflux disease
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
NSAID	Non-steroidal anti-inflammatory drugs
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
RMS	Reference Member State
SAE	Serious Adverse Event
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 Esomeprazol Cipla 10 mg, gastro-resistant granules for oral suspension in sachet, from Cipla Europe NV.

The product is primarily indicated for:

Adults

- Gastroesophageal Reflux Disease (GERD):
  - treatment of erosive reflux esophagitis
  - long-term management of patients with healed esophagitis to prevent relapse
  - symptomatic treatment of gastroesophageal reflux disease (GERD)

- In combination with appropriate antibacterial therapeutic regimens for the eradication of *Helicobacter pylori* and:
  - healing of *Helicobacter pylori* associated duodenal ulcer and
  - prevention of relapse of peptic ulcers in patients with *Helicobacter pylori* associated ulcers.

- Patients requiring continued NSAID therapy:
  - healing of gastric ulcers associated with NSAID therapy.
  - prevention of gastric and duodenal ulcers associated with NSAID therapy, in patients at risk.

- Prolonged treatment after intravenous (i.v.) induced prevention of rebleeding of peptic ulcers.

- Treatment of Zollinger Ellison Syndrome.

Adolescents from the age of 12 years

- Gastroesophageal Reflux Disease (GERD)
  - treatment of erosive reflux esophagitis
  - long-term management of patients with healed esophagitis to prevent relapse
  - symptomatic treatment of gastroesophageal reflux disease (GERD)

- In combination with antibiotics in treatment of duodenal ulcer caused by *Helicobacter pylori*.

Children between 1 and 11 years old

- Gastroesophageal Reflux Disease (GERD)
  - treatment of endoscopically proven erosive reflux esophagitis
  - symptomatic treatment of gastroesophageal reflux disease (GERD)

Children from the age of 4 years

- In combination with antibiotics in treatment of duodenal ulcer caused by *Helicobacter pylori*.

The product may also be used by patients having difficulty swallowing dispersed Esomeprazole gastro-resistant tablets.

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(1) of Directive 2001/83/EC, which concerns a generic application.

In this decentralised procedure, essential similarity is proven between the new product and the innovator product Nexium 10 mg Sachet, gastro-resistant granules for oral suspension (NL license RVG 101600), which has been registered in the Netherlands by Grünenthal B.V. by the mutual recognition procedure SE/H/0211/004/MR since 13 June 2008.

The concerned member states (CMS) involved in this procedure were France, Italy, Norway and Sweden.

II. QUALITY ASPECTS

II.1 Introduction

Esomeprazol Cipla 10 mg, are gastro-resistant granules for oral suspension presented in sachets. Each sachet contains esomeprazole magnesium dihydrate corresponding to 10 mg of esomeprazole as active substance. The product is a fine yellow powder consisting of white to pale brownish esomeprazole granules and pale-yellow inactive granules. After reconstitution, the oral suspension is opaque, pale yellow coloured, viscous liquid with suspended particles.

The excipients are:

Esomeprazole granules - glycerol monostearate (E 471), hypromellose type 2910 (E 464), magnesium stearate (E 470b), methacrylic acid - ethyl acrylate copolymer (1:1) dispersion 30 per cent (polysorbate 80 and sodium laurilsulfate), polysorbate 80 (E 433), sugar spheres (sucrose and maize starch), talc (E 553b) and triethyl citrate (E 1505).

Excipient granules - citric acid, anhydrous (E 330), glucose, crospovidone (E 1202), iron oxide yellow (E 172), hydroxypropylcellulose (silica) (E 463) and xanthan gum (E 415).

The gastro-resistant granules for oral suspension are packed in sachets, laminated with four layers i.e., polyethylene terephthalate (PET), low density polyethylene (LDPE), aluminium and low density polyethylene (LDPE). The sachets are packed in a carton box.

II.2 Drug Substance

The active substance is esomeprazole magnesium dihydrate, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a crystalline powder and is slightly soluble in water. Esomeprazole is the S-enantiomer of Omeprazole, which has one chiral centre. Esomeprazole exhibits polymorphism, it has been shown that the polymorphic form is comparable with the polymorphic form of the Certified Reference Standard (CRS). For this product, the S-enantiomer (Esomeprazole) is consistently manufactured, the R-enantiomer and polymorphic form are controlled in the drug substance specification.

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 polymorphic identity and residual solvents. 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 three full scaled batches.

Stability of drug substance

The data submitted support a retest period for the active substance of 2 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 development of the product has been described, the choice of excipients is justified, and their functions explained. The development was based on the characteristics of the reference product Nexium 10 mg. The reference drug product contains Esomeprazole magnesium trihydrate, whereas the proposed drug product contains Esomeprazole magnesium dihydrate. Furthermore, the excipients are qualitatively similar to the innovator, with the exception of the absence of hydroxypropyl cellulose in the active granules of the generic drug product. The compatibility of the excipients with the drug substance is adequately tested. Esomeprazole magnesium dihydrate was found to be incompatible with the excipients methacrylic acid-ethyl acrylate copolymer (1:1) dispersion 30 percent, citric acid anhydrous and xanthan gum. However, in the drug product, these excipients are not in direct contact with the drug substance. The manufacturing process was optimised by a risk assessment approach and several development studies were performed.

The MAH has submitted bioequivalence studies under fed and fasting conditions. For the comparison studies of the dissolution profile of the reference and drug product, *in vitro* dissolution tests were developed. The QC dissolution methods have been adequately developed and are discriminatory. The discriminatory power of the method has been demonstrated by making two batches with different compositions and showing that these batches have different dissolution profiles in both phases of the dissolution. Comparative dissolution studies at different pH levels were performed to demonstrate similarity between the product and the reference product used in the bioequivalence studies.

According to the Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms (EMA/CPMP/EWP/280/96 Corr1, section 6.9), for generic oral formulations, *in vitro* studies of the release in alcohol solutions must be performed. Alcohol induced dose dumping has been investigated for this product. For this, dissolution tests at 0.1N HCl, pH 1.2 media with 0%, 5%, 20% and 40% alcohol were performed. The dissolution profiles of the test and reference products were found comparable in the tested media from 0 to 40 % (V/V) of alcohol and for 120 minutes.

Manufacturing process

The manufacturing process is considered a non-standard process since the drug product is a modified-release product and contains Esomeprazole in low content (≤ 2% of composition). The drug product is composed of active and inactive granules. The manufacturing process consists of the following stages:

- manufacturing process of the active granules: which includes dispensing, sifting, preparation of drug dispersion, drug loading onto sugar spheres, sizing of drug loaded granules, preparation of seal coating dispersion, seal coating, sizing of seal coated granules, preparation of enteric coating dispersion, enteric coating, sizing of enteric coating granules, sifting and blending.
- manufacturing process of the inactive granules: which includes dispensing, sifting,

preparation of binder solution, mixing, wet granulation with binder solution, drying, sizing and blending.

- Packaging of the active and inactive granules: where the active and inactive granules are packed together in a sachet.

The submitted batch formula does not contain any overages. Data has been submitted for one batch produced with the maximum hold times, demonstrating that the holding times used do not affect the stability of the drug product.

The manufacturing process has not been adequately validated according to the relevant European guidelines. Instead, process validation data of the US approved product (which has the same composition as the proposed EU product) has been provided. The MAH has committed to submit post-authorisation process validation data for three consecutive commercial scale batches for the EU market, using the formulation and manufacturing process as applicable to the proposed drug product. An adequate process validation scheme has been submitted as requested.

Control of excipients

The excipients comply with Ph.Eur. requirements, except iron oxide yellow (E 172), which is tested as per specification complying to EU 231/2012. This specification is acceptable. Furthermore, a mixture containing the three excipients triethyl citrate, glycerol monostearate and polysorbate 80 is used for the esomeprazole granules. It is acceptable to define the mixture as an excipient, as sufficient information about the mixture has been submitted.

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 (powder and solution after reconstitution), fill weight, pH, identification of esomeprazole (retention time HPLC discriminating between enantiomers and HPLC not discriminating between enantiomers and UV spectrum), identification for magnesium, colour identification for iron oxide yellow, water content, assay, assay of reconstituted solution initial and after 30 minutes, dissolution (acid and buffer stage), impurities (HPLC methods I and II), uniformity of dosage units, microbial quality and assessment of packaging material. The release and shelf life acceptance criteria are not identical; assessment of packaging material is only included in the shelf-life specification and the acceptance criteria for one impurity and total impurities differ between the release and shelf-life specifications. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. The specification is acceptable.

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 non-compendial analytical methods have been provided.

Batch analytical data from four batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for four batches stored at 25°C ± 2°C/ 60% ± 5% RH (three batches 36 months, one batch 24 months), 30°C ± 2°C/ 65% ± 5% RH (three batches 12 months) and 40°C ± 2°C/ 75% ± 5% RH (6 months). The stability was tested in accordance with applicable European guidelines. No clear trends have been observed in the submitted data. Photostability studies have been performed, the results show that the product is sensitive to light. However, it has been demonstrated that the sachets provide sufficient protection from light. Furthermore, in-use stability data have been provided demonstrating that the product remains stable for 30 minutes after reconstitution, when stored at 25°C ± 2°C/ 60% ± 5% RH. On basis of the data submitted, a shelf life was granted of 2 years. The labelled storage conditions are: 'Store in the original package in order to protect against light and moisture.
Do not store above 30°C. To be used within 30 minutes after reconstitution'.

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 Esomeprazol Cipla 10 mg, has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

The following post-approval commitments were made by the MAH:

- To submitted process validation data for three consecutive commercial scale batches for the EU market, using the formulation and manufacturing process as applicable for the proposed drug product.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Esomeprazol Cipla 10 mg, is intended for generic 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 generic formulation of Nexium 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

Esomeprazol is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The member states agreed that no further clinical studies are required, besides the two bioequivalence studies, which are discussed below.

IV.2 Pharmacokinetics

The MAH conducted two bioequivalence studies (under fasted and fed conditions) in which the pharmacokinetic profile of the test product Esomeprazol Cipla 10 mg, gastro-resistant granules for oral suspension in sachet, (Cipla Europe NV, Belgium) was compared with the pharmacokinetic profile of the reference product Nexium 10 mg Sachet, gastro-resistant granules for oral suspension (former MAH AstraZeneca Ltd, UK). The active substance of the test product is esomeprazole magnesium dihydrate, while the active substance of the reference product is esomeprazole magnesium trihydrate. The choice of the reference product in the bioequivalence study has been adequately 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.

Bioequivalence studies

Study 1, single dose fasted conditions

Design

A single-dose, randomised, open label, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 20 healthy adult male subjects, aged 26-44 years. After an overnight fast of at least 10 hours, subjects were dosed with a single oral dose (1 x sachet 10 mg esomeprazole) of one of the two esomeprazole formulations. Before administration, the granules were dispersed in a container containing 15 mL of water and administered to the subjects within 10 minutes. The solution was stirred until the granules had completely dispersed and then left for a few minutes until it had thickened. The solution was stirred again immediately before administration. The container was rinsed three times with water and immediately administered to the subject. The total dosing water was 240 mL. There were two dosing periods, separated by a washout period of 8 days.

Blood samples were collected pre-dose (0 hours, taken within 120 minutes prior to dosing), at 0.33, 0.67, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 4.33, 4.67, 5, 5.5, 6, 7, 8, 10, 12, 16 and 24 hours after administration of the products.

Results

All 20 subjects completed the two periods of the study and were eligible for pharmacokinetic analysis. One subject had a serious adverse event (SAE), which was not related to the products (abnormal electrocardiogram), and was discontinued post last PK sample. The data of the subject was included in final PK and statistical analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of esomeprazole, 10 mg under fasted conditions.

Treatment N= 20	**AUC_{0-t} (ng.h/mL)**	**$AUC_{0-\infty}$ (ng.h/mL)**	**C_{max} (ng/mL)**	**t_{max} (h)**
Test	1386.15 ± 1075.87	1399.50 ± 1087.50	409.85 ± 182.67	3.00 (1.00 - 4.33)
Reference	1449.75 ± 1208.42	1464.77 ± 1223.79	437.50 ± 217.19	2.67 (1.00 - 3.67)
***Ratio (90% CI)**	99.40 (93.68 - 105.47)	---	96.27 (87.32 - 106.14)	---

$AUC_{0-\infty}$	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*

Study 2, single dose fed conditions

Design

A single-dose, randomised, open label, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fed conditions in 20 healthy adult male subjects, aged 25-44 years. After an overnight fasting of at least 10 hours and 30 minutes before dosing, subjects consumed a standardised high fat, high calorie breakfast of 973.41 Kcal within 30 minutes. 30 minutes after the start of the breakfast, subjects were dosed with a single oral dose (1 x sachet 10 mg esomeprazole) of one of the two esomeprazole formulations. Before administration, the granules were dispersed in a container with 15 mL of water and administered to the subjects within 10 minutes. The solution was stirred until the granules had completely dispersed and then left for a few minutes until it had thickened. The solution was stirred again immediately before administration. The container was rinsed three times with water and immediately administered to the subject. The total dosing water was 240 mL. There were two dosing periods, separated by a washout period of 9 days.

Blood samples were collected pre-dose (0 hours, taken within 120 minutes prior to dosing), at 0.5, 1, 1.5, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 4.33, 4.67, 5, 5.5, 6, 8, 10, 12, 16 and 24 hours after administration of the products.

Results

A total of 18 subjects completed all the periods of the study and were eligible for pharmacokinetic analysis. There were two dropouts; one subject was discontinued due to personal reasons (subject did not check in for period 2). One subject withdrew his participation from the study on his own will and was therefore not dosed in period 2.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of esomeprazole, 10 mg under fed conditions.

Treatment N= 18	AUC_{0-t} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	C_{max} (ng/mL)	t_{max} (h)
Test	956.69 ± 795.10	974.85 ± 809.87	205.01 ± 124.00	4.67 (1.50 - 5.50)
Reference	945.30 ± 802.36	960.03 ± 817.77	208.47 ± 124.94	5.00 (2.00 - 6.00)
***Ratio (90% CI)**	100.35 (89.51-112.51)	---	99.64 (85.92-115.56)	---

$AUC_{0-\infty}$	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*

The design of the studies is acceptable. Esomeprazol Cipla 10 mg is acid labile and is administered orally as enteric-coated granules. Esomeprazole may be taken without reference to food intake. From the literature it is known that food intake both delays and decreases the absorption of esomeprazole, although this has no significant influence on the effect of esomeprazole on intragastric acidity. The BE studies have been performed under fasted and fed conditions to also investigate possible food interaction. The bioequivalence studies are in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

Analytical/statistical methods

The analytical methods have been adequately validated and are considered acceptable for analysis of the plasma samples. The methods used in the studies for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Conclusion on bioequivalence studies:

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 for both studies, under fasted and fed conditions. Based on the submitted bioequivalence studies Esomeprazol Cipla 10 mg is considered bioequivalent with Nexium 10 mg.

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 Esomeprazol Cipla 10 mg. At the time of approval, the most recent version of the RMP was version 02 with data lock point 20 October 2021 and date of final sign off 17 October 2022.

Table 3. 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.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Nexium 10 mg. The MAH demonstrated through two bioequivalence studies (under fasted and fed conditions) 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 two 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

Esomeprazol Cipla 10 mg, gastro-resistant granules for oral suspension in sachet has a proven chemical-pharmaceutical quality and is a generic form of Nexium 10 mg Sachet, gastro-

resistant granules for oral suspension. Nexium 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 essential similarity has been demonstrated for Esomeprazol Cipla 10 mg, with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 7 July 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
N.A.	N.A.	N.A.	N.A.	N.A.	N.A.