21 April 2017
EMA/85635/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report on extension of Marketing Authorisation

Nexium Control

International non-proprietary name: esomeprazole

Procedure No. EMEA/H/C/002618/X/0016

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AEs	adverse events
AUC	area Under Plasma Concentration-Time Curve from Zero to Infinity
AUCinf	area under the drug concentration-time curve from time zero to infinity
AUClast	area under the drug concentration-time curve from time zero to time t, where t is the time of last measurable concentration, Cl
BMI	body mass index
Cl	last measurable concentration
Cmax	maximum observed drug concentration
CI	confidence interval
CL/F	apparent clearance (volume cleared by the system per unit time)
CR	child Resistant
CRF	case report form
CRU	clinical research unit
%CV	coefficient of variation, percent
DCT	data collection tool
ECG	electrocardiogram
EMA	European Medicines Agency
GCP	Good Clinical Practice
GERD	gastroesophageal reflux disease
GGT	gamma-glutamyl transferase
GMR	geometric mean ratio
HDPE	high density polyethylene
HIV	human immunodeficiency virus
HPC	Hydroxypropylcellulose
IB	Investigator's Brochure
ICD	informed consent document
ICH	International Conference on Harmonization
IRB	Institutional Review Board
kel	elimination rate constant defined as the negative of the regression coefficient of the best fitting regression line obtained by regressing the log-concentration during the log-linear elimination phase on time
LLOQ	lower limit of quantification

ln	natural log
MedDRA	Medical Dictionary for Regulatory Activities mL milliliter
msec	millisecond(s)
ng	nanogram
NMT	Not More Than
NOAEL	No Observed Adverse Effect Level
NOEL	No Observed Effect Level
OTC	over-the-counter
Ph. Eur.	European Pharmacopoeia
pH	hydrogen ion concentration (negative log)
PK	pharmacokinetic
PPI	proton-pump inhibitor
RM3	Rat and Mouse No. 3 Breeding Autoclavable
QC	quality control
QRS	complex consisting of Q, R, and S waves, corresponding to depolarization of the ventricles QTc corrected interval elongation
SAE	serious adverse event SD standard deviation
SD	Standard Deviation
SE	standard error
TK	Toxicokinetics
Tmax	Time taken to reach maximum plasma concentration
USP/NF	United States Pharmacopoeia/National Formulary
VRF-1	Very High Nutrient Rodent Diet

1. Background information on the procedure

1.1. Submission of the dossier

Pfizer Consumer Healthcare Ltd submitted on 22 June 2016 an extension of the marketing authorisation for Nexium Control.

The Marketing Authorisation Holder applied for the addition of a new pharmaceutical form; gastro-resistant hard capsules, associated with one strength (20 mg) and one new package size (14 capsules). The indication applied for is the same as for the already authorised presentations: “Nexium Control is indicated for the short-term treatment of reflux symptoms (e.g. heartburn and acid regurgitation) in adults.”

Furthermore, the PI is brought in line with the latest QRD template version 10.0.

The legal basis for this application refers to:

Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I of Regulation (EC) No 1234/2008, (2) point (d) change or addition of a new pharmaceutical form - Extensions of marketing authorisations.

Information on Paediatric requirements

Not applicable.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the authorised indication, which is not changing.

Scientific Advice

The MAH did not seek scientific advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Romaldas Mačiulaitis Co-Rapporteur: Robert James Hemmings

- The application was received by the EMA on 22 June 2016.
- The procedure started on 14 July 2016.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 4 October 2016 and

included the PRAC Rapporteur's first Assessment Report. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 3 October 2016.

- During the meeting on 10 November 2016, the CHMP agreed on the consolidated List of Questions to be sent to the MAH. The final consolidated List of Questions was sent to the MAH on 11 November 2016.
- The MAH submitted the responses to the CHMP consolidated List of Questions on 19 December 2016.
- The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on 1 February 2017.
- The Rapporteurs circulated the Updated Joint Assessment Report on the responses to the List of Questions to all CHMP members on 15 February 2017.
- During the CHMP meeting on 23 February 2017, the CHMP agreed on a list of outstanding issues to be addressed in writing by the MAH.
- MAH submitted the responses to the CHMP List of Outstanding Issues on 21 March 2017.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 6 April 2017.
- During the meeting on 21 April 2017, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for an extension of the marketing authorisation for Nexium Control on 21 April 2017.

2. Scientific discussion

2.1. Problem statement

Pfizer Consumer Healthcare Limited has submitted a line extension application to include a new pharmaceutical form, Nexium Control 20 mg gastro-resistant capsules (esomeprazole). Reference is made to Nexium Control 20 mg gastro-resistant tablets. Nexium Control 20 mg gastro-resistant capsules, is identical in terms of qualitative and quantitative composition of the active substances and is therefore expected to perform identically in vivo within the clinical setting.

2.1.1. Disease or condition

Gastroesophageal reflux disease (GERD) is defined as a condition that develops when the reflux of stomach contents causes troublesome symptoms and/or complications. Reflux of gastric content into the oesophagus is mediated by different mechanisms such as low basal pressure or transient relaxations of the lower oesophageal sphincter. Heartburn and acid regurgitation are the typical symptoms associated with GERD and the most common complication is reflux oesophagitis.

Nexium Control 20 mg gastro-resistant tablets are authorised in the EU for short-term treatment of reflux symptoms (e.g. heartburn and acid regurgitation) in adults.

2.1.2. Epidemiology

GERD is one of the most frequent diseases in western world, with a prevalence of 10% to 20%. In epidemiological trials it has been shown that heartburn occurs at least once per month in 30% to 40% of all adults, at least once per week in 10% to 20% of all adults and daily in 4% to 10% of all adults in the western countries.

2.1.3. Management

About the product

Nexium Control 20 mg gastro-resistant capsules provides a 20 mg dose of esomeprazole as 22.3 mg esomeprazole magnesium trihydrate in a delayed release type product.

The proposed formulation incorporates enteric coated pellets in a hard gelatine capsule. The pellets are chemically similar to those used in the approved Nexium Control 20 mg gastro-resistant tablets drug product formulation. The new formulation is a small size 5 clear capsule, within which the enteric coated pellets are visible to the consumer.

The reference product is Nexium Control 20 mg gastro-resistant tablets EMEA/H/C/002618, Marketing Authorisation number, EU/1/13/860/001-2. Nexium Control 20 mg gastro-resistant capsules are bioequivalent to Nexium Control 20 mg gastro-resistant tablets under fasted and fed conditions.

The medicinal products Nexium Control 20 mg gastro-resistant capsules, is applied for the same indication of “The short-term treatment of reflux symptoms (e.g., heartburn and acid regurgitation) in adults”.

Type of Application and aspects on development

This application has been submitted as a line extension application (EMEA/H/C/002618) of the Nexium Control 20 mg gastro-resistant tablets marketing authorisation to include a new pharmaceutical presentation, 20 mg gastro-resistant capsules. The new pharmaceutical form, 20 mg gastro-resistant capsules has been developed in order to provide an alternative to dosing for patients.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as gastro-resistant capsules containing 20 mg of esomeprazole (as magnesium trihydrate) as active substance.

Other ingredients are:

Capsule filling: glycerol monostearate 40-55, hydroxypropylcellulose , hypromellose, magnesium stearate, methacrylic acid ethylacrylate copolymer (I: I) dispersion 30 per cent, polysorbate 80, sugar spheres

(sucrose and maize starch), talc, triethyl citrate, carmine (E120), indigo carmine (E132), titanium dioxide (E171), and yellow iron oxide (E172)

Capsule shell: gelatin, indigo carmine (E132), erythrosine (E127), and allura red (E129).

Capsule printing ink: povidone, propylene glycol, shellac, sodium hydroxide, and titanium dioxide (E171)

Band: gelatin, and yellow iron oxide (E 172)

The product is available in high-density polyethylene (HDPE) bottle with an induction seal closure and child resistant cap as described in section 6.5 of the SmPC.

2.2.2. Active Substance

The active substance used in the manufacture the new pharmaceutical form gastro-resistant capsules is the same as that used in the manufacture of the currently authorised Nexium Control 20 mg gastro-resistant tablet (EU/1/13/860/001-02).

2.2.3. Finished Medicinal Product

The proposed product is a hard gelatin capsule consisting of a clear body and an amethyst-coloured cap containing a mixture of yellow and purple coloured pellets. The gelatin capsule is sealed with a yellow gelatin band. The capsule (size 5) is smaller than the currently registered tablet.

This extension application proposes to register a gastro-resistant capsule containing colour over-coated esomeprazole enteric coated pellets to be marketed as an alternate to the currently approved gastro-resistant tablet presentation.

The proposed gastro-resistant capsules use the currently approved active substance esomeprazole magnesium trihydrate. The active ingredient is a trihydrate of the alkaline magnesium salt of esomeprazole. It is thermodynamically stable and only one crystal modification of esomeprazole magnesium trihydrate has been found. The substance is crystalline as observed with powder X-ray diffraction. Esomeprazole magnesium trihydrate is non hygroscopic and has better chemical stability than the neutral form of esomeprazole during storage.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report. The components used in the non-functional colour overcoats (yellow and purple) for the enteric coated pellets are hypromellose, triethyl citrate, indigo carmine (E132), carmine (E120), yellow ferric oxide (E172) and titanium dioxide (E171). Since the colour overcoats are applied to the outer surface of the enteric coated pellets and are not in contact with the esomeprazole magnesium trihydrate contained in the enteric coated pellets, incompatibility issues between esomeprazole and the overcoat forming excipients are not expected. The colour over-coat dissolves rapidly upon contact with water so does not impact the release characteristics of the enteric coated pellets. In addition, no incompatibilities between the active substance and the other constituent excipients are known from previous experience with other esomeprazole capsule or tablet products.

The proposed finished product is built upon the existing enteric coated esomeprazole pellet formulation (gastro-resistant tablets) and manufacturing technology.

The currently approved formulation for enteric coated pellets used in the gastro-resistant tablets is slightly different from the formulation used for the enteric coated pellets used in the proposed gastro-resistant capsules. However, the manufacturing site, equipment and processes used to manufacture the enteric coated pellets are the same. The formulation differences are driven by the inherent differences in the dosage forms (i.e. the gastro-resistant capsule does not incorporate the additional tableting excipients required for the gastro-resistant tablet, and an additional overcoat is applied to the pellets).

A single dose, randomized, open label, partial replicate, 3-period crossover bioequivalence study was completed to investigate bioequivalence of the proposed dosage form (gastro-resistant capsules) to the currently approved reference product (gastro-resistant tablets). The formulation used during clinical studies is the same as that intended for marketing. The results of the bioequivalence study show that the gastro-resistant capsules are bioequivalent to the currently approved gastro-resistant tablets.

Dissolution profiles were generated using USP dissolution apparatus 2, operating at 100 rpm, and 37 ºC, using 1000 ml pH 6.8 buffer as media following a 2-hr pre-exposure to 0.1 M HCl. The use of a non Ph.Eur. method was justified as dissolution conditions used are identical to the currently approved method for the approved gastro-resistant tablets and the dissolution method is consistent with the two stage dissolution test described in Ph. Eur. 2.9.3 – Delayed-release solid dosage forms.

The finished product is packaged in high density polyethylene (HDPE) bottles with an induction sealed closure and a child resistant (CR) cap. The bottle contains a silica gel desiccant in an HDPE container. All primary packaging components meet the regulatory requirements of EU Commission Regulation as well as other regulations for packaging intended for food contact The proposed container closure system was tested for child resistance and complies with the EU requirements for ISO 8317. The data support that the proposed container closure system meets the EU child resistant requirements for re-closable containers.

Manufacture of the product and process controls

The manufacturing process includes 16 main steps. The manufacturing process for esomeprazole enteric coated pellets used in the capsules is the same as used for the tablets. This process has been validated for the tablets in full commercial production for more than 10 years. Validation of specific steps of the capsules is under way and it will be completed prior to commercialisation according to the process validation protocol provided. Process validation data is usually required at full scale for modified release products, however, as per the process validation guideline, the particular pharmaceutical process can be considered standard for the specific manufacturer based on their experience with the process for the tablet formulation and the amount of knowledge gained historically during the development of the product. Therefore it is considered that the validation of the process is satisfactory.

The in-process controls are adequate for this type of manufacturing process.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: description (visual), uniformity of dosage units by content uniformity (HPLC), identification (chiral HPLC), assay (HPLC), organic impurities (HPLC), dissolution and microbiological quality (Ph. Eur.).

Enantiomeric purity is included in the active substance specification. In addition no racemisation was observed in the manufacturing process from pure active substance to finished product. Therefore the enantiomeric purity of esomeprazole is not included in the finished product specification.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards testing has been presented.

Batch analysis results are provided for three production scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data of three pilot scale batches of finished product stored under long term conditions for 18 months at 25 °C / 60% RH and under intermediate conditions for 12 months at 30 °C / 65% RH, and for up to 6 months under accelerated conditions at 40 °C / 75% RH according to the ICH guidelines were provided. The batches are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for the same tests and analytical procedure as for release. The analytical procedures used are stability indicating.

There were not significant changes or trends observed for samples stored at long term, intermediate, and accelerate conditions.

Photostability stress testing was conducted according to the ICH guideline Q1B on one batch in the proposed HDPE bottle. No significant changes were observed in any of the parameters measured for the photostability study, therefore it is concluded the finished product is stable when exposed to light and no precautionary labelling is required. Samples from one batch packaged in the proposed HDPE bottle was also exposed to a series of three thermal cycles. The samples were subsequently analysed with regard to physical characteristics, assay, dissolution and organic impurities. All results were within the proposed specifications. Bulk product stability test results for samples taken at each process step performed at the manufacturing site were also performed. In relation to shipping stability studies, controls of critical steps and intermediates were performed and a general description of the transportation arrangements was provided. However, the CHMP recommended performing shipping stability studies and not commercialising the product until satisfactory results are obtained from the planned shipping.

Based on available stability data, the proposed shelf-life of 30 months and do not store above 30 °C as stated in the SmPC (section 6.3) are acceptable.

Adventitious agents

Gelatine obtained from bovine sources is used in the product. Valid TSE CEP from the suppliers of the gelatine used in the manufacture was provided.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the finished product has been presented in a satisfactory manner for this new pharmaceutical form. The results of tests carried out indicate consistency

and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.2.6. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

- To perform shipping stability studies and not to commercialise the product until satisfactory results are obtained from the planned shipping.

2.3. Non-clinical aspects

2.3.1. Introduction

This is a Line Extension application (EMEA/H/C/002618) of Nexium Control 20 mg gastro-resistant capsules from the original Nexium Control 20 mg gastro-resistant tablet's application. The MAH cross-referenced to the non-clinical dossier of the Nexium Control 20 mg gastro-resistant tablet application (EMEA/H/C/002618, MA number EU/1/13/860/001-2). Therefore, no new non-clinical pharmacology, pharmacokinetics and toxicology data needs to be submitted.

However, the MAH submitted a Segment III (rat pre- and post-natal) reproductive toxicology study (Study 496989), which has not been previously reviewed. Although this study is not related to the context of this Line Extension application, it has been reviewed for completeness of the toxicology.

2.3.2. Toxicology

Reproduction toxicity

The MAH submitted a Segment III (rat pre- and post-natal) reproductive toxicology study (**Study 496989**). It was a Reproductive and Developmental Toxicity -Effects on Pre- and Postnatal Development, including Maternal Function toxicity study in mated rats. The objectives of this study were: 1. characterisation of the effects on pup growth and bone morphology following maternal gestational exposure, and 2. determination of the toxicokinetic characteristics of esomeprazole magnesium trihydrate. The study consisted of 4 groups. Groups 1 (control) and 2 (TK) animals were administered 0 or 280 mg/kg/day esomeprazole respectively

from day 16 of gestation until the day of parturition. Groups 3 (control) and 4 (TK) animals were administered 0 or 280 mg/kg/day esomeprazole respectively from day 6 of gestation until the day of parturition.

All concentrations in pups from TK Groups 2 and 4 were below the limit of quantification. Following absorption, mean esomeprazole concentrations in Group 4 dams exhibited a generally bi-phasic decline whereas in Group 2 after an initial decline from 0.5 to 1 h post dose, mean concentrations remained at a relatively steady level until the end of the sample period. Mean C_{max} was comparable between groups, with total exposure to esomeprazole ($AUC_{(0-t)}$) consistently greater in Group 2. No difference in t_{max} between groups was considered. In both esomeprazole dosed groups, there was an increase in the number of animals that showed ploughing behaviour through the cage shavings immediately after dosing, this was more evident in the animals dosed from Day 6 of gestation. These signs occurred immediately after dosing and were not evident at the +1 h time-point. In both esomeprazole dosed groups, there were no effects on body weight or food consumption and group means were comparable with control values.

In esomeprazole dosed groups, group mean reticulocyte counts and red blood cell parameters (haemoglobin, haematocrit and RBCs) on day 20 of gestation were low compared to the controls, when sampled again on day 22 of lactation, the reticulocyte counts of the F_0 adult was comparable to the controls.

There was no effect of esomeprazole magnesium trihydrate on the gestation length, mean number of implants or on pre and post-implantation loss. Pup survival over Days 0-22 of lactation and pre-weaning body weights were comparable in all groups. There were no esomeprazole magnesium trihydrate microscopic findings noted in the femurs of the F_0 adults or in the F_1 pups when examined on Days 2, 10 or 22 of lactation or in the F_1 adults on Day 70. There was no effect on pup growth or on bone morphology following maternal gestational exposure of F0 females from Day 6 or 16 of gestation until parturition.

Test Group 2 animals did not have any litter losses, but in control Group 1, from ~Day 18 of gestation, weight loss was noted, many of the animals showed poor maternal care and a higher than expected number of litter losses (in 8/20 litters all pups died). Due to concerns that the RM3 diet may no longer be suitable for littering studies, the diet was changed to VRF-1 diet for the second phase of the study, and in the control Group 3 and test Group 4 animals no litter losses were recorded.

2.3.3. Ecotoxicity/environmental risk assessment

The current Line Extension application for Nexium Control 20 mg gastro-resistant capsules will be for existing patients use, as an alternative to the tablet formulation currently on the market. Therefore, no potential increase in environmental exposure is predicted on introduction of the capsule formulation and a revised environmental risk assessment (ERA) was not required by the CHMP.

2.3.4. Discussion on non-clinical aspects

No new non-clinical data were submitted in support of this line extension application and the MAH cross-references to the non-clinical dossier submitted in support of Nexium Control 20 mg gastro-resistant tablets.

An additional non-clinical study (Segment III reproductive toxicology study) was submitted to examine pre- and post-natal effects in rats, however this was not provided to support the proposed line extension. This study determined that esomeprazole even at high maternal exposures, would not adversely affect offspring bone development. No amendment of the product information was considered necessary.

A revised ERA for Nexium Control 20 mg gastro-resistant capsules was not considered necessary as no increased environmental exposure to esomeprazole was anticipated on the approval of this Line Extension application.

2.3.5. Conclusion on the non-clinical aspects

There are no non-clinical objections to the granting of the authorisation of the line extension application for Nexium Control 20 mg gastro-resistant capsules.

2.4. Clinical aspects

2.4.1. Introduction

A bioequivalence study (B5141004) has been submitted to support the line extension application for Nexium Control 20 mg gastro-resistant capsules. The bioequivalence of the test formulation (capsules) versus the reference product (tablets) has been investigated in this study.

GCP

The bioequivalence study (B5141004) was performed in accordance with GCP as claimed by the MAH

The MAH has provided a statement to the effect that studies conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Protocol No. (Country)	Study Design and Objective	Treatment Groups	No. of Subjects (by Treatment Group, Optional)	Demographics (by Treatment Group, Optional) (No. of Subjects)	Duration of Treatment	Study Start/Status	Study Report Location
Human Pharmacokinetic (PK)/ Pharmacodynamic (PD) Study Reports							
B5141004 (United States)	Phase 1, randomized, open- label, partial replicate, 2-cohort, 3-period, crossover study with at least a 7-day washout period in order to assess the bioequivalence of Nexium 20 mg minicap (banded) capsule against Nexium 20 mg gastro-resistant tablet. Primary Objective: To demonstrate bioequivalence of Nexium OTC 20 mg MiniCap (banded) capsules compared to Nexium 20 mg gastro-resistant tablet under fasted conditions. Secondary Objective: To demonstrate bioequivalence of Nexium OTC 20 mg MiniCap (banded) capsules compared to Nexium 20 mg gastro-resistant tablet under fed conditions.	Reference(1): 20 mg Nexium gastro-resistant tablet in the fasted state. Test[a] (1): Esomeprazole OTC 20 mg MiniCaps (banded) capsule (fasted) Reference (2): 20 mg Nexium gastro-resistant tablet in the fed state. Test (2): Esomeprazole OTC 20 mg MiniCaps (banded) capsule (fed)	Randomized: 135 Treated: 120 dosed and completed all 3 treatment periods	Sex: 72 M/ 63 F Mean/Median Age (min/max): 30.7/ 29.0 (18/55) years Race: W/B/A/O: 104/24/3/4	Single dose	13 Jul 2015 Start/ 03 Sept 2015 Completed	Study Report B5141004

Note: No = Number; DB = Double-blind; PC = Placebo-controlled; PG = Parallel-group; Tmt = Treatment; Grp = Group; OL = Open-label; XO = Cross-over; M = Male; F = Female; W = White; B = Black; A= Asian; O = Other; BID = Twice daily; TID = Three times daily.

a. Please note Esomeprazole OTC 20 mg MiniCaps (banded) capsule is also referred to as 20 mg esomeprazole gastro-resistant capsule.

2.4.2. Pharmacokinetics

Methods

Study design

The bioequivalence study (B5141004) was a phase I, randomized, single-dose, 3-period, 2-cohort, open label, partial replicate, crossover study to assess the bioequivalence of esomeprazole minicap (banded) capsule against Nexium 20 mg gastro-resistant tablet in healthy volunteers under fed and fasted conditions.

The primary objective of this study was to demonstrate bioequivalence of Nexium minicap (banded) capsules compared to Nexium 20 mg gastro-resistant tablets under fasted conditions.

The secondary objective was to demonstrate bioequivalence of Nexium 20 mg minicap (banded) capsules compared to Nexium 20 mg gastro-resistant tablets under fed conditions.

The pharmacokinetic endpoints were as follow:

Primary endpoints: AUClast and Cmax of the fasted cohort. Secondary endpoints: AUClast and Cmax of the fed cohort, and AUCinf of both cohorts.

Participants were randomised by computer generated randomisation schedule. The study consisted of 3 periods separated by 7 days of washout periods. There were two cohorts (fed and fasted) and the tested and reference products were administered in 3 different sequences. Subjects were housed in the clinical facility from the evening prior to investigational product administration until after 16 hours post dose in all the study periods.

Table 4 Treatment sequences in study B5141004

	Period 1	Period 2	Period 3
Cohort 1 – Fasted			
Sequence 1	A	B	B
Sequence 2	B	A	B
Sequence 3	B	B	A
Cohort 2 – Fed			
Sequence 1	C	D	D
Sequence 2	D	C	D
Sequence 3	D	D	C

The treatments (one Nexium 20 mg minicap (banded) capsule for test product and Nexium 20 mg gastro-resistant tablet for reference product both consisting of 20 mg esomeprazole magnesium trihydrate) were given in individual dose containers to each subject by oral route with 240 ml of water, in the morning to overnight fasted for at least 10 hours subjects Cohort 1 (fasting cohort) continued fasting and Cohort 2 (fed cohort) consumed a high in fat breakfast, while the dose was administered at 30 minutes from the start of the meal. No food was consumed for at least 4 hours post dose.

Blood samples were collected before dosing and up to 16 hours after each dosing period: a total of 23 (approx. 4 ml) blood samples for PK analysis were collected during each period. Blood samples were drawn pre-dose (within aprox. 60 minutes before dosing) and at 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 8, 10, 12, 14 and 16 in tubes containing sodium heparin. The tubes were inverted 5 to 8

times and placed in a cryoblock (in an upright position) or in an ice-water mixture and stored cold for up to 30 minutes prior to completing the processing procedure. Blood samples were centrifuged under refrigeration at 2500-3000 rpm at 4°C for 10-15 min within 30 minutes after the last blood sample collection of respective time point. Plasma concentrations of esomeprazole were measured using a specific and validated liquid chromatography tandem mass spectrometry assay. As this was an open-labelled clinical study, blinding was not performed.

Safety was evaluated through assessment of full physical examination, vital signs (blood pressure, pulse rate and respiratory rate), ECG and laboratory evaluation (blood and urine samples) and pregnancy tests. It was also evaluated a physical examination and monitoring for adverse events throughout the course of the study.

The following protocol deviations were reported: One subject (subject 10011097) consumed only 60% of the meal in Treatment Period 1 due to nausea and vomiting (AEs); 62 subjects had the brief physical examination conducted prior to the 16-hour blood draw at Treatment Period 3; 7 subjects had blood drawn late due to difficulties in blood drawing. Some changes happened during the conduct of the study since there were additional subjects screened in a separate group therefore the last-subject-last-visit occurred in early September 2015. Protocol deviations were minor and did not affect the overall outcome of the study.

Test and reference products

The Marketing Authorisation Holder for Nexium 20 mg gastro-resistant tablets is Pfizer Consumer Healthcare Ltd, United Kingdom. The date of approval for non-prescription use in the EU for Nexium 20 mg gastro-resistant tablets is 23rd of August 2013. Marketing Authorisation number- EU/1/13/860/001-2. The certificates of analysis of the bio-batches were provided.

Product characteristics	**Reference product**	**Test product**
Name	Nexium Control gastro-resistant tablets	Nexium minicap capsules
Strength	20 mg	20 mg
Dosage form	Gastro-resistant tablets	Gastro-resistant capsules
Batch number/Lot Number	1587-0001-004 (Pfizer)	1714-0001-006 (Pfizer)

Population(s) studied

A total of 135 subjects were screened (57 subjects in the fasted cohort and 78 subjects in the fed cohort) for 21 days and randomized to the study. The study included healthy and adult human subjects, between 18 and 55 years of age, 72 male and 63 female subjects, with a body mass index 17.5 – 29.9 kg/m2 and a total body weight >50 kg (110 lbs). The mean age (SD) was 30.7 (10.2). A total of 104 subjects in the study were White (77%), the other subjects were Black (24, 17.8%), Asian (3, 2.2%) or other race (4, 3.0%).

Table 5 Demographic and Baseline Characteristics of the study population

	All Subjects N = 135	Fasted Cohort N = 57	Fed Cohort N = 78
Gender n (%)			
Male	72 (53.3)	29 (50.9)	43 (55.1)
Female	63 (46.7)	28 (49.1)	35 (44.9)
Age (years)			
Mean (SD)	30.7 (10.2)	31.3 (10.6)	30.2 (9.9)
Median (minimum, maximum)	29.0 (18.0, 55.0)	30.0 (18.0, 55.0)	28.0 (18.0, 55.0)
Race n (%)			
White	104 (77.0)	43 (75.4)	61 (78.2)
Black	24 (17.8)	10 (17.5)	14 (17.9)
Asian	3 (2.2)	2 (3.5)	1 (1.3)
Other	4 (3.0)	2 (3.5)	2 (2.6)
Ethnicity n (%)			
Hispanic/Latino	4 (3.0)	0	4 (5.1)
Not Hispanic/Latino	131 (97.0)	57 (100)	74 (94.9)
Weight (kg)			
Mean (SD)	76.0 (12.3)	76.6 (12.4)	75.5 (12.2)
Median (minimum, maximum)	76.0 (51.8, 112.0)	76.0 (51.8, 112.0)	74.9 (52.2, 107.0)
BMI (kg/m^2)			
Mean (SD)	25.7 (3.0)	26.0 (2.9)	25.6 (3.1)
Median (minimum, maximum)	26.4 (18.3, 29.9)	26.7 (18.3, 29.8)	25.8 (19.4, 29.9)

Out of 135 subjects, 120 subjects completed all 3 periods of the study and were considered for pharmacokinetic and statistical analysis. 8 subjects discontinued the study due to AEs, 1 subject was lost to follow-up, 3 subjects were no longer willing to participate, 1 subject did not meet eligibility criteria, 2 subjects discontinued because of other reasons.

Table 6 Subject disposition and evaluation groups

	All Subjects N (%)	Fasted Cohort N (%)	Fed Cohort N (%)
Randomized	135	57	78
Completed	120 (88.9)	50 (87.7)	70 (89.7)
Discontinued	15 (11.1)	7 (12.3)	8 (10.3)
Adverse Event	8 (5.9)	4 (7.0)	4 (5.1)
Lost to Follow-up	1 (0.7)	1 (1.8)	0 (0.0)
Other	2 (1.5)	1 (1.8)	1 (1.3)
No Longer Willing to Participate in Study	3 (2.2)	1 (1.8)	2 (2.6)
No Longer Meets Eligibility Criteria	1 (0.7)	0 (0.0)	1 (1.3)
Safety Set	135 (100)	57 (100)	78 (100)
PK Set for Period 1	133 (98.5)	57 (100)	76 (97.4)
PK Set for Period 2	123 (91.1)	51 (89.5)	72 (92.3)
PK Set for Period 3	119 (88.1)	49 (86.0)	70 (89.7)

Concomitant medication (except for approved hormonal contraceptives) was not permitted to use in the study. Including over-the-counter products (within 14 days prior to the first dose of study drug and throughout the study), herbal products (within 28 days prior to the initial dose of the study medication and throughout the study) and dietary supplements (within 14 days prior to the initial dose of the study medication and throughout the study).

The patients were allowed to use acetaminophen at doses of ≤2 g/day without consulting the sponsor, as an exception. It was also agreed that a limited use of non-prescription drugs, which were not believed to affect the subject's safety or study results already approved by Sponsor was also allowed.

Table 7 Indications for non-prescription used recorded in the study

No. of subjects		**Indication**
21		Contraception
5		Headache
2		Supplement and health
7	1	Back and leg pain
	1	General aches and pain
	1	Muscle pain
	1	Polycystic ovarian syndrome
	1	Flu-like symptoms
	1	Allergy
	1	Rash

According to the protocol all prior and current concomitant drug treatments were allowed. A total of 89 subjects (65.9%) with previous or current medical conditions. 58 (43.0%) subjects had previous medical conditions and 56 (41.5%) had current medical conditions. Surgical and medical procedures (n=43, 31.9%), injury, poisoning and procedural complications (n=14, 10.4%) were the most frequently reported previous medical conditions. Immune system disorders (n=28, 20.7%), nervous system disorders (n=9, 6.7%), musculoskeletal and connective tissue disorders (n=8, 5.9%), as well and psychiatric disorders (n=7, 5.2%) were the most frequently reported medical conditions.

Analytical methods

The analysis of human plasma samples was performed. It was begun on 04 September 2015 and was completed on 23 October 2015. Plasma samples were analysed for esomeprazole concentrations, using a validated analytical assay following standard operating procedures.

Pharmacokinetic Variables

Single-dose pharmacokinetic parameters for Nexium 20 mg MiniCap (banded) capsule and Nexium 20 mg gastro-resistant tablet were calculated using non-compartmental techniques. The maximum concentration (Cmax,) and the time at which it occurred relative to the administered dose (Tmax) was determined from the observed plasma concentration-time profile over the sampling time interval. The elimination rate constant (Kel) was determined by linear regression of the terminal linear phase of the log plasma concentration-time profile. Area under the plasma concentration-time curve from time zero to time t (AUClast), where t was the time of the last measurable concentration (C1) calculated using the linear trapezoidal method. Area under the plasma concentration-time curve from time zero to infinity (AUCinf) was calculated as AUClast+(Cl/kel). The elimination half-life (t1/2) was calculated as t1/2 = 0.693/Kel. Primary parameters (AUClast and Cmax of the fasted cohort) and secondary parameters (AUClast and Cmax of the fed cohort, and AUCinf of both cohorts) were calculated using WinNonLin® 6.3 (Phoenix®) software.

Statistical methods

The comparison in fasted state of Nexium minicap (banded) capsule (test) and Nexium gastro-resistant tablet (reference) for lnCmax and lnAUClast was considered the primary bioequivalence analysis.

The comparison in the fed state of Nexium minicap (banded) capsule (test) and Nexium gastro-resistant (reference) for lnCmax, lnAUClast and lnAUCinf, and the comparison in the fasted state of test and reference products for lnAUCinf were considered the secondary bioequivalence analyses.

PK evaluable subjects within individual periods were used for these comparisons. The pre-specified criteria for bioequivalence (according to the European Medicines Agency guidelines) were as follows: (a) for AUClast and AUCinf, bioequivalence was concluded if the 90% confidence interval (CI) of the geometric mean ratio (GMR) of test to reference fell within [0.80, 1.25]. (b) For Cmax, bioequivalence was concluded if the 90% CI of the GMR of test to reference fell within [0.80, 1.25], and if the reference formulation was not highly variable, ie, within-subject coefficient of variation (%CV) for ln Cmax was $\leq$ 30%. Otherwise (ie, %CV >30%), expanded bioequivalence limits were applied; the bioequivalence range was expanded to (exp[$\pm$0.760· Swr]), but to be no wider than [0.698, 1.432]. In addition, the point estimate of the GMR had to fall within [0.80, 1.25] interval (Swr is the within subject standard deviation [SD].

Results

The pharmacokinetic results are summarised in this section.

Figure 1. Mean (± SE) Plasma Esomeprazole Concentrations (ng/ml) of Nexium Minicap (banded) Capsules and Nexium Gastro-Resistant Tablets	
Under **Fed** conditions	Under **Fasted** conditions

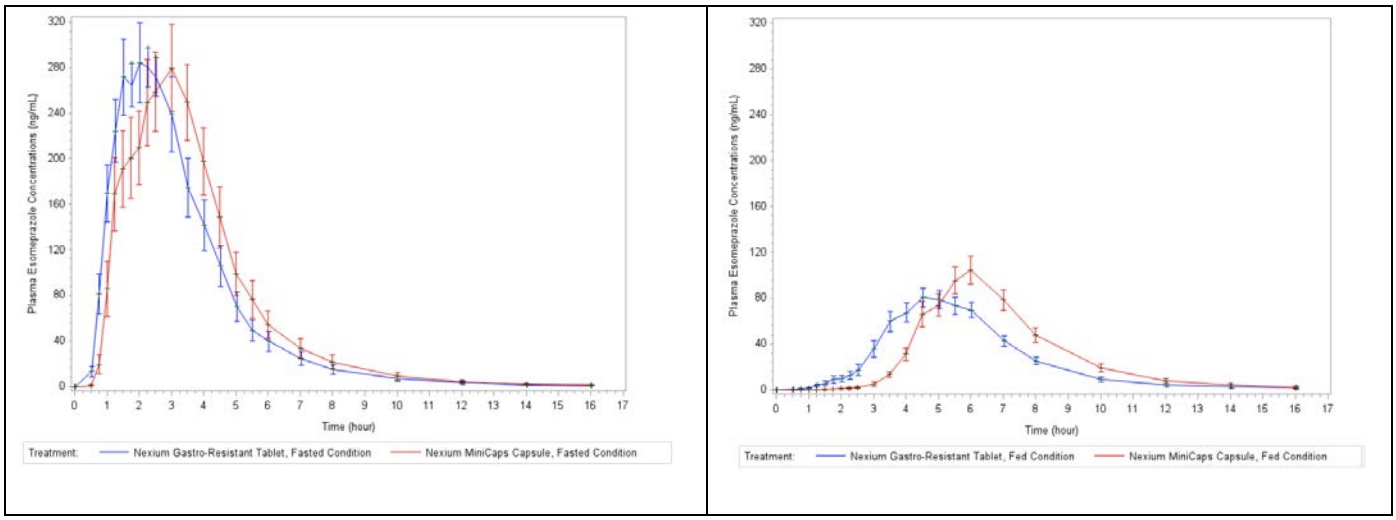

Table 8. Pharmacokinetic parameters for Esomeprazole in Fasted Cohort

Pharmacokinetic parameter	Test		Reference	
	mean	SD	mean	SD
AUC_{last} (ng*h/ml)	1037.4	845.8	1003.7	892.4
AUC_{inf} (ng*h/ml)	1041.6	851.5	1008.0	898.0
C_{max} (ng/ml)	544.9	292.9	549.8	268.5
T_{max} (h)	2.54	1.11	2.01	0.73
t1/2 (h)	1.01	0.42	0.96	0.42
CL/F (l/h)	34.61	26.42	33.78	20.74

AUC_{last}	area under the drug concentration-time curve from time zero to time of the last measurable concentration
AUC_{inf}	area under the drug concentration time curve from time zero to infinity
C_{max}	maximum observed drug concentration
T_{max}	time for maximum observed concentration
t½	elimination half-life
CL/F	volume cleared by the system

Table 9. Pharmacokinetic parameters for Esomeprazole in Fed Cohort

Pharmacokinetic parameter	Test		Reference	
	mean	SD	mean	SD
AUC_{last} (ng*h/ml)	432.6	387.0	377.6	286.7
AUC_{inf} (ng*h/ml)	484.2	421.5	406.5	342.6
C_{max} (ng/ml)	152.7	120.8	145.0	91.9
T_{max} (h)	5.88	1.06	5.02	1.32
t1/2 (h)	1.25	0.96	1.07	0.94
CL/F (l/h)	75.86	76.15	88.12	71.92

Pharmacokinetic	Test	Reference
AUC_{last}	area under the drug concentration-time curve from time zero to time of the last measurable concentration	
AUC_{inf}	area under the drug concentration time curve from time zero to infinity	
C_{max}	maximum observed drug concentration	
T_{max}	time for maximum observed concentration	
t½	elimination half-life	
CL/F	volume cleared by the system	

Table 10. Statistical Comparisons of the PK Parameters of Esomeprazole in the Fasted Cohort

Formulation	AUC_{last} (ng*h/mL)	C_{max} (ng/mL)	AUC_{inf} (ng*h/mL)
Fasted Cohort	**Nexium Minicap Capsule vs. Nexium Gastro-Resistant Tablet**		
S_{wr}/%CV		0.277/28.25%	
Test/Reference ratio (%)	1.051	0.979	1.049
90% CI (%)	(0.995, 1.110)	(0.901, 1.064)	(0.993, 1.109)
Bioequivalence Acceptance Range	(0.80, 1.25)	(0.80, 1.25)	(0.80, 1.25)
Method used	Unscaled	Unscaled	Unscaled
Outcome	Pass	Pass	Pass

Table 11. Statistical Comparisons of the PK Parameters of Esomeprazole in the Fed Cohort

Formulation	AUC_{last} (ng*h/mL)	C_{max} (ng/mL)	AUC_{inf} (ng*h/mL)
Fed Cohort	**Nexium Minicap Capsule vs. Nexium Gastro-Resistant Tablet**		
S_{wr}/%CV		0.530/56.98%	
Test/Reference ratio (%)	1.120	0.996	1.100
90% CI (%)	(1.016, 1.235)	(0.875, 1.135)	(1.011, 1.197)
Bioequivalence Acceptance Range	(0.800, 1.250)	(0.698, 1.432)	(0.800, 1.250)
Method used	Unscaled	Scaled	Unscaled
Outcome	Pass	Pass	Pass

Under the fasted conditions, the PK results demonstrated that the Nexium minicap (banded) capsule was bioequivalent to Nexium gastro-resistant tablet with respect to both primary parameters (AUClast and Cmax), as well as the secondary parameter (AUCinf). The geometric mean ratio of Nexium test-to-reference using a 90% CI met the bioequivalence criteria. T1/2 of both formulations was relatively similar. The median time to peak esomeprazole concentrations (Tmax) for Nexium minicap (banded) capsule occurred approximately 15 minutes later than that for Nexium gastro-resistant tablet. T1/2 and CL/F of both formulations were relatively similar and were in agreement with previously reported values.

In testing Cmax of esomeprazole under fed conditions it was shown to be highly variable (%CV>30%), which meant that the expanded bioequivalence limits were applied. After evaluating all secondary parameters, AUCinf, AUClast and Cmax, it was concluded that under fed conditions the Nexium minicap (banded) capsule was bioequivalent to Nexium gastro-resistant tablet. The geometric mean ratio of Nexium test-to-reference using a 90% CI met the bioequivalence criteria. The median Tmax for Nexium minicap (banded) capsule occurred 60 minutes later than that for Nexium gastro-resistant tablet.

The PK analyses demonstrated that the Nexium 20 mg minicap (banded) capsule is bioequivalent to the currently marketed Nexium gastro-resistant tablet, under both fasted and fed conditions in terms of AUClast, Cmax and AUCinf.

2.4.3. Pharmacodynamics

For this application, no new data were provided on pharmacodynamics. This is considered acceptable.

2.4.4. Discussion on clinical pharmacology

To support this application the MAH submitted the bioequivalence study to assess the bioequivalence of Nexium 20 mg capsules against Nexium 20 mg gastro-resistant tablet under fed and fasted conditions.

The study design was considered appropriate to establish PK bioequivalence of the test products. The test and reference products used in the study and the number of subjects were adequate as well. The PK variables and the statistical methods were also appropriate.

None of the deviations described was judged to affect the study results or subject safety.

The MAH addressed accordingly several issues related to data and sample management, clarified the changes introduced to the study, provided additional information about the concomitant therapies and conditions, bioanalytical methodology, individual pk parameters and clarified the differences in Tmax observed.

The assessment of the bioequivalence study complies with the Guideline on the Investigation of Bioequivalence (CPMP/QWP/EWP/1401/98 Rev. 1/Corr**). The results of the study showed the 90% confidence intervals for Cmax and AUC0-last and AUCinf fall entirely into the acceptance interval 80.00-125.00% under fasting conditions. Under fed conditions, esomeprazole Cmax was shown to be highly variable (%CV >30%), which meant that the expanded bioequivalence limits were applied in testing this parameter as prospectively anticipated in the protocol. On the basis of these results, bioequivalence between the new 20 mg capsule formulation and the 20 mg tablets of Nexium control was considered demonstrated.

2.4.5. Conclusions on clinical pharmacology

Bioequivalence between test and reference product has been demonstrated.

2.5. Clinical efficacy

For this application, no new data were provided on clinical efficacy. This was considered acceptable by the CHMP.

2.6. Clinical safety

During the bioequivalence study, 42 subjects from the total of 135 randomised patients (19 in fasted cohort and 23 in fed) experienced 74 treatment-emergent adverse events (AE). Out of them 5 (3.7%) AEs were moderate in nature and 37 (27.4%) adverse events were mild in nature. Among these, 1 AE was considered

related to treatment (1 subject experiencing rash after receiving Nexium gastro-resistant capsule in the fasted state). Neither death nor serious or severe adverse event occurred during the study.

Table 12. Summary of Adverse Events in a Study B5141004 (by Severity and Causality, in a Fasted and Fed cohorts)

	All Subjects N=135 n (%)	Fasted Cohort N=57 n (%)	Fed Cohort N=78 n (%)
Number of Treatment Emergent AEs - All Causality	74	27	47
Number of Subjects[a] with Treatment Emergent AEs - All Causality	42 (31.1)	19 (33.3)	23 (29.5)
Number of Subjects with Treatment Related AEs	1 (0.7)	1 (1.8)	0
Number of Subjects with Mild AEs	37 (27.4)	17 (29.8)	20 (25.6)
Number of Subjects with Moderate AEs	5 (3.7)	2 (3.5)	3 (3.8)
Number of Subjects with Severe AEs	0	0	0
Number of Subjects with Serious AEs	0	0	0
Number of Subjects with AEs Leading to Discontinuation	8 (5.9)	4 (7.0)	4 (5.1)
Number of Subjects Who Died	0	0	0

Source: Tables 14.3.1.1.1, 14.3.1.1.1.1, 14.3.1.1.1.2, 14.3.1.1.2, 14.3.1.1.2.1, 14.3.1.1.2.2, 14.3.1.2, 14.3.1.2.1, 14.3.1.2.2, and 14.3.1.2.
AE = adverse event; SOC = system organ class.
a. A subject may have multiple AEs for each SOC. The number of subjects counts only once within each SOC and each Preferred Term.

The most common treatment-emergent AEs were headache and nausea. Eight subjects discontinued the study due to AEs (1 event each of: headache, vomiting, rash, back pain, pyrexia, influenza-like illness, agitation, and abdominal discomfort).

Table 13. Summary of Adverse Events by in a Study B5141004 (by Incidence and SOC and preferred Term, in Fasted and Fed cohorts)

Adverse Events by SOC and Preferred Term	All Subjects N=135 n (%)	Fasted Cohort N=57 n (%)	Fed Cohort N=78 n (%)
Number of Subjects[a]	42 (31.1)	19 (33.3)	23 (29.5)
Gastrointestinal disorders	17 (12.6)	6 (10.5)	11 (14.1)
Nausea	11 (8.1)	5 (8.8)	6 (7.7)
Vomiting	5 (3.7)	2 (3.5)	3 (3.8)
Dyspepsia	3 (2.2)	0	3 (3.8)
Abdominal distension	2 (1.5)	1 (1.8)	1 (1.3)
Musculoskeletal and connective tissue disorders	3 (2.2)	3 (5.3)	0
Back pain	2 (1.5)	2 (3.5)	0
Pain in extremity	2 (1.5)	2 (3.5)	0
Nervous system disorders	24 (17.8)	8 (14.0)	16 (20.5)
Headache	21 (15.6)	7 (12.3)	14 (17.9)
Dizziness	4 (3.0)	2 (3.5)	2 (2.6)

The AEs that occurred in the study were consistent with the known safety information about known adverse events associated with treatment with esomeprazole. All physical examinations were considered as normal.

2.6.1. Discussion on clinical safety

From the 135 randomised patients total of 42 subjects (19 in fasted cohort and 23 in fed) experienced 74 treatment-emergent AE. All of them were moderate and mild in nature. Among these, only one subjects in the Capsules group, in fasted state experienced a rash 1 day after administration. Rash is described as "uncommon" AEs in the Esomeprazole SmPC. Neither death nor serious or severe adverse event occurred during the study.

The types of AEs were comparable between the two formulations and the fed/fasted states and in line with the drug class.

Therefore, the medicines were generally safe and well tolerate by the subjects during the study.

2.6.2. Conclusions on the clinical safety

The CHMP considered that there was no new relevant clinical safety information impacting on the approval of the new formulation.

2.6.3. PSUR cycle

The PSUR cycle remains unchanged.

2.7. Risk Management Plan

Safety concerns

Summary of safety concerns	
Important identified risks	Hypersensitivity reactions Gastrointestinal infections Interactions with: Warfarin or other coumarine derivatives Phenytoin Atazanavir Nelfinavir Digoxin Methotrexate Tacrolimus Clopidogrel
Important potential risks	Convulsion/seizure Off-label use Pneumonia
Missing information	Use in pregnant and lactating women Use in patients with renal impairment

Pharmacovigilance plan

There are no additional pharmacovigilance activities for this product.

Risk minimisation measures

There are no additional risk minimisation measures for this product.

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.1 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the MAH fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.9. Product information

2.9.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Nexium Control Gastro-resistant Tablets. The bridging report submitted by the MAH has been found acceptable.

3. Benefit-Risk Balance

Nexium Control 20 mg gastro-resistant tablets (esomeprazole) are approved for the short term treatment of reflux symptoms (e.g. heartburn, acid regurgitation). The proposed Nexium Control 20 mg gastro resistant hard capsules is a new pharmaceutical form identical in terms of qualitative and quantitative composition of the active substances for the same indication.

The applicant provided a bioequivalence study (B5141004) demonstrating bioequivalence of the test formulation (capsules) versus the reference product (tablets).

The design of this study was considered appropriate to establish PK bioequivalence of the test products and the assessment of bioequivalence complies with the Guideline on the Investigation of Bioequivalence (CPMP/QWP/EWP/1401/98 Rev. 1/Corr**).

Therefore the CHMP concluded that the benefit-risk of the proposed capsule formulation is in line with that of the authorised Nexium Control 20 mg gastro-resistant tablets.

3.1. Conclusions

The overall Benefit/Risk of Nexium Control 20 mg gastro resistant hard capsules is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, pharmacology and safety, the CHMP considers by consensus that the risk-benefit balance of, Nexium Control 20 mg gastro resistant hard capsules is favourable in the following indication:

Nexium Control is indicated for the short term treatment of reflux symptoms (e.g., heartburn and acid regurgitation) in adults.

The CHMP therefore recommends the extension of the marketing authorisation for Nexium Control 20 mg gastro resistant hard capsules subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product not subject to medical prescription.

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.