27 June 2013
EMA/498929/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Nexium Control

International non-proprietary name: esomeprazole

Procedure No. EMEA/H/C/002618

Note

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

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Product information

Marketing authorisation application

Name of the medicinal product:	Nexium Control
Applicant:	AstraZeneca AB Building 411A, Floor 4 S - 151 85 Södertälje SWEDEN
Active substance:	esomeprazole (as magnesium trihydrate)
International Nonproprietary Name/Common Name:	esomeprazole
Pharmaco-therapeutic group (ATC Code):	Proton pump inhibitors (A02BC05)
Therapeutic indication:	Nexium Control is indicated for the short-term treatment of reflux symptoms (e.g. heartburn and acid regurgitation) in adults.
Pharmaceutical form:	Gastro-resistant tablet
Strength:	20 mg
Route of administration:	Oral use
Packaging:	blister (PVC/PVDC)
Package sizes:	7 tablets and 14 tablets

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List of abbreviations

AAED - Astra Adverse Event Directory

AE - adverse event

ALAT - Alanine aminotransferase

ANOVA - Analysis of covariance

ASA – Acelylsalicylic acid

ASAT - Aspartate aminotransferase

AUC - Area under the plasma concentration-time curve

AUCt - Area under the plasma concentration-time curve during a dosage interval at steady state

b.i.d. - Twice daily

CgA - Chromogranin A

Cmax - Observed maximum plasma concentration

Cmin - Observed minimum plasma concentration

CNS - central nervous system

CRF - Case report form

CSR - Clinical Study Report

CYP - Cytochrome P450

CTD - Common Technical Document

DAE - Premature discontinuation of treatment with investigational product due to an adverse event (adverse events)

ECG - Electrocardiogram

ECL - enterochromaffin-like

EE - Erosive esophagitis

EGD - Esophagogastroduodenoscopy

GLP - Good Laboratory Practice

GERD - Gastroesophageal reflux disease

GCP - Good Clinical Practice

H2-RA - Histamine-2-receptor antagonist

H20 - Esomeprazole 20 mg qd

H40 - Esomeprazole 40 mg qd

H 199/18 - Esomeprazole

H+/K+-ATPase - Hydrogen/potassium adenosine triphosphatase

ICH - International Conference on Harmonisation

IEC - Independent Ethics Committee

IPA - Inhibition of platelet activation

IRB - Institutional Review Board

ITT - Intent-to-Treat

iv - intravenous

MAA - Marketing authority application

MAH - Marketing Authorisation Holder

mIPA - maximum inhibition of platelet aggregation

MTD - Maximum Tolerated Dose

NERD - Non erosive reflux disease

OAE - Other significant adverse event

OTE - Overall treatment evaluation

PD - Pharmacodynamic

PK – Pharmacokinetic

p.o. - Oral administration

PP - Per-protocol

PPB - Plasma protein binding

PPI - Proton Pump Inhibitor

Δ PRI - change in platelet reactivity index

PSUR - Periodic safety update reports

qd - Once daily

RMP - Risk management plan

SAE - Serious adverse event

SGOT - Serum glutamic oxalacetic transaminase

SGPT - Serum glutamic pyruvic transaminase

SmPC - Summary of Product Characteristics

SOC - System organ class

TK – toxicokinetic

t½ - Half-life

1. Background information on the procedure

1.1. Submission of the dossier

The applicant AstraZeneca AB submitted on 25 May 2012 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Nexium Control, through the centralised procedure under Article 3 (2) (b) of Regulation (EC) No 726/2004 (i.e. based on demonstration of interest of patients at Community level). The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 22 September 2011. The application concerns a hybrid medicinal product and refers to a reference product for which a Marketing Authorisation is or has been granted in a Member State on the basis of a complete dossier in accordance with Directive 65/65/EEC article 4.8 (equivalent to the current Art. 8.3 in Directive 2001/83/EC as amended)

The applied and approved indication reads as follows:

Short-term treatment of reflux symptoms (e.g. heartburn and acid regurgitation in adults)

The legal basis for this application refers to:

Hybrid application (Article 10(3) of Directive No 2001/83/EC).

The application is composed of administrative information, complete quality data and with appropriate own applicant's non-clinical and clinical data.

Information on paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Not applicable

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant 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 proposed indication.

Information on the reference product

The chosen reference product is:

■ Medicinal product which authorised in the Community/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Nexium, 20 mg, film-coated gastro resistant tablet
- Marketing authorisation holder: AstraZeneca AB
- Date of authorisation: 10 March 2000
- Marketing authorisation granted by: Sweden National procedure SE/H/211/01-02

- Marketing authorisation number: 15945

Scientific advice

The applicant did not seek scientific advice at the CHMP.

Licensing status

Esomeprazole has been given a Marketing Authorisation as prescription only medicine in the following countries:

Austria (28/07/2000), Belgium (11/08/2000), Cyprus (29/09/2002), Denmark (09/08/2000), Estonia (08/02/2002), Finland (31/07/2000), France (12/09/2000), Germany (26/09/2000), Greece (24/01/2001), Hungary (13/12/2001), Iceland (16/08/2000), Ireland (18/08/2000), Italy (03/01/2002), Latvia (10/04/2002), Lithuania (16/05/2001), Luxembourg (06/10/2000), Malta (14/06/2001), Netherlands (15/08/2000), Norway (21/08/2000), Poland (08/11/2001), Portugal (11/09/2000), Romania (21/05/2002), Slovenia (03/09/2002), Spain (15/09/2000), Sweden (10/03/2000 & 23/02/2001), UK (27/07/2000), Albania (15/01/2007), Algeria (16/07/2008), Argentina (10/11/2000), Armenia (07/12/2009), Aruba (11/04/2001), Australia (09/03/2001 & 28/11/2003), Azerbaijan (01/07/2008), Bahrain (13/08/2001), Belarus (30/08/2007), Benin (21/02/2005), Bosnia and Herzegovina (25/03/2008), Botswana (13/08/2007), Brazil (29/12/2000), Brunei Darussalam (29/06/2009), Burkina Faso (11/06/2004), Cambodia (21/05/2002), Cameroon (09/02/2004), Canada (17/08/2001), Chile (28/06/2002), China (16/10/2002), Colombia (16/05/2001), Congo (30/05/2003), Costa Rica (22/01/2002), Croatia (06/04/2005), Cuba (23/12/2002), Curacao (14/06/2001), Dominican Republic (09/08/2001), Ecuador (21/03/2002), Egypt (08/11/2005), El Salvador (04/03/2002), Ethiopia (12/09/2006), Gabon (27/06/2003), Georgia (10/02/2006), Ghana (01/07/2002), Guatemala (19/12/2001), Haiti (14/07/2002), Honduras (27/07/2000), Hong Kong (18/06/2001), Indonesia (26/02/2002), Iraq (19/02/2008), Israel (11/06/2001), Ivory Coast (30/08/2004), Jamaica (12/09/2001), Jordan (24/08/2002), Kazakhstan (04/09/2008), Kenya (18/06/2002), Kosovo (08/07/2011), Kuwait (28/03/2001), Lebanon (14/02/2003), Libya (27/11/2001), Macedonia (26/02/2009), Madagascar (23/05/2005), Malaysia (21/02/2002), Mali (15/09/2008), Mauritania (28/04/2004), Mauritius (09/07/2002), Mexico (18/05/2001), Morocco (24/07/2003), Namibia (14/03/2005), New Zealand (11/01/2001), Nicaragua (20/01/2002), Nigeria (08/01/2003), Oman (03/04/2002), Palestine (17/02/2004), Panama (20/07/2001), Paraguay (26/07/2004), Peru (09/05/2001), Philippines (02/08/2001), Qatar (26/01/2002), Russia (26/02/2002), Saudi Arabia (05/01/2002), Senegal (01/08/2003), Serbia (29/07/2002), Singapore (27/04/2001), South Africa (20/02/2002), South Korea (19/10/2000), Sri Lanka (13/08/2002), Sudan (01/05/2003), Switzerland (11/12/2000), Syria (25/03/2009), Taiwan (04/07/2001), Tanzania (30/09/2002), Thailand (25/04/2001), Togo (28/10/2004), Trinidad and Tobago (24/07/2001), Tunisia (10/08/2005), Turkey (21/02/2003), Uganda (06/12/2001), Ukraine (21/02/2002), United Arab Emirates (11/06/2001), Uruguay (30/04/2001), Venezuela (15/08/2001), Vietnam (24/07/2001), Yemen (09/09/2003), Zambia (21/02/2005), Zimbabwe (04/02/2005).

A Marketing Authorisation was withdrawn by the MAH post-approval in the following countries:

Czech Republic (31/12/2010), , Slovakia (12/11/2012), , Spain (21/11/2012), Bolivia (19/12/2007).

1.2. Manufacturers

Manufacturers responsible for batch release

AstraZeneca AB
Gärtunavägen
Södertälje
15185
Sweden

AstraZeneca GmbH
Tinsdaler Weg 183
22880 Wedel
Germany

AstraZeneca S. A. France
Parc Industriel Pompelle
Chemin de Vrilly
Box 1050
F-51689 Reims Cedex 2
France

AstraZeneca UK Ltd.
Silk Road Business Park
Macclesfield, Ches SK10 2NA
United Kingdom

Biofabri S.L
A Relva, s/n, O Porriño, 36400 Pontevedra
Spain

Corden Pharma GmbH
Otto-Hahn-Strasse, 68723 Plankstadt
Germany

Recipharm Monts
18, rue de Montbazon, 37260 Monts
France

1.3. 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 25 May 2012.
- The procedure started on 18 July 2012.
- The Rapporteur's initial Assessment Report was circulated to all CHMP members on

5 October 2012. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 8 October 2012.

- During the meeting on 12-15 November 2012, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 16 November 2012.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 19 February 2013.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 25 March 2013.
- During the meeting on 8-11 April 2013 the Pharmacovigilance Risk Assessment Committee (PRAC) adopted the PRAC Advice on the submitted Risk Management Plan.
- During the CHMP meeting on 22-25 April 2013, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 22 May 2013.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the list of outstanding issues to all CHMP members on 5 June 2013.
- During the meeting on 10-13 June 2013 the Pharmacovigilance Risk Assessment Committee (PRAC) adopted the PRAC Advice on the submitted Risk Management Plan.
- During the meeting on 24-27 June 2013, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Nexium Control.

2. Scientific discussion

2.1. Introduction

Problem statement

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. 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.

For many patients, acid regurgitation and heartburn can severely affect quality of life. Night-time heartburn may cause sleeping difficulties and impair next-day function. The impact on quality of life by GERD is comparable to that of more serious diseases, such as heart disease, diabetes, depression and arthritis (Wiklund et al 1998[1], Lind et al 1999[2], Gerson et al 2005[3], Vakil et al 2006[4], Jones et al 2007[5]). An improvement in the quality of life by providing effective treatment of the symptoms is therefore the predominant therapeutic goal for the treatment of acid reflux disease. Clinical studies with GERD patients showed that an appropriate inhibition of the acid secretion resulted in an effective reduction of symptoms (Richter et al 2000[6]).

Most patients do not consider treating occasional and mild heartburn, but the desire for treatment grows with increasing frequency and intensity of the symptoms. Most patients prefer self-medication for the initial treatment of heartburn symptoms and only consult a doctor if the symptoms persist (Galmiche et al 1998[7], Inadomi and Fendrick 2005[8], Bretagne et al 2007[9], Jones and Ballard 2008[10], Tytgat et al 2008[11]). Tytgat et al estimate that the number of patients who either self-medicate or are untreated is around 80%. The time lag between the first symptoms and consultation with a

[1] Wiklund I, Bardhan KD, Müller-Lissner S, Bigard MA, Bianchi Porro G, Ponce J, Hosie J, Scott M, Weir D, Fulton C, Gillon K, Peacock R. Quality of life during acute and intermittent treatment of gastro-oesophageal reflux disease with omeprazole compared with ranitidine. Results from a multicentre clinical trial. The European Study Group. Ital. J. Gastroenterol. Hepatol. 1998 Feb;30(1):19-27.
[2] Lind T, Havelund T, Lundell L, Glise H, Lauritsen K, Pedersen SA, et al. On demand therapy with omeprazole for the long-term management of patients with heartburn without oesophagitis – a placebo-controlled randomised trial. Aliment. Pharamcol. Ther. 1999;13(7):907-14.
[3] Gerson LB, Ullah N, Hastie T, Triadafilopoulos G, Goldstein M. Patient-derived health state utilities for gastroesophageal reflux disease. Am. J. Gastroenterol. 2005 Mar;100(3):524-33.
[4] Vakil N, van Zanten SV, Kahrilas P, Dent J, Jones R and the Global Consensus Group. Global Consensus Group. The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. Am. J. Gastroenterol. 2006;101:1900-20.
[5] Jones R, Liker HR, Ducrotté P. Relationship between symptoms, subjective well-being and medication use in gastro-oesophageal reflux disease. Int. J. Clin. Pract. 2007 Aug;61(8):1301-7.
[6] Richter JE, Peura D, Benjamin SB, Joelsson B, Whipple J. Efficacy of omeprazole for the treatment of symptomatic acid reflux disease without esophagitis. Arch. Intern. Med. 2000 26;160(12):1810-16.
[7] Galmiche J P, Shi G, Simon B, Casset-Semanza F, Slama A. On-demand treatment of gastrooesophageal reflux symptoms: a comparison of ranitidine 75 mg with cimetidine 200 mg or placebo. Alimentary Pharmacology & Therapeutics 1998; 12(9):909-17
[8] Inadomi J and Fendrick AM. PPI Use in the OTC Era: Who to treat, with What, and for How Long? Clin Gast and hepatology 2005;3:208-15.
[9] Bretagne JF, Honnorat C, Richard-Molard B, Soufflet C, Barthélemy P. Perceptions and practices on the management of gastro-oesophageal reflux disease: Results of a national survey comparing primary care doctors and gastroenterologists. Aliment. Pharmacol. Ther. 2007; 25(7):823-33.
[10] Jones R, Ballard K. Healthcare seeking in gastro-oesophageal reflux disease: a qualitative study. Eur. J. Gastroenterol. Hepatol. 2008 Apr:20(4):269-75.
[11] Tytgat GN, McColl K, Tack J, Holtmann G, Hunt RH, Malfertheiner P, et al. New algorithm for the treatment of gastro-oesophageal reflux disease. Aliment. Pharmacol. Ther. 2008 Feb 1;27(3):249-56.

doctor depends mainly on the intensity of the symptoms and the extent to which the symptoms interfere with daily life (Tytgat 2003[12]).

Non-prescription medicines for self-treatment of heartburn and/or acid regurgitation include antacids, histamine-2-receptor antagonists (H2-RAs) and proton pump inhibitors (PPIs). Although both having a rapid onset of action, the effect lasted longer on H2-RA therapy than on antacids, but was significantly shorter than when on PPIs. Meta-analysis found that PPIs were the most effective therapy when compared with antacids and H2-RAs. Recent clinical guidelines recommend treatment with PPIs as initial therapy for patients with symptoms impacting on their quality of life, while H2-RAs are recommended for patients whose symptoms are mild or infrequent.

About the product

Esomeprazole (the S-isomer of omeprazole) is a proton pump inhibitor, i.e., it inhibits specifically the gastric H+/K+-ATPase enzyme, which is responsible for acid secretion in the parietal cells of the stomach. The efficacy of esomeprazole for treatment of heartburn and acid regurgitation is well established. Esomeprazole as an oral formulation was first approved for marketing in Sweden in 2000, and is currently approved in more than 125 countries for various acid related disorders. The supply status in all Member States is “prescription-only medicine”.

The application is submitted through the Centralised Procedure as a hybrid application meaning that reference was made to an already approved product but that changes in the therapeutic indication compared to the reference product were applied for supported by the results of appropriate nonclinical test or clinical trials.

The reference product used for this purpose is Nexium 20 mg gastro-resistant tablets, which is approved as a prescription drug in adults for the treatment of Gastroesophageal Reflux Disease (GERD), in combination with appropriate antibacterial therapeutic regimens for the eradication of Helicobacter pylori, in patients requiring continued NSAID therapy, for prolonged treatment after i.v. induced prevention of re-bleeding of peptic ulcers, and for the treatment of Zollinger Ellison Syndrome.

The purpose of the current application for Nexium Control is to seek approval for the short term use of esomeprazole orally in the strength of 20 mg to treat reflux symptoms as a non-prescription medicine.

The claimed and approved indication reads as follows:

“Short-term treatment of reflux symptoms (e.g. heartburn and acidic regurgitation) in adults”

Type of Application and aspects on development

Relevant for the assessment are Criteria in Article 71 of Directive 2001/83/EC and the guideline on changing the classification for the supply of a medicinal product for human use (European Commission, 2006 revision)

The applicant did not receive CHMP Scientific Advice pertinent to the clinical investigation.

[12] Tytgat GN, Review article: management of mild and severe gastro-oesophageal reflux disease. Alimentary Pharmacology & Therapeutics. 2003(6); 17(Suppl 2):52-6

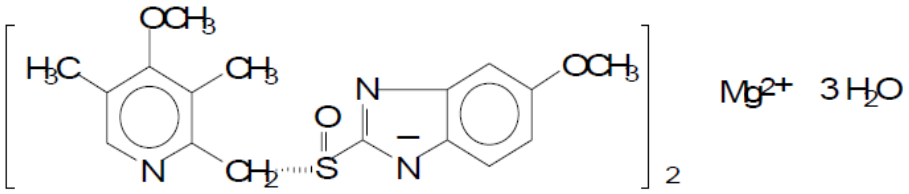
2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as gastro-resistant tablets containing 20 mg of esomeprazole (as magnesium trihydrate) as the active substance. The other ingredients are glycerol monostearate, hydroxypropyl cellulose, hypromellose, magnesium stearate, methacrylic acid, ethyl acrylate, cellulose microcrystalline, paraffin, macrogols, polysorbate 80, crospovidone, sodium stearyl fumarate, sucrose, corn starch, talc, titanium dioxide, iron oxide, triethyl citrate and hydrogen peroxide.
The esomeprazole gastro-resistant tablets 20 mg for non-prescription have the same qualitative and quantitative composition as the reference product Nexium 20 mg gastro-resistant tablets (Marketing Authorisation Holder (MAH) – AstraZeneca AB).
The gastro-resistant tablets are marketed in aluminium blister packs as described in section 6.5 of the SmPC.

2.2.1. Active substance

The chemical name of esomeprazole magnesium trihydrate is Bis(5-methoxy-2-{(S)[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl}-1H-benzimidazol-1-yl) magnesium and has the following structure:



Esomeprazole magnesium trihydrate is a white to slightly coloured crystalline powder, not hygroscopic and soluble in aqueous solutions with pH of 10.0. This active substance contains one asymmetrically substituted sulphoxide moiety which makes the molecule chiral. The Esomeprazole is the S-enantiomer of omeprazole. The enantiomeric purity of this active substance is controlled routinely by HPLC on a chiral-AGP column.
Esomeprazole magnesium trihydrate has a high degree of crystallinity and, only one crystalline form has been identified by X-ray.
A monograph of this active substance has been described in the European Pharmacopoeia.

The chemical structure elucidation has been performed by infrared spectroscopy, ultraviolet spectroscopy, ^{1}H NMR spectroscopy, ^{13}C NMR spectroscopy, optical rotation and mass spectrometry. The results of the elemental analysis are consistent with the proposed molecular formula ($C_{34}H_{36}N_6O_6S_2$ Mg • 3H2O).

Manufacture

Esomeprazole magnesium trihydrate is synthesized in four main steps using commercially available and well defined starting materials. The final active substance is purified by crystallisation. The chirality of the intermediate has an impact in the final chirality profile of the active substance. The chirality of the active substance is controlled routinely by HPLC on a chiral-AGP column and specific optical rotation. All critical steps have been identified and discussed. The manufacturing process is well described. Adequate in-process controls are applied during the synthesis. The specifications and

control methods for intermediate products, starting materials and reagents have been presented and fully described.
The characterisation of the active substance and its impurities and residual solvents are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised.

Batch analysis data are provided on three production scale batches produced by the proposed synthetic route, and the batch analysis data show that the active ingredient can be manufactured reproducibly.

The purified active substance is packed in double polyethylene tied up bags, the plastic bags are placed in polyethylene lined aluminium bags, which are welded. These are placed in plastic or steel containers for mechanical protection.

Specification

The active substance specification includes tests for: appearance (visual), identification (IR; UV, optical rotation), magnesium identity (atomic absorption spectrometry), assay (HPLC), impurities (HPLC), residual solvents (GC), enantiomeric purity (HPLC), water (KF), absorbance (UV), sulphates, titanium and cumene alcohol (GC).

The specification and analytical procedures are in line with the Ph.Eur. monograph , and includes additional testing on absorbance of solution, residual solvents, sulphates and titanium.

A detailed description for all analytical methods was provided. Full method validation data was also provided for the in-house analytical methods in accordance with the relevant ICH Guidelines. The analytical methods proposed are suitable to control the quality of the active substance. The impurity limits are acceptable and there is no concern from the point of view of safety.

All results are within the specifications and consistent from batch to batch.

Stability

Three production scale batches of the active substance packed in the intended commercial packaging (polyethylene bags) from the proposed manufacturers were put on stability testing as per ICH conditions: under long term (25°C/60%RH) for up 36 months and accelerated (40°C/75%RH) for up 6 months. The active substance used in the primary stability studies was manufactured according to the commercial process.

The following parameters were tested: assay (HPLC 98.0– 102.0%), identification (UV) and impurities (HPLC).

Forced degradation studies were conducted by exposing one batch of the active substance to high temperature, acid, base and oxidative conditions. It was only noted a slight increase of impurities, but still within specification limits of the active substance.

Photostability testing following ICH guidelines Q1B was performed on one batch of the active substance. The results showed that there are no significant changes for any of the evaluated parameters established for the stability studies.

The stability results indicate that the active substance is stable at controlled room temperature. The results justify the proposed retest period in the proposed container.

2.2.2. Finished medicinal product

Pharmaceutical development

The aim of the pharmaceutical development was to obtain gastro-resistant tablets. The active ingredient is a trihydrate of the alkaline magnesium salt of esomeprazole. This active substance is thermodynamically stable, crystalline and non-hygroscopic. The active substance is soluble in aqueous solutions. All these physicochemical properties were taken into account during the drug development. The excipients used are common for this type of dosage form and are of pharmacopoeial quality. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

This medicinal product has been developed to be a gastric acid secretion inhibitor. However, the active substance is rapidly decomposed in acidic media. Therefore, an enteric-coated formulation was developed in order to avoid any decomposition of the active substance.

The quantities of the tableting excipients were chosen so that they with good margins will form hard, fast disintegrating and non-friable tablets. Two tablet strengths of 20 mg and 40 mg have been developed. The manufacturing process and excipients used for both strengths are the same and the only difference is the quantity of the active substance. Nevertheless, the applicant intends to commercialise only the 20 mg gastro-resistant tablets.

An in vitro dissolution test method including pre-exposure in 0.1 M HCl for two hours followed by an increase of the pH to 6.8 was conducted and evaluated in terms of predictability in vivo. In addition, a bioavailability study was conducted on three tablets with different releases profiles. Moreover, the data form two previous bioavailability studies were included as supportive data. The in vitro dissolution test method provided a level A correlation for formulations having an in vitro dissolution of 70% or less at 30 minutes. Tablets that have shown a faster release rate than this upper limit were shown to have no significant differences in bioavailability. Based on the results of these studies, it was concluded that in vitro dissolution rate predicts an acceptable bioavailability properties.

Detailed information has been provided regarding the formulation development and manufacturing history in terms of the formulation, process and sites and extensive batch data confirms the consistency/uniformity of the products.

The primary packaging proposed is adequately described (Aluminium blister packs). The packaging materials comply with Ph.Eur. requirements and are adequate to support the stability and use of the product.

Adventitious agents

No excipients derived from animal or human origin have been used

Manufacture of the product

The manufacturing process consists of eight main steps. The process is considered to be a non-standard manufacturing process.

The GMP are in place to ensure the quality of the finished product. Additionally, all critical steps have been identified and the physical and chemical properties of the intermediates are controlled during the manufacturing process.

A validation study of full-scale manufacturing was performed at the manufacturing site. Major steps of the manufacturing process have been validated. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

The batch analysis data on three batches per strength show that the tablets can be manufactured reproducibly according to the agreed finished product specification, which is suitable for control of this oral preparation.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form such a as appearance (visual), uniformity of mass (Ph.Eur.), uniformity of dosage units (Ph.Eur.), identification (chiral LC), assay (HPLC), dissolution, impurities (HPLC) and microbiology (Ph.Eur.).

Batch analysis results are provided for three commercial 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 commercial batches of the finished product stored under long term conditions for 36 months at 25 ºC / 60% RH and for up to six months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided. The batches are identical to those proposed for marketing and were packed in the same primary packaging proposed for marketing.
The shelf-life specifications are identical to the release product specifications except for the limits for impurities and assay. The analytical procedures used are stability indicating.
No significant changes in specifications were noticed during the stability-testing period at long term and accelerated conditions.

In addition, one batch was exposed to light as defined in the ICH Guideline Q1B on Photostability Testing of New Drug Substances and Products. It was confirmed that the finished product is not light-sensitive.

Based on the available stability data, the shelf life and storage conditions as stated in the SmPC are acceptable.

2.2.3. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The potential impurities, by products of the synthesis and degradation products, have been discussed in detail and do not raise any safety concern. The goal of the pharmaceutical development was to obtain gastro-resistant tablets. Hence, an enteric-coated formulation was developed to avoid any decomposition of the active substance. 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.

2.2.4. Conclusions on the chemical, pharmaceutical and biological aspects

Based on the data provided the quality of this medicinal product is considered to be acceptable. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.5. Recommendation(s) for future quality development

None

2.3. Non-clinical aspects

2.3.1. Introduction

The applicant provided an acceptable summary of the pharmacology, pharmacokinetics and toxicology of esomeprazole based on published literature as well as from the reference application. No further non-clinical studies are required and the applicant has justified why no such data were provided.

Since the manufacturing of the product Nexium Control is identical to that of the Reference Product, there is no requirement to specifically address the impurity profile of the new product from a non-clinical perspective.

2.3.2. Pharmacology, Pharmacokinetics and Toxicology

Since esomeprazole is a single enantiomer of a racemate (omeprazole) that was already a marketed drug, only a limited number of nonclinical studies were necessary for the reference application. The results of the bridging studies submitted with the reference application showed that esomeprazole and omeprazole are pharmacologically and toxicologically similar at equivalent systemic exposure. Thus, the extensive nonclinical database on omeprazole was also considered relevant to the safety assessment of esomeprazole.

In summary it can be considered that due to the unique mechanism and specific effect on acid secretion, omeprazole/esomeprazole has no other significant, unrelated pharmacodynamic effects. The toxicology studies conducted for the reference application with esomeprazole indicated that this compound possesses a low systemic toxicity after both single and repeated oral administration to animals. In programs to investigate the mutagenic potentials of both esomeprazole and omeprazole it was shown that esomeprazole was not clastogenic under in vivo conditions. Based on the results in these tests, and in conjunction with the large number of mutagenicity studies previously performed on omeprazole, it was concluded that esomeprazole does not represent a genotoxic risk to man. Results in the embryo-foetal toxicity studies with esomeprazole did not indicate a risk to humans at the doses approved or proposed for use in clinical studies.

2.3.3. Ecotoxicity / environmental risk assessment

Table 1. Summary of main study results

Substance (INN / Invented Name): Esomeprazole magnesium trihydrate					
CAS-number (if available): 217087-09-7					
PBT screening		Result			**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	< 4.5			Potential PBT (N)
PBT-assessment					
Parameter	**Result relevant for conclusion**				**Conclusion**
Bioaccumulation	log K_{ow}	-			B/not B
	BCF	-			B/not B
Persistence	DT50 or ready biodegradability	-			P/not P
Toxicity	NOEC or CMR	-			T/not T
PBT-statement:	The compound is not considered as PBT nor vPvB				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
$PEC_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.1	µg/L			> 0.01 threshold (Y)
Other concerns (e.g. chemical class)					(N)
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OPPTS guideline 835.1110	$K_{d(ads)}$ = 48			
Ready Biodegradability Test	OECD 301C	BOD28/ThOD<0.6			
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50, water}$ = 2.2 to 3.7 $DT_{50, sediment}$ = 3.1 to 6.8			
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC	8.4	mg/ L	*S. capricornutum*
Daphnia sp. Reproduction Test	OECD 211	NOEC	10	mg/ L	
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC	1.0	mg/ L	*Pimephales promelas*
Activated Sludge, Respiration Inhibition Test	OECD 209	3h EC50	>100	mg/ L	
Phase IIb Studies					
Sediment dwelling organism	OECD 218	NOEC	400	mg/ kg	*Chironomus riparius*

An Environmental Risk Assessment (ERA) has been undertaken for esomeprazole in accordance with the EMA guideline. The assessment showed that the intended use of esomeprazole would result mainly in metabolites entering the environment, since it is almost completely metabolised after administration. The metabolites are predicted to partition to the aqueous phase and eventually target the aquatic environment via sewage treatment.

In the aquatic environment, esomeprazole is likely to be rapidly degraded abiotically at a neutral pH, 25°C, whereas the degradation rate is somewhat slower at lower temperatures. Esomeprazole is not readily biodegradable, however, there is evidence that the substance will partition into, and degrade

rapidly within, aquatic sediments. It is unlikely that the compound will bioaccumulate in aquatic organisms.

Only a small fraction of the compound is predicted to be removed via sewage sludge and hence exposure to the terrestrial environment is not expected to be significant.

The PEC/PNEC ratios for microorganisms, surface water, ground water and sediment are all below 0.1.

2.3.4. Discussion on non-clinical aspects

From the non-clinical point of view the esomeprazole pharmacology was adequately investigated. The toxicological properties of omeprazole have previously been extensively studied, and it has been shown that omeprazole is well tolerated in animals at dose levels that are well above those used in clinical practice. Results from the bridging studies showed that esomeprazole and omeprazole are toxicologically similar at equivalent systemic exposure.

2.3.5. Conclusion on the non-clinical aspects

The non-clinical documentation on esomeprazole, in combination with the non-clinical documentation on the racemate omeprazole, plus the extensive experience of and documentation on the clinical use of both esomeprazole and omeprazole, is considered to support the non-prescription status of 20 mg esomeprazole, once daily in adults. The environmental risk assessment based on use of esomeprazole did not identify a potential risk to the environment.

2.4. Clinical aspects

2.4.1. Introduction

This hybrid application refers to the approved product Nexium 20 mg gastro-resistant tablets and concerns a change in the indication for use as non-prescription medicine. The claimed indication is for short-term treatment of reflux symptoms (e.g. heartburn and acid regurgitation) in adults. The claimed posology is 20mg esomeprazole for a maximum of 4 weeks.

The Applicant submitted 2 Phase I Clinical Pharmacology drug-drug interaction studies and 2 identical Phase III Short-term efficacy and safety studies (QBE 0053 [Study 225] and QBE 0054 [Study 226]). The latter were considered as main studies for the claimed indication (see **Table 2)**.

As study medication esomeprazole formulated into capsules was used. Nexium gastro-resistant tablets which are referenced here were bridged to Nexium Phase III clinical trial capsules in bioequivalence studies included in the original Nexium file (SE/H/211/01-02).

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant

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

- ***Tabular overview of clinical studies***

Table 2. Tabular overview of clinical studies

Type of study	Study identifier	Location of the report in Module 5	Objective(s) of the study	Study design and type of control	Test product(s), Dosage regimen, Route of administration	No. of subjects rand/treated	Healthy subjects or diagnosis of patients	Duration of treatment	Study status; type of report
Clinical Pharmacology/ Phase I	D9612C00034	5.3.4.1	Assess the effect of esomeprazole 40 mg, omeprazole 80 mg, or lansoprazole 60 mg on the pharmacodynamic (PD) profile of clopidogrel by assessing maximum inhibition of platelet aggregation (mIPA) at Days 2, 6, 15 and 30 relative to baseline Assess the effect of esomeprazole 40 mg, omeprazole 80 mg or lansoprazole 60 mg on the pharmacokinetic (PK) profile of clopidogrel active metabolite by assessing the AUC, AUC_{0-t} and C_{max} after the loading dose of clopidogrel (Day 1) and $AUC_{0-t,ss}$ and $C_{ss,max}$ at Days 5, 14, and 29.	Open-label, randomised, 4-treatment, 3-period crossover study to assess the PD and PK interaction between clopidogrel and esomeprazole, omeprazole or lansoprazole. Each volunteer was randomized to receive a sequence of clopidogrel alone and two of the PPIs plus clopidogrel.	Clopidogrel po 300 mg loading dose on Day 1, then 75 mg daily for 28 days. Lansoprazole 60 mg po qd coadministered with clopidogrel. Omeprazole 80 mg po qd coadministered with clopidogrel. Esomeprazole 40 mg po qd coadministered with clopidogrel.	108/101	Healthy Subjects	118 days	Completed full report
Clinical Pharmacology/ Phase I	D961FC00010	5.3.4.1	Assess the effect of esomeprazole 20 mg/acetylsalicylic acid 81 mg on the pharmacodynamics of clopidogrel by assessing maximal inhibition of platelet aggregation after 9 days of clopidogrel treatment relative to baseline. Assess the effect of esomeprazole 20 mg/acetylsalicylic acid 81 mg on the pharmacokinetics of the active metabolite clopidogrel by assessing AUC, AUC_{0-last}, and $C_{ss,max}$ of the active metabolite of clopidogrel on Day 9.	Single-center, open-label, 2-way crossover study	Clopidogrel 75 mg po qd for 9 days. Clopidogrel 75 mg po qd for 4 days followed by esomeprazole 20 mg/ASA 81 mg with clopidogrel 75 mg qd for 5 days.	58/58	Healthy Subjects	18 days (two treatment periods of 9 days separated by a wash out period of 14 days)	Completed full report

Type of study	Study identifier	Location of the report in Module 5	Objective(s) of the study	Study design and type of control	Test product(s), Dosage regimen, Route of administration	No. of subjects rand/treated	Healthy subjects or diagnosis of patients	Duration of treatment	Study status; type of report
Short-term Phase III	SH-QBE 0053	5.3.5.1	Assess the efficacy, defined as complete resolution of heartburn per diary card, of both esomeprazole 40 mg qd compared to placebo qd and esomeprazole 20 mg qd compared to placebo qd of 4 weeks of treatment in patients with sGERD	Placebo-controlled randomized, double-blind, multicenter parallel-group, 4 week efficacy and safety study of esomeprazole 40 mg and esomeprazole 20 mg vs. placebo in patients with sGERD Patients were randomized on Day 1 to one of three treatment groups for 4 weeks: esomeprazole 40 mg qd, esomeprazole 20 mg qd or placebo qd.	Randomized treatment phase: Esomeprazole 40 mg capsules, Esomeprazole 20 mg capsules, Placebo capsules. Orally once daily in the morning.	368/368	Adults with symptomatic GERD with ≥ 6-month history of heartburn. episodes occurring at least 4 of the 7 days immediately preceding randomization	Up to 28 days of double-blind treatment	Completed full report
Short-term Phase III	SH-QBE 0054	5.3.5.1	Same as SH-QBE 0053	Same as SH-QBE 0053	Same as SH-QBE 0053	349/349	Same as SH-QBE 0053	Same as SH-QBE 0053	Completed full report

For the safety evaluation a review derived from the applicant's worldwide clinical trial database and post-marketing surveillance data together with a risk-benefit consideration for non-prescription status have been provided.

The applied for medicinal product and the reference product are from a quality perspective identical in terms of qualitative and quantitative composition, and manufacturing sites and processes are identical. Therefore, no bioequivalence data between the two products were required.

2.4.2. Pharmacokinetics

No new pharmacokinetic studies were conducted in support of this application and full reference was made to the available data for the reference product. This is considered acceptable.

Data on the pharmacokinetic profile of esomeprazole in line with the SmPC for the reference product relevant for this application are presented below.

Absorption

Esomeprazole, the S-isomer of omeprazole, is acid labile and is administered orally as enteric-coated granules. *In vivo* conversion to the R-isomer is negligible. Peak plasma levels occur approximately 1 to 2 hours after dose. The absolute bioavailability is 64% after a single dose of 40 mg and increases to 89% after repeated once-daily administration. For 20 mg esomeprazole the corresponding values are 50% and 68%, respectively.

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 AUC of esomeprazole magnesium decreased by 33% for a single dose and 26% at steady state on day 5 when administered after food intake compared with the fasting state, based on a single 40 mg dose. Taking into consideration that the PD effect was independent from food intake this is acceptable for the OTC status.

Elimination

Total plasma clearance of esomeprazole is about 17 L/h following a single dose and about 9 L/h after repeated administration. The plasma elimination half-life is about 1.3 hours after repeated once-daily dosing.

Almost 80% of an oral dose of esomeprazole is excreted as metabolites in the urine, the remainder in the faeces. Less than 1% of the parent drug is found in urine. The applicant explains that major metabolites of esomeprazole have no effect on gastric acid secretion.

Esomeprazole is completely metabolised by the cytochrome P450 system (CYP). The major part of the metabolism of esomeprazole is dependent on the polymorphic CYP2C19, responsible for the formation of the hydroxy- and desmethyl metabolites of esomeprazole. The remaining part is dependent on CYP3A4, responsible for the formation of esomeprazole sulphone, the main metabolite in plasma. The parameters in this section reflect mainly the pharmacokinetics in individuals with a functional CYP2C19 enzyme, ie, extensive metabolisers.

Dose proportionality and time dependencies

The pharmacokinetics of esomeprazole has been studied in doses up to 40 mg b.i.d. The AUC increases with repeated administration of esomeprazole. This increase is dose-dependent and results in a more than dose proportional increase in AUC after repeated administration. This time - and dose-dependency is due to a decrease of first pass metabolism and systemic clearance probably caused by an inhibition of the CYP2C19 enzyme by esomeprazole and/or its sulphone metabolite. Esomeprazole is completely eliminated from plasma between doses with no tendency for accumulation during once-daily administration.

Special populations

Poor metabolisers are individuals who lack a functional CYP2C19 enzyme and probably mainly catalyses esomeprazole by CYP3A4 (~2.9±1.5% of the western population). After repeated once-daily administration of 40 mg esomeprazole, the mean AUC was approximately 100% higher in poor metabolisers than in subjects having a functional CYP2C19 enzyme (extensive metabolisers). Mean peak plasma concentrations were increased by about 60%.

No studies have been performed to assess *patients with decreased renal function*. Since the kidney is responsible for the excretion of the metabolites of esomeprazole but not for the elimination of the parent compound, the metabolism of esomeprazole is not expected to be changed in patients with impaired renal function.

The CHMP noted that in a small study (Sjoevall et al., 2000[13]), the pharmacokinetics of esomeprazole, including AUC and half-life, were similar in patients with mild-to-moderate *hepatic dysfunction* (cirrhosis) and those with gastroesophageal reflux disease and normal liver function. However, significant plasma level increases were seen in patients with severe hepatic dysfunction (see **Table below**):

[13] *Sjovall H et al. Pharmacokinetics of esomeprazole in patients with liver cirrhosis. Gastroenterology 2000;118 (4; suppl 2): A346*

	DEGREE OF HEPATIC IMPAIRMENT			
PHARMACOKINETIC PARAMETER	None	Mild	Moderate	Severe
Cmax (mmol/L)	4.7	6.5	5.4	6.4
Tmax (hours)	1.6	1.7	2.3	1.8
AUC (mmol h/L	12.8	18.2	22.6	30.0
T1/2	1.5	1.3	2.4	3.1
Mmol/L = micromoles per litre				

The applicant states that the metabolism of esomeprazole is not significantly changed in *elderly subjects* (71-80 years of age). In a study performed by Hasselgren et al., 2001[14] in elderly patients Area under the curve (AUC) and maximum concentration (C-max) at steady state dosing of 40 milligrams/day were slightly higher (25% and 18%, respectively) in 13 healthy elderly subjects (mean 74 years old) compared to 36 healthy middle-aged subjects (mean 45 years old). However, between-group differences were not statistically significant, and dose adjustments are not thought to be required for elderly patients.

*Children. E*someprazole with non-prescription status is not intended for use in patients under the age of 18 years.

Pharmacokinetic interaction studies

Two specific studies were performed to assess PK/PD interaction with clopidogrel:

Study D9612C00034 was phase 1 study to evaluate esomeprazole 40 mg, omeprazole 80 mg, or lansoprazole 60 mg on PD and PK of clopidogrel in healthy volunteers. This study evaluated maximum inhibition of platelet aggregation (mIPA) as primary endpoint *(PD)*; C_{max}, t_{max}, $AUC_{(0-t)}$, AUC *(PK)*, and adverse events, clinical laboratory results, physical examinations, electrocardiograms, vital signs *(safety)* as secondary endpoints; change in platelet reactivity index (Δ PRI) and maximum inhibition of platelet aggregation and *CYP2C19* genotyping *(PD)* as exploratory endpoints.

Each volunteer was randomly assigned to receive a sequence of oral clopidogrel alone and 2 of the proton pump inhibitors + clopidogrel. The *reference treatment arm* consisted of a clopidogrel 300 mg dose on Day 1 and then clopidogrel 75 mg qd for 28 days. The 3 *test treatment arms* had the same clopidogrel dosing used in the reference treatment arm + either esomeprazole 40 mg, omeprazole 80 mg, or lansoprazole 60 mg qd for 29 days. The treatment periods were separated by washout periods of at least 14 days. Volunteers were admitted to the clinic on Days -1, 4, 13, and 28 and released on Days 2, 6, 15, and 30 after the scheduled PK and PD assessments were obtained. The study duration was approximately 146 days, including a 21-day pre-entry screening and a 7-day follow-up visit.

In total, 108 subjects were involved (63 males [58.3%] and 45 females [41.7%]), 87 (80.6%) of them completed all planned study treatments (i.e., all 3 dosing periods per protocol) and 21 (19.4%) volunteers were discontinued from the study. One SAE (spontaneous abortion) occurred after a volunteer was withdrawn due to pregnancy. One volunteer discontinued due to a SAE of schizophrenia and 5 volunteers were discontinued due to non-serious AEs.

[14] *Hasselgren G et al. Pharmacokinetics of esomeprazole are not affected by age: an assessment in the elderly. Gastroenterology 2000:118(4;suppl 2):A5698*

All 108 volunteers enrolled in the study were analysed for safety, 101 volunteers were included in PK and PD analyses.

PK. Lansoprazole, omeprazole, and esomeprazole co-administration ***significantly decreased*** exposure to the ***active metabolite of clopidogrel (H4)*** compared to clopidogrel alone on Days 5, 14, and 29, but not on Day 1.

Lansoprazole, omeprazole, and esomeprazole co-administration decreased overall exposure [**AUC(0-t)**] **of H4** on average 24%, 41%, and 38%, respectively, on Day 5, on average 24%, 46%, and 39%, respectively, on Day 14 and on average 17%, 45%, and 35%, respectively, on Day 29. Lansoprazole, omeprazole, and esomeprazole co-administration decreased maximum exposure (**Cmax**) **of H4** on average 27%, 46%, and 46%, respectively, on Day 5, on average 29%, 51%, and 43%, respectively, on Day 14 and on average 18%, 49%, and 37%, respectively, on Day 29.

The lower limit of the 90% CI of the geometric mean ratio for active metabolite (H4) $AUC_{(0-t)}$, and C_{max} comparing each proton pump inhibitor + clopidogrel (test) to clopidogrel alone (reference) was contained within the equivalence limits of 80% to 125% on Day 1 and fell below the lower bounds of the equivalence limits of 80% to 125% on Days 5, 14 and 29.

PD. *Primary variable* maximal inhibition of platelet aggregation, ***(mIPA)***. Esomeprazole and omeprazole co-administration significantly decreased mean mIPA compared to clopidogrel alone on Days 6, 15, and 30 while lansoprazole co-administration significantly decreased mean mIPA compared to clopidogrel alone on Days 2, 6, 15, and 30. The difference between the least-squares mean for clopidogrel + *lansoprazole* and clopidogrel alone represents a 15.9%, 15.0%, 20.5%, and 13.5% loss of the inhibitory effect of clopidogrel therapy on Days 2, 6, 15, and 30, respectively. The difference between the least-squares mean for clopidogrel + *omeprazole* and clopidogrel alone represents a 6.1%, 31.6%, 31.5%, and 33.1% loss of the inhibitory effect of clopidogrel therapy on Days 2, 6, 15, and 30, respectively. The difference between the least-squares mean for clopidogrel + *esomeprazole* and clopidogrel alone represents a ***1.2%, 19.9%, 32.8%, and 27.2% loss*** of the inhibitory effect of clopidogrel therapy on Days 2, 6, 15, and 30, respectively.

Secondary variables. The effect of each proton pump inhibitor on ***the inhibition of platelet aggregation*** induced by clopidogrel was virtually consistent over time; however, there seemed to be some differences in the magnitude of this effect between the different proton pump inhibitors.

Lansoprazole co-administration did not significantly increase mean (PRI - Platelet reactivity index) **ΔPRI** compared to clopidogrel alone on any study day. The magnitude of the increases in mean ΔPRI ranged from a low of 2.4% on Day 30 to a high of 4.8% on Day 6. Omeprazole co-administration significantly increased mean ΔPRI compared to clopidogrel alone by 11.8%, 13.8%, and 13.8% on Days 6, 15, and 30, respectively. Esomeprazole co-administration significantly increased mean ΔPRI compared to clopidogrel alone by 10.2%, 13.8%, and 12.8% on Days 6, 15, and 30, respectively. The magnitude of the increases in mean ΔPRI on Days 6, 15, and 30 were similar to omeprazole.

Study D961FC00010 was phase 1 study to evaluate the effect of esomeprazole 20 mg/acetylsalicylic acid (ASA) 81 mg on the PD and PK of clopidogrel on Days 1 and 9 in healthy volunteers. This study evaluated maximal inhibition of platelet aggregation (mIPA) as the primary endpoint *(PD)*, AUC, AUC0-last, and Css, max *(PK)* and adverse events, vital signs, laboratory variables, electrocardiogram, and physical examination *(safety)* as secondary endpoints; *CYP2C19* genotyping and PK/PD variables *(PD)* as exploratory endpoint.

Volunteers were randomly assigned to 1 of 2 treatment sequences (AB or BA). During Treatment A, volunteers received clopidogrel 75 mg qd for 9 days. During Treatment B, volunteers received clopidogrel 75 mg qd for 4 days followed by esomeprazole 20 mg/acetylsalicylic acid 81 mg with clopidogrel 75 mg qd for 5 days. There was a washout period of at least 14 days between each

treatment. The study duration was approximately 2.5 months, including a pre-entry visit within 28 days prior to randomization, 2 treatment periods of 9 days, a washout period of at least 14 days between the treatment periods (i.e., between the last dose in Period 1 and the first dose in Period 2), and a follow-up visit 7 to 10 days after the last dose.

In total, 58 subjects were involved (35 males [60.3%] and 23 females [39.7%]), 56 (96.6%) of them completed the study protocol. One subject withdrew after receiving all doses of treatment B and 8 days of treatment A.

PK: Administration of esomeprazole/ASA with clopidogrel reduced overall and maximum active metabolite of clopidogrel exposure ***by almost 40%*** compared to clopidogrel alone.

Pharmacogenetic results: The lowering effect of esomeprazole/ASA on active metabolite of clopidogrel exposure in the CYP2C19 poor and ultrarapid metabolizers ***did not deviate*** from that seen for the extensive metabolizers

PD: The results show there was ***no statistically significant change*** in ***mIPA*** after administration of clopidogrel with esomeprazole/ASA compared to clopidogrel administered alone.

2.4.3. Pharmacodynamics

No new pharmacodynamic studies were presented and full reference was made to the available data for the reference product. This was considered acceptable.

Mechanism of action

Esomeprazole is the *S*-isomer of omeprazole and reduces gastric acid secretion through a specific targeted mechanism of action. It is a specific inhibitor of the acid pump in the parietal cell. Both the R- and S-isomer of omeprazole have similar pharmacodynamic activity.

Esomeprazole is a weak base and is concentrated and converted to the active form in the highly acidic environment of the secretory canaliculi of the parietal cell, where it inhibits the enzyme H^+K^+-ATPase – the acid pump and inhibits both basal and stimulated acid secretion. Due to the unique mechanism and specific effect on acid secretion, omeprazole/esomeprazole have no other significant, unrelated pharmacodynamic effect.

Primary and Secondary pharmacology

Effect on gastric acid secretion: After oral dosing with esomeprazole 20 mg and 40 mg the onset of effect occurs within one hour. After repeated administration with 20 mg esomeprazole once daily (qd) for 5 days, mean peak acid output after pentagastrin stimulation is decreased 90% when measured 6 to 7 hours after dosing on day 5. After 5 days of oral dosing with 20 mg and 40 mg of esomeprazole, intragastric pH above 4 was maintained for a mean time of 13 hours and 17 hours, respectively over 24 hours in symptomatic GERD patients. The proportion of patients maintaining an intragastric pH above 4 for at least 8, 12 and 16 hours were for esomeprazole 20 mg 76%, 54% and 24%. Corresponding proportions for esomeprazole 40 mg were 97%, 92% and 56%. Using AUC as a surrogate parameter for plasma concentration, a relationship between inhibition of acid secretion and exposure has been shown.

Effects related to acid inhibition. During treatment with antisecretory drugs serum gastrin and chromogranin A (CgA) increase in response to decreased acid secretion. An increased number of enterochromaffin-like (ECL) cells, possibly related to the increased serum gastrin levels, have been observed in some patients during long-term treatment with esomeprazole. During long-term treatment with antisecretory drugs gastric glandular cysts occurs at a somewhat increased frequency.

The CHMP acknowledges that these changes are a physiological consequence of pronounced inhibition of acid secretion are benign and appear to be reversible. In addition, esomeprazole with non-prescription status is only for short-term use.

Gastrointestinal infections: In an epidemiological study Garcia Rodriguez et al[15] investigated the risk of bacterial gastroenteritis in relation to use of acid-suppressing drugs. The study was conducted as a nested case control study using the General Practice Research Database (GPRD) in UK. The study population comprised 6 414 patients with gastrointestinal bacterial infections who were matched to 50 000 controls. The results from the study showed that current use of oral PPIs (omeprazole, lansoprazole, pantoprazole, rabeprazole) was associated with an increased risk of bacterial gastroenteritis compared with non-use, regardless of the treatment duration (RR: 2.9; 95% confidence interval [CI]: 2.5-3.5), whereas no association was observed with H2RA use (RR: 1.1; 95% CI: 0.9 1.4).

Furthermore, in 2009, the applicant performed on request from a European regulatory authority a full literature review of the last 10 years (cut-off November 2008) regarding, the topic "use of PPI and *C. difficile* infection" . Although somewhat inconsistent results were revealed from the published literature and no conclusion could be drawn from in-house data, it was concluded by the applicant that it cannot be ruled out that PPI treatment may contribute to the development of *C. difficile* infection in hospitalized patients.

PD interactions. There is known secondary interaction with clopidogrel (due to PK interaction) and esomeprazole (two PK/PD interaction studies are described in the PK part of this report above).

Discussion on clinical pharmacology

The pharmacology of esomeprazole is well established and known from the application for Nexium, which is referenced here. No new studies have been conducted and a summary of the data from the reference application is supplied. The formulation of the medicine in this application and the reference are identical and therefore no bioequivalence or pharmacokinetic data is required.

The major part of the metabolism of esomeprazole is dependent on CYP2C19 which is subject to polymorphism with approximately 3% of Caucasians and 15% to 20% of Asians lacking CYP2C19 (poor metabolizers). At steady-state, the ratio of AUC in poor metabolizers to AUC in the rest of the population (extensive metabolizers) is approximately 2.

In a small study (Sjovall et al., 2000[16]) significant plasma level increases were seen in patients with severe hepatic dysfunction. Recommendation is given in the SmPC / PL that patients with severe liver impairment should be advised by a / should talk to their doctor before taking esomeprazole. Acknowledging that there are no known dose related side effects with omeprazole or esomeprazole and that for the mother compound (omeprazole) the AUC is 5-10 times higher in poor metabolisers than in the rest of the population, and it is still considered to have no implications for the posology the CHMP considers that the risk of overdosage is adequately mitigated.

The kidney is responsible for the excretion of the metabolites of esomeprazole but not for the elimination of the parent compound therefore no dose adjustment is required in patients with impaired renal function. However, due to limited experience in patients with severe renal

[15] Garcia Rodriguez LA, Ruigómez A, Panés J. Use of acid suppressing drugs and the risk of bacterial gastroenteritis. Clin Gastroenterol H 2007;5:1418-1423.
16 Sjovall H et al. Pharmacokinetics of esomeprazole in patients with liver cirrhosis. Gastroenterology 2000;118 (4; suppl 2): A346

insufficiency, such patients should be treated with caution as reflected in the SmPC. The use in Patients with renal impairment is reflected as missing information in the RMP.

In a study performed by Hasselgren et al., 2001[17] comparing elderly and middle aged patients between-group differences for Area under the curve (AUC) and maximum concentration (C-max) at steady state were not statistically significant and the CHMP agrees that dosage reductions of esomeprazole may not be necessary in geriatric patients as such for the OTC setting.

Decreased gastric acidity increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with PPIs may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter* and in hospitalised patients, also possibly *Clostridium difficile*. This is appropriately reflected in SmPC and PL for the OTC formulation and was included as a important identified risk into the RMP.

Results from studies in healthy subjects have shown a pharmacokinetic/pharmacodynamic interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and esomeprazole (40 mg p.o. daily) resulting in decreased exposure to the active metabolite of clopidogrel by an average of 40%, and resulting in decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 14%.

When clopidogrel was given together with a fixed dose combination of esomeprazole 20 mg + ASA 81 mg compared to clopidogrel alone in a study in healthy subjects there was a decreased exposure by almost 40% of the active metabolite of clopidogrel. The maximum levels of inhibition of (ADP induced) platelet aggregation in these subjects were the same in the clopidogrel and the clopidogrel + the combined (esomeprazole + ASA) product groups, likely due to the concomitant administration of low dose ASA. Based on these data, concomitant use of esomeprazole and clopidogrel should be avoided. This information is clearly described in SmPC and PL and is reflected in the RMP.

Conclusions on clinical pharmacology

The pharmacokinetics and pharmacodynamics of esomeprazole are well known from the reference product. Particularities with regards to the OTC status are appropriately reflected in SmPC, RMP and PIL.

2.4.4. Clinical efficacy

The Applicant presents the results of two studies supporting efficacy of esomeprazole for the claimed indication “short-term treatment of reflux symptoms (e.g. heartburn and acid regurgitation) in adults”.

Dose response studies

No formal dose-response studies were submitted for this application. Based on the available clinical study data, the applicant considered a daily dose of esomeprazole 20mg to be established for the short term treatment for patients with GERD, without evidence of erosive oesophagitis.

Main studies

Two phase III identical design pivotal studies were conducted: Study QBE 0053 (CSR 225) and Study QBE 0054 (CSR 226). Both of them were placebo-controlled, randomized, double-blind, multi-center, parallel-group, 4-week, efficacy and safety studies of esomeprazole 20 mg and esomeprazole 40 mg

[17] *Hasselgren G et al. Pharmacokinetics of esomeprazole are not affected by age: an assessment in the elderly. Gastroenterology 2000:118(4;suppl 2):A5698*

vs. placebo in patients with symptomatic GERD. Study sites were located in the continental USA at 26 active sites (of 26) for study 225 and at 27 active sites (of 28) for study 226. A total of 664 subjects completed the studies (344 and 320 for studies 225 and 226, respectively).

Study QBE 0053 (CSR 225) and Study QBE 0054 (CSR 226)

Methods

Study Participants

Patients with at least a 6-month history of heartburn episodes who were negative for erosive esophagitis (EE) by esophagogastroduodenoscopy (EGD) and who reported heartburn on at least 4 of the 7 days immediately preceding randomization were included. Patients were treated for 4 weeks with study medication, during which time daily diaries of heartburn occurrence and severity were kept by the patients. Patients returned for clinic visits at Week 2 and Week 4 to return diaries and any unused study medication, to be evaluated by the investigator for GERD symptoms and safety, and to complete the OTE questionnaire. Eligible patients were randomized to one of three treatment groups—H40, H20, or placebo.

Inclusion Criteria: **(1)** Adults between the ages of 18 and 75 inclusive (and of legal age to consent); **(2)** heartburn as the main symptom, defined as a burning feeling rising from the stomach or lower part of the chest up towards the neck, and presenting with macroscopically normal oesophageal mucosa, defined as absence of mucosal breaks confirmed by EGD performed within 10 days of study randomization; **(3)** a history of episodes of heartburn for 6 months or longer and **(4)** heartburn for 4 days or more during the last 7 days prior to randomisation.

Exclusion criteria: (1) any bleeding disorder or signs of GI bleeding at the time of the screening EGD or within 3 days prior to randomization; **(2)** history of or current endoscopic erosive esophagitis at screening EGD; **(3)** history of gastric or esophageal surgery, except for simple closure of perforated ulcer; **(4)** current or historical evidence (within 3 months) of the following diseases/conditions: Zollinger - Ellison syndrome, primary oesophageal motility disorders, oesophageal stricture, ulcer and/or Barrett's metaplasia, oesophageal erosion or previous gastric or duodenal surgery; **(5)** significant concurrent disease (e.g. cardiovascular, pulmonary, renal or liver disease, malignancy, unstable diabetes mellitus, any condition that may have required surgery during the study); **(6)** PPI use within 28 days prior to the baseline visit; **(7)** H2-receptor antagonist daily during the 2 weeks prior to the screening EGD or between the screening EGD and study enrolment (occasional use less than daily was permitted); **(8)** continuous treatment with nonsteroidal anti-inflammatory drugs (the use of low-dose aspirin for prophylaxis against cardiovascular diseases was allowed); **(9)** other drugs for the treatment of reflux symptoms use during the studies.

The EGD was performed on all eligible patients prior to randomization to confirm the absence of EE. Gastric biopsies were also obtained during this procedure for use in a histologic test for H. pylori.

Treatments

Patients were randomized to treatment in a 1:1:1 ratio (H40 : H20 : placebo).

Study medication or placebo (1 capsule of identical appearance) was taken orally, once daily, in the morning with a glass of water. A duration of 4 weeks was chosen for the primary efficacy evaluation as 4 weeks is an approved treatment duration for patients with symptoms of GERD, without evidence of erosive esophagitis (i.e., no oesophageal mucosal breaks). Efficacy was also assessed after 2

weeks of treatment, since it was hypothesized that esomeprazole could demonstrate efficacy after a shorter duration of treatment.

Prior and concomitant therapies: in addition to Exclusion criteria for prior therapies, during the study subjects were not allowed to use **(1)** PPIs (other than study medication); **(2)** H2-receptor antagonists; **(3)** other medications that might have affected the interpretation of the treatment outcome or were considered drug interactions in the PRILOSEC® (omeprazole) delayed-release capsules package insert.

Rescue therapy: during the study subjects were allowed to use GELUSIL tablets for acute GERD symptoms (up to 6 tablets per day). Gelusil is supposed to be an OTC product for heartburn, acid indigestion and gas. Its main ingredients are aluminium hydroxide, magnesium hydroxide and simethicone.

Objectives

Primary objective: to assess the efficacy, as defined by complete resolution of heartburn per diary card, of 4 weeks of treatment of Esomeprazole 40 mg qd compared to placebo qd and Esomeprazole 20 mg qd compared to placebo qd in subjects with GERD.

The major secondary objectives were to access the complete resolution of heartburn, the mean severity of heartburn, heartburn-free days, days without nocturnal heartburn, and two additional summaries/analyses (the mean severity of heartburn for each patient, and the percentage of patients with relief of heartburn at the end of the study).

Outcomes/endpoints

Primary efficacy endpoint: the percentage of patients who exhibited ***complete resolution*** of heartburn (no episodes of heartburn ***during the last 7 days*** of the study, according the patient diary card).

Secondary efficacy endpoints were build in accordance to secondary objectives e.g., the percentages of patients with resolution of ***GERD symptoms*** (heartburn, acid regurgitation, dysphagia, and epigastric pain) as rated by the investigator at Week 2 and Week 4. (The GERD symptoms were recalled by the patient for the 7 days prior to their study visit and documented.

The definitions for the symptoms being assessed were: (i) ***heartburn*** - a burning feeling, rising from the stomach or lower part of the chest towards the neck; (ii) ***acid regurgitation*** - flow of sour or bitter fluid into mouth; (iii) ***dysphagia*** - difficulties in swallowing, and (iv) ***epigastric pain*** - central upper abdominal pain.

The assessment of each GERD symptom was to include a rating of the overall ***severity*** of each symptom during the 7 days preceding the visit, as follows: (I) None - No symptoms; (ii) mild - awareness of symptom, but easily tolerated; (iii) moderate - Discomforting symptom sufficient to cause interference with normal activities (including sleep); (iv) severe -incapacitating symptom, with inability to perform normal activities (including sleep).

Sample size

Sample sizes of 100 per group were planned and sizes of treatment groups achieved in studies 225 and 226 are provided in Table 9.

Table 9. Number of planned, enrolled and analyzed subjects (study 225 and 226).

Study 225			
Number of Patients (Planned and Analyzed):	H 199/18 40 mg qd	H 199/18 20 mg qd	Placebo qd
Number of Patients Planned	100	100	100
Number of Patients Enrolled	123	121	124
Number of Patients Analyzed			
Efficacy: Intent-to-Treat	123	121	124
Efficacy: Per Protocol	115	117	114
Safety	122	120	123

Study 226			
Number of Patients (Planned and Analyzed):	H 199/18 40 mg qd	H 199/18 20 mg qd	Placebo qd
Number of Patients Planned	100	100	100
Number of Patients Enrolled	118	113	118
Number of Patients Analyzed			
Efficacy: Intent-to-Treat	118	113	118
Efficacy: Per Protocol	106	103	109
Safety	116	112	117

The sample size of 100 patients per treatment group assured 95% power to detect a difference in resolution rates of 60% for an esomeprazole treatment group and 30% for the placebo treatment group. This assumes a two-sided test, using the arcsine transformation, and a Bonferroni correction (ie, an alpha level of 0.025) for the two comparisons (each esomeprazole treatment group to placebo).

Randomisation

Randomization was performed at each centre using blinded blocks of 6 allocation numbers according the applicant's scheme. Patients were randomized to treatment in a 1:1:1 ratio (H40: H20: placebo). Eligible patients at each centre were given the next sequential enrolment number (001, 002, 003, etc) and the next sequential allocation number based on pre-printed numbers on the study drug labels.

Blinding (masking)

For blinding, all study drugs had the same appearance. They were packaged in bottles at Astra Hässle AB, Mölndal, Sweden. Investigators were provided with individually sealed and blinded randomization envelopes indicating the treatment allocation for each patient. All envelopes were collected and checked by the monitor at the end of the study.

Statistical methods

Intent-to Treat (ITT) population: all randomized patients, defined prior to unblinding the data.

Per Protocol population (PP): the subset of ITT patients without certain protocol deviations, defined prior to unblinding the data.

Safety population (SAF): All randomized patients who received at least one dose of study medication and for whom post-dose data were available.

Primary Efficacy Analysis: The rate of ***complete resolution*** of heartburn ***for the last 7 days*** in the study was analyzed for ITT and PP populations regarding the data from the last available 7-day period on the diary card.

Two analyses were performed: (1) A chi-square statistic was used to compare the rate of resolution of heartburn for each esomeprazole treatment group to the placebo group; (2) Hochberg's method was used to adjust for the two comparisons of interest.

Secondary Efficacy Analysis: variables were analyzed only for the ITT population, with no adjustment for multiple comparisons (only nominal p-values were presented). Chi-square statistics were used for comparisons of all dichotomous response variables. The efficacy variables based on the mean

severity of heartburn or on the percentages of days/nights without heartburn were compared using a two-way analysis of variance model (ANOVA), with main effects of investigator and treatment (used in Objectives No 3, 4, 5). A life-table approach was used to analyze the 'time to' variables; statistical comparisons were made using log-rank tests (used in Objectives No 6, 7). Investigators who contribute fewer than 5 patients to an analysis were combined in a separate 'investigator' for the analysis. To evaluate resolution of investigator-assessed GERD symptoms at 2 time points, a Cochran-Mantel-Haenszel test was used (Objective No 8). Overall treatment evaluation results were compared using a Wilcoxon rank-sum test (Objective No 9).

Subgroup analyses of the primary endpoint in the ITT population was presented descriptively for gender, age group (< 65 years, ≥ 65 years), race, investigator, and *H. pylori* status (by histology).

Safety: No inferential statistics were used. Adverse events and medical/surgical history were classified according the terminology of Astra Adverse Event Dictionary (AAED). Incidence rates of adverse event were calculated by body system and preferred term.

Safety variables including clinical laboratory tests and vital signs for the 3 treatment groups were presented using descriptive statistics. Descriptive statistics were calculated for baseline, final, and change from baseline values. 'Shift tables' presenting the frequencies of changes from within to outside of normal limits were produced for each laboratory test. Frequencies of patients having one or more potentially clinically significant results for each laboratory test were calculated using predefined criteria.

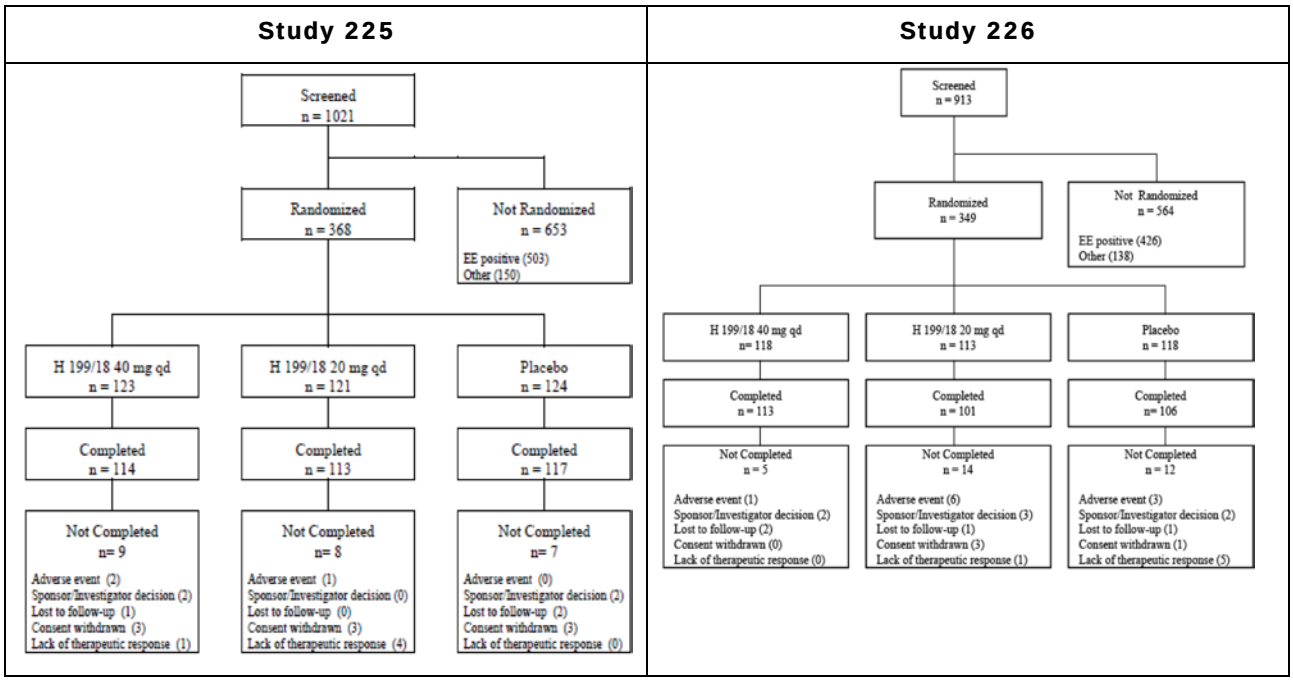
Handling the missing data and dropouts: If a diary value was missing, the maximum value of the closest prior and post diary entries was assigned. The values that were not consistent (eg, missing severity, but heartburn = Yes) were imputted and then decision was made as to the appropriateness of the data for analysis of each endpoint. Patient with less than 4 days with values or more than 2 days of imputed values was either considered a non-responder (if there was sufficient data to qalify as a non-responder), or was excluded from the analysis.

Results

Participant flow

Participants flow. In study 225, 369/1021 patients (36%) were randomized compared to 349/913 patients (38.2%) in study 226. The primary reason for non-randomizing screened patients was erosive esophagitis (EE) positive status. Of the 368 patients enrolled in **study 225**, 344 patients (93.5%) completed the study and 24 patients (6.5%) discontinued from the study before completion, mainly due to the withdrawal of consent (2.4%). Three patients (0.8%) discontinued due to an AE. Of the 349 patients enrolled in **study 226**, 320 patients (91.7%) completed the study, and 29 patients (8.3%) discontinued from the study before completion, mainly due to the occurrence of an AE (2.9%). Randomisation and discontinuation rates were comparable between the groups.

Figure 1. Subject disposition and reasons for withdrawal in study 225 and Study 226.



Recruitment

Studies 225 and 226 recruitment was initiated in February 1999, completed in June 1999.

Conduct of the study

Treatment compliance was ~90% in all 3 treatment groups. No patients were excluded from the ITT population. In **study 225**, 22/368 patients (6%) were excluded from PP population, mainly due to study drug compliance (10/368, 2.7%), medical history (7/368, 1.9%) and use of the prohibited medications prior or during the study (4/368, 1.1%). In **study 226**, 31/349 patients (8.9%) were excluded from PP population, mainly due to study drug compliance (15/349, 4.3%) and use of the prohibited medications prior or during the study (8/349, 2%). Across the three treatment groups in each study, the numbers of patients excluded were comparable. The excluded patients are comparable between groups both quantitatively and qualitatively.

Baseline data

The patients were fairly balanced among the groups as regards the gender, age, race, body weight, height, GERD history, heartburn, acid regurgitation, dysphagia, epigastric pain, *H. pylori* status (**Table 10**).

Table 10. Demographic and other baseline characteristics (ITT population, studies 225 and 226).

		Study 225			Study 226		
Demographic or Other Baseline Characteristic		**H 199/18 40 mg (N=123)**	**H 199/18 20 mg (N=121)**	**Placebo (N=124)**	**H 199/18 40 mg (N=118)**	**H 199/18 20 mg (N=113)**	**Placebo (N=118)**
Gender, n (%)							
	Male	48 (39.0%)	49 (40.5%)	46 (37.1%)	42 (35.6%)	34 (30.1%)	50 (42.4%)
	Female	75 (61.0%)	72 (59.5%)	78 (62.9%)	76 (64.4%)	79 (69.9%)	68 (57.6%)
	18-44 years	28 (37.3%)	28 (38.9%)	33 (42.3%)	36 (47.4%)	35 (44.3%)	26 (38.2%)
	≥ 45 years	47 (62.7%)	44 (61.1%)	45 (57.7%)	40 (52.6%)	44 (55.7%)	42 (61.8%)
Age (years)							
	Mean (SD)	47.2 (13.5%)	47.0 (13.4)	46.0 (12.6)	45.0 (13.1)	46.0 (14.0)	47.0 (13.2)
	Median	47.0	45.0	46.0	44.0	45.0	46.5
	Min to Max	20 – 78	21 - 75	19 - 82	19 - 77	19 - 75	21 - 77
Age category, n (%)							
	< 65 years	111 (90.2%)	104 (86.0%)	116 (93.5%)	107 (90.7%)	98 (86.7%)	106 (89.9%)
	≥65 years	12 (9.8 %)	17 (14.0%)	8 (6.5%)	11 (9.3 %)	15 (13.3 %)	12 (10.2 %)
Race, n (%)							
	Caucasian	100 (81.3%)	113 (93.4%)	104 (83.9%)	104 (88.1%)	90 (79.6%)	99 (83.9%)
	Black	17 (13.8%)	6 (5.0%)	11 (8.9%)	13 (11.0%)	19 (16.8%)	17 (14.4%)
	Asian	4 (3.3%)	0 (0.0%)	4 (3.2%)	0 (0.0%)	3 (2.7%)	1 (0.8%)
	Other	2 (1.6%)	2 (1.7%)	5 (4.0%)	1 (0.8%)	1 (0.9%)	1 (0.8%)
Body weight, lb							
	Mean (SD)	181.3 (46.8)	179.3 (38.3)	177.7 (41.0)	178.3 (43.1)	176 (40.6)	179.3 (39.3)
	Median	175.0	175.5	170.5	171.0	177.0	176.0
	Min to Max	108 - 350	105 - 299	100 - 295	100 - 294	105 - 350	109 - 300
Height, in							
	Mean (SD)	66.5 (4.4)	66.4 (3.8)	66.1 (3.7)	66.6 (3.9)	65.7 (3.4)	66.4 (4.1)
	Median	66.5	66.0	66.0	66.0	65.5	67.0
	Min to Max	54 - 78	59 - 76	58 - 76	56 - 77	60 - 75	57 - 78
GERD history, n (%)							
	<1 year	11 (8.9%)	12 (9.9%)	14 (11.3%)	10 (8.5%)	15 (13.3%)	5 (4.2%)
	1 to 5 years	58 (47.2%)	62 (51.2%)	62 (50.0%)	58 (49.2%)	44 (38.9%)	49 (41.5%)
	>5 years	54 (43.9%)	47 (38.8%)	48 (38.7%)	50 (42.4%)	54 (47.8%)	64 (54.2%)
Heartburn, n (%)							
	None	0 (0.0%)	1 (0.8%)	0 (0.0%)	1 (0.8%)	0 (0.0%)	0 (0.0%)
	Mild	14 (11.4%)	19 (15.7%)	19 (15.3%)	22 (18.6%)	9 (8.0%)	11 (9.3%)
	Moderate	81 (65.9%)	70 (57.9%)	74 (59.7%)	64 (54.2%)	62 (54.9%)	72 (61.0%)
	Severe	28 (22.8%)	31 (25.6%)	31 (25.0%)	31 (26.3%)	42 (37.2%)	35 (29.7%)
Acid regurgitation, n (%)							
	None	11 (8.9%)	16 (13.2%)	13 (10.5%)	9 (7.6%)	15 (13.3%)	8 (6.8%)
	Mild	40 (32.5%)	32 (26.4%)	34 (27.4%)	35 (29.7%)	27 (23.9%)	31 (26.3%)
	Moderate	47 (38.2%)	49 (40.5%)	57 (46.0%)	54 (45.8%)	47 (41.6%)	48 (40.7%)
	Severe	25 (20.3%)	24 (19.8%)	20 (16.1%)	20 (16.9%)	24 (21.2%)	31 (26.3%)
Dysphagia, n (%)							
	None	74 (60.2%)	74 (61.2%)	78 (62.9%)	78 (66.1%)	83 (73.5%)	83 (70.3%)
	Mild	27 (22.0%)	23 (19.0%)	25 (20.2)	26 (22.0%)	18 (15.9%)	21 (17.8%)
	Moderate	14 (11.4%)	18 (14.9%)	16 (12.9)	8 (6.8%)	9 (8.0%)	6 (5.1%)
	Severe	8 (6.5%)	6 (5.0%)	5 (4.0%)	6 (5.1%)	3 (2.7%)	8 (6.8%)
Epigastric pain, n (%)							
	None	33 (26.8%)	41 (33.9%)	40 (32.3%)	33 (28.0%)	37 (32.7%)	37 (31.4%)
	Mild	37 (30.1%)	34 (28.1%)	44 (35.5%)	37 (31.4%)	33 (29.2%)	23 (19.5%)
	Moderate	33 (26.8%)	36 (29.8)	28 (22.6%)	33 (28.0%)	31 (27.4%)	36 (30.5%)
	Severe	20 (16.3%)	10 (8.3%)	12 (9.7%)	15 (12.7%)	12 (10.6%)	22 (18.6%)
H. pylori status, n (%)							
	Negative	84 (68.3%)	82 (67.8%)	94 (75.8%)	30 (25.4%)	43 (38.1%)	38 (32.2%)
	Positive	39 (31.7%)	37 (30.6%)	29 (23.4%)	87 (73.7%)	69 (61.1%)	80 (67.8%)
	Missing	0 (0.0%)	2 (1.7%)	1 (0.8%)	1 (0.8%)	1 (0.9%)	0 (0.0%)

Numbers analysed

The numbers of the ITT population used for all primary and secondary analyses, the PP population used for the primary efficacy analysis and the SAF population for safety analyses are provided in **Table 9** above (see in ***Sample size*** of this section). Primary analysis is performed on proper population (ITT).

Outcomes and estimation

Primary efficacy parameters

The main findings of studies 225 and 226 are summarized in **Table 2**. The efficacy results of both studies were comparable

At the end of the study (last 7 days of treatment), esomeprazole 20 mg and 40 mg demonstrated a significantly better effect ($p<0.001$) compared to placebo regarding the number of patients to reach complete resolution of diary-recorded heartburn, in both ITT and PP populations in both studies. So the primary objective was achieved.

The proportion of patients with complete resolution by the end of Study 225 was 33.3% (41/123), 33.9% (41/121), and 13.7% (17/124) for treatment with esomeprazole 40 mg, esomeprazole 20 mg, and placebo, respectively. In study 226, the complete resolution was achieved in 36.4% (43/118), 41.6% (47/113) and 11.9% (14/118) of the patients, respectively.

Secondary efficacy parameters

Complete resolution of heartburn at 1, 2, and 4 weeks (diary recorded): **Study 225:** significant difference was demonstrated between the esomeprazole 40 mg and placebo groups ($p<0.001$), as well as between the esomeprazole 20 mg and placebo groups ($p<0.014$) at each of the three time points. At Weeks 2 and 4, the frequencies of patients responding to treatment in the esomeprazole 40 mg group and the esomeprazole 20 mg group are similar **Study 226:** significant difference was demonstrated between the esomeprazole 40 mg/ esomeprazole 20 mg and placebo groups ($p<0.001$) at each of the three time points. The majority of the responders achieved complete resolution in the first 2 weeks.

Table 2. Summary of efficacy results (studies 225 and 226, ITT population).

	Study 225						Study 226					
Efficacy variable	**H199/18 40 mg qd**		**H199/18 20mg qd**		**Placebo**		**H199/18 40 mg qd**		**H199/18 20 mg qd**		**Placebo**	
% of patients with complete resolution of heartburn at final visit												
% patients	33%		34%		14%		36%		42%		12%	
95 % CI	0.25, 0.417		0.255, 0.423		0.077, 0.198		0.278, 0.451		0.325, 0.507		0.06, 0.177	
p-value vs. placebo	<0.001*		<0.001*		___		<0.001*		<0.001*		___	
% patients with complete resolution of heartburn												
Week 1 - % patients/p – value vs. placebo	20%	<0.001*	10%	0.014*	2%	__	19%	<0.001*	15%	<0.001*	1%	__
Week 2 - % patients/ p –value vs. placebo	26%	<0.001*	25%	0.001*	9%	__	35%	<0.001*	36%	<0.001*	3%	__
Week 4 - % patients/ p –value vs. placebo	34%	0.001*	33%	0.001*	15%	__	40%	<0.001*	41%	<0.001*	11%	__
% patients with relief of heartburn												
Week 1 - % patients/ p –value vs. placebo	27%	<0.001*	18%	<0.001*	3%	__	29%	<0.001*	28%	<0.001*	3%	__
Week 2 - % patients/ p –value vs. placebo	35%	0.001*	35%	0.001*	17%	__	41%	<0.001*	46%	<0.001*	9%	__
Week 4 - % patients/ p –value vs. placebo	50%	<0.001*	42%	0.022*	27%	__	48%	<0.001*	52%	<0.001*	15%	__
End of Study[a] - % patients/p –value vs. placebo	46%	0.001*	44%	0.001*	26%	__	46%	<0.001*	51%	<0.001*	5%	__
Mean severity of heartburn												
Week 1 – mean/ p – value vs. placebo	0.8	<0.001*	0.9	<0.001*	1.2	__	0.8	<0.001*	0.7	<0.001*	1.3	__
Week 2 – mean/ p – value vs. placebo	0.6	<0.001*	0.6	<0.001*	1.0	__	0.6	<0.001*	0.5	<0.001*	1.1	__
Week 4 – mean/ p – value vs. placebo	0.5	0.005*	0.5	0.007*	0.8	__	0.5	<0.001*	0.4	<0.001*	1.0	__
End of Study[a] – mean/ p –value vs. placebo	0.5	0.003*	0.5	0.004*	0.8	__	0.5	<0.001*	0.5	<0.001*	1.0	__
% heartburn–free days												
Week 1 - mean/ p –value vs. placebo	47.3	<0.001*	41.9	<0.001*	24.6	__	46.2	<0.001*	49.4	<0.001*	20.7	__
Week 2 - mean/ p –value vs. placebo	53.6	<0.001*	55.3	<0.001*	37.2	__	59.0	<0.001*	63.8	<0.001*	28.2	__
Week 4 – mean/ p –value vs. placebo	62.8	0.001*	62.7	0.001*	46.4	__	66.4	<0.001*	68.0	<0.001*	36.2	__
% heartburn-free nights												
Week 1 - mean/ p –value vs. placebo	77.5	0.001*	78.7	0.001*	65.8	__	82.0	0.001	81.8	0.001	70.5	__
Week 2 - mean/ p –value vs. placebo	85.3	<0.001*	87.5	<0.001*	72.4	__	86.0	0.026*	87.3	0.009*	78.3	__
Week 4 – mean/ p –value vs. placebo	87.7	0.006*	87.7	0.006*	78.7	__	88.5	0.005*	89.9	0.002*	79.5	__
Time (days) to first resolution of heartburn & nocturnal heartburn												
Heartburn – mean/ p –value vs. placebo	7.2	0.008*	6.6	0.003*	9.9	__	6.7	0.001*	5.8	0.001*	12.3	__
Nocturnal heartburn – mean/ p –value vs. placebo	2.2	0.161	2.0	0.069	3.0	__	1.6	0.013*	1.6	0.048*	2.3	__
Time (days) to sustained resolution of heartburn and nocturnal heartburn												
Heartburn – mean/ p –value vs. placebo	15.9	<0.001*	17.3	0.001*	20.8	__	12.1	<0.001*	12.7	<0.001*	22.3	__
Nocturnal heartburn – mean/ p –value vs. placebo	8.0	0.002*	7.2	<0.001*	10.9	__	6.9	0.022*	6.2	0.006*	10.5	__
% of patients with resolution of investigator-assessed GERD symptoms												
Week 2 - % patients/ p –value vs. placebo												
Heartburn	32%	<0.001*	35%	<0.001*	11%	__	38%	<0.001*	42%	<0.001*	8%	__
Regurgitation	56%	0.004*	59%	0.001*	37%	__	61%	<0.001*	64%	<0.001*	28%	__
Dysphagia	75%	0.272	83%	0.701	81%	__	81%	0.485	89%	0.543	85%	__
Epigastric pain	58%	0.249	58%	0.673	55%	__	66%	0.081	66%	0.145	52%	__
Week 4 - % patients/ p –value vs. placebo												
Heartburn	44%	0.002*	43%	0.003*	25%	__	47%	<0.001*	54%	<0.001*	16%	__
Regurgitation	74%	0.001*	71%	<0.001*	52%	__	70%	<0.001*	76%	<0.001*	44%	__
Dysphagia	88%	0.428	89%	0.387	86%	__	86%	0.604	91%	0.142	85%	__
Epigastric pain	68%	0.961	73%	0.907	72%	__	77%	0.023*	79%	0.024*	63%	__
Analysis of overall treatment evaluation												
Week 2 (p –value vs. placebo)	<0.001*		<0.001*		___		<0.001*		<0.001*		___	
Week 4 (p –value vs. placebo)	<0.001*		<0.001*		___		<0.001*				___	

a the last 7 days of treatment
* Statistically significant, $p < 0.05$. ITT Intent to treat
H199/18 = asemapimod

Resolution of investigator-assessed GERD symptoms at week 2 and week 4: **Study 225**: the resolution results of heartburn were significantly improved for esomeprazole 40 mg and esomeprazole 20 mg compared to placebo at week 2 ($p<0.001$) and at week 4 ($p\leq0.003$), as well as of acid regurgitation at week 2 ($p\leq 0.004$) and at week 4 ($p\leq0.001$). The resolution results of dysphagia and epigastric pain were *not* significantly improved for esomeprazole 40 mg and esomeprazole 20 mg compared to placebo (see **Table 3**). **Study 226**: the resolution results of heartburn and acid regurgitation were significantly improved for esomeprazole 40 mg and esomeprazole 20 mg compared to placebo at week 2 and at week 4 ($p<0.001$). The resolution results of dysphagia were *not* significantly improved for esomeprazole 40 mg and esomeprazole 20 mg compared to placebo as well as for epigastric pain at week 2, but were improved for epigastric pain at week 4 ($p\leq0.024$) (see **Table 3**).

Table 3. Number (%) of Patients with Resolution of Investigator-Assessed GERD Symptoms at Week 2 and Week 4 (ITT Population, Studies 225 and 226).

	Study 225			**Study 226**		
GERD Symptom	Esomeprazole 40 mg qd	Esomeprazole 20 mg qd	Placebo	Esomeprazole 40 mg qd	Esomeprazole 20 mg qd	Placebo
Week 2						
	(n = 118)	(n = 118)	(n = 123)	(n = 116)	(n = 110)	(n = 113)
Heartburn p-value vs. placebo [b]	38 (32.2%) <0.001*	41 (34.7%) <0.001*	14 (11.4%)	44 (37.9%) <0.001*	46 (41.8%) <0.001*	9 (8.0%)
Regurgitation p-value vs. placebo [b]	66 (55.9%) 0.004*	69 (58.5%) 0.001*	46 (37.4%)	72 (61.1%) <0.001*	70 (63.6%) <0.001*	32 (28.3%)
Dysphagia p-value vs. placebo [b]	89 (75.4%) 0.272	98 (83.1%) 0.701	100 (81.3%)	94 (81.0%) 0.485	98 (89.1%) 0.543	96 (85.0%)
Epigastric pain p-value vs. placebo [b]	68 (57.6%) 0.249	68 (57.6%) 0.673	67 (54.5%)	76 (65.5%) 0.081	72 (65.5%) 0.145	59 (52.2%)
Week 4						
	(n = 117)	(n = 114)	(n = 117)	(n = 114)	(n = 104)	(n = 110)
Heartburn p-value vs. placebo [b]	52 (44.4%) 0.002*	49 (43.0%) 0.003*	29 (24.8%)	54 (47.4%) <0.001*	56 (53.8%) <0.001*	18 (16.4%)
Regurgitation p-value vs. placebo [b]	86 (73.5%) 0.001*	81 (71.1%) <0.001*	61 (52.1%)	80 (70.2%) <0.001*	79 (76.0%) <0.001*	48 (43.6%)

	Study 225			Study 226		
GERD Symptom	Esomeprazole 40 mg qd	Esomeprazole 20 mg qd	Placebo	Esomeprazole 40 mg qd	Esomeprazole 20 mg qd	Placebo
Dysphagia p-value vs. placebo [b]	103 (88.0%) 0.428	101 (88.6%) 0.387	100 (85.5%)	98 (86.0%) 0.604	95 (91.3%) 0.142	93 (84.5%)
Epigastric pain p-value vs. placebo [b]	80 (68.4%) 0.961	83 (72.8%) 0.907	84 (71.8%)	88 (77.2%) 0.023*	82 (78.8%) 0.024*	69 (62.7%)

b Cochran-Mantel-Haenszel test stratified by baseline rating of the symptom.

** Statistically significant, p<0.05*

Time to first resolution of heartburn and nocturnal heartburn (diary recorded): In **Study 225**: **(1)** the time to first resolution of heartburn was significantly shorter in the esomeprazole 40 mg and esomeprazole 20 mg groups vs. placebo (p=0.008 and 0.003, respectively). See **Figure 3** for graphical presentation of the results. For esomeprazole 40 mg, esomeprazole 20 mg, and placebo groups, at Day 7, 70.7%, 77.7%, and 58.1% of patients, respectively, had recorded their first resolution of heartburn (see **Table 12**). **(2)** The time to first resolution of nocturnal heartburn was *not significantly different* in the esomeprazole 40 mg and esomeprazole 20 mg groups compared to placebo group. **Study 226**: **(1)** the time to first resolution of heartburn was significantly shorter in the esomeprazole 40 mg and esomeprazole 20 mg groups vs. placebo (p=0.001). See **Figure 3** for graphical presentation of the results. For esomeprazole 40 mg, esomeprazole 20 mg, and placebo groups, at Day 7, 72.0%, 77.9%, and 51.7% of patients, respectively, had recorded their first resolution of heartburn (see **Table 12**). **(2)** First resolution of nocturnal heartburn occurred significantly sooner in the esomeprazole 40 mg and esomeprazole 20 mg groups compared to placebo group (p=0.013 and 0.048, respectively).

Table 12. Time to first resolution of heartburn and nocturnal heartburn (ITT population, studies 225 and 226).

	Study 225			Study 226		
Descriptive Statistic for First Resolution	**H 199/18 40 mg qd**	**H199/18 20 mg qd**	**Placebo**	**H 199/18 40 mg qd**	**H199/18 20 mg qd**	**Placebo**
Heartburn						
Number of patients	123	121	124	118	113	118
Cumulative percent resolved by Day 7	70.7%	77.7%	58.1%	72.0%	77.9%	51.7%
Mean days	7.2	6.6	9.9	6.7	5.8	12.3
Median number of days	3	4	5	3	3	6
p-value vs. placebo [a]	0.008*	0.003*	___	0.001*	0.001*	___
Nocturnal Heartburn						
Number of patients	123	121	124	118	113	118
Mean days	2.2	2.0	3.0	1.6	1.6	2.3
Median number of days	1	1	1	1	1	1
p-value vs. placebo [a]	0.161	0.069	___	0.013*	0.048*	___

a Log-rank test, comparison of H 199/18 treatment to placebo
* Statistically significant, p <0.05
H 199/18 = esomeprazole

Figure 3. Time to First Resolution[a] (ITT population, studies 225 and 226).

Study 225	Study 226

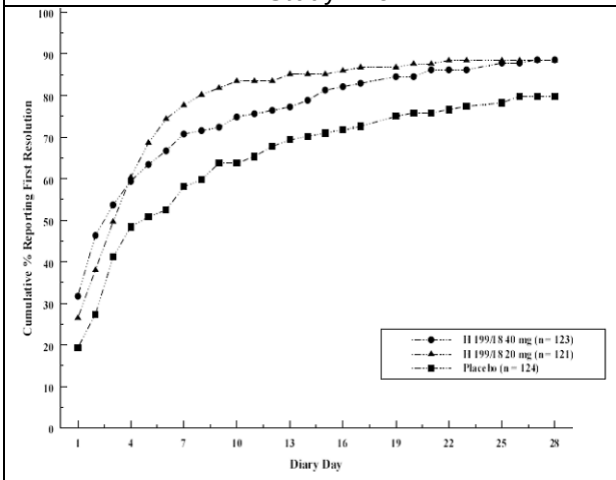
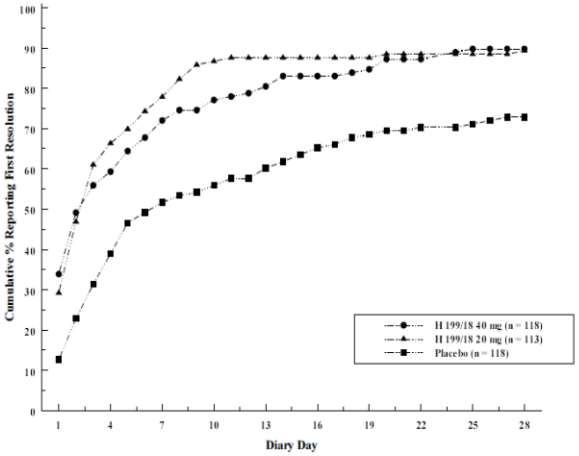

	

Figure 4 in Study 225 CSR, see CTD Module 5.3.5.1 a The time to first resolution of heartburn and nocturnal heartburn, defined as the Study Day on which heartburn severity was reported as 'No Heartburn', or nocturnal heartburn was reported as 'No'	Figure 4 in Study 226 CSR, see CTD Module 5.3.5.1 a The time to first resolution of heartburn and nocturnal heartburn, defined as the Study Day on which heartburn severity was reported as 'No Heartburn', or nocturnal heartburn was reported as 'No'

Ancillary analyses

Subgroup analysis. The applicant provided descriptive analysis of the primary endpoint (complete resolution of heartburn at the end of the study) for the ITT population for the following subgroups: gender, age group (<65 years, ≥65 years), race, and *H. pylori* status (by histology) (see **Table 16**).

Gender. In **Study 225**, 61% of patients were female and 39% were male; in **Study 226**, 64% of patients were female and 36% were male. In both studies male patients responded more favourably across all treatment groups, but the difference was not clinically meaningful.

Age group. In Studies 225 and 226, 10% and 11% of patients, respectively, were ≥65 years of age. In **study 225**, a lower response rate was observed in patients ≥65 years of age versus those <65 years of age. In contrast, in **study 226**, a higher response rate was observed in patients ≥65 years of age versus those <65 years of age. However, the small numbers of patients ≥65 years of age in both studies make these rates difficult to interpret.

Race. In both studies, only a small number of patients was non-Caucasian: 51 (14%) subjects in **Study 225** (9% Black, 2% Asian, and 2% Other) and 56 (16%) subjects in **Study 226** (14% Black; 1% Asian; 1% Other). Therefore any interpretation of rates of heartburn resolution across races is difficult.

H. pylori status. About one-third of the patients enrolled in Studies 225 and 226 were *H. pylori*-positive at baseline (by histology) (39% and 27.9%, respectively). In the placebo group, there were a larger percentage of patients who experienced complete resolution of heartburn at the final visit for patients who were H. pylori positive at baseline as compared to those who were H. pylori -negative at baseline (27.6% vs. 8.5% in study 225, respectively, and 18.4% vs. 8.8% in study 226, respectively). In the esomeprazole treatment groups, the rates for complete resolution of heartburn in *H. pylori*-positive patients were higher than those for H. pylori-negative patients.

Table 16. Number (%) of patients with complete resolution of heartburn at final visit by subgroups (ITT population, studies 225 and 226).

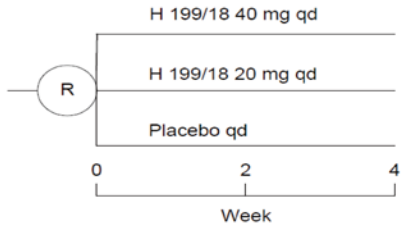
		Study 225			Study 226		
		H 199/18 40 mg	H 199/18 20 mg	Placebo	H 199/18 40 mg	H 199/18 20mg	Placebo
Gender	Male	19/48 (39.6%)	17/49 (34.7%)	9/46 (19.6%)	18/42 (42.9%)	16/34 (47.1%)	8/50 (16.0%)
	Female	22/75 (29.3%)	24/72 (33.3%)	8/78/(10.3%)	25/76 (32.9%)	31/79 (39.2%)	6/68 (8.8%)
Age	<65 yrs	38/111 (34.2%)	36/104 (34.6%)	16/116 (13.8%)	37/107 (34.6%)	39/98 (39.8%)	12/106 (11.3%)
	>65 yrs	3/12 (25.0%)	5/7 (29.4%)	1/8 (12.5%)	6/11 (54.5%)	8/15 (53.3%)	2/12 (16.7%)
Race	Caucasian	33/100 (33.0%)	39/113 (34.5%)	17/104 (16.3%)	39/104 (37.5%)	40/90 (44.4%)	10/99 (10.1%)
	Black	7/17 (41.2%)	1/6 (16.7%)	0/11 (0.0%)	3/13 (23.1%)	6/19 (31.6%)	3/17 (17.6%)
	Asian	1/4 (25.0%)	0/0 (0.0%)	4/4 (100.0%)	0/0 (0.0%)	0/3 (0.0%)	0/1 (0.0%)
	Other	0/2 (0.0%)	1/2 (50.0%)	5/5 (100.0%)	1/1 (100%)	1/1 (100%)	1/1 (100%)
Hp status	Negative	23/84 (27.4%)	26/82 (31.7%)	8/94 (8.5%)	34/87 (39.1%)	31/69 (44.9%)	7/80 (8.8%)
	Positive	18/39 (46.2%)	15/37 (40.5%)	8/29 (27.6%)	9/30 (30.0%)	15/43 (34.9%)	7/38 (18.4%)

Data from Tables 17, 18 19 and 20, Study 225 and Study 226 CSRs, see CTD Module 5.3.5.1.
H 199/18 = esomeprazole

Summary of main study(ies)

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 1. Summary of Efficacy for trial 225

Title: A comparative efficacy and safety study of H 199/18 (20 mg), H 199/18(40 mg) vs placebo in study subjects with symptomatic GERD.		
Study identifier	**SH-QBE 0053 (Study 225)**	
Design	 Figure 1 in Study 225 and Study 226 CSRs, see CTD Module 5.3.5.1 H 199/18 40 = esomeprazole 40 mg H 199/18 20 = esomeprazole 20 mg	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	4 weeks not applicable not applicable
Hypothesis	Superiority vs placebo	
Treatments groups	esomeprazole 40 mg	1 tab/d in the morning for 4 weeks; n=123
	esomeprazole 20 mg	1 tab/d in the morning for 4 weeks; n=121
	Placebo	1 tab/d in the morning for 4 weeks; n=124

Endpoints and definitions	Primary endpoint	%	% of patients who exhibited complete resolution of heartburn during the last 7 days of the study
	Secondary endpoints	%	% of patients at Week 1, Week 2, and Week 4 who exhibited complete resolution of heartburn for 7 consecutive days
		%	% of patients who exhibited relief of heartburn at Week 1, Week 2, Week 4, and for the last 7 days in the study
		mean	mean severity of heartburn at Week 1, Week 2, Week 4, and for the last 7 days in the study
		%	% of heartburn-free days at Week 1, Week 2, and Week 4
		%	% of days without nocturnal heartburn at Week 1, Week 2, and Week 4
		days	the time to first resolution of heartburn and first resolution of nocturnal heartburn
		days	the time to first sustained resolution of heartburn and first sustained resolution of nocturnal heartburn
		%	% of patients with resolution of GERD symptoms as rated by the investigator at Week 2 and Week 4
		OTE	Overall Treatment Evaluation at Week 2 and Week 4
Database lock	No information available		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat Last 7 days			
Descriptive statistics and estimate variability	**Treatment group**	**esomeprazole 40 mg**	**esomeprazole 20 mg**	**placebo**
	Number of subject	123	121	124
	% patients	33%	34%	14%
	95% CI	25.0%, 41.7%	25.5%, 42.3%	7.7%, 19.8%
	p-value	<0.001	<0.001	__
Analysis description	**Assumed main secondary endpoint: responders' rate (patients with resolution of investigator-assessed GERD symptoms)**			
Analysis population and time point description	Intent to treat **Week 2**			
GERD symptom	**Treatment group**	**esomeprazole 40 mg**	**esomeprazole 20 mg**	**placebo**
	Number of subject	118	118	123
Heartburn	n (%) patients	38 (32.2%)	41 (34.7%)	14 (11.4%)
	p-value vs placebo [a]	<0.001*	<0.001*	___
Regurgitation	n (%) patients	66 (55.9%)	69 (58.5%)	46 (37.4%)
	p-value vs placebo [a]	0.004*	<0.001*	___

Dysphagia	n (%) patients	89 (75.4%)	98 (83.1%)	100 (81.3%)
	p-value vs placebo [a]	0.272	0.701	___
Epigastric pain	n (%) patients	68 (57.6%)	68 (57.6%)	67 (54.5%)
	p-value vs placebo [a]	0.249	0.673	___
	Week 4			
	Number of subject	117	114	117
Heartburn	n (%) patients	52 (44.4%)	49 (43.0%)	29 (24.8%)
	p-value vs placebo [a]	0.002*	0.003*	___
Regurgitation	n (%) patients	86 (73.5%)	81 (71.1%)	61 (52.1%)
	p-value vs placebo [a]	0.001*	0.001*	___
Dysphagia	n (%) patients	103 (88.0%)	101 (88.6%)	100 (85.5%)
	p-value vs placebo [a]	0.428	0.387	___
Epigastric pain	n (%) patients	80 (68.4%)	83 (72.8%)	84 (71.8%)
	p-value vs placebo [a]	0.961	0.907	___
Notes	* Statistically significant, p < 0.05 [a] Cochran-Mantel-Haenszel test stratified by baseline rating of the symptom.			

Table 2. Summary of Efficacy for trial 226

Title: A comparative efficacy and safety study of H 199/18 (20 mg), H 199/18(40 mg) vs placebo in study subjects with symptomatic GERD				
Study identifier	**SH-QBE 0054 (Study 226)**			
Design	Same as in Study 225			
Hypothesis				
Treatments groups				
Endpoints and definitions				
Database lock	No information available			
Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat Last 7 days			
Descriptive statistics and estimate variability	**Treatment group**	**esomeprazole 40 mg**	**esomeprazole 20 mg**	**placebo**

	Number of subject	118	113	118
	% patients	36.4%	41.6%	11.9%
	95% CI	27.8%, 45.1%	32.5%, 50.7%	6.0%, 17.7%
	p-value	<0.001*	<0.001*	___
Analysis description	**Main secondary endpoint: responders' rate (patients with resolution of investigator-assessed GERD symptoms)**			
Analysis population and time point description	Intent to treat **Week 2**			
GERD symptom	**Treatment group**	**esomeprazole 40 mg qd**	**esomeprazole 20 mg qd**	**placebo**
	Number of subject	116	110	113
Heartburn	n (%) patients	44 (37.9%)	46 (41.8%)	9 (8.0%)
	p-value vs placebo [a]	<0.001*	<0.001*	___
Regurgitation	n (%) patients	72 (61.1%)	72 (61.1%)	72 (61.1%)
	p-value vs placebo [a]	<0.001*	<0.001*	___
Dysphagia	n (%) patients	94 (81.0%)	98 (89.1%)	96 (85.0%)
	p-value vs placebo [a]	0.485	0.543	___
Epigastric pain	n (%) patients	76 (65.5%)	72 (65.5%)	59 (52.2%)
	p-value vs placebo [a]	0.081	0.145	___
	Week 4			
	Number of subject	114	104	110

Heartburn	n (%) patients	54 (47.4%)	56 (53.8%)	18 (16.4%)
	p-value vs placebo [a]	<0.001*	<0.001*	___
Regurgitation	n (%) patients	80 (70.2%)	79 (76.0%)	48 (43.6%)
	p-value vs placebo [a]	<0.001*	<0.001*	___

Dysphagia	n (%) patients	98 (86.0%)	98 (86.0%)	93 (84.5%)
	p-value vs placebo [a]	0.604	0.142	___
Epigastric pain	n (%) patients	88 (77.2%)	82 (78.8%)	69 (62.7%)
	p-value vs placebo [a]	0.023*	0.024*	___
Notes	* Statistically significant, p < 0.05 [a] Cochran-Mantel-Haenszel test stratified by baseline rating of the symptom.			

Analysis performed across trials (pooled analyses and meta-analysis)

Efficacy results after 4 weeks in patients with partial symptom relief at 2 weeks of treatment with 20 mg esomeprazole in the pooled pivotal studies 225 and 226 (QBE-53 and –54) are displayed below (see **Table 4**).

Approximately 30% of partial responders achieved complete resolution of symptoms following an additional 2 weeks of treatment. The differences of success rates in comparison to placebo, are 25%-30% in the first two weeks, and 10-14% in the following two weeks.

Table 4

Endpoint 1 - Number (%) of Patients with Resolution of Investigator- Assessed Heartburn (last 7 days), pooled results study 225 and 226

Week	20 mg Esomeprazole			Placebo		
	n	N	%	n	N	%
Week 2	86	216	39.8	23	225	10.2
Week 4 (week 2 non-responder & resolved removed)	35	111	31.5	22	124	17.7

N=total number of patients
n=number of patients with resolution of heartburn

Endpoint 2 - Number (%) of Patients with Sustained Resolution of Heartburn (7 consecutive days), pooled results study 225 and 226

Week	20 mg Esomeprazole			Placebo		
	n	N	%	n	N	%
Week 2	79	231	34.2	23	237	9.7
Week 4 (week 2 non-responder & resolved removed)	34	117	29.1	24	125	19.2

N=total number of patients
n=number of patients with resolution of heartburn

Endpoint 3 - Number (%) of Patients with Resolution of Heartburn (last 3 days), pooled results study 225 and 226

Week	20 mg Esomeprazole			Placebo		
	n	N	%	n	N	%
Week 2	109	229	47.6	44	236	18.6
Week 4 (week 2 non-responder & resolved removed)	24	74	32.4	20	96	20.8

N=total number of patients
n=number of patients with resolution of heartburn

Clinical studies in special populations

No new studies were performed for this application. The special populations as they are assessed in the original application can be considered as acceptable.

Supportive studies

The pivotal studies were performed in non-erosive reflux disease (NERD) patients; patients with erosive esophagitis were excluded from the study following baseline endoscopy. To mimick the non-prescription situation of esomeprazole intended with the application where patients were taking the medication without prior endoscopic investigation the Applicant presented 3 bibliographical analyses (with 2 metanalyses) and 14 own studies data about several GERD populations that were considered as not tested in the same way as in pivotal studies but reasonable to expect as possible users of OTC esomeprazole (1) patients having esophageal erosions and (2) patients without baseline endoscopy and with a broad spectrum of reflux symptom frequency, severity and duration (e.g., patients with history of heartburn for at least 6 months and with prior symptomatic response to acid suppression, patients having night-time hearthburn, sleep disturbances and just seeking for the treatment at the general practitioner).

Literature Analyses:

(1) Kahrilas PJ et al 2000[18] study of erosive esophagitis (EE) was a A double-blind randomized, comparative study including Eso 40mg, 20mg and Omeprazole 20mg for 4-8 weeks (to healing) in patients 18-75 years of age with GERD symptoms and a positive endoscopy, (LA grade A-D), at least 1w before inclusion; Negative for Helicobacter pylori and No Barrett's mucosa >3cm. Study showed symptom resolution by sustained resolution (Investigator): At 4w: Eso 40mg: 65%; Eso 20mg: 61%; Ome 20mg: 57% , (p<0,005 Eso 40mg vs Ome 20mg; ns Eso20mg vs Ome 20mg); Cumulative sustained resolution (Patient diary): At 2w: Eso 40mg: 65%; Eso 20mg: 63%; Ome 20mg: 57% At

[18] Kahrilas PJ. Strategies for medical management of reflux disease. Bailliere's Clinical Gaztroenterology 2000;14(5):775-791.

4w: Eso 40mg: 74%; Eso 20mg: 70%; Ome 20mg: 67%; Healing of erosions: At 4w- Eso 40mg: 76%; Eso 20mg:71%; Ome 20mg:65% (p< 0,001 Eso 40mg vs Ome 20mg and p<0.09 Eso 20mg vs Ome 20mg); At 8w (cumulative)- Eso 40mg: 94%; Eso 20mg:90%; Ome 20mg:87% (p<0,001 Eso 40mg vs Ome 20mg; p<0,05Eso 20 vs Ome 20mg). Thus conclusion was made that Eso 40 mg qd and 20 mg qd are safe and effective treatments for healing of EE, and significantly superior to omeprazole 20 mg qd in the primary efficacy analysis, healing of EE following 4 weeks to 8 weeks of treatment. Esomeprazole was well tolerated with no unexpected findings and consistent with the known safety profile of esomeprazole '

(2) Weijenborg et al 2012[19] metaanalysis includes randomized clinical trials in patients with NERD and reflux esophagitis that evaluated the effect of short-term PPI treatment on heartburn. The proportion of individuals achieving complete relief of heartburn after 4 weeks of PPI therapy was 0.50 (0.43–0.57) in the 8 studies with uninvestigated empirically treated patients (without any endoscopy), 0.49 (0.44–0.55) in the 12 studies were patients were defined as non-erosive by negative endoscopy, 0.73 (0.69–0.77) in the 2 studies where patients were defined as nonerosive by both negative endoscopy and a positive pH-test and it was 0.72 (95% CI 0.69–0.74) in patients with reflux esophagitis (32 studies). The Applicant states that results support that the effect of PPI on symptoms is similar in uninvestigated patients treated empirically (as in the OTC setting) to the patients diagnosed as NERD based on negative endoscopy (as in the pivotal studies). It also supports that in reflux esophagitis patients the estimated complete symptom response rate after PPI therapy is higher than in patients with GERD independent if it is diagnosed by symptoms and negative endoscopy or by symptoms alone.

(3) The van Pinxteren et al 2010[20] metaanalysis demonstrated that the benefit of PPI vs. placebo was greater in studies in uninvestigated GERD patients than in studies with endoscopy verified NERD patients. Therefore it was assumed that if esomeprazole is effective and well tolerated in NERD patients (QBE-53, -54), then it will be at least as effective in uninvestigated patients that includes a mixture of erosive and non-erosive patients. The safety profile was described as similar in studies including either patients with or without esophageal erosions.

Randomized, double blind comparative studies:

(1-2) Two, almost identically designed, studies D961AC00001 and D9612L00122 represent a special subgroup of uninvestigated reflux patients i.e. those who have *night-time heartburn* and sleep disturbances. The studies included 950 US patients having at least a 3 month history of GERD including frequent night-time heartburn (2-3/week) with related sleep disturbances and moderate or severe night-time heartburn with sleep disturbances at least 3 of the last week prior to randomization. The patients in the two studies were randomized to receive esomeprazole (20 and 40 mg in study D961AC00001, and 20 mg in study D9612L00122) and placebo, all for 4 weeks. Patients symptoms were evaluated after 2 and 4 weeks, using diary cards (symptom relief defined as max 1 day with mild symptoms last week).

Results: nighttime heartburn relief (a) in *Study D961AC00001:* Eso 40mg: 53.1%, Eso 20 mg: 50.5% , placebo: 12.7% (p < 0.0001); (b) in *Study D961AC00122:* Eso 20 mg: 34.3% vs. placebo: 10.4% (p < 0.0001). Thus the evaluation of 24h heartburn relief is comparable with the results in the pivotal studies. The treatment was well tolerated in this uninvestigated patient population.

[19] Weijenborg P, Cremonini F, Smout A, Bredenoord A. PPI therapy is equally effective in welldefined non-erosive reflux disease and in reflux esophagitis: a meta-analysis.
[20] van Pinxteren B, Sigterman KE, Bonis P, Lau J, Numans ME. Short-term treatment with proton pump inhibitors, H2-receptor antagonists and prokinetics for gastro-oesophageal reflux disease-like symptoms and endoscopy negative reflux disease. Cochrane database of systematic reviews. 2010, Issue11. Art.No.: CD002095. DOI: 10.1002/14651858.CD002095.pub4.

(3-4) The two identical phase III randomised, double blind, placebo-controlled, parallel group studies D961RC00001 and D961RC00002 were recently conducted in the US. According to the applicant the design of the studies was similar to previously conducted registration trials for this indication performed for other PPIs in the US and it is in accordance with FDA's expectation to include subjects who are likely to self-treat for *frequent heartburn* with nonprescription medications *without consulting a prescriber*. Approximately 340 patients were randomized in each study. The primary objective of the studies was to determine the efficacy of esomeprazole 20 mg once daily over a 14-day regimen for the treatment of frequent heartburn (≥2 times a week).

Results**:** percentage heartburn free 24 hour day (LS mean) *Study 01*: Eso 20 mg 46,1% , placebo: 33% ($p < 0.0001$); *Study 02*::Eso 20 mg: 48% vs. placebo: 33% ($p < 0.0001$). Thus, esomeprazole was significantly more effective than placebo. Esomeprazole treatment was generally well tolerated and there were no new or significant findings with regard to safety.

(5) In a double blind, randomized study (D9612L00064) 369 US patients with a history of heartburn for at least 6 months and with prior symptomatic response to acid suppression were included *without baseline endoscopy*. The requirement for a positive esophageal acid perfusion test aimed to include patients whose symptoms were most likely related to acid reflux. Patients were randomized to either esomeprazole 20 mg od, 40 mg od or 40 mg bid. Symptoms were evaluated using diaries after 4 weeks.

Results: Mean % of sustained resolution of HB: 20mg 48%; 40mg 44% ; 40mg bid 41%; Mean % of patients with HB relief: 20mg 59% ; 40mg 52% ; 40mg bid 54%; Cumulative daily sustained resolution rate: 20 mg 62.8%; 40mg 52.0%; 40 mg bid 62.0%; Mean number of days to the first day of the first 7-day period of sustained resolution: 20 mg 14.7; 40mg 14.0; 40 mg bid 15.5; Mean number of days to the first day of the first 7-day period of relief: 20 mg 12.1; 40mg 12.5; 40 mg bid 12.9; Mean % of heartburn-free days: 20 mg 66.5%; 40mg 62.4%; 40 mg bid 67.8%; Mean % of heartburn-free nights: 20 mg 80.8%; 40mg 78.0%; 40 mg bid 88.2%. The results show that each of the treatment doses of esomeprazole to a similar extent decreased reflux symptoms in comparison to baseline. All treatments were well tolerated in this uninvestigated patient population.

Open label studies:

To further describe the safety and efficacy of esomeprazole in a large segment of uninvestigated reflux patients the applicant presented seven studies in uninvestigated patients without any baseline endoscopy and with a *broad spectrum* of reflux symptom frequency and severity, seeking for treatment at the general practitioner from many different countries in Europe. The studies were all designed to have two parts, an initial 4 week part and a second maintenance part.

(1-2) In two studies (D9612L00109, D9612L00111) a total of 3133 uninvestigated patients consulting a general practitioner for symptoms attributed to gastroesophageal reflux, as judge by the investigator, were investigated. During the initial non-blinded period all patients were treated with either esomeprazole 20 mg or 40 mg. After 4 weeks treatment the patients symptoms were evaluated according to the endpoint of this phase (max 1 or 2 days of mild symptom last week). Symptom free patients were then randomized into the second maintenance phase given either esomeprazole 20 mg od or 20 mg on-demand or antacids during 12 weeks. Results from the initial period is applicable here.

Results: Study D9612L00109: Basal GERD severity: Heartburn Moderate 64% Severe 25%; Symptom resolution At 4 weeks 20mg Eso: Treatment success 88.0%; No Hb 74%, Mild 17%, moderate/Severe 4%; 40mg Eso: Treatment success 82.1% No Hb 77%, Mild 26%, moderate/severe 7%. *Study D9612L00111:* Basal heartburn severity: In the 20 mg, 22% mild , 73% with moderate 6% with severe, in the 40 mg, 4% mild 55% with moderate 41% with Severe; Symptom resolution

At 4 weeks: 20mg Eso: Treatment success: 86% 40mg Eso: Treatment success: 80% In 20+40mg (total): 85%. The results from the initial study part demonstrated a decrease in reflux symptoms in comparison to baseline, without a significant difference between the 20 mg and 40 mg doses. In these studies esomeprazole was well tolerated with no unexpected findings and consistent with the known safety profile of esomeprazole.

(3-7) In a group of five similar studies (ACH-QBE-0101, CR BU-NEG-0005, IE-ESO-0001, CBNEG-0001, LH-NEG-0020) in a total of 7721 uninvestigated patients seeking primary care for symptoms suggestive of gastroesophageal reflux for at least three days during the last seven days were investigated. During the initial non-blinded period all patients were treated with esomeprazole 40 mg. After 4weeks treatment the patients symptoms were evaluated to the endpoint of this phase (max 1 day mild symptom last week). In the second maintenance part of the study patients free from symptoms were randomized to either esomeprazole 20mg as continuous treatment or as on-demand treatment for 6 months. Results from the initial period is applicable here.

Results: Efficacy: Basal heartburn severity: Moderate / severe in 85,5% of the patients Symptom resolution (all five studies) At 4 weeks: Symptom-free patients (40mg): 90%. Safety: ACH-QBE-0101: Adverse event (AE) during entire study period 6month were reported by 21%, Most common AEs were diarrhoea 2,2%, headache; 2,0%, and nausea 1,9%. There were 62 SAEs, deemed unrelated to study drug. BU-NEG-0005: AE during the initial 4w period was reported by 35%. Most common AEs were diarrhoea 7%, headache 13%, and respiratory infection 10%. There were 10 (1%) SAEs, deemed unrelated to study drug; IE-ESO-0001AE, the initial 4w period, were reported by 19,4% and there were 2 SAEs, deemed unrelated to study drug Most common AEs were Nausea 1,9%, Headache 1,4% Diarrhoea 0,6%; CB-NEG-0001: AE during entire study period 6month was reported by 48%. Most common AEs from the Respiratory and GI systems. There were 91(3,2%) SAEs, deemed unrelated to study drug. Results from the initial study part show substantial decrease of reflux symptoms in comparison to baseline. Esomeprazole treatments were well tolerated, consistent with the known safety profile of esomeprazole.

Non comparative studies

Studies D9914C00002 and GB-QBE-001 evaluated both patients with and without erosions, the two usual subpopulations within the uninvestigated reflux population. In these two studies the patients were endoscoped at baseline however all patients were treated and evaluated irrespectively of if they had erosions or not and together they could mimic the uninvestigated population.

(1) The D9914C00002 (Diamond study) included 308 patients seeking primary care consultation for upper abdominal symptoms persistent at least 2 times/week for 4 weeks and three or more occasions with at least mild symptoms last week. The great majority of patients had reflux symptoms as the most bothersome symptoms, although in addition other upper GI symptoms were often presented as well. The design included sequentially two single blinded 2 week study periods with placebo and esomeprazole 40 mg respectively. Symptom evaluations were done using patient reported outcome measurements. Further, an endoscopy, a pH test and questionnaires were performed but the results were blinded to the patients during the study.

Results: Based on all data 66% of the patients were defined as having GERD; At 4 week Response to PPI (40mg) - 48% of all patients ; group response: EE 57%, NERD 49%, non-GERD 35%, $p<0,1$ EE vs non-GERD Placebo response total 13% (GERD 13%, non-GERD 14%); The pattern of heartburn relief was similar to other studies in patients with or without GERD diagnosis confirming the applicability of esomeprazole treatment in patient populations when no endoscopy is performed

before treatment initiation like in the OTC patient group. Esomeprazole was well tolerated, consistent with the known safety profile of esomeprazole.

(2) In the GB-QBE-001 (ProGERD) study 6509 patients in Germany, Switzerland and Austria referred to endoscopy due to reflux symptoms. Open treatment with esomeprazole was allocated based on the result of the endoscopy, 40 mg for 4-8 weeks for patients with reflux esophagitis and 20 mg during 2-4weeks in NERD patients. Symptoms were evaluated by the endpoint of complete symptom resolution (no symptom last week) after 2 weeks for all patients, after 4 weeks in all patients with erosions and in non-erosive patients with persistent symptoms at 2 weeks, and after 8 weeks in patient that still had erosions at 4 weeks.

Results: Efficacy: Symptom resolution: At 2weeks Complete resolution of heartburn: 61% of EE patients (40mg); 59% of NERD patients (20mg); At last visit Complete resolution of heartburn: 70% of EE patients and 65% of NERD patients; Healing EE: At 4weeks: 78% healed; At 8weeks: 88% healed. High level results demonstrated decrease in reflux symptoms, in comparison to baseline, but without a significant difference between 20 mg and 40 mg (at 2 weeks). An increased proportion of patients reached symptom relief after 4 weeks compared to after 2 weeks. Esomeprazole was well tolerated with no unexpected findings and consistent with the known safety profile of esomeprazole.

2.4.1. Discussion on clinical efficacy

Design and conduct of clinical studies

In the pivotal studies (QBE 0053 (study 225) and QBE 0054 (study 226)), the safety and efficacy of 4 weeks' treatment with esomeprazole 20 mg or 40 mg with regard to reflux symptoms (heart burn and acid regurgitation) was studied. These two phase III pivotal studies were of identical design. Both of them were continental USA, placebo-controlled, randomized (1:1:1), double-blind, multi-center, parallel-group, 4-week, efficacy and safety studies of esomeprazole 20 mg and esomeprazole 40 mg vs. placebo in patients with symptomatic GERD. Subjects selected to the studies had at least a 6-month history of heartburn, were negative for erosive oesophagitis at endoscopy (non-erosive reflux disease (NERD) patients) and reported at least 4 days with heartburn in the week prior to the inclusion. Both studies were properly sized, no protocol amendments were issued for both studies and there were no changes made to the analyses specified in the Data Analysis Plan completed prior to the data being unblinded.

The effect was assessed by patient daily diary heartburn scoring and by investigator-recorded symptoms scoring. Patient symptom scoring (self-assessment of symptom frequency and severity with help of a questionnaire) has been widely used in clinical studies and recognized as a useful aid for the diagnosis of reflux disease. Efficacy data are based on proper ITT population (all randomized patients, defined prior to unblinding the data) assessing primarily the rate of *complete resolution* of heartburn *for the last 7 days* in the study based on the data from the last available 7-day period on the diary card. Patients are fairly balanced among the groups as regards the gender, age, race, body weight, height, GERD history, heartburn, acid regurgitation, dysphagia, epigastric pain, *H. pylori* status.

Efficacy data and additional analyses

Only the data for the 20-mg dosing are relevant for the present application. The proportion of patients with complete resolution by the end of Study 225 was 33.9% (41/121) and 13.7% (17/124) for treatment with esomeprazole 20 mg, and placebo, respectively. In study 226, the complete resolution was achieved in 41.6% (47/113) and 11.9% (14/118) of the patients, respectively. At the end of the study (last 7 days of treatment), esomeprazole 20 mg demonstrated a significantly better

effect ($p<0.001$) compared to placebo regarding the number of patients to reach complete resolution of diary-recorded heartburn, in both ITT and PP populations in both studies. Therefore, the primary objective was achieved. This primary endpoint was further supported by the majority of secondary efficacy parameters.

The CHMP noted that the pivotal studies were performed in non-erosive reflux disease (NERD) patients and that more than half of the screened patients were not eligible for the studies due to "silent" erosions. To elaborate the effects of esomeprazole in case of the non-prescription setting where patients were taking the medication without prior endoscopic investigation (i.e. in patients with reflux esophagitis as well as in other GERD subpopulations in un-investigated patients), the applicant presented 3 bibliographical analyses (with 2 meta-analyses) and 14 own studies with data about several investigated and un-investigated populations with reflux symptoms. The results from these studies were comparable to the results from the pivotal studies in terms of showing an effect of esomeprazole on symptom relief in patients with heartburn and/or acid regurgitation with a similar safety profile as shown with esomeprazole in the prescription drug development. Based on this review the CHMP agrees on the extrapolation of the pivotal study results to the patient population who will obtain a PPI as non-prescription medicine.

As a general principle for non-prescription medicines and particularly in the context of the indirect danger of having a more serious underlying condition that needs medical attention present in partial responders, the CHMP noted that the treatment duration should be adequately limited in an OTC setting. According to the pivotal studies efficacy was shown already at week 2 for two variables (% of patients with complete resolution of heartburn and % of patients with relief of heartburn). Furthermore, time (days) to first resolution of heartburn and nocturnal heartburn was 6.6 and 2 for Study 225 and 5.8 and 1.6 for Study 226. Time (days) for sustained resolution of heartburn and nocturnal heartburn was 17.3 and 7.2 for Study 225 and 12.7 and 6.2 for Study 226.

To justify the claim of the additional two weeks (i.e. a maximum of 4 weeks in partial responders) the Applicant reviewed efficacy results in patients with partial symptom relief at 2 weeks of treatment with 20 mg esomeprazole in the pooled pivotal studies 225 and 226 (QBE-53 and –54). Between 29% - 32% (depending on the definitions of symptom resolution [i.e., investigator assessed resolution (no symptoms during the last week), or daily diary card of partial responders achieved complete resolution of symptoms following an additional 2 weeks of treatment. However, the differences of success rates in comparison to placebo were 25%-30% in the first two weeks, and only 10-14% in the following two weeks. The NNT (Number needed to treat) in the second two weeks is therefore considered to be clearly diminished. Therefore, the CHMP concluded that the treatment duration should be limited to two weeks and that the product information should indicate that if no symptom relief is obtained within 2 weeks of continuous treatment, the patient should be instructed to consult a doctor. The CHMP also noted that this is in line with the recommendation for the non-prescription medicine containing omeprazole, the parent compound of esomeprazole, in the same indication.

Conclusions on the clinical efficacy

The applicant has presented the relevant efficacy data which shows that esomeprazole is effective in GERD when compared to placebo and that resolution rates with the 20mg dose are clinically relevant. This is further supported by post approval data gathered from the meta-analyses and studies presented bridging the results of the pivotal studies to the uninvestigated patient population who will seek OTC PPI medication.

With regards to the initially claimed posology (2 weeks of treatment and additional 2 weeks in partial responders) the CHMP was of the view that it is to be taken into consideration that good efficacy is shown already after 2 weeks and only numerical improvement in partial responders achieving complete resolution of symptoms following an additional 2 weeks of treatment could be shown. Therefore, the treatment duration should be limited to two weeks and that the product information should indicate that if no symptom relief is obtained within 2 weeks of continuous treatment, the patient should be instructed to consult a doctor.

2.5. Clinical safety

Patient exposure

As of 31 August 2011, oral esomeprazole is estimated to have a cumulative exposure of approximately 70.5 million patient-years worldwide since first approval.

In addition more than 90 000 patients/subjects were exposed to esomeprazole in clinical trials as of 10 September 2011 (see Table 19).

Table 19 Esomeprazole exposure (all clinical trial populations)

Esomeprazole exposure in AZ studies	No of patients/subjects
Total	90833
Oral	88925
Intravenous	1904
Oral up to 40 mg daily	85281
Oral 41-79 mg daily	38
Oral 80 mg daily	3572
Oral more than 80 mg daily	34
Oral less than 12 months exposure	87652
Oral 12 months exposure	1058
Oral more than 12 months exposure	219

The safety population in the submitted two pivotal studies (470 patients) is presented below to be regarded as supportive.

In the pooled safety population of studies 225 and 226 a total of 710 subjects with diagnosis of symptomatic GERD were included. Of these, 240 received placebo and 470 received treatment with esomeprazole; 232 patients were exposed to the proposed dose range (20 mg) of esomeprazole, the others (238) to esomeprazole 40 mg. Of the 717 randomized patients, 7 patients did not have a documented dose of study medication and were therefore excluded from the safety population. The pooled mean exposure was 28 days. For this application the safety analyses were performed using the safety population, which included all randomized patients treated with at least one dose of study medication (esomeprazole or placebo) and for whom post-dose data were available. Treatment groups were generally well balanced with respect to all demographic characteristics. Demographic distribution is representative to EU population.

Adverse events

As of 31 August 2011 the applicant had, in total, obtained approximately 51000 spontaneously reported case reports concerning AEs (both serious and non-serious) from post-marketing experiences (including reports from consumers and Patient Assistance Programs) of esomeprazole around the world.

The 10 most commonly reported AEs were drug dose omission, drug ineffective, diarrhoea, headache, gastroesophageal reflux disease, nausea, abdominal pain upper, dyspepsia, malaise and abdominal pain. In the reports of drug dose omission (that the patients do not take their medication regularly, eg, due to cost) approximately one third of the patients also reported gastroesophageal reflux disease. Other commonly reported events in the reports of drug dose omission were dyspepsia, malaise, vomiting, abdominal pain upper and drug ineffective.

Table S 11 Esomeprazole ten most common AEs

AE SOC Abbreviation	AE Preferred Term	Case Count
Inj & P	Drug dose omission	4779
Genrl	Drug ineffective	4234
Gastr	Diarrhea	3862
Nerv	Headache	3440
Gastr	Gastroesophageal reflux disease	3078
Gastr	Nausea	2878
Gastr	Abdominal pain upper	2725
Gastr	Dyspepsia	2596
Genrl	Malaise	2048
Gastr	Abdominal pain	2030

In the pivotal studies overall, 285/710 patients (40%) experienced at least 1 AE. The rate of subjects reporting AEs was following: esomeprazole 40 mg (42%), 20 mg (38.8%), placebo (39.6%). There were no apparent differences between the esomeprazole treatment groups and the placebo group in the proportions of patients reporting at least one AE or in the proportions of patients reporting a serious AE. There were no deaths in the studies. Relatively few patients discontinued treatment due to an AE (see **Table 6**).

Table 6. Summary of AEs (studies 225 and 226, pooled data).

	H 199/18 40 mg qd N=238		H 199/18 20 mg qd N=232		Placebo N=240	
No. (%) of patients with:						
any AE	100	(42.0)	90	(38.8)	95	(39.6)
fatal serious AE	0		0		0	
non-fatal serious AE	3	(1.3)	0		2	(0.8)
drug stopped due to AE	3	(1.3)	7	(3.0)	3	(1.3)
AE with severe intensity	16	(6.7)	16	(6.9)	12	(5.0)
Total no. of AEs recorded	160		183		146	

Table 6:5 in Addendum - Summary of Safety, included in the original file SE/H/211/01-02
H 199/18 = esomeprazole

The most common AEs were in the GI disorders SOC, overall (154/710, 21%) and in each treatment group. The frequency of GI disorder AEs was higher in the esomeprazole groups compared with

placebo, but AEs increase with dose was not observed: esomeprazole 40 mg (22.3%), 20 mg (24.6%), placebo (18.3%).

The most common AE by preferred term was headache, reported in 5.5% of esomeprazole 40 mg patients, 7.8% of esomeprazole 20 mg patients, and 7.5% of placebo patients. The following the most frequent AEs were of GI disorders SOC (abdominal pain, diarrhoea and nausea) and were reported at a slightly higher frequency in the esomeprazole 20 mg group compared to esomeprazole 40 mg and placebo groups.

In the pivotal studies, 31% of the subjects experienced any AE during the first 2 weeks of esomeprazole treatment compared to 15% during Day 15-28 of treatment. The proportion of subjects with any AE was similar to those in the placebo group. No SAEs were recorded in the esomeprazole treatment group **(Table 6).**

The percentage of related AEs as judged by the investigator were higher in the esomeprazole groups in the pooled pivotal studies, the relative difference was bigger in the second 2 weeks in pooled pivotal studies (~7% and 3% vs. ~16% and 13% for esomeprazole and placebo). The larger data set consisting of 13 pooled studies presented in table 7 below no such pattern is seen.

Table 6 **Number (%) of patients who had an adverse event in any category (safety population) pooled data from pivotal studies SH-QBE-0053, SH-QBE-0054**

	Day 0-14				Day 15-28			
	Esomeprazole 20 qd		Placebo qd		Esomeprazole 20 qd		Placebo qd	
Category of adverse events[a]	(n=232)		(n=240)		(n=223)		(n=228)	
Any adverse events	71	(30.6)	70	(29.2)	34	(15.3)	36	(15.8)
Serious AEs	0		1	(0.4)	0		1	(0.4)
Serious AEs leading to death	0		0		0		0	
Serious AEs not leading to death	0		1	(0.4)	0		1	(0.4)
Discontinuation of study treatment due to AEs	6	(2.6)	2	(0.8)	2	(0.9)	1	(0.4)
Other significant AEs	0		0		0		0	
Related AEs[b]	38	(16.4)	31	(12.9)	15	(6.7)	7	(3.1)
Severe AEs	14	(6.0)	6	(2.5)	2	(0.9)	7	(3.1)

[a] Patients with multiple events in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories.
[b] Related AEs are those for which there was a possible relationship to investigational product as judged by the investigator.

In pooled data from 13 clinical studies with 20 mg esomeprazole treatment 16% of the subjects had any AE during the first 2 weeks of treatment while 0.6% of the subjects had any SAE. During Day 15-28 of treatment 12% the subjects had any AE and 0.6% of the subjects had any SAE **(Table 7)**.

Table 7 **Number (%) of patients who had an adverse event in any category (safety population) pooled data from 13 studies**

	Day 0-14				Day 15-28			
Category of adverse events[a]	Esomeprazole 20 qd (n=2917)		Placebo qd (n=2932)		Esomeprazole 20 qd (n=2805)		Placebo qd (n=2772)	
Any adverse events	463	(15.9)	478	(16.3)	335	(11.9)	401	(14.5)
Serious AEs	17	(0.6)	18	(0.6)	16	(0.6)	14	(0.5)
Serious AEs leading to death	1	(<0.1)	1	(<0.1)	1	(<0.1)	0	
Serious AEs not leading to death	17	(0.6)	17	(0.6)	15	(0.5)	14	(0.5)
Discontinuation of study treatment due to AEs	55	(1.9)	77	(2.6)	24	(0.9)	45	(1.6)
Other significant AEs	0		0		0		0	
Related AEs[b]	130	(4.5)	127	(4.3)	61	(2.2)	48	(1.7)
Severe AEs	48	(1.7)	39	(1.3)	16	(0.6)	22	(0.8)

[a] Patients with multiple events in the same category are counted only once in that category.
Patients with events in more than 1 category are counted once in each of those categories.
[b] Related AEs are those for which there was a possible relationship to investigational product as judged by the investigator.
Pooled data from 13 studies: D9617C00011, D961FC00003, D961HC00001, SH-NEN-0001, SH-NEN-0002, SH-NEN-0003, SH-NEN-0004, SH-NEN-0013, SH-NEN-0014, SH-QBE-0014, SH-QBE-0015, SH-QBE-0053, SH-QBE-0054.

Tabulated list of adverse reactions

The following adverse reactions have been identified or suspected in the clinical trials programme for esomeprazole and post-marketing. The reactions are classified according to MedDRA frequency convention: very common ≥ 1/10; common ≥1/100 to <1/10; uncommon ≥1/1000 to <1/100; rare ≥1/10,000 to <1/1,000; very rare <1/10,000; not known (cannot be estimated from the available data).

	Common	Uncommon	Rare	Very rare	Not known
Blood and lymphatic system disorders			leukopenia, thrombocytopenia	agranulocytosis, pancytopenia	
Immune system disorders			hypersensitivity reactions e.g. fever, angioedema and anaphylactic reaction/shock		
Metabolism and nutrition disorders		peripheral oedema	hyponatraemia		hypomagnesaemia; severe hypomagnesaemia can correlate with hypocalcaemia; hypomagnesaemia may also result in hypokalaemia
Psychiatric disorders		insomnia	agitation, confusion, depression	aggression, hallucinations	

	Common	Uncommon	Rare	Very rare	Not known
Nervous system disorders	headache	dizziness, paraesthesia, somnolence	taste disturbance		
Eye disorders			blurred vision		
Ear and labyrinth disorders		vertigo			
Respiratory, thoracic and mediastinal disorders			bronchospasm		
Gastrointestinal disorders	abdominal pain, constipa-tion, diarrhoea, flatulence, nausea/ vomiting	dry mouth	stomatitis, gastrointestinal candidiasis		microscopic colitis
Hepatobiliary disorders		increased liver enzymes	hepatitis with or without jaundice	hepatic failure, hepatic encephalopathy in patients with pre-existing liver disease	
Skin and subcutaneous tissue disorders		dermatitis, pruritus, rash urticaria	alopecia, photosensitivity	erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN)	
Musculoskeletal and connective tissue disorders			arthralgia, myalgia	muscular weakness	
Renal and urinary disorders				Interstitial nephritis	
Reproductive system and breast disorders				gynaecomastia	
General disorders and administration site disorders			malaise, increased sweating		

According to the SmPC of the reference product the majority of ADRs are mild and transient in nature, the most frequent being headache and gastrointestinal disorders, ie, abdominal pain, diarrhoea, flatulence, nausea/vomiting and constipation. No dose-related adverse reactions have been identified.

Serious adverse event / deaths / other significant events

Deaths. No deaths were reported in Study 225 and Study 226.

Serious AE other than deaths. In total, 5 serious AEs (SAEs) were reported in studies 225 and 226. All SAEs were single events. The most frequent SAEs were GI disorders SOC (2 subjects) and myo-endo-pericardial & valve disorders SOC (2 events occurred in one patient).

In general serious or severe AEs and interactions following administration of esomeprazole are rare. All identified adverse drug reactions are included in the Product information. Details of all important identified risks and all potential risks with esomeprazole are presented in the RMP.

Laboratory findings

Haematology and clinical chemistry: Baseline values for all variables in Study 225 and Study 226 were similar between treatment groups. Mean changes were small and similar across three treatment groups in each study. Expected dose-related mean changes in serum gastrin were found in both studies. Isolated values outside reference range were found in both studies, but findings weren't statistically significant. Laboratory findings did not raise any additional issues for esomeprazole.

Agranulocytosis is included in the SmPCs for esomeprazole and the frequency is considered to be very rare, <1/10000. No cases have been reported within the applicant's clinical programme. In total 128 medically confirmed AEs of agranulocytosis had been received up to 10 September 2012. Of these, 127 were serious and 1 was non-serious from marketed use. The risk of Agranulocytosis is reflected in the RMP. Hypomagnesaemia is included in the SmPCs for esomeprazole and the frequency has been estimated to 'not known'. No cases have been reported within the applicant's clinical programme. In total 66 medically confirmed AEs of hypomagnesaemia had been received as of 10 September 2012. Of these, 36 were serious and 29 were non-serious from marketed use, and 1 was an SAE from an AstraZeneca sponsored clinical trial.

Safety in special populations

See also pharmacology part of this report above.

Elderly

The safety events for elderly patients from pooled data from 24 placebo-controlled clinical studies with esomeprazole comprising 9877 patients treated with esomeprazole and 5551 patients treated with placebo was presented by age groups. The number of patients in the age group >65 was 2851 and 1637 for esomeprazole and placebo respectively. See **Table 2.**

Table 2 **Number (%) of patients with the most commonly reported adverse events, presented by Preferred Term (Esomeprazole Placebo Pool)**

Drug:	Esomprazole		Placebo		Esomprazole		Placebo		Esomprazole		Placebo		Esomprazole		Placebo	
Age:	Less than 65				65-74				75 - 84				85 and above			
Mean no. of treatment days:	98		87		140		131		146		130		138		115	
Total no. of patients with AE:	*3149*	*(44.8)*	*1685*	*(43.1)*	*1026*	*(48.1)*	*564*	*(46.0)*	*315*	*(46.4)*	*184*	*(48.4)*	*18*	*(47.4)*	*17*	*(56.7)*
No. of patients with AE per 100 treatment years:	*167*		*181*		*125*		*128*		*116*		*136*		*125*		*180*	
Preferred term	(n=7026)		(n=3914)		(n=2134)		(n=1227)		(n=679)		(n=380)		(n=38)		(n=30)	
Headache	331	(4.7)	148	(3.8)	58	(2.7)	34	(2.8)	11	(1.6)	8	(2.1)	1	(2.6)	1	(3.3)
Diarrhoea	262	(3.7)	94	(2.4)	86	(4.0)	27	(2.2)	37	(5.4)	10	(2.6)	1	(2.6)	0	
Nausea	266	(3.8)	129	(3.3)	81	(3.8)	44	(3.6)	25	(3.7)	18	(4.7)	1	(2.6)	2	(6.7)
Abdominal distension	243	(3.5)	129	(3.3)	91	(4.3)	41	(3.3)	20	(2.9)	12	(3.2)	1	(2.6)	1	(3.3)
Dyspepsia	191	(2.7)	165	(4.2)	73	(3.4)	65	(5.3)	16	(2.4)	16	(4.2)	1	(2.6)	3	(10.0)
Nasopharyngitis	196	(2.8)	111	(2.8)	40	(1.9)	36	(2.9)	10	(1.5)	6	(1.6)	2	(5.3)	1	(3.3)
Bronchitis	112	(1.6)	65	(1.7)	42	(2.0)	23	(1.9)	10	(1.5)	8	(2.1)	2	(5.3)	0	
Gastrooesophageal reflux disease	91	(1.3)	80	(2.0)	54	(2.5)	45	(3.7)	18	(2.7)	16	(4.2)	2	(5.3)	0	
Gastritis erosive	47	(0.7)	40	(1.0)	55	(2.6)	33	(2.7)	17	(2.5)	7	(1.8)	2	(5.3)	1	(3.3)
Hypertension	61	(0.9)	20	(0.5)	38	(1.8)	15	(1.2)	9	(1.3)	8	(2.1)	1	(2.6)	3	(10.0)
Oedema peripheral	31	(0.4)	8	(0.2)	16	(0.7)	9	(0.7)	8	(1.2)	6	(1.6)	0		2	(6.7)
Vertigo	22	(0.3)	9	(0.2)	11	(0.5)	5	(0.4)	8	(1.2)	2	(0.5)	2	(5.3)	0	

Included in the table are AEs reported for at least 4 % of the patients in any column. The events are sorted by decreasing frequency for all esomeprazole treated patients, irrespective of age category.
The esomeprazole placebo pool comprises 24 studies: D9611C00002, D9614C00096, D9617C00011, D9618C00001, D961FC00003, D961HC00001, D9914C00001, SD-NED-0021, SD-NED-0022, SD-NEE-0003, SH-NEN-0001, SH-NEN-0002, SH-NEN-0003, SH-NEN-0004, SH-NEN-0013, SH-NEN-0014, SH-QBE-0010, SH-QBE-0012, SH-QBE-0014, SH-QBE-0015, SH-QBE-0022, SH-QBE-0053, SH-QBE-0054, SH-QBE-0065

The AE rates were evenly distributed across all age groups and the overall AE profile is similar for esomeprazole and placebo, with headache, nausea and diarrhoea being the most commonly reported.

Paediatric population

Esomeprazole is not foreseen to be used in the non-prescription setting in the paediatric population below 18 years of age.

Pregnancy and Lactation

A moderate amount of data on pregnant women (between 300-1000 pregnancy outcomes) indicate no malformative or feto/ neonatal toxicity of esomeprazole. Provided data from the Swedish birth registry showed a 1.7% rate of congenital malformations in case of esomeprazole that is in the range of background rate of ~2.8% reported in the literature. As a precoutionary measure the product information states that use during pregnancy and lactation is not recommended.

Safety related to drug-drug interactions and other interactions

Medicinal products with pH dependent absorption

Gastric acid suppression during treatment with esomeprazole and other proton pump inhibitors (PPIs) might decrease or increase the absorption of medicinal products with a gastric pH dependent absorption. As with other medicinal products that decrease intragastric acidity, the absorption of medicinal products such as ketoconazole, itraconazole and erlotinib can decrease during treatment with esomeprazole and the absorption of digoxin can increase during treatment with esomeprazole. Concomitant treatment with omeprazole (20 mg daily) and digoxin in healthy subjects increased the bioavailability of digoxin by 10% (up to 30% in two out of ten subjects). Digoxin toxicity has been rarely reported.

Antiretroviral drugs

Omeprazole has been reported to interact with some protease inhibitors. The clinical importance and the mechanisms behind these reported interactions are not always known. Increased gastric pH during omeprazole treatment may change the absorption of the protease inhibitors. Other possible interaction mechanisms are via inhibition of CYP2C19. For atazanavir and nelfinavir, decreased serum levels have been reported when given together with omeprazole.

Due to the similar pharmacodynamic effects and pharmacokinetic properties of omeprazole and esomeprazole, concomitant administration with esomeprazole and atazanavir is not recommended and concomitant administration with esomeprazole and nelfinavir is contraindicated.

Drugs metabolized by CYP2C19

Esomeprazole inhibits CYP2C19, the major esomeprazole metabolising enzyme. Thus, when esomeprazole is combined with drugs metabolised by CYP2C19, such as diazepam, citalopram, imipramine, clomipramine, phenytoin etc., the plasma concentrations of these drugs may be increased and a dose reduction could be needed.

Interaction with clopidogrel and submitted studies has been described in the pharmacology part of this report.

Unknown mechanism

As reflected in the SmPC, when given together with PPIs, methotrexate levels have been reported to increase in some patients. In high-dose methotrexate administration a temporary withdrawal of esomeprazole may need to be considered.

Effects of other drugs on the pharmacokinetics of esomeprazole

Esomeprazole is metabolised by CYP2C19 and CYP3A4. Concomitant administration of esomeprazole and a CYP3A4 inhibitor, clarithromycin (500 mg b.i.d), resulted in a doubling of the exposure (AUC) to esomeprazole. Concomitant administration of esomeprazole and a combined inhibitor of CYP2C19 and CYP 3A4 may result in a more than doubling of the esomeprazole exposure. The CYP2C19 and CYP3A4 inhibitor voriconazole increased omeprazole AUCt by 280%. A dose adjustment of esomeprazole is not regularly required in either of these situations. However, dose adjustment should be considered in patients with concomitant severe hepatic impairment.

Drugs known to induce CYP2C19 or CYP3A4 or both (such as rifampicin and St. John's wort) may lead to decreased esomeprazole serum levels by increasing the esomeprazole metabolism.

2.5.1. Post marketing experience

Esomeprazole is currently not approved for non-prescription use hence there is no post-marketing experience. However, the parent compound omeprazole is approved and marketed for use in the OTC setting. To give further assurance on the issue of incorrect self-assessment the Applicant provided post marketing data on the adverse event profile of non-prescription omeprazole, including the type of reports received and about changes in the type of events following non-prescription availability in the US.

In Table 2 the 15 most commonly reported AE MedDRA PTs for PRILOSEC OTC, omeprazole Rx pre-launch of PRILOSEC OTC and omeprazole Rx post-launch of PRILOSEC are shown (data derived from

AstraZeneca safety database SAPPHIRE). The percentage of the total number of AE Preferred terms is also displayed.

'Drug ineffective' is the most commonly reported AE for both PRILOSEC OTC and omeprazole Rx (both pre and post launch of PRILOSEC OTC). The AE term *'drug ineffective'* for Rx constitutes a much higher percentage post launch than pre-launch of PRILOSEC OTC. The percentage reported for *'drug ineffective'* for PRILOSEC OTC (13.8) is comparable with the percentage for Rx post-launch (17.8), which could indicate a change in the overall reporting pattern. As shown in Table 2 a majority of the 15 most commonly reported AEs in each group are either listed (entered with *italic* font in Table 2) in the
Company Core Data Sheet for omeprazole and/or likely related to the background disease (entered with **bolded** font in Table 2). Overall no significant difference between the patterns of ADR reports for prescription and non-prescription omeprazole can be seen.

Table 2 Post marketing data on the adverse event profile of omeprazole

PRILOSEC OTC (cumulative up to 31 Oct 2012)		**Omeprazole Rx* pre-launch PRILOSEC OTC (cumulative up to 14 Sep 2003)**		**Omeprazole Rx* post-launch PRILOSEC OTC (15 Sep 2003 – 31 Oct 2012)**	
AE MedDRA PT	Number of PTs (%)	AE MedDRA PT	Number of PTs (%)	AE MedDRA PT	Number of PTs (%)
Drug ineffective	1 811 (13.8)	Drug ineffective	1 590 (5.9)	Drug ineffective	3 257 (17.8)
Diarrhoea	429 (3.3)	*Diarrhoea*	1 105 (4.1)	**Gastrooesophageal reflux disease**	825 (4.5)
Incorrect drug administration duration	410 (3.1)	*Headache*	932 (3.5)	*Dyspepsia*	487 (2.7)
Inappropriate schedule of drug administration	392 (3.0)	*Abdominal pain*	723 (2.7)	*Malaise*	404 (2.2)
Gastrooesophageal reflux disease	323 (2.5)	*Nausea*	691 (2.6)	*Vomiting*	314 (1.7)
Abdominal pain upper	315 (2.4)	*Dizziness*	526 (2.0)	*Abdominal pain upper*	307 (1.7)
Nausea	302 (2.3)	*Rash*	519 (1.9)	*Nausea*	287 (1.6)
Headache	278 (2.1)	*Alopecia*	443 (1.6)	*Diarrhoea*	267 (1.5)
Dizziness	251 (1.9)	*Abdominal pain upper*	363 (1.4)	*Abdominal discomfort*	239 (1.3)
Dyspepsia	246 (1.9)	*Constipation*	361 (1.3)	Pain	209 (1.1)
Malaise	220 (1.7)	*Flatulence*	319 (1.2)	*Headache*	199 (1.1)
Vomiting	211 (1.6)	Abdominal distension	317 (1.2)	Drug effect decreased	194 (1.1)
Incorrect dose administered	191 (1.5)	*Vomiting*	304 (1.1)	Chest pain	181 (1.0)
Chest pain	145 (1.1)	Chest pain	301 (1.1)	Drug dose omission	166 (0.9)
Abdominal discomfort	138 (1.0)	*Pruritus*	301 (1.1)	*Dizziness*	138 (0.8)

*Footnote:** There is also a wide use of omeprazole generics. In terms of volume of global sales of prescribed omeprazole during 2011, approximately 4% came from AstraZeneca omeprazole and 96% from generic. It could be anticipated that some of the AEs reported to AstraZeneca, directly or via regulatory authority line listings, could relate to generic omeprazole. All omeprazole AE reports received by AstraZeneca are entered into SAPPHIRE.

2.5.2. Discussion on clinical safety

As of 31 August 2011, oral esomeprazole is estimated to have a cumulative exposure of approximately 70.5 million patient-years worldwide since first approval. The exposure of esomeprazole in clinical trials exceeding the 90 000 patients/subjects in clinical trials makes robust database to argue for risk profiling in general.

The majority of adverse reactions identified or suspected in the clinical trials programme for esomeprazole and post-marketing of ADRs are mild and transient in nature, the most frequent being headache and gastrointestinal disorders, ie, abdominal pain, diarrhoea, flatulence, nausea/vomiting and constipation. No dose-related adverse reactions have been identified.

Accordingly the most common AE by preferred term in the pooled pivotal trials was headache, and the following most frequent AEs were of GI disorders SOC (abdominal pain, diarrhoea and nausea)

reported at a slightly higher frequency in the esomeprazole 20 mg group compared to esomeprazole 40 mg and placebo groups.

AE rates from a pool of placebo controlled studies comprising 9877 patients treated with esomeprazole and 5551 patients treated with placebo are evenly distributed across all age groups and the overall AE profile is similar for esomeprazole and placebo, with headache, nausea and diarrhoea being the most commonly reported.

To better profile the safety findings between the 2nd and 4th week of treatment a comparative safety analysis, both in pooled clinical studies with esomeprazole and in the pivotal studies was performed. Both analyses demonstrate fewer adverse events during Day 15-28 of treatment compared to the first 2 weeks of treatment. In total, serious and severe AE were comparable to placebo during the second two weeks. Overall the safety profile shown in these analyses was considered not to be worse as compared to the first two weeks.

The applicant provided information on interactions in line with the approved SmPC for the reference product. Gastric acid suppression during treatment with esomeprazole and other proton pump inhibitors (PPIs) might decrease or increase the absorption of medicinal products with a gastric pH dependent absorption. When esomeprazole is combined with drugs metabolised by CYP2C19, the major esomeprazole metabolising enzyme, the plasma concentrations of these drugs may be increased and a dose reduction could be needed.

Further, Omeprazole has been reported to interact with some protease inhibitors. Due to the similar pharmacodynamic effects and pharmacokinetic properties of omeprazole and esomeprazole, concomitant administration with esomeprazole and atazanavir is not recommended and concomitant administration with esomeprazole and nelfinavir is contraindicated.

The identified and potential interactions which have been considered as the most important due to e.g., a narrow therapeutic range and/or risk for serious complications are reflected appropriately in the RMP. All known interactions are listed in the SmPC/Package Leaflet and the risk is considered adequately balanced for OTC use.

Post marketing data provided by the applicant on the adverse event profile of non-prescription omeprazole demonstrate that there is no significant difference between the patterns of ADR reports for prescription and non-prescription omeprazole. As esomeprazole is an isomer of omeprazole, the data provide reassurance that the adverse event profile for esomeprazole is unlikely to change significantly if the product were to be available without prescription.

From the safety database all the adverse reactions reported in clinical trials and post-marketing have been included in the Summary of Product Characteristics.

2.5.3. Conclusions on the clinical safety

The safety profile of esomeprazole for the treatment of GERD is well characterised and does not reveal new safety signals for self-therapy. Based on the available information the product information it is considered appropriate to provide guidance for the safe use of the medicine in the non-prescription setting.

2.6. Legal status

The applicant requested the supply of the medicinal product to be classified as non-prescription medicine meaning that the criteria of Article 71 of Directive 2001/83/EC, as amended, do not longer apply to esomeprazole for short-term treatment of reflux symptoms. For the assessment of this

request the criteria as laid down in the Commission Guideline on Changing the Classification for the Supply of a Medicinal Product for Human Use (European Commission, 2006 revision) apply.

First criterion: Directly or indirect danger, even when used correctly, if utilised without medical supervision

Direct danger

Side effect profile: Most of the effects that can occur during short-term use of esomeprazole 20 mg tablets are mild, self-limiting and not dependent on dosage. The most frequent of these side effects occur in the gastrointestinal tract (such as abdominal pain, diarrhoea, constipation, flatulence, nausea and vomiting) or manifest themselves as unspecific symptoms such as headache. General toxicity of esomeprazole when used correctly can be considered low, and there is no nonclinical or clinical evidence of organ damage caused by this drug substance.

Due to the unique mechanism and specific effect on acid secretion the risk of severe side effects of Type A or Type B[21] is low and very low respectively. The proposed dose of 20 mg per day does not need to be adjusted in patients with impaired kidney or liver function.

Carcinogenicity, embryotoxicity and foetotoxicity: clinical experience with long-term therapy has not given any evidence for a carcinogenic potential. Neither nonclinical studies nor clinical epidemiological studies have shown any relevant reproductive toxic or genotoxic effects, and both nonclinical and clinical data show that the risks associated with taking esomeprazole during pregnancy are very low. Esomeprazole with non-prescription status is not intended for use during pregnancy or lactation due to limited clinical data on exposed pregnancies as reflected in the Product Information.

Interactions of esomeprazole with commonly used medicines are rare. All known interactions are listed in the Package Leaflet, and patients who are taking certain medications will be advised to consult a pharmacist or doctor before taking esomeprazole. Esomeprazole may affect the pharmacokinetics of other drugs via e.g., its acid-inhibitory effect or metabolic pathways, and dose-adjustments might be needed. In addition, other drugs might affect the pharmacokinetics of esomeprazole. Appropriate advice is given in PIL and SmPC and the risk of interactions is reflected in the RMP.

The safety profile of esomeprazole is comparable to the one of other PPI treatments already approved for use in the OTC setting.

Indirect danger

As recommended in clinical guidelines (Flook et al 200822, Tytgat et al 2008[23], Holtmann et al 2011[24]) diagnostic measures are often not initiated before a short term course of treatment with a PPI has been completed in patients with typical reflux symptoms (heartburn / regurgitation) and no alarm symptoms, even when under medical supervision.

Diseases that in similarity to GERD may include symptoms of heartburn and acid regurgitation are Peptic ulcers, Barrett's esophagus and Malignant esophageal or gastric disorders. Patients with peptic ulcers most often have epigastric pain as the dominant symptom and heartburn only as a secondary symptom. Patients with Barrett's esophagus could have heartburn and acid regurgitation but

21 Type A: those that result from exaggeration of a medicinal product's expected pharmacological actions when given in the usual therapeutic dose; normally dose dependent. Type B those that represent a novel response not expected from known pharmacological action.

22 Flook N, Jones R, Vakil N. Approaches to gastresopageal reflux disease in primary care. Can Fam Physician 2008;54:701-5.

[23] Tytgat GN, McColl K, Tack J, Holtmann G, Hunt RH, Malfertheiner P, et al. New algorithm for the treatment of gastro-oesophageal reflux disease. Aliment. Pharmacol. Ther. 2008 Feb 1;27(3):249-56.

[24] Holtmann G, Biguard M-A, Malfertheiner P, Pounder R. Guidance on the use of over-the counter proton pump inhibitors for the treatment of GERD. Int J Clin Pharm 2011 33: 493-500.

symptoms recur after ending a short term treatment, and the progression from normal to Barrett's mucosa and further to dysplasia is a slow process, with a progression rate of at most 1% and 0.5% per year, respectively. The occurrence of malignant disorders in the esophagus and stomach without other so-called "alarm" symptoms, such as unintentional weight loss, recurrent vomiting, dysphagia, bloody stool or vomit, fever, jaundice or anaemia *is rare*. In addition, symptomatic GERD does not progress in the long-term and the risk of developing pathogenic mucosal changes is low.

The Package Leaflet includes clear instructions for the patient not to start self-medication if certain specified alarm symptoms, are present or occur during treatment. Furthermore, the duration of has been limited to 2 weeks and patient are advised to consult a doctor if no symptom relief is obtained within 2 weeks of continuous treatment; this information is included in the Package Leaflet.

Self-assessment

International guidance for self-assessment: according to an international consensus conference, the initial medical treatment of GERD is based on the detection and description of the symptoms by the patient (Vakil et al 2006[25]). Heartburn and acid regurgitation, the typical well defined and documented symptoms of GERD, can easily be assessed by the patients themselves. Signs and symptoms that should initiate a physician-driven investigation, such as alarm symptoms and lack of treatment effect, are also easily recognizable by patients.

Experience with self-therapy: epidemiological studies on the treatment of symptoms during self-medication confirm the ability of patients to independently detect and treat these symptoms. A self-medication study has shown that the majority of patients used self-medication for the symptoms of heartburn as intended, according to the indication and dosage instructions, and if not free from symptoms after 14 days followed the recommendations of the patient information leaflet and consulted a doctor (Fendrick et al 2004[26]).

Risk and consequences of incorrect use

The three main risks' areas on incorrect use for esomeprazole OTC (i) overdose, (ii) pregnancy and lactation, (iii) use in children are discussed below together with considerations to risk management through product information to patients.

Overdose: Results from non-clinical studies indicate that esomeprazole has a low acute toxicity by the oral route. Clinical experience of doses in excess of 240 mg/day is limited. The symptoms described in connection with oral ingestion of 280 mg have been gastrointestinal symptoms and weakness. The ingestion of a single dose of 800 mg in an attempt to commit suicide by a patient with a medical history of psychiatric disease has been reported. No symptoms were reported. The patient was hospitalised, clinical monitoring and lavage of the stomach were performed and the patient recovered.

The pack sizes are 7 x 20 mg tablets and 14 x 20 mg tablets, i.e., the maximum pack size will contain a total of 280 mg esomeprazole. Thus, even if all the tablets in an entire pack were to be ingested in a single dose, this would only just exceed the maximum daily recommended dose (240 mg in Zollinger-Ellison syndrome patients) and would not raise any major safety concerns.

Pregnancy and lactation:

[25] Vakil N, van Zanten SV, Kahrilas P, Dent J, Jones R and the Global Consensus Group. Global Consensus Group. The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. Am. J. Gastroenterol. 2006;101:1900-20.
[26] Fendrick AM, Shaw M, Schachtel B, Allgood L, Allgood G, Grender J, Peura D. Selfselection and use patterns of over-the-counter omeprazole for frequent heartburn. Clin. Gastroenterol. Hepatol. 2004 Jan;2:17-21.

Although clinical data on exposure to esomeprazole during pregnancy are limited, esomeprazole taken during the fertile period or during early pregnancy has not been associated with any significant teratogenic risk. The Package Leaflet explicitly states that esomeprazole with non-prescription status is not intended for use during pregnancy and lactation. Thus, accidental ingestion of esomeprazole during conception or early pregnancy represents an acceptably low risk.

Children:

In Europe, esomeprazole is approved for treatment of GERD in children aged from 1 year to adolescence. In addition, esomeprazole has been approved in the US for children aged from 1 month. The adverse event pattern has been similar to that in adults, both in clinical trials and in case reports from marketed use and no particular safety concerns have been raised for the paediatric population. No findings in juvenile toxicity studies have indicated any specific risk in the paediatric population. The applied non-prescription medicine is not intended for use in children <18 years. The Package Leaflet explicitly states that esomeprazole with non-prescription status is not intended for use in self-medication of children under 18 years of age. In view of this clear labelling and also considering the available information on paediatric use, the risk of causing harm due to unintentional intake by children is considered as low.

Suitability of patient information

The package leaflet and the labelling are considered adequate to contribute effectively to the safe and effective use of the medicine including appropriate guarding that the non-prescription medicine is not used where it is contraindicated or unsafe. The written information clearly expresses when the medicinal product should not be used. An appropriate user testing of the package leaflet has been performed in accordance with the legislation.

Second criterion: Known incorrect use

Esomeprazole does not produce euphoric, stimulant, sedative or other addictive effects most commonly associated with abuse or misuse. No potential for misuse for illegal purposes has been identified.

Third criterion: Activity or side-effects which require further investigation

The active substance esomeprazole, in comparable indication, is approved throughout Europe since 2000 and is now approved in 117 countries worldwide. The side effect profile of esomeprazole is well investigated and well understood. The medicinal product will not be available without prescription in a new strength, at a new dose, using a new route of administration, new age group or for a new indication.

Conclusion:

The available experience with esomeprazole 20 mg orally is considered sufficient for assessing the proposed non-prescription status, and the documented use relevant for the proposed indication, treatment duration and age group of the medicine. Overall, the CHMP considers that the supply as non-prescription medicine is appropriate. It is noted that specific aspects of the national implementation of a non-prescription status vary amongst Member States.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

PRAC Advice

Based on the PRAC review of the Risk Management Plan version 8.4 the PRAC considers by consensus that the risk management system for esomeprazole (Nexium Control) for the short-term treatment of reflux symptoms (e.g. heartburn and acid regurgitation) in adults is acceptable.

This advice is based on the following content of the Risk Management Plan:

Safety concerns

Summary of the 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 plans

Table 2.2: Planned and Ongoing studies in the PhV development plan

Activity / Study title	**Objectives**	**Safety concerns addressed**	**Status Planned, started,**	**Date for submission of interim or final reports (planned or actual)**
Two prospective pharmacoepidemiology studies of the safety of long-term treatment with esomeprazole in children (category 3). (D9612N00014) (D9612N00016)	To describe the co-morbidity and other characteristics of children that are prescribed esomeprazole for the first time and to compare these patients with those who are prescribed other acid-suppressing drugs for the first time. To estimate the occurrence of prespecified outcomes among children being prescribed esomeprazole and other acid suppressing drugs for the first time.	Long-term treatment in children	Started	Last annual study report Q4 2012. Results available Q4 2015.
An observational cohort study on the association between acid suppressing drugs in pregnancy and asthma in the offspring (category 3). (D9612N00018)	To estimate the association between prenatal exposure to PPIs and the risk of asthma during childhood. To estimate the association between prenatal exposure to histamine2-receptor antagonists (H2RAs) and the risk of asthma during childhood.	Use of acid-suppressing drugs in pregnancy and childhood asthma	Planned start Q1 2013	Results available Q4 2014 (planned)
An observational cohort study with a nested case control analysis on acid suppressing drugs and seizures (category 3). (D9612N00017)	To estimate the incidence of seizure in the general population and stratified by epilepsy status. To estimate the relative risk of seizure associated with use of PPI and	Use of acid-suppressing drugs and seizures	Planned start Q1 2013	Results available Q4 2014 (planned)

Activity / Study title	Objectives	Safety concerns addressed	Status Planned, started,	Date for submission of interim or final reports (planned or actual)
	H2RA and stratified by epilepsy status.			

*Category 1 are imposed activities considered key to the benefit risk of the product.
Category 2 are specific obligations
Category 3 are required additional PhV activity (to address specific safety concerns or to measure effectiveness of risk minimisation measures)

The PRAC, having considered the data submitted, was of the opinion that the proposed post-authorisation PhV development plan is sufficient to identify and characterise the risks of the product.

The PRAC also considered that routine PhV is sufficient to monitor the effectiveness of the risk minimisation measures.

Risk minimisation measures

Summary table of Risk Minimisation Measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risks		
Hypersensitivity reactions ,	Text in SmPCs section 4.4 Special warnings and precautions for use Text in PIL	None applicable
Gastrointestinal infections	Text in SmPCs and PIL	None applicable
Interaction with warfarin or other coumarine derivatives	Text in SmPCs section 4.5 Interaction with other medicinal products and other forms of interaction Text in PIL	None applicable
Interaction with phenytoin		None applicable
Interaction with atazanavir	Text in SmPCs section 4.4 Special warnings and precautions for use and in section 4.5 Interaction with other medicinal products and other forms of interaction Text in PIL	None applicable
Interaction with nelfinavir	Text in SmPCs section 4.3 Contraindications Text in PIL	None applicable
Interaction with digoxin	Text in SmPCs section 4.5 Interaction with other medicinal products and other forms of interaction Text in PIL	None applicable
Interaction with methotrexate		None applicable
Interaction with tacrolimus	A variation for prescribed esomeprazole will be submitted. Text included in the proposed SmPC for esomeprazole for non-prescription use	None applicable
Interaction with clopidogrel	Text in SmPCs section 4.4 Special warnings and precautions for use and in section 4.5 Interaction with other medicinal products and other forms of interaction Text in PIL	None applicable
Important potential risk		
Convulsion/Seizure	None applicable	None applicable
Off-label use	Clear instructions regarding use in the SmPC, PIL and in package text	None applicable
Pneumonia	None applicable	None applicable
Missing information		
Use in pregnant and lactating women	Text in SmPC section 4.6 Pregnancy and lactation Text in PIL	None applicable
Use in patients with renal impairment	Text in SmPC section 4.2 Posology and method of administration	None applicable

The PRAC, having considered the data submitted, was of the opinion that the proposed risk minimisation measures are acceptable. The RMP is acceptable.

The CHMP endorsed this advice without changes.

PSUR submission

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list)) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet 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.*

3. Benefit-risk balance

Benefits

Beneficial effects

The efficacy of esomeprazole for treatment of heartburn and acid regurgitation as prescription only medicine is well established. The pivotal studies, designed to show short term efficacy on reflux symptoms, were performed in patients negative for erosive oesophagitis at endoscopy. In this studies Esomeprazole 20 mg was significantly more effective compared to placebo in patient daily diary symptom scoring regarding the number of patients to reach complete resolution of heartburn, relief of heartburn, days without heartburn and mean heartburn severity scoring. Also the number of patients with investigator-recorded resolution of heartburn and/or regurgitation was significantly better after esomeprazole 20 mg than after placebo.

Data from meta-analyses and studies presented by the applicant from several investigated and uninvestigated GERD populations could show comparable results in terms of showing an effect of esomeprazole on symptom relief in patients with heartburn and/or acid regurgitation and bridging to the uninvestigated patient population who will seek OTC PPI medication is accepted.

Since most patients obtained complete relief of their reflux symptoms already within 2 weeks of use and only numerical improvement in partial responders achieving complete resolution of symptoms following an additional 2 weeks of treatment could be shown, a maximum treatment duration of 2 weeks is considered appropriate for the non-prescription setting.

Uncertainty in the knowledge about the beneficial effects

Esomeprazole as an oral formulation was first approved for marketing in Sweden in 2000, and is currently approved in more than 125 countries for various acid related disorders. The efficacy of esomeprazole for treatment of heartburn and acid regurgitation is well established.

Risks

Unfavourable effects

The safety and tolerability of esomeprazole are well established and supported by post-marketing experience. The majority of adverse reactions identified or suspected in the clinical trials programme for esomeprazole and post-marketing of ADRs are mild and transient in nature, the most frequent being headache and gastrointestinal disorders, i.e. abdominal pain, diarrhoea, flatulence, nausea/vomiting and constipation. No dose-related adverse reactions have been identified.

The SmPC and Package Leaflet provide appropriate information and guidance regarding the management of the safety profile. This includes information on interactions for which patients who are taking certain medications will be advised to consult a pharmacist or doctor before taking esomeprazole.

Uncertainty in the knowledge about the unfavourable effects

Although clinical data on exposure to esomeprazole during pregnancy are limited, esomeprazole taken during the fertile period or during early pregnancy has not been associated with any significant teratogenic risk. The Package Leaflet explicitly states that esomeprazole with non-prescription status is not intended for use during pregnancy and lactation.

The kidney is responsible for the excretion of the metabolites of esomeprazole but not for the elimination of the parent compound therefore no dose adjustment is required in patients with impaired renal function. However, due to limited experience in patients with severe renal insufficiency, such patients should be treated with caution as reflected in the SmPC and outlined in the RMP.

Importance of favourable and unfavourable effects

The clinical study data submitted demonstrate that esomeprazole 20 mg qd is effective in the short-term treatment of reflux symptoms (e.g. heartburn and acid regurgitation) in adults. The rate of improvement from the pivotal trials was highest during the first two weeks of treatment.

There is a long-standing safety experience with prescription esomeprazole and its safety profile is well characterized and similar to omeprazole which is authorized for 2 weeks OTC use in various EU countries.

Information about the duration of the treatment and limitations that require the patient to minimise the risk for an indirect danger and incorrect use are included in the product information.

Benefit-risk balance

Based on the available clinical efficacy and safety data, and taking into consideration the criteria as laid down in the Commission Guideline on Changing the Classification for the Supply of a Medicinal Product for Human Use the benefit-risk balance for the OTC use of esomeprazole in the short term treatment of reflux symptoms in adults is considered to be positive.

Discussion on the benefit-risk assessment

GERD is a frequent disease with heartburn and acid regurgitation as typical reflux symptoms, which for many patients can severely affect quality of life. Tytgat et al[27] estimate that the number of patients who either self-medicate or are untreated is around 80%. Most patients initially self-medicate for GERD symptoms and consult a doctor only if the symptoms persist. Furthermore for consumers without a regular physician, accessing a prescriber may be difficult, time-consuming, and expensive. The individual may elect to tolerate the symptoms, assuming them to be self-limiting, and will bear the potential consequences of resultant morbidity[28]. In this respect self-therapy facilitates the start of the treatment and is in the interest of the community to minimise the burden in starting therapy.

Diagnosis and treatment follow the scientific knowledge and international consensus guidelines that recommend starting diagnosis and treatment of GERD primarily based on patient reported symptoms and initiate early invasive investigations, such as endoscopy, only if alarm features are present (Dent et al 1999[29], NICE guideline 17[30], 2004, DeVault et al 2005[31], Wang and Hunt 2008[32]). This is also reflected in the recommendations in several OTC guidelines, supporting initial self-medication and the contact with a physician only if symptoms persist (Flook et al 2008[33], Tytgat et al 2008, Holtmann et al 2011[34], Haag et al 2009[35]).

Non-prescription medicines for self-treatment of heartburn and/or acid regurgitation include antacids, histamine-2-receptor antagonists (H2-RAs) and proton pump inhibitors (PPIs). Recent clinical guidelines recommend treatment with PPIs as initial therapy for patients with symptoms impacting on their quality of life.

The efficacy of esomeprazole for short-term treatment of reflux symptoms in adults has been demonstrated in a population representative for OTC use. Most patients in the pivotal trials obtained complete relief of their reflux symptoms already within 2 weeks of use and only numerical improvement in partial responders achieving complete resolution of symptoms following an additional 2 weeks of treatment could be shown. Therefore, in the OTC setting the treatment duration can be limited to 2 weeks.

[27] Tytgat GN, McColl K, Tack J, Holtmann G, Hunt RH, Malfertheiner P, et al. New algorithm for the treatment of gastro-oesophageal reflux disease. Aliment. Pharmacol. Ther. 2008 Feb 1;27(3):249-56.
28 Brass EP et al. Improving the Decision-Making Process for Nonprescription Drugs: A Framework for Benefit–Risk Assessment. Clinical Pharmacology & Therapeutics (2011); 90 6, 791–803. doi:10.1038/clpt.2011.231
[29] Dent J, Brun J, Fendrick AM, Fennerty MB, Janssens J, Kahrilas PJ, Lauritsen K, Reynolds JC, Shaw M, Talley NJ on behalf of The Genval Workshop Group. An evidence-based appraisal of reflux disease management - the Genval Workshop Report. Gut.1999; 44 (Suppl. 2):S1-S16.
[30] NICE clinical guideline 17. Dyspepsia: management of dyspepsia in adults in primary care. National Institute for Clinical Excellence, August 2004. (www.nice.org.uk/CG017quickrefguide)
[31] DeVault KR. Castell DO. American College of Gastroenterology Updated guidelines for the diagnosis and treatment of gastroesophageal reflux disease. American Journal of Gastroenterology. 2005;100(1):190-200.
[32] Wang C. Hunt R Medical Management of Gastroesophageal Reflux Disease. Gastroenterol Clin N Am 2008;37:879- 899
[33] Flook N, Jones R, Vakil N. Approaches to gastresopageal reflux disease in primary care. Can Fam Physician 2008;54:701-5.
[34] Holtmann G, Biguard M-A, Malfertheiner P, Pounder R. Guidance on the use of over-the counter proton pump inhibitors for the treatment of GERD. Int J Clin Pharm 2011;33: 493-500.
[35] Haag S, Andrews JM, Katelaris P,Gapasin J, Galmiche JP, Hunt R, Layer P, Malfertheiner P, Holtmann G. Management of Reflux Symptoms with Over-the-Counter Proton Pump Inhibitors: Issues and Proposed Guidelines Digestion 2009;80:226-234

Indirect danger by masking a more serious underlying condition that needs medical attention with symptomatic treatment can derive from the OTC status of a medication. Diseases that in similarity to GERD may include symptoms of heartburn and acid regurgitation are Peptic ulcers, Barrett's oesophagus and malignant oesophageal or gastric disorders. The Package Leaflet includes clear instructions for the patient not to start or continue self-medication if certain specified alarm symptoms are present or occur during treatment and to consult a doctor. Signs and symptoms that should initiate a physician-driven investigation, such as alarm symptoms and lack of treatment effect, are also easily recognizable by patients.

Also the risk and consequences of incorrect use need to be considered for the OTC setting. Based on post marketing data the risk of organ toxicity is considered low, by either accidentally or deliberately exceeding the maximum daily dosage. Symptoms described in connection with oral ingestion of 280 mg have been gastrointestinal symptoms and weakness. Therefore characteristics of esomeprazole do not imply any particular concern as regards the potential for overdose. Additionally the proposed small pack size minimizes the risk for abuse or misuse.

Overall, the CHMP considers that the supply of esomeprazole 20mg Gastro-resistant tablets as non-prescription medicine is appropriate. No additional risk minimisation activities are required beyond those included in the product information.

4. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Nexium Control in the short-term treatment of reflux symptoms (e.g. heartburn and acid regurgitation) in adults is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal products not subject to medical prescription

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list)) provided for under Article 107c(7) of Directive 2001/83/EC and 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.

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Additional risk minimisation measures**

Not applicable

- **Obligation to conduct post-authorisation measures**

Not applicable

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.