

Public Assessment Report

Scientific discussion

October 2009

Nexium, Axiago, Esopral, Refexxin (esomeprazole)

**SE/H/211/04/MR, SE/H/234/04/MR, SE/H/262/04/MR,
SE/H/251/04/MR**

The mutual recognition procedure was finalised at the 16th of April 2008. This module reflects the scientific discussion up to October 2009 for the approval of Nexium, Axiago, Esopral, Refexxin. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

AstraZeneca AB, Sweden has applied for marketing authorisation of a line extension of Nexium (esomeprazole) and the duplicates Axiago, Esopral and Refexxin. Esomeprazole is a proton pump inhibitor, ie, it inhibits specifically the gastric H⁺/K⁺-ATPase enzyme, which is responsible for acid secretion in the parietal cells of the stomach.

The extension concerned new pharmacological formulation, 10 mg gastro resistant granules for oral administration. The application also concerned the indication “short-term treatment of gastroesophageal reflux disease (GERD) and erosive esophagitis (EE) in pediatric patients 1 to 11 years of age, inclusive”. For the GERD indication, Nexium tablets are approved from the age of 12 since July 2006. The application for the Nexium line extension was approved on 23 November 2007 in Sweden.

The product contains the active substance esomeprazole magnesium trihydrate and well-known pharmaceutical excipients. The formulation consists of two drug product intermediates, esomeprazole gastro-resistant granules and excipient granules for oral suspension, which are filled in a single-use aluminium foil sachet. Prior to administration the full contents of one sachet are added to water to form a viscous suspension.

The submitted studies were in accordance with GMP, GLP and GCP procedures.

II. QUALITY ASPECTS

II.1 Introduction

Finished product is presented in the form of Gastro-resistant granules for oral suspension containing 10 mg of esomeprazole magnesium trihydrate.

The excipients used for manufacturing Esomeprazole Sachets comply with Ph Eur (except for the colouring agent iron oxide, yellow, which complies with EC directive 95/45/EC). No excipients used in Esomeprazole Sachets are of human or animal origin.

Esomeprazole pellets and excipient granules are packed into a sachet made out of an aluminium laminate.

II.2 Drug Substance

Esomeprazole magnesium trihydrate is a white to slightly coloured crystalline powder. The substance contains 3 moles of water of solvation. The molecule contains one asymmetrically substituted sulfoxide moiety, which makes the molecule chiral. In esomeprazole the sulphur atom has the S-configuration. Esomeprazole is the S-enantiomer of omeprazole.

The route of synthesis has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The active substance specification includes relevant tests and the limits for impurities/degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies under ICH conditions have been conducted and the data provided are sufficient to confirm the retest period.

II.3 Medicinal Product

Esomeprazole Sachets have been developed as a paediatric dosage form alternative to the approved drug product esomeprazole gastro-resistant tablets, containing the same drug substance, esomeprazole magnesium trihydrate.

The formulation consists of 2 intermediates, esomeprazole pellets and excipient granules, which are filled in an aluminium sachet. Prior to administration the full contents of 1 sachet are added to water to form a viscous suspension. The suspension has been shown to be suitable for administration by spoon, drinking or through enteric tubes.

The manufacture of the esomeprazole pellets consists of several consecutive steps. The manufacturing process for the excipient granules is a conventional wet granulation process.

The manufacturing process for the drug product, Esomeprazole Sachets is a filling process where the esomeprazole pellets and excipient granules are filled into the sachets. The first step is to form a sachet sealed on 3 sides. In the next step a dose of the esomeprazole pellets is metered, weighed and filled into the sachet.

The manufacturing processes have been sufficiently described and critical steps identified. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification.

Specification for the intermediates

The quality of the 2 intermediates is controlled through release testing against specifications assigned to each of the 2 intermediates, refer to.

The specification and control tests applied for the esomeprazole pellets and excipient granules, are considered to be acceptable. The limits for each specification test are achievable by the production process and are supported by stability study data from both the finished product and esomeprazole pellets/ Excipient granules. The methodology for the esomeprazole pellets and excipient granules have been validated to meet the general requirements of the ICH Guideline, Q2B.

Specification for the drug product

The specification and control tests applied for the finished product at time of release and throughout the life of the product, are in compliance with general pharmacopoeial standards (including Ph Eur) and ICH guidelines (Q3B and Q6A). The limits for each specification test are achievable by the production process and are supported by stability study data (except the limit for total impurities and the lower limit for the assay). The methodology for the drug product has been validated to meet the general requirements of the ICH Guideline, Q2B.

Stability of the drug product

The stability data provided support the proposed shelf-life of 36 months.

III. NON-CLINICAL ASPECTS

III.1 Introduction

The following new non-clinical studies have been conducted in support of the new paediatric dosage form: toxicity and toxicokinetic studies in neonatal/juvenile rats and dogs, *in vitro* investigation of cytochrome P450 enzyme activities and the metabolic stability of esomeprazole in liver microsomes from juvenile dogs and plasma protein binding studies. In addition, two pharmacodynamic studies were submitted.

III.2 Pharmacology

The gastric acid antisecretory effect of the S-enantiomer (esomeprazole), the racemate (omeprazole) and the R-enantiomer (R-omeprazole, H 199/19) have been studied *in vivo* in rats and dogs. The results showed that both the racemate omeprazole and its two enantiomers esomeprazole (the S-enantiomer) and the R-enantiomer are potent inhibitors of gastric acid secretion. In conclusion, the enantiomers, esomeprazole and H199/19, and the racemate, omeprazole, demonstrate similar pharmacodynamic effects.

III.3 Pharmacokinetics

In juvenile rats and dogs, the exposure to esomeprazole was generally comparable between males and females. For esomeprazole, there was a slight tendency towards a higher exposure in female than in male rats at the highest dose level on Dose Day 28. The exposure generally increased more than proportionally to the increase in dose in juvenile rats and dogs. A decrease in exposure was seen during the study time periods. For both species, the AUC values at the end of the study were more than 10-fold lower than those observed on Dose Day 1. This decrease in exposure was also significant in dogs that were dosed with esomeprazole only once every 14 days. While the decrease was most prominent in neonatal/juvenile dogs, it was also noted in young adult dogs.

The plasma protein binding levels for esomeprazole were similar (about 90%) in neonatal, juvenile and young adult rats. The degree of binding in dogs of different ages from neonatal to young adults was about 85% to 90%, and did not seem to vary with age. Since the protein binding levels were constant it cannot explain the decreased exposure to esomeprazole. The activity of EROD (reflecting CYP1A1/2) increased 6- to 11-fold and the activity of in CZXH (reflecting CYP2E1) increased slightly in neonatal/juvenile dogs that were treated once daily or once every 14 days between 10 and 65 days post-partum, and in young adult dogs dosed once daily. In neonatal/juvenile dogs dosed twice daily, the activity of EROD and CZXH also increased. Nonetheless, the *in vitro* hepatic intrinsic clearance-rate of esomeprazole was largely unaffected and not related to age or dosing regimen (daily vs. intermittently, or once daily vs. twice daily). The metabolic profiles of esomeprazole *in vitro* were similar regardless of the gender, treatment/vehicle, dosing regimen or age of the pups. Hence, the decrease in exposure seems not to be caused by autoinduction of esomeprazole-metabolising CYP enzymes. Consequently, the decrease in exposure of esomeprazole in neonatal/juvenile or young adult dogs was not related to the dosing regimen or plasma protein binding, or to the hepatic microsomal clearance of esomeprazole.

The reason behind the decreased exposure during the course of the toxicity studies in neonatal/juvenile animals is unknown but may be attributable to age development of physiological functions during the maturation process as suggested by the Applicant.

III.4 Toxicology

In juvenile rats, esomeprazole has been studied in two 1-month repeat dose toxicity studies which also included recovery periods of 1 or 3-months. In addition, omeprazole was included

in one of the studies for comparison. At the start of the dosing the pups were 7 days old. The timing of dosing was considered adequate in relation to the intended use in children. Mortality was induced at the highest tested dose of esomeprazole, 800 µmol/kg. The only treatment-related clinical sign was fur staining in most of the pups given 800 µmol/kg esomeprazole prior to weaning, and also occasionally post-weaning in a few males. A decrease in body weight gain was also seen at 800 µmol/kg esomeprazole. The target organs after esomeprazole administration were the hematopoietic system (hypochromic, microcytic anemia), stomach (increased weight, increases in ECL parameters, increased gastrin levels), kidneys (increased weight, renal pelvis dilation), and liver (increased weight, increases in serum AST, ALP, cholesterol and iron). The findings were all shown to be fully reversible after recovery.

Extensive examinations/observations were performed in order to be able to follow pre- and post-weaning physical and reflexological development, post-weaning behavioural performance and visual function in the growing rats. No treatment-related effects were noted in any group in any of these investigations.

In juvenile dogs, one 3-month study with and without 3 months of recovery was performed. At the start of the dosing the pups were 10 days old. The timing of dosing was considered adequate in relation to the intended use in children. In addition, two complementary studies, 2 and 3-months, were performed with emphases on the toxicokinetics of esomeprazole, cytochrome P450 activities and in vitro metabolism of esomeprazole in various ages of dogs and after different dosing regimens.

Mortality was induced at the highest tested dose of esomeprazole, 160 µmol/kg. In dogs, treatment-related clinical signs (including CNS signs), a dose-related decrease in body weight gain and growth, haematological changes indicating a mild, microcytic, hypochromic anaemia and substantial, treatment-related increases in gastrin secretion following treatment were all fully reversible. The target organs were primarily the stomach (increased weight, increase in the reference (tissue) volume of the stomach, increase in the mucosal height).

In dogs, the development of the puppies was followed by detailed clinical observation and monitoring body weight and growth, and also by a similar examination/observation program including nursing behaviour, physical and reflexological development, pre- and post-weaning behaviour and neurological examination. No treatment-related effects were noted in any group in any of these investigations, in either species.

No ECL-cell hyperplasia or other gastric histopathological changes were noted on light microscopic examination of the stomach specimens in any animal, in either rats or dogs. The only clear gastric changes noted in the juvenile rats consisted of a low-degree increase in ECL-cell total volume and number. These small changes could no longer be detected in the esomeprazole-treated animals following the 1- or 3-month dose-free recovery period, but small increases compared to the controls were evident in the omeprazole-treated rats. All these small changes noted from the morphometry were of too low a magnitude to be detected by light microscopical examination. The lack of gastric histopathological changes in the esomeprazole-treated neonatal/juvenile dogs indicates that young dogs are not more susceptible to proliferative changes in the gastric mucosa following esomeprazole treatment, compared to adult dogs.

In conclusion, no new or unexpected toxicity findings after esomeprazole administration were observed in the juvenile rats and dogs as compared to the adult animals. Esomeprazole and omeprazole induced a similar toxicological profile. The NOAEL after esomeprazole administration were 270 µmol/kg in rats and 80 µmol/kg in dogs. The exposure margins observed in juvenile animals/children were similar to the exposure margins seen in adult

animals/adult GERD patients. The SPC section 5.3 has been updated with the following text “No new or unexpected toxicity findings were observed in juvenile rats and dogs, after administration of esomeprazole for up to 3 months, as compared to the adult animals.” The application is recommended for approval from a preclinical point of view.

III.5 Ecotoxicity/environmental risk assessment

The ERA has been prepared in accordance with the guideline EMEA/CHMP/SWP/4447/00.

IV. CLINICAL ASPECTS

IV.1 Introduction

The clinical development program in 1 to 11 year old pediatric patients is consistent with the principles presented in the ICH Guidance E11 Clinical Investigation of Medicinal Products in the Pediatric Population (July 2000), the more recent EMEA Guideline on the Role of Pharmacokinetics in the Development of Medicinal Products in the Paediatric Population (2006), and the FDA Written Request for pediatric studies Amendment #3 (2005). In addition, the program reflects the standard of care used in the treatment of pediatric GERD as reflected in the NASPGHAN (Rudolph et al 2001) and ESPGHAN guidelines (Vandenplas et al 1993). One clinical study, Study D9614C00097, was included in this submission together with a pharmacokinetic study, Study D9614C00099.

IV.2 Pharmacokinetics

The submitted study reports show that bioequivalence has been shown between the gastroresistant granules and capsules marketed in the US or the gastroresistant tablet marketed within the EU. Bioequivalence has also been shown between opened and intact capsules, as used in one of the clinical studies (study D9614C00099). This has been shown under single-dose fasting conditions. It has not been evaluated how concomitant intake of food will affect the bioavailability of esomeprazole granules. The food-effect is likely to be similar to the effect on the capsules and tablets and is probably not clinically relevant.

The 10 mg dose applied in children weighing ≥ 10 - < 20 kg for appears to give similar exposure of esomeprazole as 20 mg q.d. in adults. The indication down to 10 kg bodyweight reflects the lack of data in children with a lower bodyweight than 10 kg and the lack of appropriate formulation in lighter, ie younger, children. The study results roughly support similar pharmacokinetics at 1mg/kg down to the age of at least 8 months. The data are difficult to interpret due to the low number of subjects, the high inter-individual variability and the dose dependent pharmacokinetics. The 20 mg dose administered to children aged 6-11 years appears not to give as high exposure as 40 mg q.d. in adults. However, this is a between study comparison and the number of children was low (n=6).

IV.3 Pharmacodynamics

Study SH-NEC-0001

This was a study to assess the pharmacokinetics and pharmacodynamics of esomeprazole investigating its efficacy in controlling intragastric pH in infants below the age of 24 months. Fifty patients were randomised to treatment and 45 completed the study (39 of these 45 patients were ≤ 12 months of age). Treatment with esomeprazole 0.25 mg/kg or esomeprazole 1.0 mg/kg once daily increased, compared with baseline, the percentage of time the intragastric pH was > 4 during 24-hour pH-monitoring. The 1.0 mg/kg dose showed a statistically significantly longer time with intragastric pH > 4 as compared with the 0.25 mg/kg dose. Both

esomeprazole doses reduced the percentage of time the intra-esophageal pH was <4, with no difference between the doses.

IV.4 Clinical efficacy

One clinical study, Study D9614C00097, was submitted together with the pharmacokinetic study D9614C00099 (discussed above).

Study D9614C00097

Study D9614C00097 was a multicenter, double-blind, parallel-group study to evaluate the safety and clinical outcome of esomeprazole treatment for 8 weeks in patients with GERD. It was primarily a safety study and included clinical outcomes as a secondary objective.

The study population was children of both sexes, ages 1 to 11 years, who had endoscopically proven GERD. A total of 109 subjects were randomised and 101 completed the study. Fifty-three patients had erosive esophagitis and the remaining part had non-erosive esophagitis. Endoscopically proven GERD was required to objectively define the study population and adequately characterize the disease in this age group. The treatment period in this study was 8 weeks. The dosage used was 5 mg or 10 mg in patients <20 kg and 10 mg or 20 mg in patients ≥ 20 kg. In the lower weight group, 48 patients were between 1 and 5 years and two patients were between 6 and 11 years. In the higher weight group, 55 patients were between 6 and 11 and 5 subjects between 1-5 years of age.

Table 1 (Table 26 in CSR)

Table 26	Summary of outcome for patients who had EE at baseline and had a follow-up endoscopy—ITT population									
	Esomeprazole dose groups									
	5 mg Wt <20 kg (N=11)		10 mg Wt <20 kg (N=11)		10 mg Wt ≥20 kg (N=10)		20 mg Wt ≥20 kg (N=13)		Total (N=45)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Improved	11	(100.0)	9	(81.8)	9	(90.0)	13	(100.0)	42	(93.3)
Improved but not resolved	0		0		0		2	(15.4)	2	(4.4)
Resolved	11	(100.0)	9	(81.8)	9	(90.0)	11	(84.6)	40	(88.9)
No improvement (same as baseline)	0		2	(18.2)	1	(10.0)	0		3	(6.7)
Worsened	0		0		0		0		0	

Wt is weight.

Table is derived from [Table 11.2.7.1](#).

Symptoms were significantly reduced over the treatment period in all treatment arms. In addition, after 8 weeks of esomeprazole treatment, EE was improved or resolved in over 80% of the 45 patients who had EE at baseline and who had an endoscopy at their final visit. These data indicate that esomeprazole is effective in GERD in this population as well as in adults.

IV.5 Clinical safety

The safety profile in 1 to 11 year old children is consistent with the known safety profile of esomeprazole. No new safety signals were identified. The frequency of adverse events seems not to be dose dependent. There were no deaths in Study D9614C00097.

There were 2 serious adverse events (SAEs) that occurred during or after study treatment and 1 SAE that occurred during the screening endoscopy (before the patient was randomized). The SAEs were not considered to be treatment related. There were 4 patients with discontinuations

due to AEs (DAEs). The DAEs of 3 of these patients were not considered to be treatment related. One DAE patient had AEs of asthenia, nausea, and viral infection that were considered as possibly treatment related. These events all resolved within 1 day of onset.

The frequencies of AEs were approximately 20% higher in the ≥ 20 kg treatment groups than in the < 20 kg treatment groups. This may be due to the fact that the mean age of patients in the ≥ 20 kg treatment groups was 8.4 years, while the mean age of patients in the < 20 kg treatment group was 2.3 years. There are some differences between these age populations, such as school attendance, daily environment, developmental abilities, etc, which may have affected the AE reporting. Although a difference was observed in the frequencies of overall AE reporting, the frequencies of treatment-related AEs were similar across the 2 weight strata. There were no clinically important findings or trends in hematology, clinical chemistry, urinalysis, vital signs, or physical examination (including medical history) observed across or within the esomeprazole treatment groups.

In summary, no new safety concerns have been raised in this clinical study programme or in reports from off-label use.

IV.6 Discussion on the clinical aspects

In the main Study D9614C00097, symptoms were significantly reduced over the treatment period in all treatment arms. In addition, after 8 weeks of esomeprazole treatment, EE was improved or resolved in over 80% of the 45 patients who had EE at baseline and who also had an endoscopy at their final visit. It can be concluded that esomeprazole is effective in GERD in this population as well as in adults. It has been shown in the supportive Study SH-NEC-0001 that esomeprazole raises the intra-gastric and intra-esophageal pH in children aged 1-24 months.

The safety profile in 1 to 11 year old children is consistent with the known safety profile of esomeprazole. No new safety signals were identified. The frequency of adverse events seems not to be dose dependent. The frequencies of AEs were approximately 20% higher in the ≥ 20 kg treatment groups than in the < 20 kg treatment groups. This may be due to the difference in age between the 2 treatment groups (mean age of 8.4 years vs. 2.3 years). Overall, no new safety concerns have been raised in this clinical study programme or in reports from off-label use.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Esomeprazole is the enantiomer of the racemate omeprazole which has been marketed for many years and is approved in most EU countries from the age of 1 or 2 for the treatment of GERD. Omeprazole is approved in a couple of EU countries for newborns and has been used off label in other countries for this population. However, the lack of an age-appropriate formulation has precluded the approval of omeprazole for the use in children below the age of 2 by the FDA and in most EU countries. Here, the MAH has developed an age-appropriate formulation for children, gastroresistant granules for oral suspension, which is acknowledged.

In the preclinical studies, no new or unexpected toxicity findings were observed in the juvenile rats and dogs as compared to the adult animals after esomeprazole administration. The exposure margins observed in juvenile animals/children were similar to the exposure margins seen in adult animals/adult GERD patients. From a preclinical point of view, the line extension of Nexium can be recommended for market authorisation.

In the uncontrolled Study D9614C00097, patients were treated for 8 weeks. Esophageal erosions were healed 40 of the 45 patients who had a follow up endoscopy. No new safety problems have evolved and the secondary efficacy endpoints strongly indicate a good treatment effect, which is expected. No major difference between the different doses was seen either concerning efficacy or safety. The dosage used was 5 mg or 10 mg in patients <20 kg and 10 mg or 20 mg in patients ≥ 20 kg. Doses over 1 mg/kg/day have not been studied. Therefore, MAH has agreed to an indication for children ≥ 10 kg (1-11 years of age) and has presented an acceptable SmPC suggestion on this issue.

The relative lack of efficacy data is acceptable considering the fact that GERD pathophysiology is assessed to be equal to the adult population. The ICH Guideline E11 is also referring to “when a medicinal product is to be used in the pediatric population for the same indication(s) as those studied and approved in adults, the disease process is similar in adults and pediatric patients, and the outcome of therapy is likely to be comparable, extrapolation from adult efficacy data may be appropriate”.

It is, however, important to restrict the use to only children with proven GERD. Considering the fact that GERD symptoms may be chronic and sometimes require retreatment or long-term treatment, a long-term safety study is proposed, and it is considered that the population of children below the age of 6 constitute the main concern due to lack of long-term safety data for PPIs in general and for esomeprazole in particular.

A way to collect long-term safety data in this patient group could preferably be made in a separate EU RMP plan for this new age group as proposed in the Guideline on Conduct of Pharmacovigilance for Medicines used in the Pediatric Population (EMA/CHMP/PhVWP/235910/2005) together with the routine PSURs every 3rd year. The initiated epidemiological study of natural history of newly diagnosed GERD in children and adolescents in general practice as outlined by the MAH and including 5000 patients is endorsed.

Overall, the benefit/risk balance for this product is considered positive.

User testing of the package leaflet has been performed.

The benefit/risk ratio is considered positive and “Nexium, 10 mg, gastro-resistant granules for oral suspension” is recommended for approval.

Specific obligations, follow-up measures

The Applicant agreed to provide results from the epidemiological study of natural history of newly diagnosed GERD in children and adolescents in general practice, to collect long term safety data on Nexium for children through a prospective epidemiology study and to update the Risk Management Plan. As of October 2009 an updated RMP is under preparation. The results from the epidemiological study of natural history has been provided. The prospective epidemiology study is progressing according to plan and results will be submitted when available.

The Applicant also received a list of CMC commitments during the MRP. Those have been fulfilled and/or are progressing.

VI. APPROVAL

The Mutual recognition procedure for Nexium (and duplicates), 10 mg, gastro-resistant granules for oral suspension was successfully finalised on 2008-04-16. The approved indication is as follows:

Nexium oral suspension is primarily indicated for treatment of GERD in children 1-11 years old.

Gastroesophageal Reflux Disease (GERD)

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

Nexium oral suspension may also be used by patients having difficulty swallowing dispersed Nexium gastro-resistant tablets. For indications in patients from the age of 12 years reference is made to the Nexium gastro-resistant tablet SmPC.

Public Assessment Report – Update

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
						Y/N (version)