Public Assessment Report for paediatric studies submitted in accordance with Article 46 of Regulation (EC) No1901/2006, as amended

Nexium esomeprazole magnesium

SE/W/0006/pdWS/002

Marketing Authorisation Holder: AstraZeneca AB

Rapporteur:	Sweden
Finalisation procedure (day 90):	2017-03-06

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ADMINISTRATIVE INFORMATION

Invented name of the medicinal product:	Nexium
INN (or common name) of the active substance(s):	esomeprazole magnesium
MAH:	AstraZeneca AB
Currently approved Indication(s)	Nexium oral suspension is primarily indicated for: o Paediatric population ☐ Children 1 – 11 years old: Gastroesophageal Reflux Disease (GERD) ☐ - treatment of endoscopically proven erosive reflux esophagitis ☐ - symptomatic treatment of gastroesophageal reflux disease (GERD) ☐ Children over 4 years of age: In combination with antibiotics in treatment of duodenal ulcer caused by Helicobacter pylori o Adults and adolescents from the age of 12 years: For indications in patients from the age of 12 years reference is made to the Nexium gastro-resistant tablet SmPC. ☐ Nexium tablets are indicated in adults for: o Gastroesophageal Reflux Disease (GERD) ☐ - treatment of erosive reflux esophagitis ☐ - long-term management of patients with healed esophagitis to prevent relapse ☐ - symptomatic treatment of gastroesophageal reflux disease (GERD) o In combination with appropriate antibacterial therapeutic regimens for the eradication of Helicobacter pylori and: ☐ - healing of Helicobacter pylori associated duodenal ulcer and ☐ - prevention of relapse of peptic ulcers in patients with Helicobacter pylori associated ulcers o Patients requiring continued NSAID therapy ☐ - Healing of gastric ulcers associated with NSAID therapy. ☐ - Prevention of gastric and duodenal ulcers

	associated with NSAID therapy, in patients at risk. o Prolonged treatment after i.v. induced prevention of rebleeding of peptic ulcers. o Treatment of Zollinger Ellison Syndrome ☐ Nexium tablets are indicated in adolescents from the age of 12 years for: o Gastroesophageal Reflux Disease (GERD) ☐ - treatment of erosive reflux esophagitis ☐ - long-term management of patients with healed esophagitis to prevent relapse ☐ - symptomatic treatment of gastroesophageal reflux disease (GERD) o In combination with antibiotics in treatment of duodenal ulcer caused by Helicobacter pylori
Pharmaco-therapeutic group (ATC Code):	A02B C05
Pharmaceutical form(s) and strength(s):	Granules for suspension, 10 mg, and capsules, 10 mg and 20 mg

I. EXECUTIVE SUMMARY

The MAH has submitted the final study report from the Japanese paediatric study D961TC00002.

No SmPC and PL changes are proposed.

II. RECOMMENDATION

The results of the paediatric study do not influence the benefit-risk of esomeprazole
The benefit-risk remains unchanged.
No further action is required

III. INTRODUCTION

On 26 August 2016, the MAH submitted a clinical study report concerning a completed paediatric study performed in Japan for esomeprazole magnesium, D961H (Nexium®), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

The MAH stated that the submitted paediatric study does not influence the benefit risk for esomeprazole and that there is no consequential regulatory action.

IV. SCIENTIFIC DISCUSSION

IV.1 Information on the pharmaceutical formulation used in the study(ies)

Granules for suspension, 10 mg, and capsules, 10 mg and 20 mg were used.

IV.2 Clinical aspects

1. Introduction

- The MAH submitted the final report for study D961TC00002:

- An open-label, parallel-group, multi-centre, phase I/III study to assess the safety, pharmacokinetics, pharmacodynamics and efficacy of repeated once-daily oral administration of D961H 10 mg and D961H 20 mg in Japanese paediatric patients 1 to 14 years old (n=50) with gastrointestinal acid related diseases

2. Clinical study D961TC00002

- **Description**

Study D961TC00002 was an open-label, parallel-group, multi-centre, phase I/III study in Japanese paediatric patients with gastrointestinal acid related diseases.

➢ Methods

- Objectives

The primary objective was to assess the safety and tolerability of repeated once-daily oral administration of esomeprazole 10 mg and 20 mg by the assessment of adverse events, laboratory variables and vital signs.

Secondary objectives were:

PK

To assess the pharmacokinetics with the PK parameters [AUC □ (AUC during a interval), AUCt, Cmax, tmax, t1/2, apparent total clearance (CL/F) and apparent volume of distribution during terminal phase (Vz/F)] of esomeprazole after at least 5 days of repeated oral administration of D961H 10 mg and D961H 20 mg.

To assess the pharmacokinetics with the PK parameters (AUC □, AUCt, Cmax, t and t1/2) of the 5-hydroxy and sulphone metabolites of esomeprazole after at least 5 days of repeated oral administration of D961H 10 mg and D961H 20 mg.

PD

To assess percentages of time with intragastric pH > 4 and pH > 3, and median intragastric pH during 12-hours by intragastric pH monitoring at pre-dose and after at least 5 days of repeated oral administration of D961H 10 mg and D961H 20 mg in a subset of patients.

Efficacy

To assess the clinical outcome by the assessment of presence/absence and severity of upper gastrointestinal symptoms (heartburn, epigastric pain, upper abdominal discomfort and regurgitation) compared to baseline after 1, 4 and 8 weeks administration of D961H 10 mg and D961H 20 mg.

- Study design

The study was an open-label, parallel-group, multi-centre study.

- Study population /Sample size

Fifty Japanese paediatric patients aged 1 to 14 years old (mean/median age 9.5 years) who either had a diagnosis of or were suspected to have gastric ulcer, duodenal ulcer, anastomotic ulcer, non-erosive reflux disease, reflux esophagitis or Zollinger-Ellison syndrome were included.

- Treatments

Patients were treated with oral esomeprazole for 8 weeks (median exposure duration 56 days). Of the patients who gave consent, those aged 1 year or more and weighted ≥10 kg and <20 kg were automatically allocated to Group 1 (patients weighing less than 10 kg were excluded). Patients weighing more than 20 kg (inclusive) were randomized to Groups 2 to 5, based on their age, see Table 2.

Table 1. Treatment groups

Group	Patient		Number of target patient	Administration
	Age	Weight		
1	≥ 1year	<20 kg	5 to 10	One sachet of D961H granule for suspension 10 mg was orally administered once daily after breakfast for 8 weeks.
2	≥ 1year to 11 years	≥20 kg	10	One capsule of D961H capsule 10 mg was orally administered once daily after breakfast for 8 weeks.
3	≥1 year to 11 years	≥20 kg	10	One capsule of D961H capsule 20 mg was orally administered once daily after breakfast for 8 weeks.
4	12 to 14 years	≥20 kg	10	One capsule of D961H capsule 10 mg was orally administered once daily after breakfast for 8 weeks.
5	12 to 14 years	≥20 kg	10	One capsule of D961H capsule 20 mg was orally administered once daily after breakfast for 8 weeks.

- Outcomes/endpoints

The objectives and outcome variables are presented in Table 3.

Table 2. Objectives and outcome variables

Objective Priority	Type	Description	Outcome Variable Description
Secondary	Efficacy	To assess the clinical outcome by the assessment of presence/absence and severity of upper gastrointestinal symptoms (heartburn, epigastric pain, upper abdominal discomfort and regurgitation) compared to baseline after 1, 4 and 8 weeks administration of D961H 10 mg and D961H 20 mg.	Presence/absence and intensity of upper gastrointestinal symptoms (heartburn, epigastric pain, upper abdominal discomfort and regurgitation) assessment by the investigators and patient diaries
Exploratory	Efficacy	To assess the clinical outcome of oral administration of D961H 10 mg and D961H 20 mg according to the EGD findings in a subset of patients.	Endoscopic presence/absence of GU, DU, AU or RE
Secondary	PK	To assess the pharmacokinetics with the PK parameters of esomeprazole after at least 5 days of repeated oral administration of D961H 10 mg and D961H 20 mg.	AUC_τ, AUC_t, C_{max}, t_{max}, $t_{1/2}$, CL/F and V_z/F
Secondary	PK	To assess the pharmacokinetics with the PK parameters of the 5-hydroxy and sulphone metabolites of esomeprazole after at least 5 days of repeated oral administration of D961H 10 mg and D961H 20 mg.	AUC_τ, AUC_t, C_{max}, t_{max}, and $t_{1/2}$
Secondary	PK	To investigate the effect of CYP2C19 polymorphism on the PK.	AUC_τ, AUC_t, C_{max}, t_{max}, $t_{1/2}$, CL/F and V_z/F
Secondary	PD	To assess percentages of time with intragastric pH > 4 and pH > 3, and median intragastric pH during 12-hours by intragastric pH monitoring at pre-dose and after at least 5 days of repeated oral administration of D961H 10 mg and D961H 20 mg in a subset of patients.	The percentages of time with intragastric pH >4 and pH>3 (percent of the time) and median intragastric pH during 12 hours at pre-dose and after at least 5 days of repeated oral administration of D961H 10 mg and D961H 20 mg in a subset of patients.
Secondary	PD	To investigate the effect of CYP2C19 polymorphism on the PD.	The percentages of time with intragastric pH >4 and pH>3 (percent of the time) and median intragastric pH during 12 hours at pre-dose and after at least 5 days of repeated oral administration of D961H 10 mg and D961H 20 mg in a subset of patients.
Primary	Safety, Tolerability	To assess the safety and tolerability of repeated once daily oral administration of D961H 10 mg and D961H 20 mg in Japanese paediatric patients aged 1 to 14 years old who either have a diagnosis of or are suspected to have GU, DU, AU, NERD, RE or Zollinger-Ellison syndrome.	Adverse events, clinical laboratory values, vital signs

- Statistical Methods

PK

Descriptive statistics was used.

Efficacy variables:
The cumulative sustained resolution rates and the median time to sustained resolution were calculated by Kaplan-Meier method for each treatment group. For intensity of each gastrointestinal symptom (assessment by the investigators and by the patient diaries), the number and percentage of disappearance or aggravation of each symptom at Week 1, 4 and 8 of D961H administration compared to baseline were summarised for each treatment group. The mean scores for changes in the intensity of each upper gastrointestinal symptom were analysed using a paired t-test for each treatment group.

PD and safety variables:
Descriptive statistics was used.

➢ Results

- Recruitment/ Number analysed

Overall there were 55 patients screened and 50 were enrolled from 20 sites in Japan. Of enrolled patients, 47 patients (94.0%) completed the study and 3 patients (6.0%) discontinued the study due to AEs (one patient in Group 3) or patient decision (each 1 patient in Group 1 and 4).

All 50 registered patients were included in the safety analysis set and FAS. Of these, two patients were excluded from the PK analysis set due to the lack of PK samples and 48 patients were included in the PK analysis set. PD analysis set consisted of five patients who consented to gastric pH monitoring procedure and had available PD data.

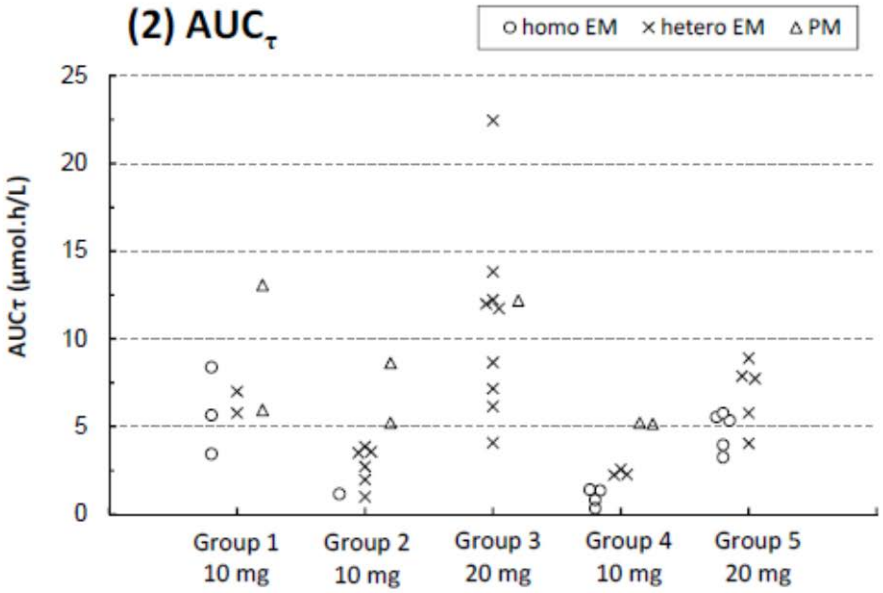
- Baseline data

There was an even distribution of males (48%) and females (52%) and all patients were Japanese (100%).

The most common qualifying disease was Non-erosive reflux disease in Group 1, 3 and 4 [each 6 patients (60%)], Reflux esophagitis in Group 2 [5 patients (50%)] and Gastric ulcer in Group 5 [5 patients (50%)]. In total, 5 patients (10%) had positive H. pylori test; 2 patients (20.0%) in Group 1, each 1 patient (10.0%) in Group 2, 3 and 5.

- PK results

Individual AUC_{τ} values of esomeprazole:



Group 1, Age: >=1 year, Weight: <20 kg, D961H sachet 10 mg
Group 2, Age: >=1 year to 11 years, Weight: >=20 kg, D961H capsule 10 mg
Group 3, Age: >=1 year to 11 years, Weight: >=20 kg, D961H capsule 20 mg
Group 4, Age: 12 to 14 years, Weight: >=20 kg, D961H capsule 10 mg
Group 5, Age: 12 to 14 years, Weight: >=20 kg, D961H capsule 20 mg

Between the same dose groups, the younger groups showed a lower CL/F of esomeprazole than older groups. However, the age-dependency was eliminated when CL/F was normalized by body weight.

The paediatric exposures were considered to be included in the range of adult exposures reported with 10 to 40 mg dose levels.

- PD results

Based on 2 patients in Group 2, 2 patients in Group 3 and 1 patient in Group 5, the percentages of time with intragastric pH > 4 and pH > 3 were 51.2% to 98.3% and 65.4% to 99.0% across groups, respectively. The median of intragastric pH during 12 hours was 4.10 to 7.10.

- Efficacy results

Among patients who had any gastrointenstinal symptoms at baseline, most patients became asymptomatic. The majority of patients who had no symptoms at baseline did not develop symptoms during the course of the trial.

- Safety results

A total of 33 patients (66.0%) reported one or more AE during the study. The most common AE was nasopharyngitis (22%, see Table 4.

Table 3. Adverse events reported by 2 or more patients by SOC and PT (safety analysis set)

System organ class / Preferred term	Number (%) of patients Group 1 (N=10)	Group 2 (N=10)	Group 3 (N=10)	Group 4 (N=10)	Group 5 (N=10)	Total (N=50)
Patients with any AE	8 (80.0)	8 (80.0)	5 (50.0)	5 (50.0)	7 (70.0)	33 (66.0)
Infections and infestations	7 (70.0)	7 (70.0)	2 (20.0)	2 (20.0)	3 (30.0)	21 (42.0)
Nasopharyngitis	1 (10.0)	4 (40.0)	2 (20.0)	1 (10.0)	3 (30.0)	11 (22.0)
Upper respiratory tract infection	1 (10.0)	1 (10.0)	0 (0.0)	1 (10.0)	0 (0.0)	3 (6.0)
Gastroenteritis	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (10.0)	2 (4.0)
Pneumonia	2 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.0)
Gastrointestinal disorders	2 (20.0)	2 (20.0)	3 (30.0)	2 (20.0)	5 (50.0)	14 (28.0)
Diarrhoea	1 (10.0)	0 (0.0)	2 (20.0)	0 (0.0)	1 (10.0)	4 (8.0)
Nausea	0 (0.0)	1 (10.0)	0 (0.0)	0 (0.0)	2 (20.0)	3 (6.0)
Abdominal pain	0 (0.0)	0 (0.0)	1 (10.0)	0 (0.0)	1 (10.0)	2 (4.0)
Vomiting	2 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.0)
Nervous system disorders	0 (0.0)	2 (20.0)	0 (0.0)	0 (0.0)	2 (20.0)	4 (8.0)
Headache	0 (0.0)	2 (20.0)	0 (0.0)	0 (0.0)	2 (20.0)	4 (8.0)
Respiratory, thoracic and mediastinal disorders	2 (20.0)	1 (10.0)	0 (0.0)	1 (10.0)	0 (0.0)	4 (8.0)
Upper respiratory tract inflammation	0 (0.0)	1 (10.0)	0 (0.0)	1 (10.0)	0 (0.0)	2 (4.0)
Immune system disorders	1 (10.0)	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.0)

A patient can have one or more preferred terms reported under a given system organ class.
Group 1, Age: >=1 year, Weight: <20 kg, D961H sachet 10 mg
Group 2, Age: >=1 year to 11 years, Weight: >=20 kg, D961H capsule 10 mg
Group 3, Age: >=1 year to 11 years, Weight: >=20 kg, D961H capsule 20 mg
Group 4, Age: 12 to 14 years, Weight: >=20 kg, D961H capsule 10 mg
Group 5, Age: 12 to 14 years, Weight: >=20 kg, D961H capsule 20 mg
Data from Table 59

Three patients reported an SAE during the study (anaphylactic reaction, asthma and irritable bowel syndrome). None of the SAEs were judged by investigators to be causally related to the study drug.

Of all AEs, 3 events (abdominal pain, diarrhoea and photosensitivity reaction) in 2 patients were judged by investigators to be causally related to the study drug.

Discontinuations of investigational drug due to AEs were 2 events (abdominal pain and diarrhoea) in one patient, which were judged by the investigator to be causally related to the study drug.

No safety concerns were raised in any of the treatment group in this study. Esomeprazole in dose of 10 or 20 mg once daily was well tolerated in Japanese paediatric patients aged 1-14 years.

3. Discussion on clinical aspects

In Japanese paediatric patients with acid-related diseases aged 1 to 14 years, treatment with esomeprazole capsule or sachet 10 mg or 20 mg once daily for 8 weeks, did not raise any safety concerns and were well tolerated.

The upper gastrointestinal symptoms in paediatric patients were reduced after the treatment for 8 weeks. These data including esophagogastroduodenoscopy finding suggested that esomeprazole 10 and 20 mg once daily was effective in Japanese paediatric patients.

The PD variables (time with pH more than 4) demonstrated acid suppression, which seems in general to be in line with corresponding adult data.

The paediatric exposures are considered to be included in the range of adult exposures reported with 10 to 40 mg dose levels.

The MAH's conclusion

The results from the submitted study D961TC00002 in Japanese children are in accordance with the previous adult and paediatric studies. The observed safety profile of oral esomeprazole is consistent with its known safety profile and no new safety concerns were raised.

Esomeprazole is approved for use in children from 1 year of age in EU and the submitted paediatric study does not influence the benefit risk for esomeprazole. Accordingly, it is AstraZeneca's opinion that no amendment to the SmPC is warranted.

V. MEMBER STATES OVERALL CONCLUSION AND RECOMMENDATION

The MAH's conclusion that the results of the paediatric study do not influence the benefit-risk of esomeprazole is supported.

- **Overall conclusion**

The benefit-risk remains unchanged.

- **Recommendation**

No further action required