European Medicines Agency

Doc. Ref. EMEA/688217/2009
P/209/2009

EUROPEAN MEDICINES AGENCY DECISION

of 30 October 2009

on the acceptance of a modification of an agreed Paediatric Investigation Plan for esomeprazole sodium, esomeprazole magnesium trihydrate (Nexium and associated names), (EMEA-000331-PIP01-08-M01) in accordance with Regulation (EC) No 1901/2006 of the European Parliament and of the Council as amended

(ONLY THE ENGLISH TEXT IS AUTHENTIC)

DISCLAIMER: This Decision does not entitle to the rewards and incentives referred to in Title V of Regulation (EC) No 1901/2006, as amended.

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THE EUROPEAN MEDICINES AGENCY,

Having regard to the Treaty establishing the European Community,

Having regard to Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use as amended and amending Regulation (EEC) No. 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004[1],

Having regard to Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency[2],

Having regard to the decision P/107/2009 of the European Medicines Agency on 19 June 2009,

Having regard to the application submitted by AstraZeneca AB on 10 July 2009 under Article 22 of Regulation (EC) No 1901/2006 as amended proposing changes to the agreed Paediatric Investigation Plan,

Having regard to the opinion of the Paediatric Committee of the European Medicines Agency, issued on 18 September 2009, in accordance with Article 22 of Regulation (EC) No 1901/2006 as amended,

Having regard to Article 25 of Regulation (EC) No 1901/2006 as amended,

WHEREAS:

(1) The Paediatric Committee of the European Medicines Agency has given an opinion on the acceptance of changes to an agreed Paediatric Investigation Plan,

(2) It is therefore appropriate to adopt a Decision on the acceptance of changes to an agreed Paediatric Investigation Plan.

[1] OJ L 378, 27.12.2006, p.1
[2] OJ L 136, 30.4.2004, p. 1

HAS ADOPTED THIS DECISION:

Article 1

Changes to the agreed Paediatric Investigation Plan for esomeprazole sodium, esomeprazole magnesium trihydrate, (Nexium and associated names), gastro-resistant tablets, gastro-resistant granules for oral suspension, powder for solution for injection and infusion, intravenous use (esomeprazole sodium), oral use (esomeprazole magnesium trihydrate), the details of which are set out in the Opinion of the Paediatric Committee of the European Medicines Agency annexed hereto, together with its appendices, are hereby accepted.

Article 2

This decision, that supersedes previous decision of the European Medicines Agency P/107/2009, as far as the agreed changes to the Paediatric Investigation Plan for esomeprazole sodium, esomeprazole magnesium trihydrate, (Nexium and associated names) are concerned, is addressed to AstraZeneca AB, Södertälje, S-151 85, Sweden.

Done at London, 30 October 2009

For the European Medicines Agency
Thomas Lönngren
Executive Director

(Signature on file)

European Medicines Agency
Pre-authorisation Evaluation of Medicines for Human Use

Doc. Ref. EMEA/PDCO/499183/2009
EMEA-000331-PIP01-08-M01

OPINION OF THE PAEDIATRIC COMMITTEE ON THE ACCEPTANCE OF A MODIFICATION OF AN AGREED PAEDIATRIC INVESTIGATION PLAN

Scope of the application

Active substance(s):
Esomeprazole sodium
Esomeprazole magnesium trihydrate

(Invented) name:
Nexium and associated names

Condition(s):
1. Gastro-oesophageal reflux disease
2. Gastric ulcer
3. Duodenal ulcer
4. Peptic ulcer, site unspecified
5. Zollinger-Ellison syndrome

Pharmaceutical form(s):
Gastro-resistant tablets
Gastro-resistant granules for oral suspension
Powder for solution for injection and infusion

Route(s) of administration:
Intravenous use (esomeprazole sodium)
Oral use (esomeprazole magnesium trihydrate)

Name/corporate name of the PIP applicant:
AstraZeneca AB

Information about the authorised medicinal product:
See Annex II

Basis for opinion

Pursuant to Article 22 of Regulation (EC) No 1901/2006 as amended, AstraZeneca AB submitted to the EMEA on 10 July 2009 an application for modification of the agreed paediatric investigation plan with a deferral and a waiver as set out in the EMEA decision P/107/2009 of 19 June 2009. The application for modification proposed changes.

The procedure started on 23 July 2009.

A meeting with the Paediatric Committee took place on 17 September 2009.

Scope of the modification

Pharmacovigilance.

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Opinion

1. The Paediatric Committee, having assessed the application in accordance with Article 22 of Regulation (EC) No 1901/2006 as amended, recommends as set out in the appended summary report:

- to agree to the changes proposed by the applicant regarding the measures and the timelines of the paediatric investigation plan.

The Icelandic and the Norwegian Paediatric Committee members agree with the above-mentioned recommendation of the Paediatric Committee.

2. The measures and timelines of the paediatric investigation plan and the subsets of the paediatric population and conditions covered by the waiver are set out in the Annex I.

This opinion is forwarded to the applicant and the Executive Director of the Agency, together with its annexes and appendix.

London, 18 September 2009

On behalf of the Paediatric Committee
Dr Daniel Brasseur, Chairman

(Signature on file)

ANNEX I

THE MEASURES AND TIMELINES OF THE AGREED PAEDIATRIC INVESTIGATION PLAN AND THE SUBSET(S) OF THE PAEDIATRIC POPULATION AND CONDITION(S) COVERED BY THE WAIVER

A. CONDITION(S)

1. Gastro-oesophageal reflux disease
2. Gastric ulcer
3. Duodenal ulcer
4. Peptic ulcer, site unspecified
5. Zollinger-Ellison syndrome

B. WAIVER

- **Condition**

1. Gastro-oesophageal reflux disease

The waiver applies to:
All subsets of the paediatric population from birth to less than one year, for Gastro-resistant tablets and Gastro-resistant granules for oral suspension, on the grounds that the specific medicinal product is likely to be ineffective;
and all subsets of the paediatric population from 1 year to less than 18 years for Gastro-resistant tablets and Gastro-resistant granules for oral suspension on the grounds that the specific medicinal product does not represent a significant therapeutic benefit over existing treatments for paediatric patients.

2. Gastric ulcer
3. Duodenal ulcer
4. Peptic ulcer, site unspecified

- **Indication a) Treatment of ulcer associated to H pylori infection.**

The waiver applies to:
All subsets of the paediatric population from birth to less than 1 year of age for Gastro-resistant tablets and Gastro-resistant granules for oral suspension, on the grounds that the specific medicinal product is likely to be ineffective;
and all subsets of the paediatric population from birth to less than 18 years for IV administration: Powder for solution for injection and infusion, on the grounds that the specific medicinal product does not represent a significant therapeutic benefit over existing treatments for paediatric patients.

- **Indication b) Prevention and healing of gastric and duodenal ulcers associated with NSAID therapy, in patients at risk c) Treatment and Prevention of rebleeding of peptic ulcers.**

The waiver applies to:
All subsets of the paediatric population from birth to less than 18 years of age for oral administration: Gastro-resistant tablets and Gastro-resistant granules for oral suspension and IV administration: powder for solution for injection and infusion, on the grounds that the specific medicinal product does not represent a significant therapeutic benefit as clinical studies are not feasible.

5. Zollinger-Ellison syndrome

The waiver applies to:
All subsets of the paediatric population from birth to less than 18 years of age for oral administration: Gastro-resistant tablets and Gastro-resistant granules for oral suspension and IV administration: Powder for solution for injection and infusion, on the grounds that the specific medicinal product does not represent a significant therapeutic benefit as clinical studies are not feasible.

C. PAEDIATRIC INVESTIGATION PLAN

1) Condition to be investigated

2. **Gastric ulcer**
3. **Duodenal Ulcer**
4. **Peptic Ulcer**

- **Proposed PIP indication**

  Eradication of Helicobater pylori associated with duodenal ulcer and prevention of relapse of peptic ulcers, in combination with appropriate antibacterial therapeutic regimens.

- **Subset(s) of the paediatric population concerned by the paediatric development**

  From 1 year to less than 18 years.

- **Formulation(s)**

  Gastro-resistant granules for oral suspension.
  Gastro-resistant tablets.

Data from pharmacokinetic studies for esomeprazole described below together with omeprazole data for H pylori indication should be submitted as part of the variation application to support extrapolation of data.

- **Studies**

Area	Number of studies	Description
Clinical	3	Open-label, single center, repeated dose PK study conducted in patients aged 1 year to less than 12 years, with GERD or symptoms of GERD. Randomised, open-label, single and repeated dose PK study conducted in adolescents aged 12 to less than 18 years who have GERD or symptoms of GERD. Double blind, randomized, three way cross over comparative study of Esomeprazole and Omeprazole with regard to effect on intragastric pH.

2) Condition to be investigated

1. **Gastro-oesophageal reflux disease**

- **Proposed PIP indication**

  Treatment of endoscopically-proven erosive reflux oesophagitis, treatment of erosive reflux oesophagitis, long-term management of patients with healed oesophagitis to prevent relapse.

- **Subset(s) of the paediatric population concerned by the paediatric development**

  From 1 year to less than 18 years.

- **Formulation(s)**

  Powder for solution for injection and infusion, intravenous use.

- **Studies**

Area	Number of studies	Description
Quality		Not applicable.
Non-clinical		Not applicable
Clinical	**2**	Randomised, Open-Label, Multi-National Study to Evaluate the Pharmacokinetics of Repeated Once-Daily Intravenous Doses of Esomeprazole Sodium in Patients from birth to less than 18 years
		Pharmacoepidemiological cohort study

Measures to address long term follow-up of potential safety issues in relation to paediatric use:	**Yes**
Date of completion of the paediatric investigation plan:	**By November 2009**
Deferral for some or all studies contained in the paediatric investigation plan:	**Yes**

ANNEX II

INFORMATION ABOUT THE AUTHORISED MEDICINAL PRODUCT

EU Number	Invented name Name	Strength	Pharmaceutical Form	Route of administration	Package size
N/A	Nexium	40 mg	Powder for solution for injection and infusion	IV	N/A
N/A	Nexium	10 mg	Gastro-resistant granules for oral suspension	Oral	N/A
N/A	Nexium	20 mg	Gastro-resistant tablets	Oral	N/A
N/A	Nexium	40 mg	Gastro-resistant tablets	Oral	N/A