European Medicines Agency

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EUROPEAN MEDICINES AGENCY DECISION

of 19 June 2009

on the agreement of a Paediatric Investigation Plan and on the granting of a deferral and on the granting of a waiver for esomeprazole sodium, esomeprazole magnesium trihydrate (Nexium and associated names), (EMEA-000331-PIP01-08) 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 application submitted by AstraZeneca AB on 26 June 2008 under Article 16(1) of Regulation (EC) No 1901/2006 as amended also requesting a waiver under Article 13 of said Regulation and a deferral under Article 20 of said Regulation,

Having regard to the Opinion of the Paediatric Committee of the European Medicines Agency, issued on 30 April 2009, in accordance with Article 18 of Regulation (EC) No 1901/2006 as amended, and Article 13 of said Regulation and Article 21 of said Regulation**,**

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 agreement of a Paediatric Investigation Plan and on the granting of a deferral and on the granting of a waiver.

(2) It is therefore appropriate to adopt a Decision granting a Paediatric Investigation Plan.

(3) It is therefore appropriate to adopt a Decision granting a deferral.

(4) It is therefore appropriate to adopt a Decision granting a waiver.

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

HAS ADOPTED THIS DECISION:

Article 1

A Paediatric Investigation Plan for esomeprazole sodium, esomeprazole magnesium trihydrate, 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, is hereby agreed.

Article 2

A deferral for esomeprazole sodium, esomeprazole magnesium trihydrate, 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, is hereby granted.

Article 3

A waiver for esomeprazole sodium, esomeprazole magnesium trihydrate, 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, is hereby granted.

Article 4

This decision is addressed to AstraZeneca AB, Södertälje, S-151 85, Sweden.

Done at London, 19 June 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/192854/2009
EMEA-000331-PIP01-08

OPINION OF THE PAEDIATRIC COMMITTEE ON THE AGREEMENT OF A PAEDIATRIC INVESTIGATION PLAN AND A DEFERRAL AND A WAIVER

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 16(1) of Regulation (EC) No 1901/2006 as amended, AstraZeneca AB submitted for agreement to the EMEA on 26 June 2008 an application for a paediatric investigation plan for the above mentioned medicinal product and a deferral under Article 20 of said Regulation and a waiver under Article 13 of said Regulation.

The procedure started on 31 July 2008.

Supplementary information was provided by the applicant on 18 February 2009.

A meeting with the Paediatric Committee took place on 29 of April 2009.

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Opinion

1. The Paediatric Committee, having assessed the proposed paediatric investigation plan in accordance with Article 17 of Regulation (EC) No 1901/2006 as amended, recommends as set out in the appended summary report:

- to agree the paediatric investigation plan in accordance with Article 18 of said Regulation,

- to grant a deferral in accordance with Article 21 of said Regulation,

- to grant a waiver for one or more subsets of the paediatric population in accordance with Article 13 of said Regulation and concluded in accordance with Article 11(1)(a) of said regulation, on the grounds that the specific medicinal product is likely to be ineffective or unsafe in part or all of the paediatric population and Article 11(1)(c) of said Regulation, on the grounds that the specific medicinal product does not represent a significant therapeutic benefit over existing treatments for paediatric patients,

- to grant a product-specific waiver for some subsets of the paediatric population on its own motion in accordance with Article 12 of said Regulation and concluded in accordance with Article 11(1)(a) of said regulation, on the grounds that the specific medicinal product is likely to be ineffective or unsafe in part or all of the paediatric population and Article 11(1)(c) of said Regulation, on the grounds that the specific medicinal product does not represent a significant therapeutic benefit over existing treatments for paediatric patients.

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

2. 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 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, 30 April 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

- **Conditions**

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	**1**	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

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
SE/H/0211/003	Nexium	40 mg	Powder for solution for injection and infusion	IV	1 vial
SE/H/0211/004	Nexium	10 mg	Gastro-resistant granules for oral suspension	Oral	28 sachets carton
SE/H/0211/001	Nexium	20 mg	Gastro-resistant tablets	Oral	28 tablet
SE/H/0211/002	Nexium	40 mg	Gastro-resistant tablets	Oral	28 tablet