

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-101

CROSS DISCIPLINE TEAM LEADER REVIEW

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research

DIVISION OF GASTROENTEROLOGY DRUGS

DATE: February 8, 2008

FROM: Hugo E. Gallo-Torres, MD, PhD, PNS
Division of Gastroenterology Products [HFD-180]
DGDP/ODE III

TO: DIVISION FILES, NDA 22-101

SUBJECT: GI Team Leader Recommendations for Regulatory Action
[Complete Response to AE letter on December 27, 2007]
PDUFA Goal date: February 27, 2007

APPLICANT: AstraZeneca LP
Wilmington DE 19803-8355
Regulatory Contact: George Kummeth
Global Director Regulatory Affairs

DRUG: NEXIUM (esomeprazole magnesium) For Delayed-Release Oral Suspension

INDICATION: Short-term treatment of GERD and healing of erosive esophagitis in patients 1 to 11 years old inclusive

**Documents Considered
in this review:**

1. July 27 Approvable Letter
2. December 27, 2007 Complete response to July 27 AE Letter
3. November 16, 2007 4-Month Safety Update
4. Annotated Labeling

BACKGROUND/INTRODUCTION

On September 27, 2006, AstraZeneca submitted NDA 22-101 for NEXIUM® (esomeprazole magnesium) For Delayed-Release Oral Suspension as an alternative esomeprazole formulation. NDA 22-101 provides for new delayed-release granules for an oral suspension formulation of NEXIUM. Also submitted with NDA 22-101 were revisions to the pediatric section of the package insert to add information regarding the use of NEXIUM in patients 1 to 11 years old inclusive, for the short-term treatment of GERD and healing of erosive esophagitis.

The Agency sent an Approvable Letter on 27 July 2007. The AE was given due to pending issues surrounding cardiac safety. The Agency also sent a fax, dated December 18, 2007, regarding the legal advice from the Chief Counsel's Office about the initial approval date.

The cardiac safety issues have been resolved.

The current Class 1 resubmission¹ includes:

1) a 4-month safety update report for NDA 22-101.

and

2) a revised Package Insert and labels/cartons²

II. PURPOSE OF THE MTL SECONDARY REVIEW

The purpose of the MTL review is to assess the safety information in the 4-MSU, to assess the acceptability of the proposed labeling revisions and all together, to evaluate the adequacy of the information submitted in the sponsor's complete response to our July 27 Approvable Letter, so as to formulate a recommendation for regulatory action.

III. REVIEW OF THE 4-MONTH SAFETY UPDATE

It is worth noting that a previous 4-MSU was submitted 24 January 2007 for the period covering 1 March 2006 to 1 December 2006. No new safety concerns were discovered.

The current 4-MSU summarizes safety information for the delayed-release oral suspension NEXIUM formulation³ received by AstraZeneca covering 02 December 2006 to 31 October 2007.

1. Adverse events from clinical studies

The sponsor notes that between the period of 02 December 2006 and 31 October 2007 there have been no studies conducted nor initiated in children 1 through 11 years old with this new formulation of NEXIUM Delayed Release Granules.

- All relevant safety, exposure, and adverse event data were presented in the Clinical Study Report in Module 5 of NDA 22-101

¹ This electronic submission has been scanned using Symantec AntiVirus, Version 10.1.5.5001 (Corporate Edition), with a virus definition file dated 12/18/2007 rev 7. No viruses were detected, and AstraZeneca certifies that the submission is virus-free.

² The package insert is being submitted in WORD format and SPL for ease of review. The labels and cartons are provided as PDF documents.

³ This formulation has been approved in Canada but has not been launched

2. Literature search

The sponsor conducted a search of the scientific/medical literature from 02 December 2006 Through 31 October 2007 to identify any relevant safety information with the use of any oral formulation of esomeprazole in pediatric patients.

- The search was performed utilizing Ovid and Planet (AstraZeneca's in-house database for indexing biomedical literature).
- The search did not provide any new or relevant safety information in the 1-11 year-old pediatric patient population receiving esomeprazole

3. Post-marketing safety data

According to the information provided by the sponsor, during the 02 December 2006 and 31 October 2007 period, there were **16 spontaneous post-marketing AE reports involving oral esomeprazole in pediatric patients** ≤ 11 years of age.

- One of these 16 reports involved the suspension formulation of esomeprazole.
- 6 of these reports were serious, but either contained limited information for causality assessment or a causal relationship to esomeprazole was considered unlikely based upon time to onset and exposure duration.
- The remaining 10 reports either contained limited information for causality assessment or had other more likely explanations for the events.
- 6 of the 16 reports involved young children who accidentally ingested NEXIUM that was intended for someone else. Only one of these reports described an AE (**2007UW22251-vomiting**) other than the accidental ingestion. A search of the scientific/medical literature for this reporting period did not identify any new or relevant safety information in this age group following exposure to esomeprazole.

Additional details related to this information are addressed below. As already noted, during the mentioned period covering 02 December 2006 to 31 October 2007, a total of 16 spontaneous adverse event reports involving the use of **any oral formulation of esomeprazole in pediatric patients** ≤ 11 years of age were identified from the AstraZeneca Global Drug Safety Database.

- One report (2007UW23353 [pain, drug ineffective] involved the use of esomeprazole suspension [40 mg/daily, oral for ca. 3 months]⁴.
- 13 of the 16 reports involved patients 1 to 11 years of age.
- In one of these 16 reports, the age of the child was not specified.

⁴In this report, there is limited information available for assessment. A question arose regarding the patient receiving complete dose of medication.

- 2 of the 16 reports involved neonates who were exposed to esomeprazole in utero.
- 6 of the 16 reports involved young children who accidentally ingested esomeprazole intended for someone else.

-- Esomeprazole doses ranged from 20 mg daily to a single 80 to 120 mg accidental overdose.

-- Duration of therapy ranged from 1 day to 19 months.

-- Time to event onset, from initiation of therapy or exposure, ranged from 1 day to 2 years. -- The most commonly reported indication for use was GERD. The information that follows was excerpted from sponsor's

Table 1⁵ Summary of spontaneous pediatric (≤11 years of age) adverse event reports received and entered into the AstraZeneca Global Safety Database from 02 December 2006 to 31 October 2007

- 6 of the 16 reports described 6 serious AEs, as follows:

Report Id #	Adverse Event ^a
2007AC01645 Neonate/Male	asthma
2007CG00800 10 y old/Male	constipation
2007SE04445 3 y old/Male	accidental overdose
2007UW18503 2 y old/UNK sex	accidental exposure
2007UW22019 Neonate/Male	syndactyly ^b
2007UW23196) 11 y old/Female	hallucination ^c

^aPreferred Term

^bThe baby was exposed to esomeprazole in utero for six weeks from approximately 22 to 24 weeks gestation until birth. He was born with syndactyly of the left hand and fourth and fifth digits. The mother had two previous normal deliveries.

Company comment: The differentiation of the fingers into individual appendages usually occurs during the sixth and eighth weeks of embryologic development. In this report, the baby was exposed to esomeprazole at approximately 22 to 24 weeks gestation until birth, thus it is unlikely that esomeprazole exposure in utero led to syndactyly. The reviewer agrees with the sponsor's assessment.

^c Patient experienced hallucinations, which were an increasing distraction at school and at home. Concomitant medications included montelukast, fluticasone propionate, cetirizine and tolterodine.

Company comment: Time relationship to esomeprazole therapy is unknown as is the child's medical history. Hallucination is a labeled event in the Nexium USPI. In the current report, there is limited information available for assessment. Additionally, hallucinations have also been reported with montelukast, cetirizine and tolterodine. Adverse event was considered serious due to unspecified disability.

⁵ This Table consists of four columns: First Column [Report Id#, Country/Source, Age/Gender]
Second Column [Dose/Schedule, Route/Duration, Indication]
Third Column [AEs (Preferred Term), Time to onset, Outcome]
Fourth Column [Abbreviated narrative, Company comment]

This Table also included Clinical Summary Narratives and Company Comments.

Summary

Overall, a review of these 16 adverse event reports in pediatric patients ≤11 years of age did not identify any new safety concerns.

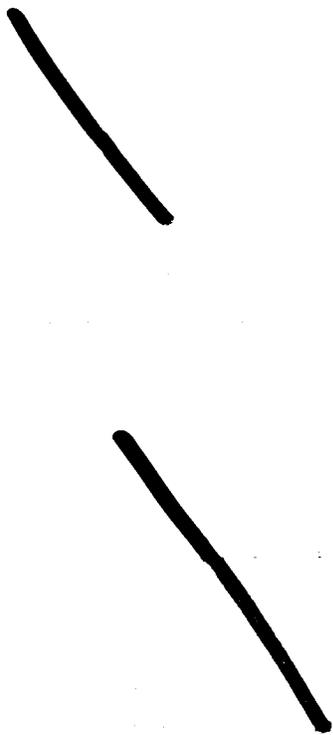
Conclusion on 4-Month Safety Update

The reviewer agrees with the sponsor that, based on the information presented and reviewed for this reporting period, no new safety concerns were identified for oral esomeprazole use in children 1 to 11 years of age, inclusive.

IV. PERTINENT LABELING REVISIONS

The sponsor's proposed labeling revisions have been incorporated into the **ANNOTATED LABELING VERSION**. The latter is included as an Attachment to the current review. Information added was discussed among the multiple disciplines internally and reflect the input of the pertinent disciplines at the time the AE letter was sent to the sponsor.

For completeness of review purposes, the labeling revisions related to the current submission [use of NEXIUM in patients 1 to 11 years old inclusive, for the short-term treatment of GERD and healing of erosive esophagitis] are excerpted below, as included within the Section/Subsection of the labeling⁶.



b(4)

⁶ Sections/Subsections of the Annotated Labeling that are not added or modified or do not contain information related to the current application are not listed/addressed in the current MTL's review.

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Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

concomitant control.

V. MTL's RECOMMENDATIONS FOR REGULATORY ACTION

Approval of NDA 22-101 is recommended.

NDA 22-101, submitted September 27, 2006, requested revisions to the pediatric Section/Subsections of the package insert. The aim of these revisions is to add information regarding the use of NEXIUM® in patients 1 to 11 years old, inclusive, for the short-term treatment of GERD and healing of erosive esophagitis.

The [initial] submission of September 27, 2006 was assessed as **approvable**⁷ to be modified to **approval** once issues regarding serious cardiac events observed in long-term studies with omeprazole and esomeprazole [SOPRAN and LOTUS studies in adult patients with GERD] have been settled. This initial recommendation for regulatory action was based on a) bioavailability Study 9614C00099; safety information from Study D9614C00097; and c) the similarity of pathogenesis of GERD between adult and pediatric patients 1 to 11 years old.

The current recommendation for **approval** of NDA 22-101 is further based on the sponsor's Complete Response dated December 27, 2007 to the Agency's approvable letter of July 27, 2007.

As requested by the Agency, the Complete Response included a 4-month safety update with literature publications and Post-marketing Safety Information in general and data on the use of the drug in pediatric populations in particular.

No new safety concerns have been identified.

The current evaluation also includes a review of the Labeling revisions related to the requested new use.

In short, there are no unsettled efficacy or safety issues.

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MORreview by Dr. Wen-Yi Gao, signed off into DFS July 19, 2007; the MTL agreed with this recommendation [Signed off into DFS July 23, 2007]; July 27, 2007 AE letter to sponsor by Dr. Joyce Korvick.

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Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

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/s/

Hugo Gallo Torres
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MEDICAL OFFICER