

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-101**

**SUMMARY REVIEW**

**MEMORANDUM**

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

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**DATE:** 2/27/08

**FROM:** Joyce A Korvick, MD, MPH  
DGP/ODE III

**SUBJECT:** Deputy Division Director Approval Recommendation  
NDA 22-101

**APPLICANT:** AstraZeneca LLP

**DRUG:** Nexium® (esomeprazole magnesium)  
For Delayed-Release Oral Suspension, 10 mg

**DIVISION RECOMMENDATION:**

The medical review team has completed the review including the review of the potential cardiovascular risk in adults, and recommended approval of this NDA. I am in agreement with this recommendation.

**Regulatory History:**

This is a two month resubmission of NDA 22-101 based on the approvable letter sent to the sponsor 7/27/08. Outstanding issues at that time included finalization of package insert and package labeling. The following is excerpted from my memo dated 7/27/07 (see Appendix A for previous review details).

“Since the Nexium label is a unified label including adult indications and higher dosing, it will be important to finalize the review of the final report of cardiac safety data submitted July 25, 2007. It would be difficult at this time to recommend labeling in pediatric patients 1 to 11 years of age given this potential serious risk. If the review of these studies determines that the risk is low or non-existent, minor labeling negotiations will need to proceed due to the fact that labeling negotiations at this time are fairly mature but not complete.”

The final review of cardiac safety was completed and a public announcement was made regarding the findings.

Here is a summary of the activity regarding cardiac safety:

“On December 10, 2007, FDA announced the completion of its review of the submitted adult safety data for the drugs Prilosec (omeprazole) and Nexium (esomeprazole). FDA stated that we continue to believe that long-term use of omeprazole or esomeprazole is not likely to be associated with an increased risk of heart problems and recommends that

healthcare providers continue to prescribe and patients continue to use these products in the manner described in the labeling for the two products. Previously, on May 29, 2007, AstraZeneca, the manufacturer of Prilosec (omeprazole) and Nexium (esomeprazole), sent FDA and other regulatory authorities world-wide their preliminary review of new data from two small long-term clinical studies in patients with severe gastroesophageal reflux disease (GERD). The results from the study of Prilosec and analyses from an ongoing study of Nexium raised concerns that long-term use of Prilosec or Nexium may have increased the risk of heart attacks, heart failure, and heart-related sudden death in those patients taking either one of the drugs compared to patients who received surgery. On August 9, 2007 FDA released an "Early Communication of an Ongoing Safety Review" of both Nexium and Prilosec. The agency's initial review determined that there was no increased risk of heart problems associated with long-term use of these two products.

**Use of Nexium for Treatment of GERD in pediatric patients 1 to 11 years of age.**

The use of Nexium in pediatric patients 1 to 11 years of age for short-term treatment of GERD is supported by extrapolation of previous study results in adults to the pediatric population, and safety and pharmacokinetic studies performed in pediatric patients. In one study, 109 pediatric patients with a medically confirmed diagnosis of GERD ages 1 to 11, were treated with Nexium once-a-day for up to 8 weeks to evaluate its safety and tolerability. Most of these patients demonstrated healing of their esophageal erosions after 8 weeks of treatment. Data from the pharmacokinetic studies support dosing with 10 milligrams (mg) or 20 mg daily in this age group. This dose is lower than the 20 mg or 40 mg recommended for pediatric patients 12 to 17 years of age. (For further details refer to the Medical Officer Review).

It should be noted that while this NDA specifically refers to the oral suspension, it is part of a unified label which included 20 and 40 mg capsules. If a pediatric patient in this age group could safely swallow this formulation the 20 mg capsule would be effective since they are bioequivalent based upon data supporting a previous approval of this oral suspension.

The safety and effectiveness of Nexium for the treatment of symptomatic GERD in patients less than one year of age or for other pediatric uses have not been established.

During this submission the physician labeling was finalized and agreements were made regarding packaging.

Please refer to approval letter (2/27/08) including the attached approved physician labeling for specific details regarding the label.

(Please note that additional details are provided in my previous review attached in Appendix A.)

APPENDIX A

MEMORANDUM

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

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**DATE:** 7/27/07

**FROM:** Joyce A Korvick, MD, MPH  
DGP/ODE III

**SUBJECT:** Deputy Division Director Approvable Comments  
NDA 22-101  
(Resubmission)

**APPLICANT:** AstraZeneca LLP

**DRUG:** Nexium® (esomeprazole magnesium)  
For Delayed-Release Oral Suspension, 10 mg

**DIVISION RECOMMENDATION:**

The medical review team has recommended approvable pending resolution of the serious cardiac safety issues that have arisen external to this NDA. I am in agreement with this recommendation

Outstanding issues regarding this NDA include finalization of package insert and package labeling. Since the Nexium label is a unified label including adult indications and higher dosing, it will be important to finalize the review of the final report of cardiac safety data submitted July 25, 2007. It would be difficult at this time to recommend labeling in pediatric patients 1 to 11 years of age given this potential serious risk. If the review of these studies determines that the risk is low or non-existent, minor labeling negotiations will need to proceed due to the fact that labeling negotiations at this time are fairly mature but not complete. This could be a two-month resubmission.

**I. Regulatory History:**

Nexium (Delayed Release Capsules) is currently approved for the following indications:

- Reflux Disease (GERD): Healing of Erosive Esophagitis, Maintenance of Healing of Erosive Esophagitis, Symptomatic Gastroesophageal Reflux Disease
- Risk Reduction of NSAID – Associated Gastric Ulcer

- H. pylori Eradication to Reduce the Risk of Duodenal Ulcer Recurrence
- Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome.

The current application is for the treatment of GERD in the pediatric population aged 1 to 11 years. This claim is based upon the similarity in disease process between adults and children, a phase III safety/exposure study and 3 pharmacokinetic studies. This results of these studies provide for dosing recommendations for this age group on a “by weight basis”. This 10 mg formulation was produced to address the needs in this younger age group.

The proposed dosing is as follows:

Short-term treatment of symptomatic GERD: 10 mg; Once daily up to 8 weeks.

Healing of Erosive Esophagitis:

weight < 20 kg: 10 mg; once daily up to 8 weeks.

weight ≥ 20 kg: 10 or 20 mg; once daily up to 8 weeks.

#### **DISCIPLINE REVIEW SUMMARY AND COMMENTARY:**

##### **A. OPDRA/DDMAC/DMETS/SEALD:**

There were no major issues raised by these consults. The current label is being changed into the PLR format and therefore extensive comments were received from the SEALD Team and incorporated into the labeling.

##### **B. Chemistry and Manufacturing:**

The reviewers recommended approval. The 10 mg formulation is acceptable.

##### **C. Pre-Clinical Phamacology/Toxicology:**

This was found to be acceptable and appropriate by the reviewers..

##### **D. Biopharmaceutics:**

The proposed dosing regimens of 10 mg QD (for all patients in the specified age range) and 20 mg QD (for healing of erosive esophagitis in patients weighing ≥ 20 kg) are reasonable based on the PK findings from Study D9614C00099. The appropriateness of the above proposed dosing regimens based on the dose-response trial is being evaluated by the Medical Officer of HFD-180.

##### **E. Clinical/Statistical:**

As described above, the clinical data presented in approximately 150 pediatric patients 1 to 11 years of age support the safety and effectiveness in this population. However, the current report of an imbalance in serious cardiac events from two controlled clinical trials in adults needs to be resolved before labeling can be extended to this young and vulnerable age group. If it is found that these studies do not show an imbalance, or they

are flawed in some serious way that the interpretation does not lead to a new cardiac signal, it would be appropriate to finalize this labeling and approve the drug in this age group.

**F. Pediatric Use:**

Currently there is an ongoing WR for GERD in pediatric patients. The other indications have been waived due to the small number of pediatric patients in those diseases.

**II. Labeling Recommendations:**

Recommendations were sent to the sponsor dated July 26, 2007. These are near final; one area to resolve is the representation of the clinical study design.

**III. Deficiencies:**

1. Finalization of the package insert and carton labeling.
2. Resolution of reports of serious cardiovascular adverse events in adults due to an imbalance in two adult clinical trials (SOPRAN, LOTUS). Review of final safety report is currently ongoing in the division. Additional labeling may be needed.

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Joyce Korvick  
2/27/2008 02:24:05 PM  
MEDICAL OFFICER  
dep dir approval memo