

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER: 21-153/ 21-154**

**MICROBIOLOGY REVIEW(S)**

**MICROBIOLOGY REVIEW**  
**DIVISION OF SPECIAL PATHOGENS AND IMMUNOLOGIC DRUG PRODUCTS**  
**(HFD-590)**

**NDA #:** #21-154

**REVIEWER:** Peter A. Dionne  
**CORRESPONDENCE DATE:** 28-FEB-00  
**CDER DATE:** 28-FEB-00  
**REVIEW ASSIGN DATE:** 01-MAR-00  
**REVIEW COMPLETE DATE:** 04-MAY-00

**SPONSOR:** AstraZeneca LP  
725 Chesterbrook Blvd  
Wayne, PA 19087-5677

**CONTACT PERSON:** Kathryn Kross  
Director Regulatory Affairs  
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**SUBMISSION REVIEWED:** Original NDA for *H. pylori* eradication

**DRUG CATEGORY:** Proton pump inhibitor

**INDICATIONS:** This application: *Helicobacter pylori* Eradication in Patients with Duodenal Ulcer Disease

**DOSAGE FORM:** Delayed-Release Capsules—20 mg and 40 mg/capsule

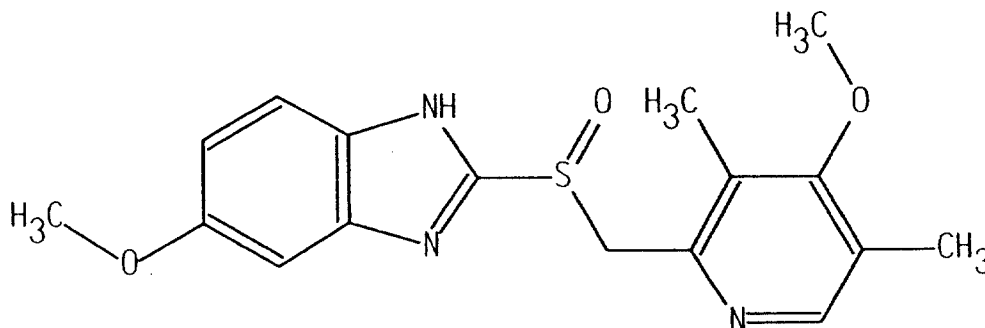
**DRUG PRODUCT NAME**

**PROPRIETARY:** NEXIUM™ Delayed-Release Capsules

**NONPROPRIETARY/USAN:** Esomeprazole magnesium

**CHEMICAL NAME:** bis (5-methoxy-2-[(S)-[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole-1-yl) magnesium trihydrate


**STRUCTURAL FORMULA:**



**Molecular Formula:** C<sub>34</sub>H<sub>36</sub>N<sub>6</sub>O<sub>6</sub>S<sub>2</sub>Mg•3H<sub>2</sub>O

**Molecular Weight:** 767.2

**NDA #21-154**  
**AstraZeneca LP**  
**Nexium™ (esomeprazole magnesium) for *H. pylori***

**SUPPORTING DOCUMENTS:** IND  -H 199/18 for eradication of *H. pylori* in *H. pylori* infected patients.

**REMARKS/COMMENTS:**

This is an original New Drug Application for H 199/18 (esomeprazole magnesium) 20 mg and 40 mg Delayed-Release Capsules in combination with antibiotics (clarithromycin and amoxicillin) for the eradication of *Helicobacter pylori* in patients with duodenal ulcer disease or a history of duodenal ulcer disease. This drug is the S-enantiomer of omeprazole, which is approved for this indication.

**CONCLUSIONS:**

1. About 15% of the *Helicobacter pylori* isolates in the clinical trials were resistant (MIC  $\geq 1$   $\mu\text{g/mL}$ ) to clarithromycin pre-treatment. The distribution of pre-treatment clarithromycin MIC values was bimodal. One population had MIC values of  $\leq 0.125$   $\mu\text{g/mL}$  and the other population had MIC values of  $\geq 8$   $\mu\text{g/mL}$ . A few isolates had MIC values between these two populations. Patients with isolates that had high clarithromycin MICs did not have their *Helicobacter pylori* eradicated as readily as those with isolates with low clarithromycin MIC values. All but one *H. pylori* isolate in the clinical trials was susceptible (MIC  $\leq 0.25$   $\mu\text{g/mL}$ ) to amoxicillin. Eradication rates did not seem to be related to amoxicillin MIC values.
2. Treatment with triple therapy [HAC] (esomeprazole+amoxicillin+clarithromycin) eradicated *H. pylori* better (89% of the clarithromycin-susceptible isolates and 83% of the amoxicillin-susceptible isolates were eradicated) than dual treatment [HC] with esomeprazole+clarithromycin (61% of the clarithromycin-susceptible isolates and 54% of the amoxicillin-susceptible isolates were eradicated). Treatment with esomeprazole alone did not eradicate *H. pylori*.
3. Treatment with triple therapy did not lead to a significant development of isolates with clarithromycin resistance. Of 197 patients in the HAC group with susceptible baseline isolates only two patients had isolates that developed resistance to clarithromycin. Treatment did not lead to amoxicillin-resistance.
4. Treatment with esomeprazole plus clarithromycin alone led to a significant number of isolates that developed resistance to clarithromycin. Of 153 patients in the HC group with susceptible baseline isolates 23 patients had isolates that developed resistance to clarithromycin. Treatment did not lead to amoxicillin-resistance.

**NDA #21-154**  
**AstraZeneca LP**  
**Nexium™ (esomeprazole magnesium) for *H. pylori***

**RECOMMENDATIONS:**

The application is approvable from the microbiological viewpoint under section 505(b) of the Act. Minor changes should be made to the microbiology subsection of the label.

[ ]

**APPEARS THIS WAY  
ON ORIGINAL**