Emerging Drug List
Esomeprazole Magnesium

Canadian Coordinating Office for Health Technology Assessment

No. 12 July 2001

Generic (Trade Name)**:** Esomeprazole magnesium (Nexium®)

Manufacturer: AstraZeneca Canada Inc. (Mississauga, ON)

Indication:
- for acute and maintenance treatment of gastroesophageal reflux disease (GERD)
- for maintenance treatment of erosive esophagitis, and
- in combination with amoxicillin and clarithromycin, for eradication of *Helicobacter (H.) pylori* in the treatment of duodenal ulcer

Current Regulatory Status (in Canada and abroad): Esomeprazole is currently awaiting approval with the Therapeutic Products Directorate in Canada. It is expected to be launched in 2001. Esomeprazole has been available in the U.S. since March 31, 2001.

Description: Esomeprazole is a new proton pump inhibitor (PPI) that is the S-isomer of omeprazole. The recommended dosage is 20 to 40 mg orally, once daily (in a delayed-release formulation) for four to eight weeks for healing erosive esophagitis, with the possibility of an additional four to eight weeks if necessary. The dose for maintenance healing of erosive esophagitis is 20 mg per day for six months and for symptomatic GERD, it is four weeks of 20 mg per day with an additional four weeks, if needed. For eradication of *H. pylori*, 20 mg esomeprazole twice daily in combination with amoxicillin 1000 mg twice daily and clarithromycin 500 mg twice daily, all for 7 days is recommended. In the U.S., esomeprazole is available in 20 and 40 mg delayed-release capsules.

Current Existing Treatments: Gastroesophageal reflux disease can be treated with antacids, histamine-2 (H_2) receptor blockers (cimetidine, ranitidine, famotidine and nizatadine) and PPIs (omeprazole (Losec®), lansoprazole (Prevacid™) and pantoprazole (Pantoloc®). The PPIs decrease the recurrence rate for erosive and severe esophagitis more effectively than the H_2 receptor blockers. For the treatment of peptic ulcer disease the H_2 receptor blockers, PPIs, bismuth, misoprostol (Cytotec®) and sucralfate (Sulcrate®) all have a role to play.

Cost: Esomeprazole is currently not available in Canada; hence there is no Canadian cost information at this time.

Evidence: Esomeprazole has been evaluated in a number of clinical trials. A large study of 1960 patients with GERD confirmed by endoscopy were randomized to once daily esomeprazole 20 or 40 mg or omeprazole 20 mg for eight weeks in a multicentre, double-blind trial. At week four, patients on esomeprazole 40 mg had a significantly higher rate of healing (75.9%) than those on omeprazole 20 mg (64.7%) (p # 0.05).The esomeprazole 40 mg produced significantly greater results for all the secondary variables including heartburn resolution, time to first resolution of heartburn and percentage of heartburn-free days.

Esomeprazole 40 mg was compared with omeprazole 20 mg once daily in 2,425 patients with erosive esophagitis in an eight-week, well designed trial. At week four, 81.7% of patients on esomeprazole 40 mg were healed compared to 68.7% of patiented treated with 20 mg omeprazole ($p < 0.001$).

Significantly more patients were healed with esomeprazole (93.7%) compared to omeprazole (84.2%) at week eight ($p < 0.001$). Esomeprazole 40 mg was also shown to be significantly more effective than omeprazole for all secondary endpoints that evaluated heartburn resolution, including percentage of heartburn-free days and nights, time to first resolution and time to sustained resolution.

Esomeprazole was evaluated as part of a seven-day triple therapy for the eradication of *H. pylori* in patients with duodenal ulcer disease (but no currently active ulcer). Eradication was defined as a negative C-urea breath test for *H. pylori* at both four and eight weeks after

ESOMEPRAZOLE MAGNESIUM

completing therapy. Esomeprazole 20 mg, twice daily was compared to omeprazole 20 mg, twice daily. Treatment included amoxicillin 1000 mg twice daily and clarithromycin 500 mg twice daily. Differences in eradication rates were not statistically significant with 90% and 88% eradication in the esomeprazole and the omeprazole groups, respectively.

Adverse Effects: Esomeprazole is generally well-tolerated. The most commonly observed adverse effects with esomeprazole 20 or 40 mg daily include headache, respiratory infection, sinusitis, flatulence and diarrhea. The rate of occurrence was similar in those taking omeprazole 20 mg daily. Esomprazole is metabolized by CYP2C19 and CYP3A4. The combined use of esomeprazole with clarithromycin 500 mg twice daily and amoxicillin 1000 mg twice daily for seven days resulted in a 70% increase in the AUC and an 18% increase in the C_{max} for esomeprazole. The AUC for 14-hydroxy-clarithromycin increased by 19%. These effects are not expected to produce significant safety concerns and are less than those produced with the combined use of omeprazole 40 mg daily with clarithromycin 500 mg three times daily. In clinical trials using combination therapy with esomeprazole, clarithromycin and amoxicillin, no adverse events specific to the combinations were observed. In patients receiving triple therapy for *H. pylori*, tolerability of the esomeprazole-containing regimen was similar to omeprazole-based triple therapy.

Conclusion: Esomeprazole has significant efficacy in treating GERD and as maintenance treatment of patients with healed erosive esophagitis. Esomeprazole provided effective symptom control in GERD with on-demand use. Esomeprazole 20 mg twice daily eradicated *H. pylori* as well as omeprazole 20 mg twice daily in a triple therapy regimen that included amoxicillin 1g twice daily and clarithromycin 500 mg twice daily. It is well-tolerated with a similar side effect profile to omeprazole. Overall, it appears to offer similar, and in some cases superior, benefits to omeprazole.

References:

Kahrilas PJ, Galk GW, Johnson DA et al. Esomeprazole improves healing and symptom resolution as compared with omeprazole in reflux esophagitis patients: a randomized controlled trial. Aliment Pharmacol Ther 2000;14:1249-58.

Richter JE, Kahrilas PJ, Johanson J et al. Efficacy and safety of esomeprazole compared with omeprazole in GERD patients with erosive esophagitis: a randomized controlled trial. Am J Gastroent 2001; 96(3):656-65.

Talley NJ, Lauritsen K, Tunturi-Hihnalas H et al. Esomeprazole 20 mg maintains symptom control in endoscopy-negative gastro-oesophageal reflux disease: a controlled trial of 'on-demand' therapy for 6 months. Aliment Pharmacol Ther 2001;15:347-54.

VeldhuyzenVan Zanten S, Lauritsen K, Delchier JC et al. One-week triple therapy with esomeprazole provides effective eradication of Helicobacter pylori in duodenal ulcer disease. Aliment Pharmacol Ther 2000; 14:1605-11.

Laine L, Fennerty MB, Osato M et al. Esomeprazole-based Helicobacter pylori eradication therapy and the effect of antibiotic resistance: results of three US multicenter, double-blind trials. Am J Gastroent 2000;95(12):3393-98.

Spencer C, Faulds D. Esomeprazole. Drugs 2000;60(2):321-29.

Personal communication with Medical Information Department, AstraZeneca., Mississauga, ON. May 22, 2001.

Nexium® Product Information (U.S.) internet site: http://www.astrazeneca-us.com/cgi-bin/az-

ISSN 1496-8398 (online only)