PUBLIC SUMMARY DOCUMENT
Product: ESOMEPRAZOLE magnesium trihydrate, tablet (enteric coated), equivalent to 20 mg esomeprazole, Nexium®
Sponsor: AstraZeneca Pty Ltd
Date of PBAC Consideration: November 2005

1. Purpose of Application

The application sought the listing of esomeprazole magnesium trihydrate 20 mg for the healing of peptic ulcers associated with non-steroidal anti-inflammatory drug NSAID (non-selective and COX-2 selective) therapy.

2. Background

The PBAC originally considered esomeprazole at its meeting held in March 2001. Esomeprazole was listed as a restricted benefit on 1 August 2002 for the healing of gastroesophageal disease for the 40 mg strength and for maintenance of healed gastro-oesophageal disease for the 20 mg strength.

3. Registration Status

Esomeprazole is registered by the Therapeutic Goods Administration (TGA) for the following indications:

Gastro-Oesophageal Reflux Disease (GORD):

- treatment of erosive reflux oesophagitis;
- long-term management of patients with healed oesophagitis to prevent relapse;
- symptomatic treatment of gastro-oesophageal reflux disease (GORD).

In combination with appropriate antibiotics for:

- healing of duodenal ulcer associated with Helicobacter pylori;
- eradication of Helicobacter pylori in patients with active or healed peptic ulcer.

Short-term treatment of upper gastrointestinal symptoms associated with non-steroidal anti-inflammatory drug (NSAID) (non-selective and COX-2 selective) therapy.

Healing of gastric ulcers associated with non-steroidal anti-inflammatory drug NSAID (non-selective and COX-2 selective) therapy.

Prevention of gastric and duodenal ulcers associated with non-steroidal anti-inflammatory drug NSAID (non-selective and COX-2 selective) therapy in patients at risk.

4. Listing Requested and PBAC's View

Restricted benefit

Healing of peptic ulcers associated with non-steroidal anti-inflammatory drug NSAID (non-selective and COX-2 selective) therapy

NOTE: Helicobacter pylori eradication therapy should be considered.

See Recommendations and Reasons for the PBAC's view.

5. Clinical Place for the Proposed Therapy

Esomeprazole would provide an alternative to other proton pump inhibitors for the treatment of peptic ulcers not caused by *H. pylori* infection.

6. Comparator

The submission nominated omeprazole as the main comparator. This was considered appropriate by the PBAC.

7. Clinical Trials

The submission presented an indirect comparison using ranitidine as the common reference. The primary evidence consisted of two randomised trials of esomeprazole 20 mg daily versus ranitidine 150 mg twice daily and one randomised trial of omeprazole 20 mg daily versus ranitidine 150 mg twice daily. Four randomised trials comparing omeprazole 20 mg daily with ranitidine 150 mg twice daily and one randomised trial comparing pantoprazole 40 mg daily and ranitidine 300 mg daily were provided as supporting evidence.

Details of the trials provided as primary evidence are as follows

Trial/First author	Protocol title	Publication citation
Trial 0005 AstraZeneca Study Report SH-NEN-0005	A comparative efficacy and safety study of Nexium (esomeprazole magnesium) delayed-release capsules (40mg qd and 20mg qd) versus ranitidine (150mg bid) for the healing of NSAID-associated gastric ulcers when daily NSAID use is continued.	
Trial 0006 AstraZeneca Study Report SH-NEN-0006	A comparative efficacy and safety study of Nexium (esomeprazole magnesium) delayed-release capsules (40mg qd and 20mg qd) versus ranitidine (150mg bid) for the healing of NSAID-associated gastric ulcers when daily NSAID use is continued.	
Yeomans N	A comparison of omeprazole with ranitidine for ulcers associated with nonsteroidal antiinflammatory drugs.	N Engl J Med 1998;338:719-26

8. Results of Trials

The results of the comparative randomised trials used as primary evidence are shown below**.**

Trial	Treatment n/N (%)	Ranitidine n/N (%)	ARD (95% CI)	RR (95% CI)	p-value
SUBMISSION ANALYSIS					
Esomeprazole					
Week 4					
Trial 0005	109/140 (77.9)	88/134 (65.7)	*12.2% (1.5%, 22.7%)*	1.19 (1.02, 1.38)	
Trial 0006	100/150 (66.7)	77/149 (51.7)	*15.0% (3.8%, 25.8%)*	1.29 (1.06, 1.56)	
Pooled				**1.23 (1.09, 1.39)**	
Week 8					
Trial 0005	122/140 (87.1)	98/134 (73.1)	*14.0% (4.6%, 23.5%)*	1.19 (1.06, 1.34)	
Trial 0006	117/150 (78.0)	106/149 (71.1)	*6.9% (-3.0%, 16.7%)*	1.10 (0.96, 1.25)	
Pooled				**1.14 (1.04, 1.25)**	
Omeprazole – Yeomans 1998 – sub-set of gastric ulcer patients					
Week 4	47/70 (67.1)	35/70 (50)	*17.1% (0.7%, 32.6%)*	1.34 (1.01, 1.79)	
Week 8	59/70 (84.3)	45/70 (64.3)	*20.0% (5.6%, 33.9%)*	1.31 (1.07, 1.60)	
TRIAL ANALYSIS					
Esomeprazole					
Week 4					
Trial 0005	109/138 (79)	88/132 (66.7)	NR	NR	0.023
Trial 0006	100/138 (72.5)	77/139 (55.4)	NR	NR	0.003
Week 8					
Trial 0005	122/138 (88.4)	98/132 (74.2)	NR	NR	0.003
Trial 0006	117/138 (84.8)	106/139 (76.3)	NR	NR	0.073
Omeprazole – Yeomans 1998					
Week 4	47/70 (67.1)	35/70 (50)	NR	NR	NR
Week 8	59/70 (84.3)	45/70 (64.3)	NR	NR	<0.001

ARD = absolute risk reduction; NR = not reported; RR = relative risk reduction; estimates in italics calculated during the evaluation

The event rates for ranitidine were generally similar across the esomeprazole versus ranitidine and the omeprazole versus ranitidine trials. Trial 0005 demonstrated a statistically significant advantage for esomeprazole over ranitidine at both 4 and 8 weeks; in Trial 0006, the advantage was apparent only at 4 weeks and not 8 weeks. The pooled data conclude a statistically significant advantage of esomeprazole over ranitidine therapy at both 4 and 8 weeks. Omeprazole showed statistically significantly higher ulcer healing rates than ranitidine at both 4 and 8 weeks (Yeomans trial).

The adverse events seen in the trials were as expected based on the established profiles of the drugs and the characteristics of the enrolled populations, mainly arthritis sufferers with peptic ulcer disease.

9. Clinical Claim

The submission claimed esomeprazole was no worse than omeprazole in terms of effectiveness and toxicity. The PBAC accepted this claim.

10. Economic Analysis

The submission sought listing on a cost-minimisation basis with esomeprazole 20 mg daily for 4 to 8 weeks considered equi-effective to omeprazole 20 mg daily for 4 to 8 weeks.

A preliminary economic evaluation was not presented.

11. Estimated PBS Usage and Financial Implications

The submission estimated that the number of prescriptions would be > 200,000 in Year 4 of listing with the absolute cost estimated to the PBS between $5 million to $10 million in Year 4 of listing.

The submission claimed that all esomeprazole 20 mg use will be as direct substitution of currently available peptic ulcer indicated proton pump inhibitors and therefore the net change in usage of proton pump inhibitors for this indication following listing for esomeprazole will be zero. The PBAC noted the zero cost calculation may be true if use is restricted to 4 to 8 weeks' therapy of 20 mg/day for ulcer healing, but was of the view that there was considerable potential for usage beyond the requested restriction.

12. Recommendation and Reasons

Listing was recommended on a cost-minimisation basis, concluding that the indirect comparison via a ranitidine comparator arm presented in the submission indicated that esomeprazole was no worse than omeprazole in the treatment of gastric ulcer. The equi-effective doses were esomeprazole 20 mg daily for 4 to 8 weeks and omeprazole 20 mg daily for 4 to 8 weeks.

The PBAC considered it appropriate for the restriction to align as far as possible with the PBS restrictions for the current listed proton pump inhibitors in the treatment of gastrointestinal ulcers. The Committee noted that the majority of gastric ulcers not associated by H. pylori are caused by non-steroidal anti-inflammatory drugs.

Recommendation

ESOMEPRAZOLE MAGNESIUM TRIHYDRATE, tablet (enteric coated), equivalent to 20 mg esomeprazole

Extend listing to include the following restriction:

Restriction:	Restricted benefit Initial treatment of gastric ulcer. NOTE Helicobacter pylori eradication therapy should be considered. No applications for increased maximum quantities and/or repeats will be authorised.
Maximum quantity	30
Repeats:	1

13. Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

14. Sponsor's Comment

AstraZeneca agrees with the PBAC's decision and looks forward to the listing of esomeprazole 20mg for the treatment of gastric ulcers.