PUBLIC SUMMARY DOCUMENT

Product: Naproxen and esomeprazole, tablet, 500 mg-20 mg (as magnesium trihydrate), Vimovo®

Sponsor: AstraZeneca Pty Ltd

Date of PBAC Consideration: March 2012

1. Purpose of Application

The resubmission requested a Restricted Benefit listing for the symptomatic treatment of osteoarthritis, rheumatoid arthritis or ankylosing spondylitis in a patient who requires a non-steroidal anti-inflammatory drug (NSAID) and is at high risk of developing gastrointestinal complications.

2. Background

At its August 2011 Special meeting, the PBAC rejected an application for naproxen and esomeprazole fixed dose combination (FDC) tablet because the comparator was inappropriate. The PBAC did not accept celecoxib as the appropriate main comparator. Consistent with its Guidelines, the Committee considered the appropriate comparator to be meloxicam, as it was the most commonly prescribed NSAID on the PBS.

The PBAC accepted that the evidence supported a conclusion that the naproxen/esomeprazole FDC was as effective as naproxen alone, or celecoxib in the symptomatic treatment of osteoarthritis and rheumatoid arthritis. However, the PBAC noted that paracetamol was the drug of choice for osteoarthritis and that NSAIDs should only be used in patients with osteoarthritis who have true inflammatory symptoms.

The PBAC considered that the evidence provided in the submission to support the claims that naproxen/esomeprazole FDC was superior to naproxen and non-inferior to celecoxib with respect to gastrointestinal toxicity, using the surrogate outcome of endoscopically-detected ulcers, was less convincing than the Committee's previous acceptance of directly assessed improvements in the patient-relevant composite outcome of "perforations, ulcerations and bleeds" (PUBs) for meloxicam and in the even more patient-relevant composite outcome of "complicated PUBs", also called "perforations, obstructions and bleeds" (POBs) or, in the key celecoxib randomised trial evidence, "clinically significant upper gastrointestinal events" (CSUGIEs). The PBAC recalled that both these composite outcomes had accepted definitions, and that any effect on either composite outcome became more clinically important the longer it was maintained. The PBAC also recalled that part of the reason for the lower price of meloxicam compared to celecoxib was that clear evidence for celecoxib in prospectively defined and adequately powered trials was more convincing than a meta-analysis of under-powered randomised trials relying on a post-hoc analysis of collated adverse event reports across the trials.

Overall, when considering any of these aspects, the PBAC indicated that it would prefer the best available evidence reporting directly patient relevant outcomes for the naproxen/esomeprazole FDC. More convincing evidence would demonstrate a statistically significant improvement over naproxen alone when directly assessing a patient-relevant composite outcome and would present a comparison with meloxicam.

3. Registration Status

Naproxen and esomeprazole fixed dose combination was TGA registered on 25 October 2011 for the following indication:

> "patients with an increased risk of gastrointestinal ulceration, who require NSAID therapy for symptomatic management of rheumatoid arthritis, ankylosing spondylitis and osteoarthritis with an inflammatory component AND in whom lower doses of naproxen or other NSAIDs have proven insufficient. If a total daily dose of 1 gram naproxen is not required, Vimovo should NOT be used."

4. Listing Requested and PBAC's View

Restricted Benefit

Symptomatic treatment of osteoarthritis, rheumatoid arthritis or ankylosing spondylitis in a patient who requires a non-steroidal anti-inflammatory (NSAID) and is at high risk of gastrointestinal complications.

Note:

The use of naproxen and esomeprazole magnesium trihydrate for the treatment of the following conditions is not subsidised through the PBS:

a) Acute pain;
b) Soft tissue injury;
c) Arthrosis without an inflammatory component.

For use as sole PBS-subsidised proton pump inhibitor therapy.

The PBAC did not comment on the requested restriction.

5. Clinical Place for the Proposed Therapy

Ankylosing spondylitis is a type of inflammatory arthritis that targets the joints of the spine. It particularly affects the sacroiliac joint where the spine attaches to the pelvis. Symptoms include back pain, stiffness and reduced mobility in the spine. NSAIDs, including cyclooxygenase (Cox) inhibitors, are the recommended first-line treatment for patients with ankylosing spondylitis who have pain and stiffness.

Osteoarthritis is a disease of the joints where cartilage has broken down, causing pain and stiffness in the joint. Non-pharmacological interventions such as weight loss and exercise form the basis of first-line treatment. For patients experiencing persistent symptoms, simple analgesia in the form of regular paracetamol represents the mainstay of pharmacological therapy. For those patients who do not experience adequate pain relief with paracetamol or whose disease exhibits an inflammatory component, NSAID therapy may be initiated following assessment of cardiovascular and gastrointestinal risk.

Rheumatoid arthritis is a disease in which inflammation (pain, heat and swelling) affects the joints and other organs of the body. The hands, feet and knees are commonly affected. Stiffness in the joints is common, especially in the morning. Remission is the goal of treatment of rheumatoid arthritis and as such, disease modifying anti-rheumatic drugs (DMARDs) are the mainstay of therapy. NSAIDs are an effective therapy for improving the symptoms and thus, are used early in the condition, prior to initiation of DMARD therapy

and also intermittently during disease flares or transient worsening of join pain and/or swelling.

The resubmission proposed that combining a proton pump inhibitor with an NSAID in a sequential release dose form, from which naproxen is only released in the presence of gastroprotective levels of esomeprazole addresses both the local and systemically mediated mechanisms of NSAID-associated gastropathy, whilst also addressing issues with respect to adherence to gastroprotective therapy.

6. Comparator

As in the previous submission, the resubmission nominated celecoxib as the main comparator.

The PBAC considered that a mixed comparator of both meloxicam and celecoxib would be more appropriate than celecoxib alone. See *Recommendation and Reasons*.

7. Clinical Trials

The basis of the resubmission was six randomised controlled trials:

- Two trials directly comparing the naproxen/esomeprazole FDC with naproxen alone (Trials 301 and 302);
- Two trials directly comparing the naproxen/esomeprazole FDC with celecoxib (Trials 307 and 309); and
- Two trials directly comparing celecoxib with naproxen (Goldstein 2001 and Simon 1999).

Trials 301, 302, 307 and 309 were presented in the previous submission.

Details of the trials presented are below.

Trials and associated reports identified by the resubmission

Trial ID/First author	Protocol title/ Publication title	Publication citation
Direct randomised trials – naproxen/esomeprazole FDC versus naproxen alone		
301	Clinical study report PN400-301 A 6-month, phase 3, randomised, double-blind, parallel-group, controlled, multi-centre study to evaluate the incidence of gastric ulcers following administration of either PN400 or naproxen in subjects who are at risk for developing NSAID-associated ulcers.	*Aliment Pharmacol Ther*. 2010; 32(3):401-13 *Arthritis Rheum*. 2009;60:842
302	Clinical study report PN400-302 A 6-month, phase 3, randomised, double-blind, parallel-group, controlled, multi-centre study to evaluate the incidence of gastric ulcers following administration of either PN400 or naproxen in subjects who are at risk for developing NSAID-associated ulcers.	*Aliment Pharmacol Ther.* 2010; 32(3):401-13 *Arthritis Rheum.* 2009;60:842
Direct randomised trials – naproxen/esomeprazole FDC versus celecoxib		
307	Clinical study report PN400-307	*Curr Med Res Opin.* 2011; 27(6):1243-53

Trial ID/First author	Protocol title/ Publication title	Publication citation
	Randomised, double-blind, parallel group, placebo-controlled, multi-centre study evaluating the efficacy of PN400 BID and celecoxib 200mg QD in patients with osteoarthritis of the knee.	*Arthritis Rheum.* 2010; 62:937
309	Clinical study report PN400-309 Randomised, double-blind, parallel group, placebo-controlled, multi-centre study evaluating the efficacy of PN400 BID and celecoxib 200mg QD in patients with osteoarthritis of the knee.	*Curr Med Res Opin*. 2011; 27(6):1243-53 *Arthritis Rheum.* 2010; 62:937
Direct randomised trials – celecoxib versus naproxen		
Goldstein J L 2011	Reduced incidence of gastroduodenal ulcers with celecoxib, a novel cyclooxygenase-2 inhibitor, compared to naproxen in patients with arthritis	*Am J Gastroenterol.* 2001; 96(4) 1019-27
Simon L S 1999	Anti-inflammatory and upper gastrointestinal effects of celecoxib in rheumatoid arthritis: A randomized controlled trial.	*JAMA* 1999; 282(20): 1921-8

8. Results of Trials

The table below summarises the results for the primary endpoint of endoscopically detected ulcers in the indirect comparison of naproxen/esomeprazole fixed dose combination versus celecoxib.

Results of endoscopically detected ulcers in the indirect comparison: naproxen/esomeprazole FDC versus celecoxib

Trial	FDC n/N (%)	Naproxen n/N (%)	Celecoxib n/N (%)	RR (95% CI)	OR (95% CI)
Cumulative incidence of gastric ulcers at 3 months					
Trial 301	4/218 (1.8)	42/216 (19.4)	-	**0.09 (0.03, 0.26)**	**0.08 (0.03, 0.22)**
Trial 302	10/210 (4.8)	37/210 (17.6)	-	**0.27 (0.14, 0.53)**	**0.23 (0.11, 0.48)**
			Pooled	**0.17 (0.06, 0.49)**	**0.14 (0.05, 0.43)**
Goldstein (400)	-	37/267 (13.9)	6/270 (2.2)	**0.16 (0.07, 0.37)**	**0.14 (0.06, 0.34)**
		Indirect comparison (FDC versus celecoxib 400mg)		1.06 (0.28, 4.06)	1.00 (0.25, 3.98)
Cumulative incidence of duodenal ulcers at 3 months					
Trial 301	1/218 (0.5)	11/216 (5.1)	-	**0.09 (0.01, 0.*68*)**	**0.09 (0.1, 0.67)**
Trial 302	2/210 (1.0)	11/210 (5.2)	-	**0.18 (0.04, 0.*79*)**	**0.17 (0.04, 0.79)**
			Pooled	**0.*13* (0.04, 0.*44*)**	**0.*13* (0.04, *0.44*)**
Goldstein (400)	-	12/267 (4.5)	4/270 (1.5)	0.33 (0.11, 1.01)	0.32 (0.10, 1.00)
		Indirect comparison (FDC versus celecoxib 400mg)		*0.39 (0.08, 2.01)*	*0.41 (0.08, 2.14)*
Cumulative incidence of gastroduodenal ulcers at 3 months					
Trial 301	5/218 (1.8)	52/216 (19.4)	-	**0.10 (0.04, 0.23)**	**0.07 (0.03, 0.19)**
Trial 302	12/210 (4.8)	44/210 (17.6)	-	**0.27 (0.15, 0.50)**	**0.23 (0.12, 0.45)**
			Pooled	**0.17 (0.06, 0.48)**	**0.14 (0.04, 0.42)**
Simon (200)	-	36/137 (26.3)	9/148 (6.1)	**0.23 (0.12, 0.46)**	**0.18 (0.08, 0.39)**
		Indirect comparison (FDC versus celecoxib 200mg)		0.74 (0.21, 2.55)	0.78 (0.19, 3.21)
Goldstein (400)	-	*109/267 (40.8)*	*24/269 (8.9)*	***0.21 (0.15, 0.33)***	***0.14 (0.09, 0.23)***
Simon (400)	-	*36/137 (26.3)*	6/145 (4.1)	***0.14 (0.06, 0.32)***	***0.11 (0.04, 0.26)***
			Pooled celecoxib (400)	***0.20 (0.14, 0.28)***	***0.13 (0.09, 0.20)***
		Indirect comparison (FDC versus celecoxib 400mg)		*0.85 (0.29, 2.54)*	*1.08 (0.31, 3.73)*
Cumulative incidence of gastroduodenal ulcers at 3 months in patients receiving concomitant low dose aspirin (LDA)					
Trial 301	0/53 (0.0)	12/51 (23.5)	-	**0.04 (0.00, 0.63)**	**0.03 (0.00, 0.51)**

Trial 302	1/46 (2.2)	16/51 (31.4)	-	**0.07 (0.01, 0.50)**	**0.05 (0.01, 0.38)**
			Pooled	**0.06 (0.01, 0.29)**	**0.04 (0.01, 0.22)**
Goldstein (400)	-	12/28 (42.9)	7/29 (24.1)	0.56 (0.26, 1.22)	0.42 (0.14, 1.32)
Indirect comparison (FDC versus celecoxib 400mg)				**0.11 (0.17, 0.68)**	**0.10 (0.01, 0.64)**

Text in italics: modified during evaluation. Recalculated figures and corrected figures from published reports

The resubmission also presented a mixed treatment comparison versus multiple comparators including NSAID ± PPI, COX-2 selective agents ± PPI, Arthrotec® (a FDC of diclofenac and misoprostol) and placebo. From the results of the mixed treatment comparison, the resubmission concluded that the naproxen/esomeprazole FDC was clearly differentiated from NSAIDs for the gastrointestinal safety outcomes assessed. Statistically significant results were shown for gastroduodenal ulcers in the comparison versus NSAIDs. Comparisons versus other agents were not statistically significantly different. The results of the mixed treatment comparison were consistent with previously published data showing that addition of a PPI significantly reduced the risk of symptomatic ulcers and endoscopic ulcers compared with using an NSAID alone.

For PBAC's view, see Recommendation and Reasons.

The PBAC noted that a new Periodic Safety Update Report was included in the resubmission, but no new toxicity data were presented. The PBAC considered that the safety profiles of naproxen alone and esomeprazole alone are well known and the adverse events reported in the included trials did not indicate that there were any additional safety issues with the fixed dose combination. A 12-month open label safety study of the FDC also reported safety data that was consistent with those reported in the clinical trials.

9. Clinical Claim

The resubmission described the naproxen/esomeprazole FDC as non-inferior to celecoxib in terms of comparative effectiveness on all primary (pain and function) measures and non-inferior in a number of gastrointestinal safety and tolerability measures. The resubmission also described the naproxen/esomeprazole FDC as being superior to naproxen for the incidence of endoscopically detected ulcers. The PBAC considered there was insufficient evidence to establish that observed differences in the surrogate outcome, endoscopically-detected ulcers, accurately predicted the extent of differences in the risk of clinically relevant changes in symptomatic gastrointestinal events.

The PBAC had previously agreed that naproxen with esomeprazole was non-inferior to celecoxib and naproxen in terms of comparative effectiveness on all primary (pain and function) measures.

10. Economic Analysis

The resubmission presented a cost minimisation analysis. The equi-effective doses were estimated as naproxen 500 mg/esomeprazole 20 mg in a fixed dose combination twice daily and celecoxib 200 mg daily.

11. Estimated PBS Usage and Financial Implications

The submission estimated the likely number of patients per year to be greater than 200,000 in Year 5 of listing with net savings to the PBS.

The PBAC considered that the submission's estimates of net savings with listing naproxen/esomeprazole were unlikely. See *Recommendation and Reasons.*

12. Recommendation and Reasons

The PBAC recalled that it had not accepted celecoxib as the main comparator from the previous submission. The PBAC noted that the resubmission disputed its previous decision that meloxicam is an appropriate comparator on the grounds of comparative Cox-2 selectivity, comparative gastrointestinal (GI) safety, market share and the recommendations made in the Gastroenterological Society of Australia's guidelines which position non-selective NSAIDs + PPI as an alternative to coxibs in at-risk patients. However, the PBAC was not convinced that the resubmission had provided sufficient evidence to conclude that celecoxib alone was the only appropriate comparator.

Consistent with its 2004 review of the Cox-2 agents, the PBAC considered that meloxicam lies between traditional NSAIDs and Cox-2 specific agents with direct trial evidence of a lower incidence of perforations, ulceration and bleeds (PUBs) but not direct trial evidence of a lower incidence of the more patient-relevant composite outcome of perforation, obstructions and bleeds (POBs). Celecoxib is a Cox-2 selective inhibitor with direct trial evidence of a lower incidence of clinically significant upper gastrointestinal events (CSUGIEs, considered equal to POBs). Further, meloxicam is more commonly prescribed and therefore has a larger market share than celecoxib. Therefore, the PBAC concluded that a mixed comparator of both meloxicam and celecoxib would be more appropriate than celecoxib alone. The PBAC noted that as one consequence of the 2004 review of Cox-2 agents, celecoxib retained a higher price than meloxicam because it had superior evidence of a favourable effect on more patient-relevant gastrointestinal outcomes than was available for meloxicam.

The PBAC noted the addition of two new studies, Goldstein (2001) and Simon (1999), to inform the indirect comparison of naproxen/esomeprazole with celecoxib via naproxen. The indirect analysis showed no statistically significant difference between naproxen/esomeprazole and celecoxib in the number of endoscopically-detected ulcers, however the PBAC noted that the analysis was limited by differences in baseline characteristics and the celecoxib doses used in the trials.

The PBAC further noted that the resubmission did not present any data relating to the incidence of PUBs, POBs or CSUGIEs, the most patient-relevant outcomes. The resubmission argued that endoscopically detected ulcers are a valid surrogate outcome for clinically relevant GI outcomes (PUBs, POBs or CSUGIEs), on the grounds of biological plausibility and evidence of a comparable treatment effect on both the surrogate outcome and the final outcomes of interest. The submission also stated that the FDA recommends the use of endoscopically detected ulcers as an appropriate endpoint for evaluating products intended to prevent NSAID associated upper GI toxicity.

Overall, the PBAC considered there was insufficient evidence to establish that observed differences in the surrogate outcome, endoscopically-detected ulcers, accurately predicts the extent of differences in the risk of clinically relevant changes in symptomatic gastrointestinal events.

The PBAC recalled that it had previously considered that the basis of comparison of GI events between celecoxib and naproxen/esomeprazole was less convincing than the Committee had previously relied upon for its recommendations for either meloxicam or

celecoxib, which were made on the basis of directly observed patient relevant outcomes (PUBs, POBs and CSUGIEs) in randomized trials. Overall, the PBAC remained unconvinced by the resubmissions justification for continuing to use endoscopically-detected ulcers as a surrogate outcome to establish non-inferiority.

The PBAC considered that the net savings with listing naproxen/esomeprazole were unlikely. The PBAC considered that usage of the product would be high, particularly if it substitutes for cheaper NSAIDs, and is prescribed for those patients not currently taking concurrent PPIs with NSAIDs and for those patients requiring high doses of naproxen for short periods of time.

The PBAC rejected the resubmission on the basis of an inappropriate comparator, uncertainty regarding the validity of the surrogate outcome, for the purposes of demonstrating noninferiority of more patient-relevant outcomes, and resultant uncertainty in the proposed cost-minimisation analysis and an expectation that listing as requested could result in increased costs both overall and also to the PBS.

In making this recommendation the PBAC noted the consumer comments on this item.

Recommendation:
Reject

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 – March 2012

AstraZeneca will continue to work with the PBAC to make Vimovo available on the PBS for patients with arthritis who are at increased gastrointestinal risk from NSAID therapy.

ADDENDUM

PUBLIC SUMMARY DOCUMENT

Product: Naproxen and esomeprazole, tablet, 500 mg-20 mg (as magnesium trihydrate), Vimovo®
Sponsor: AstraZeneca Pty Ltd
Date of PBAC Consideration: November 2012

1. Purpose of Application

The minor re-submission sought a Restricted Benefit listing for the symptomatic treatment of osteoarthritis, rheumatoid arthritis or ankylosing spondylitis in a patient who requires a non-steroidal anti-inflammatory drug and is at increased risk of gastrointestinal ulceration. The re-submission also requested PBAC advice under section 101(4AC) of the *National Health Act 1953*.

2. Listing Requested and PBAC's View

Restricted Benefit
Symptomatic treatment of osteoarthritis, rheumatoid arthritis or ankylosing spondylitis in a patient who requires a non-steroidal anti-inflammatory (NSAID) and is at an increased risk of gastrointestinal ulceration in whom lower doses of naproxen or other NSAIDs are insufficient.

Note:
The use of naproxen and esomeprazole for the treatment of the following conditions is not subsidised through the PBS:

a) Acute pain;
b) Soft tissue injury;
c) Arthrosis without an inflammatory component

For use as sole PBS-subsidised proton pump inhibitory therapy.

3. Summary of Submission

The minor resubmission presented a revised pricing proposal and provided additional discussion on the hierarchy of clinical evidence for naproxen with esomeprazole FDC relative to that previously considered by the PBAC in relation to celecoxib and meloxicam to provide context to the revised pricing proposal.

4. Estimated PBS Usage and Financial Implications

The estimated extent of use and financial implications section was updated to reflect the revised pricing proposal, actual changes to the PBS prices of proton pump inhibitors and meloxicam, and potential changes to the PBS prices for other relevant proton pump inhibitors. The submission claimed that market uptake assumptions were revised to align with the assumptions previously used by the DUSC, and attempted to address concerns expressed during the previous evaluation regarding anticipated uptake and substitution patterns for naproxen with esomeprazole FDC.

The likely number of patients per year was estimated in the submission to be greater than 200,000 in Year 5, at an estimated net cost saving per year to the PBS in the range of $10 - $30 million in Year 5.

The Committee was concerned that the financial impact of the proposed listing requires further analysis and evaluation, which was not possible in the context of a minor re-submission. The analysis and evaluation should take into account the issues raised in previous evaluations and the ongoing reductions in the PBS-prices of some proton-pump inhibitors and NSAID medicines.

5. Recommendation and Reasons

The PBAC noted that the minor re-submission offered a revised price which was weighted based on a mixed comparator of celecoxib and meloxicam. The Committee noted the re-submission stated that this revised pricing proposal was intended to address the issues around the appropriate comparator for the naproxen with esomeprazole combination and the uncertainty relating to the use of surrogate outcome to support the therapeutic claims for this combination relating to gastrointestinal (GI) safety. However, the Committee considered that

the new weighted price proposal did not adequately address all areas of concern with this listing proposal.

In particular, PBAC was concerned that the proposed combination does not satisfy the minimum requirements for combination products to be eligible for consideration for PBS listing, as detailed in Part IV of the PBAC Guidelines. The PBAC considered that criterion (b), which requires "*the component products should preferably be on the PBS*" is only partially met, in that although both components are PBS-listed, esomeprazole is not PBS-subsidised for prevention of GI complications resulting from therapy with non-steroidal anti-inflammatory drugs (NSAIDs). Criterion (c) "*restrictions for the component products should be consistent with those proposed for the combination*", is also not satisfied for the same reason.

Additionally, criterion (g) "*the combination should not result in inappropriate dosing of either component, nor contain components which require individual titration"* was not considered satisfied by PBAC, as the combination product is only available for use in patients requiring a twice daily dose of naproxen 500 mg, whereas in clinical practice a considerable proportion of patients derive additional benefit from a single daily dose of slow-release naproxen 750 mg or 1,000 mg, both of which are PBS-listed, compared to a twice daily 500 mg dose. Furthermore, although the sponsor claims the proposed restriction will ensure the combination is only used in patients at increased risk of GI ulceration who require 1 g of naproxen daily, in accordance with the TGA approved indication, the lack of availability of a combination presentation containing a smaller amount of naproxen will result in some patients being inappropriately started on 1 g naproxen/day.

The PBAC recalled the evidence presented in terms of health outcomes by celecoxib and meloxicam, which forms the basis of the current pricing structure for the two medicines – perforation, obstruction and bleeds (POB) or clinically significant upper gastrointestinal events (CSUGIEs) for celecoxib and perforations, ulceration and bleeds (PUBs) for meloxicam. The PBAC recalled its March 2012 advice, that overall, there was insufficient evidence to establish that observed differences in the surrogate outcome, endoscopically-detected ulcers, accurately predicts the extent of differences in the risk of clinically relevant changes in symptomatic gastrointestinal events. The PBAC was unconvinced by the additional justification given in the re-submission for using endoscopically-detected ulcers as a surrogate outcome to establish non-inferiority.

The Committee did not agree with the weighting suggested in the revised pricing proposal, but given that this is not the only outstanding issue of concern to PBAC, it would not be appropriate for the PBAC to propose an alternative weighting at this time, as requested by the sponsor in its pre-PBAC response.

Lastly the Committee was concerned that the financial impact of the proposed listing requires further analysis and evaluation, which was not possible in the context of a minor re-submission. The analysis and evaluation should take into account the issues raised in previous evaluations and the ongoing reductions in the PBS-prices of some proton-pump inhibitors and NSAID medicines.

The PBAC therefore rejected the re-submission on the basis that not all PBAC criteria for combination products are met; continuing uncertainty regarding the validity of the surrogate

outcome for the purposes of demonstrating non-inferiority of more patient-relevant outcomes, and the resultant impact on the cost-minimisation analysis; and continuing concern that the listing could result in increased costs to the PBS.

The PBAC considered that these reasons for rejection could only be addressed in a major submission which is subject to full evaluation. This major submission should additionally provide information which will enable the Committee to satisfy itself that therapy with esomeprazole for prevention of GI complications resulting from NSAID treatment meets the statutory requirements for listing on the PBS in terms of effectiveness and cost. Also, any submission seeking PBAC advice under s101(4AC) of the *National Health Act 1953* on the basis of improved compliance should follow the approach set out in the Compliance to Medicines Working Group report to PBAC.

The PBAC requested the Secretariat to provide an update of the current restrictions and utilisation for the entire class of proton pump inhibitors.

In making this recommendation the PBAC noted the consumer comments on this item.

Recommendation:
Reject

6. 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.

7. Sponsor's Comment – November 2012

The sponsor did not provide further comment.