Public Summary Document

Product: Naproxen and Esomeprazole, tablets, 500 mg-20 mg (as magnesium trihydrate), Vimovo® - Independent Review Report
Sponsor: AstraZeneca Pty Ltd
Date of PBAC Consideration: July 2013

1. Purpose of Application

To consider the findings of the Independent Review Report on naproxen with esomeprazole for the symptomatic treatment of osteoarthritis, rheumatoid arthritis or ankylosing spondylitis.

2. Background

This product has been considered three times by the PBAC.

At its August 2011 Special meeting, the PBAC considered a major submission that sought a Restricted Benefit listing for the treatment of osteoarthritis, rheumatoid arthritis or ankylosing spondylitis in patients at risk of developing non-steroidal anti-inflammatory drugs (NSAID) associated gastric and/or duodenal ulcers. The PBAC rejected the submission because the comparator was inappropriate and there were no data to make a recommendation.

At its March 2012 meeting, the PBAC considered a major resubmission that sought a Restricted Benefit listing for the symptomatic treatment of osteoarthritis, rheumatoid arthritis or ankylosing spondylitis in a patient who requires an NSAID and is at high risk of developing gastrointestinal complications. 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 non inferiority of more patient-relevant outcomes, and resultant uncertainty in the proposed cost-minimisation analysis. The PBAC also considered it possible that listing as requested could result in increased costs both overall and also to the PBS.

At its November 2012 meeting, the PBAC considered a minor re-submission seeking a Restricted Benefit listing for the symptomatic treatment of osteoarthritis, rheumatoid arthritis or ankylosing spondylitis in a patient who requires an NSAID and is at high risk of developing gastrointestinal complications. The re-submission also requested PBAC advice under section 101(4AC) of the *National Health Act* 1953.

The PBAC rejected the re-submission on a number of grounds. Firstly, not all PBAC criteria for combination products were met. Secondly, there was concern that listing could result in increased costs to the PBS. Lastly there was continuing uncertainty regarding the validity of using a surrogate outcome for the purposes of demonstrating non-inferiority of more patient-relevant outcomes. The latter impacted on the interpretation of the cost-minimisation analysis. The PBAC considered that these reasons for rejection could only be addressed in a major submission which is subject to full evaluation.

AstraZeneca applied for Independent Review on 4 January 2013 and asked that all three submissions and associated PBAC documentation be included in the review.

There were three grounds for review with a number of subordinate issues raised within all three submissions. The grounds of review nominated by the sponsor were as follows:

a. PBAC Criteria for Fixed Dose Combination Products
PBAC's conclusion "that not all PBAC criteria for combination products are met" inappropriately applies the information requests as outlined on pages 211-212 of Part IV of the *Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee* (PBAC) (Version 4.3) as minimum mandatory requirements for combination products to be eligible for consideration by the PBAC for PBS listing.

b. Validity of the surrogate outcome and non-inferiority
PBAC's conclusion that there is "continuing uncertainty regarding the validity of the surrogate outcome for the purposes of demonstrating non-inferiority of more patient-relevant outcomes" (Ratified minutes of the November 2012 PBAC meeting, page 2, paragraph 4) is based on insufficiently robust data which has been taken out of context.

c. Continuing concern that the listing of Vimovo® could result in increased costs to the PBS
PBAC's conclusion that there is "continuing concern that the listing could result in increased costs to the PBS" is unable to be reconciled with any costing analysis available.

3. Registration Status

Naproxen and esomeprazole fixed dose combination (FDC) 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

The submission to the November 2012 PBAC meeting sought the following listing:

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 ulcerations in whom lower doses of naproxen or other NSAIDS are insufficient.

Note:
The use of naproxen and esomeparazole 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.

5. Independent Review Recommendations

The full text of the review is available at
http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/public-summary-documents-by-product [link under 'N' still to be created by PBD webmaster]

The Independent Review made four detailed recommendations and a further overall recommendation.

Recommendation 1
That sufficient resources be devoted to the preparation of PBAC minutes to improve the detail, accuracy and clarity of the minutes.

Recommendation 2
That the PBAC amends Part IV of the Guidelines to make explicit any minimum requirements that must be met by Fixed Dose Combination products.

Recommendation 3
Considering surrogates
Future submissions that involve drugs with surrogate outcomes should include a table that summarises information about the five Parts of the Surrogate to Final Outcomes Working Group (STFOWG) report.

Recommendation 4
Non-inferiority for drugs with multiple outcomes
For drugs with multiple outcomes and for which economic analysis by cost-minimisation is being proposed, it would be helpful to have an explicit process of considering at least all the primary outcomes and deciding for which non-inferiority needs to be assessed. This is particularly important for combination drugs, especially when the two drugs are being used to affect different outcomes. This process could be incorporated into PBAC Guidelines and the cost-minimisation checklist.

Overall Recommendation
That the matters raised in this Independent Review are best addressed in a major submission, informed by a pre-submission meeting.

6. PBAC Discussion

The PBAC considered each recommendation, the advice of its Drug Utilisation Subcommittee (DUSC) and Economics Subcommittee (ESC), and the sponsor's pre-subcommittee response, pre-PBAC response and hearing.

Recommendation 1
That sufficient resources be devoted to the preparation of PBAC minutes to improve the detail, accuracy and clarity of the minutes.

The PBAC considered that the Review highlighted the need to ensure the clearest communication of its reasoning and decisions through the Committee Minutes and noted that the Department was evaluating the resources available for this task.

The PBAC noted that the increasing complexity of sponsors' submissions had in some cases led to Commentaries of substantial length. The Committee considered that revision of the PBAC Guidelines is warranted to ensure that the submission and evaluation documentation best support the PBAC's recommendations on the suitability of a drug product for subsidy.

Recommendation 2
That PBAC amends Part IV of the Guidelines to make explicit any minimum requirements that must be met by Fixed Dose Combination (FDC) products.

The PBAC noted the Review's conclusion that the term "information requests" in the PBAC Guidelines was ambiguous. However, the PBAC considered that the intent of the Guidelines remained clear. A submission for a fixed dose combination should include information relevant to all of the information requests in the PBAC Guidelines. The PBAC noted that instead of the term "minimum requirements", the term "criteria" would effectively communicate the Committee's intent that a submission should address all the points of the Guidelines' information requests.

The PBAC noted the Review's conclusion that the presentation of the information requests in the PBAC Guidelines differs in format to the document used during the evaluation process, although the specific points are consistent in both formats. The PBAC considered that the format of both documents could be harmonised to eliminate any future confusion.

The PBAC noted that the Guidelines review is being overseen by the PBAC Guidelines Working Group and considered that matters related to the Guidelines referred to in the Independent Review should be addressed by the Guidelines Working Group as a priority.

Recommendation 3
Considering surrogates
Future submissions that involve drugs with surrogate outcomes should include a table that summarises information about the five Parts of the STFOWG report.

The Review considered the validity of endoscopically-detected ulcers as a surrogate for patient relevant outcomes previously accepted by the PBAC such as Perforations, Ulcers and Bleeds (PUBs) or Perforations, Obstructions and Bleeds (POBs). The Review used the framework of the Surrogate to Final Outcomes Working Group in its assessment and recommended that this framework should be used by PBAC for future assessment of all surrogate outcomes. The PBAC agreed with this recommendation and noted that it would be a matter to be taken up by the Guidelines Working Group, including the feedback already received from Medicines Australia on this topic.

The Review noted indirect evidence presented by the sponsor, based on a systematic review, that treatment with NSAIDs resulted in increased risk for all four levels of harm: endoscopic ulcers, clinically diagnosed ulcers, perforations/bleeding and deaths. Evidence was also presented that endoscopic ulcers and upper gastrointestinal bleeding are associated with other variables, such as age and previous history.

Overall, the Review concluded that there were insufficient grounds for the PBAC to dismiss the use of endoscopic ulcers as a surrogate for clinically relevant upper gastro-intestinal (UGI) outcomes.

The PBAC noted the accumulation of evidence, since its last consideration of celecoxib, to support the use of endoscopically-detected ulcers as a surrogate measure and accepted the recommendation of the Independent Review. The PBAC considered however that the risk differences between the various gastrointestinal outcomes may vary and that the risk reduction for endoscopically detected ulcers may be greater than for more patient relevant outcomes.

The PBAC noted the advice of the ESC that there may be additional outcomes relevant to any consideration of the combination of naproxen and esomeprazole, including those presented in a recent meta-analysis (CNT collaboration, May 30 2013). The PBAC agreed that an updated summary of the estimates of comparative effects of naproxen versus 'coxibs' for these outcomes should be provided for any future consideration of the combination product.

Recommendation 4
Non-inferiority for drugs with multiple outcomes
For drugs with multiple outcomes and for which economic analysis by cost-minimisation is being proposed, it would be helpful to have an explicit process of considering at least all the primary outcomes and deciding for which non-inferiority needs to be assessed. This is particularly important for combination drugs, especially when the two drugs are being used to affect different outcomes. This process could be incorporated into PBAC Guidelines and the cost-minimisation checklist.

The Independent Review concluded that there was inadequate information on which to judge the non-inferiority of naproxen with esomeprazole compared to celecoxib in regard to gastrointestinal outcomes. The PBAC agreed with this conclusion. The PBAC also noted the remark in the Independent Review that the wide confidence intervals for the indirect comparison of Vimovo with celecoxib for upper gastrointestinal outcomes may not support a conclusion of non-inferiority for that outcome, and that therefore the validity of a cost-minimisation approach to the economic evaluation is not adequately justified.

The PBAC recalled that in all of its previous considerations of Vimovo it had not accepted that celecoxib was the sole comparator. In its August 2011 rejection of Vimovo the PBAC considered that meloxicam was the appropriate comparator. In March 2012 and November 2012 the PBAC accepted that celecoxib was part of a mixed comparator, together with meloxicam. The PBAC noted that the Review did not address the issue of Vimovo's comparison with meloxicam, and reaffirmed its view that meloxicam remained a comparator as the most frequently prescribed NSAID.

Review of November 2012 rejection of Vimovo minor submission

The PBAC re-examined its rejection of Vimovo in November 2012 in the light of the findings of the Review, including the analysis and conclusions contained in the Review Report and the Review's recommendations.

The PBAC noted that the purpose of esomeprazole in this FDC would be to prevent NSAID-induced gastropathy. The PBAC recalled that it has to date not seen convincing evidence of the cost-effectiveness of proton pump inhibitors (PPIs) for this indication, and that therefore use of PPIs for this indication is outside the PBS listings for this drug class.

The PBAC accepted that endoscopically detected ulcers may be considered a surrogate for patient-relevant outcomes such as PUBs and POBs. The PBAC noted however that the submission had not established the non-inferiority of Vimovo with regard to this surrogate.

The PBAC reiterated that it did not accept that celecoxib was the sole comparator for Vimovo. The PBAC had previously accepted that a mixed comparator was appropriate, and noted that meloxicam is the most commonly-prescribed NSAID. The PBAC noted that the Review did not address the issue of the FDC's comparative effectiveness and safety against meloxicam, either separately or as a mixed comparator.

The PBAC noted the Review's conclusion that only extreme assumptions of market growth and price reductions in celecoxib (with and without PPIs) and NSAIDs (with and without PPIs) demonstrated the potential to make the PBS listing of Vimovo a net cost rather than a net save. The PBAC noted also the advice of the DUSC in relation to the analyses presented in the Independent Review.

DUSC advised the PBAC that on the basis of historical volatility in the NSAID market, current patterns of NSAID doses, and plausible switching scenarios following the potential listing of Vimovo (from lower to higher doses of naproxen, and from non-subsidised to subsided use), a 9.4% growth in the NSAID market is well within the bounds of plausibility.

DUSC considered that use in acute musculoskeletal conditions is still a key concern, notwithstanding the Sponsor's response that Vimovo would not be suitable for acute use. Such use would increase costs to the PBS over the currently available therapies.

Overall, the PBAC did not accept the Review's conclusion that the most plausible scenario in the event of PBS listing of Vimovo was a net saving to the PBS. The PBAC agreed with the DUSC that there are plausible scenarios where the projected cost saving would not be realised and a net cost to the PBS would result.

The PBAC recalled the claim of improved compliance in the November 2012 submission, and noted the Review's conclusions that 'by implication FDC products do provide improvements in adherence'. The PBAC noted that the DUSC disagreed, and noted that the Independent Review did not comment on the relative compliance benefit of taking one tablet of the FDC twice daily versus taking two tablets of the component products once daily. The PBAC considered that there was no evidence to support a claim that the formulation of Vimovo improved compliance and that any such evidence would need to be provided according to the standards described in the Compliance to Medicines Working Group report.

Overall Recommendation
That the matters raised in this Independent Review are best addressed in a major submission, informed by a pre-submission meeting.

The PBAC confirmed its November 2012 rejection of the submission for the listing of Vimovo. The PBAC agreed with the Review's overall recommendation that the matters raised in the Independent Review are best addressed in a major submission, informed by a pre-submission meeting.

The PBAC considered that the following points should be addressed in a future major submission for listing Vimovo:

Fixed Dose Combination criteria
The PBAC considered that a future submission should provide information addressing all points of the criteria for Fixed Dose Combination products in the PBAC guidelines. The PBAC recalled that a particular concern in its November 2012 consideration of Vimovo was the fact that the purpose of the PPI component was to prevent NSAID-induced gastropathy, and that therefore the PBS-subsidised indication for esomeprazole as part of the FDC would not be consistent with the indication of the single-ingredient product. The cost-effectiveness of esomeprazole in this indication would therefore need to be established.

The proposed population
The PBAC considered that estimates of the proposed population need to take account of the true likely extent of use of the product. The PBAC considered that the utilisation estimates should address:
- Use in acute inflammatory conditions
- Patients switching from lower doses of naproxen, in the absence of a formulation providing a dose below the daily maximum
- Patients switching from over the counter NSAID therapy to PBS-subsidised Vimovo®

Comparator
The PBAC considered that a future submission should appropriately be based on an analysis with meloxicam as the major component of a mixed comparator, together with celecoxib. The PBAC reiterated that it considered meloxicam a comparator on the basis of market data showing it to be the most commonly prescribed NSAID, and therefore was the therapy most likely to be replaced.

Comparative effectiveness and non-inferiority
The PBAC considered that evidence for the comparative effectiveness and safety of Vimovo against both meloxicam and celecoxib would be required for the following outcomes:
- Pain
- Gastrointestinal outcomes
- Cardiovascular outcomes

The PBAC considered that the sponsor should propose non-inferiority limits for minimum clinically important differences for each outcome. If surrogate outcomes, including endoscopically-detected ulcers, are used, then the submission should include an assessment of each proposed surrogate according to the framework used in the STFOWG report. As endoscopic ulcers have been assessed against this framework in the Independent Review, the PBAC would accept them as an adequate surrogate outcome.

Claimed compliance advantage

The PBAC considered that should the sponsor choose to maintain a claim of improved compliance for Vimovo, suitable evidence, as noted above, should be presented to establish that a dosing regimen of one tablet twice daily provides advantage over a regimen of two tablets once daily.

Details of Risk Share proposal
The PBAC requested that the sponsor provide details of a proposed risk share agreement to contain the risk to the Commonwealth of greater than expected utilisation, should Vimovo be successful in achieving PBS listing.

8. 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

AstraZeneca recommends that this document be read in conjunction with the published full report of the Independent Review, the AstraZeneca application for the Independent Review, and the AstraZeneca pre-subcommittee response, with specific focus on the Reviewer's conclusions as well as the recommendations.