AstraZeneca Australia thanks the reviewers for their Report of an Independent Review of the PBAC's considerations of submissions requesting the inclusion of Vimovo® (naproxen 500mg + esomeprazole 20mg) tablets on the Schedule of Pharmaceutical Benefits for patients with osteoarthritis, rheumatoid arthritis or ankylosing spondylitis who are at risk of developing NSAID-related gastrointestinal ulceration (hereafter referred to as the Review). AstraZeneca also thanks the PEB and the PBAC for this opportunity to respond to the Review.

Introduction

The minutes from the most previous PBAC consideration of Vimovo® in November 2012 state that the PBAC "*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.*"

These reasons for rejection were the subject of the Independent Review. Although the Review does not and, more importantly, cannot direct the PBAC to make a different decision, the Review does outline a number of areas where the PBAC's consideration of Vimovo® was deficient:

(i) In regard to the issue of the manner in which the criteria for Fixed Dose Combination (FDC) were applied by the PBAC
(ii) In regard to the PBAC's consideration as to whether the outcome of endoscopic ulcers is reliable and repeatable as a surrogate for clinically relevant upper gastrointestinal (UGI) events
(iii) In regard to the PBAC's conclusions with respect to financial implications

Each of these issues is discussed in greater detail, and specific requests are made of the PBAC, in the numbered points below. As can be seen, these issues relate directly to each of the reasons given for rejection in the PBAC minutes from November 2012 (the last meeting at which Vimovo® was considered). **Given the findings of the Review, AstraZeneca requests that PBAC reconsider the PBS listing of Vimovo at the July meeting, recalling AstraZeneca's offer of a Risk Share Arrangement and pricing proposal as previously communicated (and as described below)**.

Recent submission – considered November 2012

AstraZeneca's decision to prepare a minor submission emerged directly from the post rejection meeting on 17 April 2012. AstraZeneca acknowledges that these meetings are held without prejudice. AstraZeneca was advised that a minor resubmission with a revised pricing proposal would be an appropriate way to address the outstanding issues (comparator, endpoints, and price). Hence, a minor submission offering a price reduction and reiterating the offer of a Risk Share Arrangement was assembled and submitted for consideration by the PBAC in November 2012.

The fundamental components of AstraZeneca's minor submission are presented here.

- Proposed wording (summarized in Table 1) the minor submission expressed AstraZeneca's willingness to work with the Secretariat and the Restrictions Working Group to revise the PBS restriction, including listing as a Streamlined Authority, if necessary.
- Comparator - The PBAC has considered a mixed comparator of celecoxib and meloxicam to be appropriate.
- Endpoints - The PBAC remained unconvinced by the claim in the re-submission to the March 2012 meeting that endoscopically-detected ulcer was a valid surrogate for clinically relevant UGI events. Following the post-rejection meeting, AstraZeneca understood that this issue could be dealt with via a pricing proposal.
- Pricing - The minor resubmission offered a price reduction for Vimovo® based on a cost-minimisation analysis versus celecoxib 73% and meloxicam 27%. Financial analysis demonstrated that the PBS listing of Vimovo® would result in cost-savings for the PBS.
- Risk share Arrangement - The minor submission also confirmed *that if "the Committee is of the opinion that an RSA is required for Vimovo, AZA is prepared to negotiate such an agreement in good faith."*

AZA notes that, in May 2013, the NPS, in its monthly e-newsletter for Australian health professionals (NPS Direct) contained an article (available at http://www.nps.org.au/publications/health-professional/nps-direct/2013/cv-risk-and-nsaids [Last accessed: 25 May 2013]) discussing the growing body of evidence showing that NSAIDs are associated with an increased risk of cardiovascular events, with some associated with greater risk than others. The article notes that "one large meta-analysis [Trelle et al, BMJ, 2011] has suggested that for all NSAIDs except naproxen [emphasis added] the increased risk of CV events exceeds 30%" and also advises that risks of gastrointestinal bleeding and peptic ulcer disease may be mitigated by "by using proton pump inhibitors concomitantly." There is clearly a clinical need for the

use of this medicine.

The pricing proposal and the expression of willingness to engage in a RSA are current and still on offer, from AstraZeneca's perspective.

The Independent Review

The following is a more detailed discussion of the key issues addressed in the Review and AstraZeneca's comments.

1. PBAC Criteria for Fixed Dose Combination (FDC) products

AZ request of PBAC on this issue : **1)** considering the findings of the Independent Review, please clarify which of the criteria, if any, is considered mandatory for a combination product to be eligible for a positive PBAC recommendation, **2)** if not all criteria are mandatory, please clarify whether the fact that Vimovo® does not satisfy some of the criteria remains a reason for rejection, **3)** if so, please be explicit about which are the key criterion/criteria, and why non compliance is sufficient for Vimovo to be rejected, while other products have been listed despite the failure to satisfy the same criterion/criteria (see Attachment 1).

The Review (on p12 and pp26-27) finds that the reference to the criteria for FDC products as "minimum requirements" in the PBAC minutes (and other documents including the PBAC Secretariat Overview and the PES Commentary on the submission to the March 2012 PBAC meeting) is *"not accurate"*. Although not considered in the Review, AstraZeneca suggests that it is possible that the *"internal document which PBAC uses to assess products"*, referred to by Review (on p12), is based on an out-of-date version of the PBAC Guidelines (September 2002 – available at http://www.health.gov.au/internet/main/publishing.nsf/Content/health-pbs-general-pubs-guidelines-index.htm/$FILE/guidelines.pdf [Last accessed: 25 May 2013]) because Appendix A to that version of the PBAC Guidelines did refer to the criteria as "minimum requirements" and also used the alpha referencing questioned in the Review (on p27 and pp32-33). The stipulation that all these criteria are required to be satisfied for a combination product to be eligible for consideration by the PBAC was removed with issuance of the 2008 edition of the PBAC Guidelines. Presumably, this was to give the PBAC flexibility to permit it to be able to list products that did not satisfy all the criteria where it considered there was good reason to do so. Several combination products have been listed on the PBS that did not satisfy the same criteria considered not considered to be satisfied by Vimovo®, as summarised in Attachment 1. In line with the Review's recommendations, ***it is requested that the PBAC clarify which of the criteria, if any, is considered mandatory*** for a combination product to be eligible for a positive recommendation by the PBAC. Where the PBAC considers that it is appropriate that there should be some flexibility around the need for a criterion to be satisfied, ***the PBAC is requested to clarify whether the fact that Vimovo® does not satisfy some of the criteria remains a reason for rejection***. If so, ***the PBAC is requested to be explicit about which, and why the criterion/criteria which are not satisfied is sufficient for the request for listing for Vimovo® to be rejected but was not sufficient grounds in cases where products have been listed despite the failure to satisfy the same criterion/criteria (see Attachment 1)***.

AstraZeneca is disappointed and surprised that the Review (on p29) considers that the "PBAC is not required to demonstrate consistency in decision-making". Although AstraZeneca understands that the PBAC should have flexibility in the application of the criteria for FDC products, AstraZeneca considers that consistency in decision-making has been, and should continue to be, one of the objectives to which the PBAC should aspire. AstraZeneca considers that where the PBAC, for some good reason that can be articulated, makes a determination that a particular criterion does not need to be satisfied then sponsors bringing other products to market where the same reasoning applies should also expect to not be required to satisfy the same criterion.

2. Validity of the proposed surrogate measure (PSM) - endoscopic ulcers - as a surrogate for the target clinical outcome (TCO)- clinically relevant upper gastrointestinal events

AZ request of PBAC on this issue: 1) considering the Independent Review findings, please revisit the conclusion with respect to the validity of the surrogate relationship between endoscopic ulcer and clinically relevant UGI outcomes, 2) If the PBAC remains unconvinced please explain why it remains unconvinced and explicitly state what further evidence needs to be presented for the PBAC to accept the claim of a surrogate relationship between endoscopic ulcer and upper GI events

AstraZeneca notes that, in relation to the consideration as to whether the outcome of endoscopic ulcers is reliable and repeatable as a surrogate for clinically relevant UGI events (Part 1 of the Report of the Surrogate to Final Outcome Working Group [STFOWG]), the Review (on pp14&37) finds that "*information from the single small study mentioned by the PBAC is insufficient to outweigh the information about the appropriateness of the PSM presented in the other parts of the framework*". It also notes that, in relation to the consideration as to whether the biological reasoning and

epidemiological evidence is sufficient to support the claim of a surrogate relationship (Part 2 of the STFOWG), the Review (on pp15&38) finds that the "*comments by PBAC on Part Two are insufficient evidence to dismiss the use of endoscopic ulcers as a surrogate for clinically relevant UGI outcomes*". The Review also indicates that Parts 3, 4 and 5 of the STFOWG are reasonably met. Overall, the Review (on pp16&42) finds that *"it seems reasonable to use endoscopic ulcers as a surrogate for clinically relevant upper gastrointestinal outcomes"*. However, the Review (on pp16&43) notes that "*as part of its responsibilities, PBAC will still need to decide whether the evidence is sufficiently strong for them to accept the use of endoscopic ulcers as a surrogate*" and lists a number of factors that this judgment should take into account. ***The PBAC is requested, on the basis of the Review, to revisit its conclusion with respect to the validity of the surrogate relationship between endoscopic ulcer and clinically relevant UGI outcomes. If the PBAC considers that it remains unconvinced about the validity of endoscopic ulcer as a surrogate for UGI events, then the PBAC is requested to explain why it remains unconvinced and to explicitly state whether the PBAC considers that, given the available evidence, it would not be possible for sufficient evidence to be presented for acceptance of the claim of a surrogate relationship between endoscopic ulcer and upper GI events, such that it would be futile for AstraZeneca to assemble a re-submission. If it is that the PBAC considers that it cannot accept the claim that endoscopic ulcers is a valid surrogate for UGI events because of the extent of uncertainty around the specific nature of the relationship, then the PBAC is requested to explain why this issue could not be addressed by appropriate sensitivity analysis.***

3. Minimally clinically important difference (MCID) in endoscopic ulcer outcomes for determination of non-inferiority

AZ request of PBAC on this issue: 1) please confirm that the key issue was the validity of the claim that endoscopic ulcer is a valid surrogate for clinically relevant UGI events, 2) please clarify whether Vimovo® can be recommended for listing only if there is no degree of uncertainty associated with the claim of non-inferiority, and why the previously offer to enter a Risk Share Arrangement does not address any residual uncertainty

The ground for rejection relating to the surrogate outcome is stated in the ratified minutes from the November 2012 consideration of Vimovo as follows:

"…continuing uncertainty regarding the validity of the surrogate outcome for the purposes of demonstrating non-inferiority of more patient relevant outcomes." (p2)

Furthermore, the PBAC minutes from August 2011, state that PBAC "*acknowledged that the naproxen/esomeprazole FDC is likely to be non-inferior to celecoxib, but that this conclusion was based on less convincing outcomes than the Committee had previously relied upon for either meloxicam or celecoxib*".

These statements suggest that the PBAC's issue with the non-inferiority claim relates to the validity of endoscopic ulcers as a surrogate. ***The PBAC is requested to confirm that the key issue with the non-inferiority claim is related to concerns about the validity of endoscopic ulcers as a valid surrogate for clinically relevant UGI events.***

AstraZeneca acknowledges the findings of the Review with respect to the setting of non-inferiority limits for the indirect comparison versus celecoxib for the outcome of gastroduodenal ulcers (p46). However, we feel it is also important to consider that this was only one of the many sources of evidence provided to support this claim. Specifically:

- Evidence from RCTs which directly compared the effect of Vimovo and celecoxib on pre-specified NSAID-associated UGI AEs (presented in the original submission and major resubmission)
- A mixed treatment comparison which compared the effect of Vimovo versus celecoxib ± PPI, NSAIDs ± PII and Arthrotec (diclofenac and misoprostol FDC) (presented in the major resubmission)
- Real world evidence from good quality observational studies which showed that either celecoxib monotherapy or the addition of a PPI to an NSAID are effective strategies for reducing the incidence of patient-relevant clinical outcomes such as GI haemorrhage, perforation or hospitalisation associated with peptic ulcer disease and that the magnitude of the risk reduction observed is comparable (0.2-0.6 for coxibs and 0.2-0.5 for NSAID + PPI) (presented in the minor resubmission)

Accordingly, AstraZeneca seeks clarification from the PBAC as to what further information is required to address any residual uncertainty related to the non-inferiority claim (presuming endoscopic ulcers are found to be a valid surrogate) and why the previous (and currently standing) offer to enter a Risk Share Arrangement was not considered as sufficient to address remaining uncertainty.

4. Financial implications

AZ request of PBAC on this issue: 1) In light of the unequivocal findings of the Independent Review, if the PBAC continues to have concerns about the potential for increased costs for the PBS as a consequence of the PBS listing of Vimovo®, please share the basis of these concerns so that, should AstraZeneca decide to assemble a resubmission, further sensitivity analyses can be conducted and presented, in addition to the already proposed Streamlined Authority listing and RSA.

AstraZeneca notes that the Review (on p19) finds that "*there was no documented evidence before PBAC to support the claim that listing Vimovo® on the PBS would result in increased costs to the PBS*". The Review notes that only extreme assumptions (unlikely to be valid in practice) result in an analysis that is not cost saving.

AstraZeneca is perplexed by the Chair of the PBAC's explanation to the Reviewers (on p19) on how the PBAC arrived at the conclusion that Vimovo® might be associated with increased costs to the PBS. The explanation was that "*In the absence of proposals such as a financial cap or authority restrictions, the committee concluded use in practice would in turn increase the costs to the PBS*". In fact, both of these options have been proposed by AstraZeneca. The Managing Director of AstraZeneca, Mr. Mark Fladrich, at its hearing before the PBAC for Vimovo® on 8 March 2012, indicated to the Committee that AstraZeneca would be prepared to enter into risk-share arrangements that would mitigate the risk of increased costs for the PBS. This preparedness to enter into a risk-share arrangement was confirmed on p40 of the minor submission where it was stated that *if "the Committee is of the opinion that an RSA is required for Vimovo, AZA is prepared to negotiate such an agreement in good faith."* AstraZeneca also articulated its preparedness to consider an Authority Restriction on p5 of the minor submission where it was stated that *"AZA is committed to supporting the use of Vimovo in a manner which is consistent with the principles of QUM. As such, we would like to take this opportunity to express our willingness to work with the Secretariat and the Restrictions Working Group to devise a PBS restriction which most clearly supports this objective, including listing as a Streamlined Authority"*.

The Review found that "…the PBAC conclusion is unable to be reconciled with any costing analysis available." (p54). However, if the PBAC continues to have concerns about the potential for increased costs for the PBS as a consequence of PBS listing of Vimovo® the PBAC is requested to express clearly the scenarios under which the incremental cost are deemed to be possible so that, AstraZeneca is provided with an opportunity to propose measures to address these, notwithstanding the already proposed Streamlined Authority listing and RSA.

Conclusion

Following consideration at the November 2012 meeting, the PBAC recommended rejection of the application seeking listing for Vimovo on the PBAC on the grounds 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." (p2) The Review concluded the following with respect to each of these grounds:Regarding the FDC criteria, "Part IV of the Guidelines lists informational requests only, with no indication that there are minimum requirements." (p12)

- "…it seems reasonable to use endoscopic ulcers as a surrogate for clinically relevant upper gastrointestinal outcomes." (p16)
- "There was no documented evidence before PBAC to support the claim that listing Vimovo on the PBS would result in increased costs to the PBS" (p19)

The Independent Review has provided an external assessment of each of the grounds cited for rejection and has reached a different conclusion to the PBAC. Although of course the ultimate decision with respect to recommendations for PBS listing of products resides with the Committee, given the findings of the Review, AstraZeneca requests that PBAC reconsider its reasons for rejection, recalling AstraZeneca's offer of a Risk Share Arrangement and pricing proposal as previously communicated, and recommend the PBS listing of Vimovo as previously requested. We respectfully question the recommendation of the Review that these issues need to be addressed via a major submission given that two major submissions and one minor submission have already been lodged for Vimovo and as such, a significant amount of evidence has already been presented with respect to these issues. As such, AstraZeneca seeks the opportunity to address any residual issues with the application via a less onerous mechanism.

Table 1: Proposed PBS listing

Name, Restriction, Manner of administration and form	Max. Qty	No of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer	
naproxen 500 mg with esomeprazole magnesium trihydrate 20 mg tablet, 60	1	3	$28.77	Vimovo	AstraZeneca
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					

Attachment 1

Assessment of Vimovo® versus PBAC criteria for FDC products and examples of combination products that have been listed on the PBS despite not satisfying the PBAC criteria for FDC products

Criterion description	Vimovo®	Examples of combination products listed on the PBS that do not satisfy the PBAC criteria for FDC products					
		Aspirin with clopidogrel	Juvicor (simvastatin with sitagliptin)	Seretide (Fluticasone with salmeterol)	Duodart (Dutasteride + tamsulosin)	ZanExtra (lercanidipine with enalapril)	Ramipril with felodipine
(a) The product should be approved or is recommended for approval by the TGA and meets all clinical criteria required by the TGA.	√	√	√	fluticasone (as Flixotide®) is not TGA-approved for use in COPD.	√	√	√
(b) The component products should preferably be listed on the PBS.	esomeprazole is not PBS-subsidised for prevention of GI complications	clopidogrel is not PBS listed for treatment following stent insertion	√	salmeterol is not PBS listed for COPD.	tamsulosin is listed on the RPBS, it is not listed on the PBS.	√	√
(c) Restrictions for the component products should be consistent with those proposed for the combination.	not satisfied for the same reason (as above)	clopidogrel is not PBS listed for treatment following stent insertion	√	salmeterol is not PBS listed for COPD and fluticasone (as Flixotide®) is not TGA-approved for use in COPD.	tamsulosin is listed on the RPBS, it is not listed on the PBS.	√	√
(d) The doses of the listed component products and the proposed combination should be consistent.	√	√	not available in combination with sitagliptin 50 mg or 25 mg, being therefore unsuitable for patients with moderate to severe renal insufficiency..	√	√	patients may need lercanidipine 20mg	patients may need other combinations e.g. 5 mg/2.5 mg or may need ramipril 10 mg
e) There should be additive (not necessarily synergistic) beneficial effectiveness of the components.	√	√	The PBAC considered that the submission did not	√	√	√	√

			demonstrate additive benefits of FDC sitagliptin/simvastatin.				
(f) The combination should not encourage or result in an inappropriate increase in overall utilisation of the components, nor inappropriate use of one or both components in specific patient groups.	√	√	The PBAC considered that there is a risk that sitagliptin may be used earlier in the treatment algorithm than specified in the PBS restriction	√	√	√	√
(g) The combination products should not result in inappropriate dosing of either component, nor contain components which required individual dose titration.	only available for use in patients requiring a twice daily dose of naproxen 500 mg	√	The PBAC considered that on balance the risk of inappropriate dosing with a sitagliptin/simvastatin FDC was low.		√	patients may need lercanidipine 20mg	patients may need other combinations e.g. 5 mg/2.5 mg or may need ramipril 10 mg
(h) The combination product should not result in unnecessary proliferation of product and/or dose forms.	√	√	The PBAC was not convinced of a pressing clinical need for a sitagliptin/simvastatin FDC but accepted that there may be a need to reduce pill burden in some patients with diabetes who require a statin	√	√	√	√