INDEPENDENT REVIEW
May 2013

PHARMACEUTICAL BENEFITS SCHEME

NAPROXEN with ESOMEPRAZOLE

Names of reviewers redacted

Contents

REQUESTED LISTING

Submission type *(new drug application, changes to listings, resubmissions)*	**Drug Name, form(s), strength(s) and Sponsor** *(Drug name, form, strength, Trade name®, Sponsor)*	**Drug Type and Use** *(What is the drug used to treat?)*	**Purpose of Submission**
Review	NAPROXEN with ESOMEPRAZOLE, tablet, 500 mg – 20 mg (as magnesium trihydrate), Vimovo®, AstraZeneca Pty Ltd	Symptomatic treatment of osteoarthritis, rheumatoid arthritis or ankylosing spondylitis	Report on the Independent Review for naproxen with esomeprazole for the symptomatic treatment of osteoarthritis, rheumatoid arthritis or ankylosing spondylitis.

Name	Naproxen with esomeprazole magnesium trihydrate
Restriction	N/A
Strength	500mg/20mg
Maximum quantity	60
No. of repeats	3
Dispensed price for maximum quantity (DPMQ)	$28.77
Proprietary name	Vimovo®
Manufacturer	AstraZeneca Pty Ltd
Section 100	N/A

SCOPE OF THE REVIEW

History of submissions

AstraZeneca have applied for a listing for Vimovo® on three occasions, twice as a major submission and lastly, on advice, as a minor submission. An abbreviated summary of the PBAC decisions on these three submissions follows. The full minutes are on the PBAC website.

August 2011 Major Submission

The PBAC ... rejected the submission because the comparator was inappropriate and there were no data to make a recommendation.

March 2012 Major submission

The PBAC rejected the submission on the basis of: …

- Inappropriate comparator
- Uncertainty regarding the validity of the surrogate outcome…
- Resultant uncertainty in the proposed cost-minimisation analysis…
- An expectation that listing as requested could result in increased costs both overall and also to the PBS.

November 2012 Minor submission

The PBAC rejected the submission on the basis of:

- Inappropriate comparator
- Uncertainty regarding the validity of the surrogate outcome…
- Resultant uncertainty in the proposed cost-minimisation analysis
- An expectation that listing as requested could result in increased costs both overall and also to the PBS.

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

Grounds for Review

There are three grounds for review with a number of subordinate issues raised within them. The grounds of review are as follows:

1. **PBAC Criteria for Fixed Dose Combination Products**

   PBAC's conclusion "that not all PBAC criteria for combination products are met" (Ratified minutes of the November 2012 PBAC meeting, page 2, paragraph 4) 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.

2. 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.

3. 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" (Ratified minutes of the November 2012 PBAC meeting, page 2, paragraph 4) is unable to be reconciled with any costing analysis available.

The complete Independent Review Request is at Attachment 5.

DESCRIPTION OF THE REVIEW

Approach to the Review

The Review covers three disparate grounds and as a result three Secondary Reviewers were engaged to support the Primary Reviewer who brings health economic expertise:

- Epidemiological expertise to review non-inferiority and surrogate outcomes;
- Pharmacological expertise to provide input on utilisation and on the various comparators to Vimovo®;
- Public administration expertise in the use and purpose of guidelines by committees with a statutory role.

Reviewers

Names and short biography of reviewers redacted

Structure of the report

Upon investigation, many of the issues have a common theme. Accordingly the report is structured with an overview in the main body which draws together the findings on each ground, but which also makes some overarching comments where there are common themes.

Each report by a Secondary Reviewer is attached in full.

General process

The list of materials considered by all reviewers is at Attachment 4. The individual reviewer reports include:

- the answers to questions asked of the department or the Sponsor
- file notes of consultations
- any other material considered in the review.

There was one meeting of all reviewers with the Convenor, and a regular teleconference with each reviewer to monitor progress. The Primary Reviewer also met weekly with [*names of reviewers redacted*].

PRIMARY REVIEWER REPORT

Introduction

The framework for this Independent Review has been informed by the two important processes that underpin the Pharmaceutical Benefits Advisory Committee (PBAC) and its sub-committees – the technical assessment of submissions and the deliberations and judgement that underpin PBAC recommendations.

The technical assessment of submissions is supported by the *Guidelines for preparing submissions to the PBAC* (Version 4.3). It is the Guidelines that advise PBAC and Sponsors alike of what constitutes best practice in **comparing** the product under consideration to another currently listed medicine (the comparator). The Guidelines form one major point of reference for all three grounds of our review. The other is the *Report of the Surrogate to Final Outcome Working Group* (STFOWG) – a framework for evaluating proposed surrogate measures and their use in submissions to the PBAC (2009). The STFOWG report provides the major point of reference for the second ground of the review that deals with surrogates outcomes and non-inferiority. The 'Parts' of the STFOWG framework, which map against the Steps (1-3) from the Guidelines 'Use of surrogate outcomes to estimate final outcomes' (Pages 108 – 109), produce a summary framework for our evaluation.

The information contained in each of the two major and one minor submission is subject to processes overseen by PBAC and its secretariat that involve critical appraisal, deliberation, reasoning and decision making. The first part of the process evaluates the validity of information used to make judgments; the second integrates multiple criteria in forming the recommendation by PBAC. We have reviewed all documents related to both the technical assessment of the information contained in each of the three submissions and the PBAC deliberations, reasoning and recommendation as reflected in the formal minutes of PBAC meetings, noting the response of the Sponsor in each instance.

Above all this is regulation and legislation that mandates the process of listing medicines on the PBS. The outcome of the process is published and open for all to see. In short, PBAC has the right to decide and a responsibility to explain.

PBAC's right to decide and responsibility to explain

Our assessment of the first ground of the review "PBAC Criteria for Fixed Dose Combination Products" focuses on the PBAC's responsibility to explain its deliberations, reasoning and recommendation in a clear and open manner. It also addresses the requirements for assessing Fixed Dose Combination (FDC) drugs, which relates to Part IV of the Guidelines and specifically to PT1.1 "Matters to consider for the listing of fixed combination products" and the table on 'Information requests' (page 211).

The responsibility to explain in a clear and open manner goes to the heart of the matters assessed in this Independent Review of PBAC's decision on the Vimovo® applications. PBAC were working well within their responsibilities in their continued rejection of the Vimovo® application for listing on the PBS. However our review finds that in this instance, the PBAC has not adequately explained its decision to reject the Vimovo® application. The reasons for the decision to reject the Vimovo® application could have been explained in the minutes in a more consistent, transparent and timely manner.

Judgment under conditions of uncertainty

Whilst judgment in the face of uncertainty characterizes every decision to a list a new product on the PBS, there were a number of aspects of the Vimovo® submission that compounded the level of uncertainty for PBAC. Decisions must be made on the basis of the best available evidence – the question is whether that evidence is good enough to satisfy a claim for non-inferiority.

Our assessment of the second ground of the review "Validity of the surrogate outcome and non-inferiority" focuses on the extent to which the information presented in the submissions fulfils the parts of the STFOWG framework for evaluating proposed surrogate measures and their use in submissions to the PBAC. We also assess the level of evidence presented by the Sponsor to establish non-inferiority and likewise assess PBAC's evaluation of that evidence. Our review includes an assessment of whether sources of uncertainty have been adequately explained and communicated in the minutes of PBAC. The second ground of the review reinforces our view that PBAC has the right to decide and a responsibility to explain.

Future demand and financial impact

The overall net cost to the PBS of listing Vimovo® is a function of price (of the product and its comparator/competitors) and quantity (uptake and substitution). The third ground of the review "Continuing concern that the listing of Vimovo® could result in increased costs to the PBS" focuses the evidence used to support this claim. The reviewers used the Sponsor's Section E financial impact model to conduct further one-way sensitivity analyses in an attempt to establish the likely cause of concern about increasing costs.

The following three sections summarises our approach, conclusions and recommendations relating to each of the three substantive grounds for the review. The companion reports prepared by the primary and secondary reviewers provide further detail on our analysis of each of the three grounds for the Independent Review.

The first ground for review relates to the PBAC Guidelines.

PBAC Criteria for Fixed Dose Combination Products

Minimum Requirements

There is some ambiguity on the requirements for assessing Fixed Dose Combination (FDC) drugs, which relates to Part IV of the Guidelines and specifically to PT1.1 "Matters to consider for the listing of fixed combination products" and the table on 'Information requests' (page 211).

What is stated in the Guidelines as information requests had, by the 3rd Minor Submission, been represented in the minutes as a set of minimum requirements. This is not an accurate representation of the content of the Guidelines.

The information available suggests that the following sequence of events has occurred:

- PBAC has used the eight information requests on at Pt1.1 of Part IV of the Guidelines to develop eight requirements which it determined that fixed dose combination products must satisfy. These are referred to as 'minimum requirements for combination products to be eligible for consideration for PBS listing' in an internal document which PBAC uses to assess products.
- PBAC decided that Vimovo® did not satisfy the 'minimum requirements'.
- The PBAC Minutes, PBAC Sec OVR and March 2012 Commentary have referenced the 'minimum requirements' to Part IV of the Guidelines.

This reference to the Guidelines in the minutes is not accurate, as Part IV of the Guidelines lists information requests only, with no indication that there are minimum requirements. It is the Guidelines themselves that should remain the authoritative source for best practice in the preparation of a submission to the PBAC. It is within the PBAC charter to use internal documents to assist in considering submissions, but where they become mandatory the Guidelines should be amended to reflect this fact. PBAC should also consider making it clear that meeting such criteria would not, of itself, guarantee a positive recommendation as there may be other relevant matters that the PBAC would consider on a case-by-case basis.

Disclosure

Secondly, the PBAC requirement for meeting all criteria of Pt1.1 only emerged on the 3rd Vimovo® submission. Given the cost, effort and time involved in the preparation and evaluation of a submission for listing a new product on the PBS, the formal (committee-based) and informal (pre- and post-submission meetings) meetings are both exemplar processes for assessing the expected value of information within the overall remit to consider the clinical, economic and other aspects of a new product for listing on the PBS. The processes are exemplars in the sense that PBAC strives for transparency in its proceedings consistent with the secrecy provision of the Act. That openness promotes resource effective and accountable behaviour by PBAC. We acknowledge the value of PBAC's approach to work with a Sponsor through the pre- and post-PBAC meetings to clarify

issues, highlight uncertainties and strive for early formal disclosure of the reasons for its decisions.

Consistency

Thirdly, the issue of consistency of PBAC's decision making with respect to fixed dose combination products was considered by the Review team. All things being equal, identical FDCs being considered for listing in the context of a static market would result in the same conclusion. But all things are not equal and consistency in decision-making is difficult to achieve in the context of emerging products in dynamic markets. Comparison is the main objective of the PBAC processes for listing a new product on the PBS Section 101 3(A) of the National Health Act says 'For the purpose of deciding whether to recommend to the Minister that a drug or medicinal preparation, or a class of drugs and medicinal preparations, be made available as pharmaceutical benefits under this Part, the Committee shall give consideration to the effectiveness and cost of therapy involving the use of the drug, preparation or class, including by comparing the effectiveness and cost of that therapy with that of alternative therapies, whether or not involving the use of other drugs or preparations.'

Conclusions

In this instance PBAC documentation did not ensure that minimum requirements and/or threshold issues were communicated to the applicant early in the assessment process.

In general, the quality and clarity of the minutes regarding the Vimovo® applications could have been improved. As drafted, the minutes conflate technical requirements of the Sponsor with PBAC judgments about evidence. Also, the reasons for PBAC decisions related to the Vimovo® application were not as adequately communicated in writing to the Sponsor as they could have been. For example, the persistent use of the word 'uncertainty' in the minutes obscures the need to explain the reasoning used and conclusions reached by PBAC.

Just and accountable decision making

In light of our observations we suggest that the basic principles of just and accountable decision-making generally afford the applicant the right to:

- Know what criteria they must satisfy;
- Be heard - to provide information and argue their case;
- Know what information has been considered in making the decision; and
- Know the reasons for the decision.

This leads us to the following recommendations:

Recommendation 1

We recommend that sufficient resources be devoted to the preparation of PBAC minutes to improve the detail, accuracy and clarity of the minutes.

Recommendation 2

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

Validity of the surrogate outcome and non-inferiority

The technical assessment of the information contained in the submission consists of multi-staged evaluation of the validity and usefulness of information for the purpose of comparison – comparing the new product to current therapy. This process is underpinned by the Guidelines for preparing submissions that represent 'best practice' and allow the PBAC to make the necessary comparison. The decision making itself requires the PBAC to assess and weight the multiple criteria that form the basis for a recommendation. All of which is done knowing that uncertainty characterizes every aspect of the process, from assessing the validity of the information, the known and predicted outcomes of the product and the nature of decision making itself.

In the case of Vimovo® PBAC expressed continuing uncertainty regarding the validity of endoscopically-detected ulcers as a surrogate outcome for the purposes of demonstrating non-inferiority of more patient-relevant outcomes. At the heart of the matter are two issues. The first issue is the validity of the surrogate measure: whether it provides an adequate measure by which to judge the effect of the drug on more patient-relevant relevant outcomes. The second issue is whether non-inferiority against the comparator has been adequately assessed.

Validity of the surrogate in principle

Our assessment of the validity of the surrogate outcomes was conducted within the PBAC framework for evaluating surrogates. The framework included elements (Part 1-5) proposed by the *Report of the Surrogate to Final Outcome Working Group* (STFOWG) – a framework for evaluating proposed surrogate measures and their use in submissions to the PBAC (2009), which map against the Steps (1-3) from the Guidelines 'Use of surrogate outcomes to estimate final outcomes' (Pages 108 – 109) producing a summary framework for our evaluation.

Working through parts one to five of the framework, Part One includes the definition, selection and measurement of the potential surrogate marker (PSM) and the target clinical outcome (TCO). The main issue here is the repeatability of the measure. The Sponsor does not present any measure of repeatability but states that the assessment of PSM is standardized in the trials. Material before PBAC suggests that there is poor repeatability on the basis of one small study published as an abstract. The information from the single small study in the PES commentary is insufficient to outweigh the information about the appropriateness of the PSM presented in the other parts of the framework. This is reflected by the STOFWG comment: "If relevant meta-regression data from multiple randomised trials

supporting the link between the comparative treatment effect on the PSM and the comparative treatment effect on the TCO are available for Part Three ….the amount of information needed for 1A.6 is reduced." [1.A.6 is "An assessment of the validity, reliability and responsiveness of the method for measuring the PSM."].

Part Two addresses biological reasoning and epidemiological evidence supporting the relationship between the PSM and TCO, independent of any intervention. The Sponsor presents indirect evidence 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. They also present evidence that endoscopic ulcers and upper gastrointestinal bleeding are associated with other variables, such as age and previous history. The PES/PBAC comment that not all endoscopic ulcers will progress to clinical ulcers is based on a textbook reference (MacDonald). Progression of all endoscopic ulcers to clinical ulcers is not a necessary criterion to justify the use of a surrogate. The issue is not prediction of clinical ulcers in individuals, but whether the PSM shows the same relationships to other variables as the TCO in population studies. The relationship of surrogate and clinically relevant outcomes to NSAIDs is consistent in direction, though not in apparent magnitude.

The comments by PBAC on Part Two are insufficient evidence to dismiss the use of endoscopic ulcers as a surrogate for clinically relevant upper gastro-intestinal (UGI) outcomes.

The most important and relevant part of the framework to our Review is Part Three – the randomized trial evidence using other medicines to show that there is a basis to conclude that a comparative treatment effect on the proposed surrogate measure (PSM) has satisfactorily predicted a comparative treatment effect on the target clinical outcome (TCO). Ideal evidence would be direct, based on studies in which the endoscopic ulcers and clinical endpoints were measured on the same patients randomized to treatment options. The STFOWG suggested hierarchy of evidence ranges from Level I (multi-trial meta-regression) the strongest to Level IV (no randomized trial data) the weakest. Direct evidence is unavailable. The Sponsor provides indirect evidence [drug effects on PSM and on TCO from different trials] from a review of multiple trials and extra information from Gastrointestinal Drug Advisory Committee (GIDAC) documents to FDA. The PES commentary for the March 2012 meeting comments on the fact that the RRs for COX-2 selective inhibitors compared with NSAIDs are generally smaller [greater relative risk reduction] for endoscopic ulcers than for clinically relevant outcomes. They suggest that overestimation by using endoscopically detected ulcers may have an impact on establishing non-inferiority.

The PES also point out that the confidence intervals (CIs) are very wide for the study on clinically relevant outcomes in the study of high-risk patients comparing naproxen + esomeprazole vs. naproxen alone.

The Reviewer notes that direct evidence is lacking and unlikely to be obtainable. The indirect evidence points towards endoscopic ulcers showing similar results to clinical endpoints, based on the point estimates, for several drugs which are designed to avoid the UGI complications of conventional NSAIDs. If the effect of these drugs is greater on the PSM than the TCO, it will make for a more stringent test of non-inferiority.

Though not ideal, the evidence is considered acceptable to fulfil Part Three of the STFOWG.

Part Four addresses the level of support for why the relationship between comparative treatment effects on the PSM and TCO with other medicines is likely to apply to the proposed product. The information in Part Three above seems to hold reasonably for drugs such as celecoxib [the major comparator] and there is some evidence that the effect is similar for naproxen plus esomeprazole. Within the constraints of the information available in Part Three, there are no additional concerns about Part Four.

Part Five includes relevant considerations for incorporation of the comparative treatment effect based on the PSM in the economic evaluation. Good quantitative direct evidence on the relative effects of the drugs on the PSM and TCO is lacking. However, the indirect evidence suggests that the effect of drugs will be similar or less on clinically relevant outcomes than on endoscopic ulcers. The available evidence suggests it would be reasonable to consider Part Five as sufficiently well addressed to assess non-inferiority on endoscopic ulcers as a surrogate for clinically relevant outcomes.

Conclusions

Although evidence from studies assessing clinically relevant outcomes is clearly always preferable, it seems reasonable to use endoscopic ulcers as a surrogate for clinically relevant upper gastrointestinal outcomes based especially on Parts Two and Three, the most important parts of the STFOWG report.

However, PBAC will still need to judge whether the evidence is sufficiently strong for them to accept the use of endoscopic ulcers as a surrogate. This judgement needs to take into account that:

- Surrogates are most useful when the clinically relevant outcomes are distant in time. In that case, the use of surrogates can appreciably shorten the duration of studies. If the clinically relevant outcomes occur in a similar timescale to the surrogates, they may still have the advantage of requiring smaller sample sizes in randomised trials.
- Evidence has accumulated, since PBAC decisions were made about celecoxib, to support the use of endoscopic ulcers as a surrogate.
- Getting better [direct] evidence about the value of the surrogate as a predictor of clinically relevant outcomes is unlikely. [STFOWG Part Two]
- Because endoscopic ulcers as a surrogate is becoming more widely accepted, it is difficult now to mount studies to get direct evidence on clinically relevant outcomes. [STFOWG Part Three]

Adequacy of assessment of non-inferiority

PBAC Guidelines say that a Sponsor should explain and justify the non-inferiority threshold difference in treatment effect between the proposed drug and its main comparator, and provide a point estimate of the difference, with its 95% confidence interval, to assess whether the confidence interval overlaps the threshold.

This has been done for outcomes related to the naproxen component of Vimovo®, and are presented in the cost-minimisation checklist. The upper gastro-intestinal outcomes are of obvious importance for this drug combination, as stated by the Sponsor. However, non-inferiority limits have not been provided for the ulcer outcomes. Confidence intervals [based on indirect comparison via naproxen] of Vimovo® and celecoxib for gastroduodenal ulcers at 3 months are wide [Risk Ratio 0.85 (CI 0.28 2.56)]. This suggests an economic analysis based on cost-minimisation is not well justified.

Conclusion

Non-inferiority limits for upper gastrointestinal outcomes need to be proposed and justified. Using their usual methods and cost-minimisation checklist, PBAC then can consider the quality of the evidence and the confidence limits around the estimated difference in ulcer outcomes between Vimovo® and comparator products to decide whether non-inferiority is a reasonable assumption.

A judgement then needs to be made about the appropriate economic evaluation, with sensitivity analyses to reflect the uncertainty about the differences in gastrointestinal outcomes between Vimovo® and comparator products. The sensitivity analyses could reflect both the statistical uncertainty of the estimated surrogate outcome, as well as any uncertainty about how the result on the surrogate outcome translates to clinically relevant outcomes.

Recommendations

The following are recommendations for PBAC submissions prompted by consideration of this request for Independent Review.

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.

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.

Continuing concern that the listing of Vimovo® could result in increased costs to the PBS.

The grounds for PBAC's continuing concern that the listing of Vimovo® on the PBS could result in increased costs to the PBS relates specifically to factors associated with uncertainty in the Sponsor's assumptions relating to expected use and price. Those factors include growth in the NSAID market itself, Vimovo®'s share of the markets and the specific assumptions regarding uptake and substitution patterns for Vimovo®, price weighting of Vimovo®, the proportion of patients currently on celecoxib + PPI (Proton-pump Inhibitor) or nsNSAID (non-selective non-steroidal anti- inflammatory drug) + PPI who have at least 1 gastrointestinal (GI) risk factor, known statutory price reductions for rabeprazole and esomeprazole and further price reductions of NSAIDs.

From the first to the third submissions PES/PBAC expressed concerns about the potential for Vimovo® to increase overall net costs to the PBS. At no point could we locate any information in the documents provided to the review team that supported this claim. There was one direct request from PBAC to the Sponsor to use an alternate set of assumptions on market uptake and substitution. These assumptions were provided by DUSC and the Sponsor complied with the request. The results did not change the conclusion that Vimovo® produced an overall negative net cost (cost saving) to the PBS. Another request from PBAC asked the Sponsor to include known statutory price reductions in rabeprazole and esomeprazole. The results did not change the conclusion that Vimovo® produced an overall negative net cost (cost saving) to the PBS.

The Sponsor correctly states the request from PBAC to include in further analysis on 'the ongoing reductions in the PBS prices of some PPIs and NSAID medicines' is not consistent with the Guidelines that specify the use of constant prices and zero inflation in estimating the overall net cost to the PBS. As PBAC was concerned about the impact of future price reductions of NSAIDs then they have the right to request the information. But in this instance it has not been accompanied by their responsibility to explain the reasons for the request.

The Primary Reviewer sought a meeting with the Chair of the PBAC to clarify how PBAC arrived at the conclusion in the minutes of PBAC meeting that Vimovo® would increase the overall net cost to the PBS.

The Primary Reviewer was advised that, following the Sponsor lodging a minor submission (as suggested by the Department of Health and Ageing in a pre-submission meeting), the application could not been returned to DUSC for further analysis of utilization against the latest financial impact costings. As a result, the PBAC had to form a view about the utilization figures. 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.

Conclusions

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 PES and PBAC accepted the Section D and Section E information with just a few minor corrections, the validity of the Sponsor's financial estimates model was not questioned and the Sponsor responded appropriately to PBAC requests for it to model the financial impact using revised assumptions.

While the Committee was entitled to make that judgement based on the expertise of its members, this could have been explained more clearly in the minutes.

Addendum

As an independent exercise the Review team used the Sponsor's model to conduct a series of one-way sensitivity analyses to ascertain the possible causes of concern about cost increases in listing Vimovo® on the PBS. Only the extreme assumptions about market growth and price reductions in celecoxib +/- PPIs and NSAIDs +/- PPI demonstrated the potential to flip the Overall Net Cost to the PBS from negative (cost saving) to positive (cost inducing). The full details of this analysis are contained in the companion report on costings.

Overall Conclusion

There are few mandated approaches to the evidence-based evaluation of a new product that are as well tried and tested as that led by the PBAC. Its longevity is testament to the rigour and credibility of the PBAC process. Indeed it is the pillars of PBAC, the guidelines for best practice and critical appraisal that guided us in our review of the issues raised by the Sponsor. The application of those principles and practice in this instance (with Vimovo®) could have been improved by clear and more open communication of the deliberations and reasons for the conclusions reached by PBAC. Where PBAC exercises its right to request further information or highlight issues in the interests of managing the level of uncertainty around its decision, then there is a responsibility to explain those reasons to the Sponsor,

particularly where it involves a departure from the Guidelines. The minutes of PBAC meetings should fully reflect the reasoning used and conclusions reached by PBAC.

The Guidelines provide support for best evaluation practice. We have identified a deficiency in the current Guideline for Fixed Dose Combination Products as to what constitutes 'minimum requirements'. We recommend that this deficiency be fixed.

PBAC is required to make judgments based on the best available evidence now. Only PBAC can decide where it sets the threshold for acceptable evidence. Even with the best available evidence and full compliance by the Sponsor with best practice (as embodied in the Guidelines) there will be times when the best available evidence is not enough to justify a recommendation.

Given the evidence, PBAC will need to decide whether it is sufficiently strong for them to accept the use of endoscopic ulcers as a surrogate. Then information about proposed non-inferiority limits for upper gastrointestinal outcomes and their justification need to be supplied. Using their usual methods, PBAC then can consider the confidence limits around the estimated difference in Ulcer outcomes between Vimovo® and comparator products to decide whether non-inferiority is a reasonable assumption.

The previous step will determine whether cost-minimisation is appropriate or what type of economic modelling is necessary, and what sensitivity analyses should be included to reflect the uncertainty about the differences in gastrointestinal outcomes between Vimovo® and comparator products.

Finally, markets are inherently dynamic and predictions for use, price and financial impact on the PBS may be uncertain. If there are concerns about the assumptions used in the Section E financial modelling then they need to be expressed clearly and preferably quantified.

Overall Recommendation

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

Attachment 1

PBAC CRITERIA FOR FIXED DOSE COMBINATION PRODUCTS

Report prepared by *Name of reviewer redacted*

PBAC CRITERIA FOR FIXED DOSE COMBINATION PRODUCTS

Reviewer

Name of reviewer redacted

Matters detailed in the Independent Review Request

This report focuses on the first ground for review;

> PBAC Criteria for Fixed Dose Combination Products
> PBAC's conclusion "that not all PBAC criteria for combination products are met" (Ratified minutes of the November 2012 PBAC meeting, p2, paragraph 4) inappropriately applies the information requests as outlined on p211-212 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.

The Sponsor raised three specific concerns in relation to the matter:

1. That the Pharmaceutical Benefits Advisory Committee's (PBAC's) conclusion 'that not all PBAC criteria for combination products are met' inappropriately applied the information requests as outlined in Part IV of the Guidelines for preparing submissions to the PBAC as minimum mandatory requirements for combination products to be eligible for consideration for PBS listing. The description of these information requests as 'minimum requirements' is inappropriate and overstates the standing of these criteria. There is no indication in the PBAC Guidelines that all these requirements must be satisfied for a combination product to be eligible for consideration by PBAC;

2. The PBAC requirement for meeting all criteria only emerged on the 3rd (minor) submission. In terms of procedural fairness it should have emerged at the first (major) submission. The criteria which Vimovo® was deemed not to have satisfied has not been consistently stated during the evaluation; and

3. PBAC's description and application of the 'information requests' in Part IV of the Guidelines as 'minimum requirements that combination products need to satisfy in order to be eligible for consideration by PBAC', is inconsistent with previous PBAC decisions, whereby combination products which do not meet all the criteria have not only been considered by the PBAC but also listed on the PBS.

Reviewer's understanding of the matters to be reviewed

Part IV of the Guidelines for preparing submissions to the PBAC including major submissions involving economic analysis (page 211) lists matters to consider for the listing of fixed combination products. There are eight matters listed under the title of 'information requests'. In the Minutes of the PBAC meeting held on 7-9 November 2012, PBAC referred to these information requests as minimum requirements for combination products to be eligible for consideration for PBS listing. The application for review raises the following questions:

- What is the meaning of PBAC's reference to the information requests as "minimum requirements"? Does this decision overstate the standing of the information requests as presented in the Guidelines?
- Did PBAC communicate its concerns and requirements consistently to the Sponsor throughout the assessment process?
- Is PBAC required to apply these minimum requirements consistently?

Status and purpose of the PBAC Guidelines

The PBAC Guidelines state that, since January 1993, it has been mandatory for companies making submissions to PBAC to follow the Guidelines. The current Guidelines, released in December 2008, are described as Version 4.3. Vimovo® is subject to the Version 4.3 Guidelines (referred to in this report as 'the Guidelines'). PBAC is an independent statutory body established on 12 May 1954 under section 101 of the *National Health Act 1953*. The Guidelines do not require ministerial or parliamentary approval. There is no legislative requirement for the Guidelines nor are the Guidelines drawn from any legislative instruments.

The purpose of the Guidelines, as stated at Section 2, is to provide practical information for the pharmaceutical industry in making a submission to PBAC. It is further stated that the Guidelines are also intended to help PBAC assess submissions and provide information to other interested stakeholders. The Guidelines specify the information to be included in a submission and how the content is to be structured in a submission.

Section 4.6 states that it is in the interests of the community, industry and PBAC that uniformity be maintained in the way that economic analyses are conducted and evaluated. However it is also stated that there will continue to be flexibility in the interpretation of these Guidelines, to help industry and government to further increase their experience of, and expertise in, the techniques of economic evaluation.

What are information requests?

The term 'information request' is used throughout the Guidelines. The term is not listed in the glossary; therefore a definition is not available to the Sponsor. Section 2.3 of the Guidelines advises that the Guidelines include a series of requests for specific types of information. The stated aim is to provide an ordered series of reference points (requests for information) against which the specific information presented in a submission can be assessed to ensure that the submission is complete.

Section 2.3 provides further advice on how to discriminate between different information requests. It states that the default writing style for requests uses the imperative voice; therefore the reader should interpret these imperative statements as indicating what **should** be provided. In two instances, the request includes the word '**must**' and failure to comply with these requests is sufficient to render the submission unacceptable, and for the submission to be returned to the Sponsor. In some other instances, there is no basis to indicate a preference for one type of information over another. In these instances, options about what **could** be presented are usually given.

The information requests in this case relate to eight matters listed in the table on Part IV 1.1 titled 'Matters to consider for the listing of fixed combination products'. As the table does not include the words 'must' or 'could' the reader assumes that the imperative applies, therefore the information should be provided. In the absence of a definition, it is necessary to rely on the instructions Section 2.3 to determine whether specific information requests must, should or could be provided. In the present case, the Sponsor did provide information addressing the eight matters in the table.

Are information requests the same as minimum requirements?

The Minutes of the November 2012 PBAC meeting state that the re-submission was rejected on the basis, among other things, that not all PBAC criteria for combination products are met.

The Minutes refer to page 3 of the PBAC Secretariat Overview (SEC OVR) and p 20 of the March 2012 Commentary.

The PBAC SEC OVR 7.10.3 contains a table of eight matters listed (a) – (h) under the heading of *Combination Products.* The sentence preceding the table says "Part IV of the December 2008 PBAC Guidelines specifies a number of minimum requirements that combination products need to satisfy in order to be eligible for consideration by the PBAC". However there is no reference in Part IV of the Guidelines to 'minimum requirements'.

The following table compares the table at 1.1 of Part IV of the Guidelines with the table at 7.10.3 of the PBAC SEC OVR. Although the matters in the two tables are generally consistent, albeit re-numbered, PBAC has distilled specific matters and expressed them as requirements which 'should' or should not' achieve certain outcomes.

Table 1: Comparison of PBAC Guidelines and PBAC SEC OVR 7.10.3

Part IV PBAC Guidelines	PBAC SEC OVR 7.10.3
Comply with all information requests in Parts I-III of these Guidelines where applicable	
Provide information as part of the response to Part II, Subsection A.2 to show that combination product has been approved by the TGA, and meets all clinical criteria required by the TGA. Confirm that any requested restriction is consistent with any restriction for each component of the combination product	(a) The product should be approved or is recommended for approval by the TGA and meets all clinical criteria required by the TGA. (c) Restrictions for the component products should be consistent with those proposed for the combination.
For each component of the combination product, provide information as part of the response to Part II, subsection A.3 to show that:	
- it is (preferably) listed on the PBS or funded on the NIP.	(b) The component products should preferably be listed on the PBS.
- the doses are consistent with the doses of the combination product	(d) The doses of the listed component products and the proposed combination should be consistent.
Also as part of the response to Part II, Subsection A.3, show that listing the combination product would not result in:	
-Inappropriate dosing of ether component (eg the combination product should not contain components for which individual dose titration is preferable)	(g) The combination products should not result in inappropriate dosing of either component, nor contain components which required individual dose titration.
- unnecessary proliferation of products or dose forms.	(h) The combination product should not result in unnecessary proliferation of product and/or dose forms.
As part of the response to Part II, Subsection A.4, identify the main comparator products and explain the reasons for the selection of these comparators.	
Provide data as part of submission section B to show additive (not necessarily synergistic) beneficial effectiveness of the components.	(e) There should be additive (not necessarily synergistic) beneficial effectiveness of the components.
Substantiate any claims of improved patient convenience or compliance in terms of their impact on improving health outcomes (as part of the response to submission sections B or C), reducing provision of other health care resources (as part of submission sections B, C or D), or reducing expenditure in the Australian Government health budget (as part of submission section E).	
Provide an analysis as part of submission section E to show that listing the combination product would not encourage or result in an inappropriate increase in overall use of its individual components, nor in inappropriate use of one or more of those components in specific patient groups.	(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 March Commentary, at 7.4, provides an analysis of Vimovo® against each of the criteria listed in the table at 7.10.3 of the SEC OVR. I note that the expressed purpose of the Commentary is to provide feedback to the Sponsor on the submission, as it is prepared during the evaluation stage and the focus is on the submission itself rather than the proposed drug.

The information available suggests that the following sequence of events has occurred:

- PBAC has used the eight information requests at 1.1 of Part IV of the Guidelines to develop the requirements which it determined that combination products must satisfy. These are referred to as 'minimum requirements for combination products to be eligible for consideration for PBS listing' in an internal document which PBAC uses to assess products.
- PBAC decided that Vimovo® did not satisfy the 'minimum requirements'.
- The PBAC Minutes, PBAC SEC OVR and March 2012 Commentary have referenced the 'minimum requirements' to Part IV of the Guidelines.

Conclusion

The reference to the Guidelines in the minutes is not accurate, as Part IV of the Guidelines lists information requests only, with no indication that they are minimum requirements.

I do not accept the Sponsor's assertion that PBAC's decision overstates the standing of these criteria. The PBAC Guidelines advise that information addressing the eight matters should be provided in order for PBAC to undertake an informed assessment. However the Guidelines do not prescribe PBAC's decision-making, they relate only to the development of submissions.

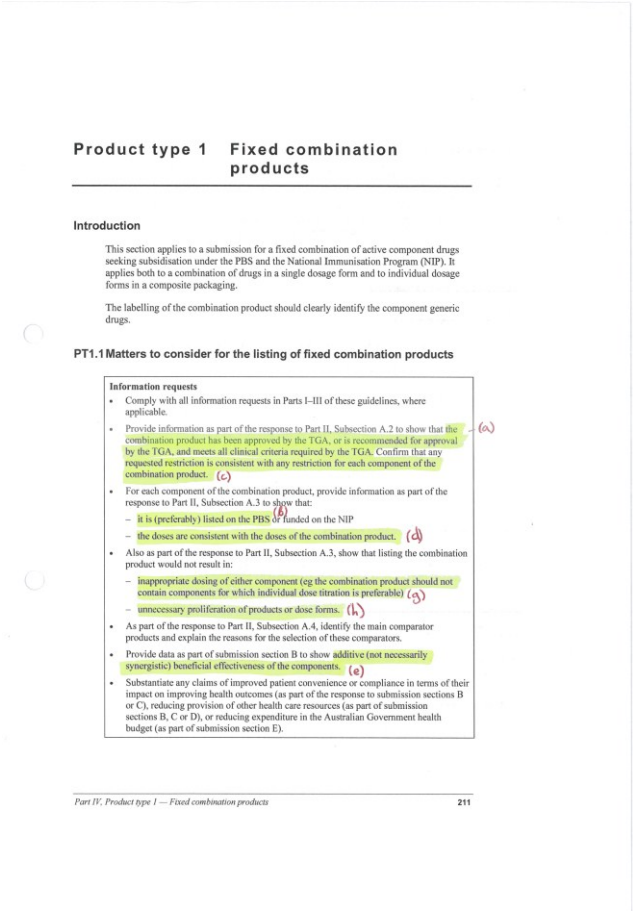
It is within PBAC prerogative to develop internal working documents that assist its consideration of submissions, and to develop minimum criteria submissions must satisfy. Even with minimum criteria, I would note that PBAC still has the right to determine the criteria a drug must satisfy, on a case by case basis.

Nevertheless, I consider that PBAC has not been transparent in communicating its requirements and reasoning to the Sponsor. The basic principles of just and accountable decision-making generally afford the Sponsor the right to:

- Know what criteria they must satisfy;
- Be heard - to provide information and argue their case;
- Know what information has been considered in making the decision; and
- Know the reasons for the decision.

In the context of the Guidelines, I find that the articulation of PBAC's decision is confusing, as it has conflated the requirement for the Sponsor to provide information with PBAC's decision-making considerations.

The Minutes contain two anomalies. Firstly, they refer to information requests in Part IV as 'minimum requirements' - which is not an accurate representation of the content of the Guidelines. Secondly, they reference a document which was not available to the Sponsor.



Product type 1 Fixed combination products

Introduction

This section applies to a submission for a fixed combination of active component drugs seeking subsidisation under the PBS and the National Immunisation Program (NIP). It applies both to a combination of drugs in a single dosage form and to individual dosage forms in a composite packaging.

The labelling of the combination product should clearly identify the component generic drugs.

PT1.1 Matters to consider for the listing of fixed combination products

Information requests

- Comply with all information requests in Parts I–III of these guidelines, where applicable.
- Provide information as part of the response to Part II, Subsection A.2 to show that the combination product has been approved by the TGA, or is recommended for approval by the TGA, and meets all clinical criteria required by the TGA. Confirm that any requested restriction is consistent with any restriction for each component of the combination product. (c) (a)
- For each component of the combination product, provide information as part of the response to Part II, Subsection A.3 to show that: (b)
  - it is (preferably) listed on the PBS or funded on the NIP
  - the doses are consistent with the doses of the combination product. (d)
- Also as part of the response to Part II, Subsection A.3, show that listing the combination product would not result in:
  - inappropriate dosing of either component (eg the combination product should not contain components for which individual dose titration is preferable) (g)
  - unnecessary proliferation of products or dose forms. (h)
- As part of the response to Part II, Subsection A.4, identify the main comparator products and explain the reasons for the selection of these comparators.
- Provide data as part of submission section B to show additive (not necessarily synergistic) beneficial effectiveness of the components. (e)
- Substantiate any claims of improved patient convenience or compliance in terms of their impact on improving health outcomes (as part of the response to submission sections B or C), reducing provision of other health care resources (as part of submission sections B, C or D), or reducing expenditure in the Australian Government health budget (as part of submission section E).

Part IV, Product type 1 — Fixed combination products 211

Table 2: Document provided by Department to explain alpha numbering in Minutes of November 2012 meeting

There is also a third table, provided to the Reviewer by the Department to the Independent Review in response to a question about the source of the alpha referencing contained in the PBAC Minutes of the November 2012 meeting. This is at Table 2.

Although the 'matters' are common across the three tables, they are expressed as information requests in the publicly available Guidelines and the document provided by the department (Table 2), and expressed as minimum requirements in the document which was not publicly available. For this reason, the Sponsor could not have known that there were eight 'minimum requirements' which the product was required to satisfy.

The Guidelines state at 1.4 that PBAC is conscious of the need to be as open as possible in its proceedings consistent with the secrecy provisions of the Act.

The above events resulted in the Sponsor not knowing what criteria PBAC required to be satisfied. Accordingly, I find that PBAC was not as open in its proceedings in this matter as it should have been.

Recommendation

If PBAC has decided that there are criteria which must be satisfied for combination products to be eligible for consideration for PBS listing, then those requirements should be explicit in the PBAC Guidelines. PBAC should also consider making it clear that meeting such criteria would not, of itself, guarantee a positive recommendation as there may be other things PBAC would consider on a case-by-case basis.

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

Did PBAC communicate its concerns and requirements consistently to the Sponsor throughout the assessment process?

The table below shows that PBAC's requirement for Vimovo® to satisfy the minimum requirements discussed above was first communicated to the Sponsor after the 3rd submission was considered by PBAC.

Table 3: Reasons for rejecting Vimovo® application

PBAC decision	Précis of reasons for rejection as expressed in meeting Minutes
August 2011 (major submission)	The nominated main comparator was inappropriate and there were no data presented versus the comparator which PBAC considered to be appropriate.
March 2012 (major re-submission)	The comparator was inappropriate. Uncertainty regarding the validity of the surrogate outcome, for the purposes of demonstrating no inferiority of more patient-relevant outcomes, and resultant uncertainty in the proposed cost-minimisation analysis. An expectation that listing as requested could result in increased costs both overall and also to the PBS.
November 2012 (minor re-submission)	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. Continuing concern that the listing could result in increased costs to the PBS.

It is noted that the March 2012 PES Commentary referred to the need for the product to satisfy the minimum requirements. This may have put the Sponsor on notice regarding the threshold issues, however the PBAC Minutes of the March 2012 meeting do not refer to 'minimum requirements'.

The available information indicates that PBAC did not clearly communicate to the Sponsor from the outset the minimum requirements and threshold issues which would underpin its consideration of the application. While the first PBAC decision identified the inappropriate comparator as the reason for rejection, subsequent meetings identified additional concerns, with the need to satisfy minimum requirements only being communicated after the 3rd submission.

Conclusion

The Sponsor has a right to know what criteria must be satisfied. The Sponsor was placed in the position of developing re-submissions to address a particular deficiency, then finding that new deficiencies were identified which the re-submission did not address. As a

consequence the standards of evidence determined by PBAC were not transparent to the Sponsor.

PBAC routinely uses both formal and informal communication processes to advise Sponsors of threshold issues and concerns. This is good practice in accordance with PBAC's stated commitment to transparency. In this instance, PBAC's communication with the Sponsor was less than optimal, as threshold issues were not communicated to the Sponsor early in the process nor were they communicated consistently throughout the process.

Is PBAC required to apply these minimum requirements consistently?

PBAC is required to consider the effectiveness and cost of a proposed PBS listing compared with other therapies. PBAC is not required to demonstrate consistency in decision-making. The relevant factors influencing decision making by PBAC do not include consistency. See Table 4 below.

Table 4: Factors PBAC are required to take into account in making decisions

- it is needed for the prevention or treatment of significant medical conditions not already covered, or inadequately covered, by drugs in the existing list and is of acceptable cost-effectiveness
- it is more effective or less toxic (or both) than a drug already listed for the same indications and is of acceptable cost-effectiveness
- it is at least as effective and safe as a drug already listed for the same indications and is of similar or better cost-effectiveness.
A new drug that is less effective and/or more toxic than a drug already listed for the same indications might be considered for listing. In such a circumstance, other supportive factors would be needed to justify a recommendation, for example, if the new drug would decrease the overall costs of therapy and/or if it were restricted to a subsequent line of therapy after the more effective or less toxic therapy.

In fact, consistency could be counterproductive given the diversity of products and the dynamic nature of the market. PBAC is required to make judgments about weightings applied in its decision making process, and these judgments may be influenced by a number of factors.

Conclusion

Accordingly, the Sponsor's claim that the PBAC decision is inconsistent with previous PBAC decisions does not have merit.

Reviewer's summary of findings on this aspect of the Review

The community expects that individuals and bodies with decision-making authority exercise their power in a just and accountable manner. Put simply, decision makers should not only **be** fair, they should be **seen** to be fair.

PBAC has the right to determine the standards of evidence it requires on a case by case basis, and the decision making process is quite distinct from the requirements for submissions as detailed in the Guidelines.

I do not accept the Sponsor's assertion that PBAC's decision overstates the standing of these criteria because this confuses information requests for the purpose of making a submission with the actual decision making considerations. The Guidelines do not prescribe PBAC's decision making processes, and PBAC has the right to develop minimum requirements which it determines Fixed Combination Products must meet. However I consider that PBAC was not transparent about these minimum requirements and that this lack of transparency confused the Sponsor.

I do not accept the Sponsor's contention that PBAC has been inconsistent in its assessment of combination products, as there is no requirement for PBAC to be consistent in decision-making. Furthermore, consistency in decision-making is difficult to achieve, and potentially undesirable, in the context of emerging products in a dynamic market.

Nevertheless, I find that PBAC was not transparent in its communication of its requirements and its decisions. As a result, the Sponsor made 3 submissions without being fully informed of the criteria which PBAC required the product to satisfy. The PBAC Guidelines state that PBAC is conscious of the need to be as open as possible in its proceedings consistent with the secrecy provisions of the Act. In this instance PBAC was not as transparent as it should have been.

Annexure 1: Material used in preparing the report

Information provided to the reviewer by the Department of Health and Ageing in response to a number of questions follows. (Answers are in italics)

12 February 2013 - Questions

1. Could you confirm that the PBAC Guidelines on the web (version 4.3 December 2008) are the latest and are used by the PBAC? *Yes*

2. The following text is an excerpt from the PBAC Guidelines, pp. 211-212 of Part IV version 4.3, December 2008[1]. Could you please advise me whether any of the material in that excerpt is a legislative requirement or similar? *No*

3. Can you advise whether there is another document which assigns alphas to the information requests? The PDF document and the web document use dot points, while the PBAC short minutes uses (b) (c) etc. If there is another document, could you provide a copy of that please? If there is no other document, and the PBAC have used alphas for convenience, could I please have an annotated copy of the excerpt so I am sure that reviewers are pointed in the right direction.

The November 2012 PBAC meeting short minutes refer to PBAC Guidelines Part IV, PBAC Secretariat Overview (PBAC SEC OVR 7.10.3) and PBAC Secretariat March 2012 Commentary (7.4.COM.20). The 'alpha' criteria (b), (c) and (g) refer to a suite of eight criteria that have been developed by Pharmaceutical Evaluation Branch for the PBAC, ESC and DUSC to assist them with assessment of combination products. They provide more detail on the application of the eight criteria set out in the PBAC Guidelines (Part IV Product type 1 Fixed Combinations products). However, the numbering does not match the eight criteria in the PBAC Guidelines (Part IV). An annotated extract of the PBAC Guidelines (Part IV) correlating it to the criteria referred to in the Overview and Commentary is attached[2].

4. The PBAC minutes say, and I quote 'criterion (c) "restrictions for the component products should be consistent with those proposed for the combination", is also not satisfied...'. I would appreciate advice from the department of the source and authority for that wording, and a copy of the relevant document.

As noted above, the source and authority of criterion (c) is the PBAC Guidelines. Pharmaceutical Evaluation Branch prepared it for the PBAC, ESC and DUSC to assist them with assessment of combination products. These criteria have been adopted by PBAC in previous assessments.

[1] This is the text in column 1 of Table 1
[2] This is Table 2

5. Could you also advise if there is a glossary or similar that would explain the term 'information request' or the expectations of how that term should be interpreted.

There is no explanation of the term 'information request' in the Glossary to the PBAC Guidelines or in other PBAC documentation. It is the title of the section of the PBAC Guidelines which summarise the nature of information that may be required for specific product types.

18 March 2013 Questions

1. Page 11 of the Guidelines (the December 2008 official version on the web) state that the Guidelines were endorsed by ESC and PBAC. Please confirm that they were not required to be approved by the Minister and/or other Parliamentary process.

There is no requirement for Ministerial or Parliamentary approval of the Guidelines for Preparing Submissions to the Pharmaceutical Benefits Advisory Committee (PBAC Guidelines). They provide practical information for the pharmaceutical industry for making a submission to PBAC. Although the Guidelines have been written for the pharmaceutical industry, they are also intended to help PBAC assess submissions and, provide information to other interested stakeholders, including clinical and patient groups, and the general community.

2**.** Are the Guidelines in whole or part referenced in the Act or any other legislative instrument/determination? *No*.

3. Is there existing legal advice regarding the status of the Guidelines? If so, is this available?

Pharmaceutical Evaluation Branch cannot recall any such advice. Legal Services Branch has advised that they have conducted a search of LSB records and also could not find any advice regarding the status of the Guidelines.

4. The PBAC has described the information requests in Part IV of the Guidelines as minimum requirements that combination products must satisfy in order to be eligible for consideration by PBAC. Has this issue been raised previously in relation to other applications?

Yes. These minimum requirements ensure standard information is considered by PBAC before it takes into account any other issues.

24 April 2013 Questions

1. The PBAC SEC OVR of the March 2012 meeting includes a table at 7.10.3 which lists 8 requirements (a) - (h).

- When was this list of requirements first developed?
- What document is this table found in?
- Has this table been released to industry at any time?

PBAC Secretariat advises that the table on page PBAC SEC OVR 7.10.3, sets out requirements which are specified in the December 2008 PBAC Guidelines Part IV (Information requests for specific product types). Whilst the exact format of the table is not presented, the requirements match the information requests in the box under PT1.1 Matters to consider for the listing of fixed combination products. (The secretariat also notes that PBAC SEC OVR 7.10.3 is from the November 2012 PBAC meeting.)'

Attachment 2

VALIDITY OF THE SURROGATE OUTCOME AND NON-INFERIORITY

Report prepared by | *Name of reviewer redacted*

Validity of the surrogate outcome and non-inferiority

Reviewer

Name of reviewer redacted

Matter detailed in the Independent Review Request

This report addresses the second ground for review:

> 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) which the Sponsors say is based on insufficiently robust data taken out of context.

The Sponsor raised a specific concern in relation to the matter: whether the evidence cited by the PES and accepted by the PBAC to repudiate the validity of endoscopic ulcers as a valid surrogate endpoint is of sufficient rigour and did the PES and therefore the Committee interpret this evidence appropriately.

Reviewer's understanding of the matter to be reviewed

There are two separate issues in the statement that there is *"continuing uncertainty regarding the validity of the surrogate outcome for the purposes of demonstrating non-inferiority of more patient-relevant outcomes ".* The first issue is the validity of the surrogate measure: whether it provides an adequate measure by which to judge the effect of the drug on more patient-relevant outcomes. To address this issue, I assess the quality of evidence presented by both the Sponsor and PES/PBAC. The second issue is whether non-inferiority against the comparator has been adequately assessed. I now deal with each of these.

Abbreviations and terms used in this report

- CI: 95% confidence interval
- Clinically relevant outcomes [for upper gastro-intestinal outcomes]: patient-relevant outcomes such as "perforations, obstructions and bleeds" (POBs), "perforations, ulcerations and bleeds" (PUBs), or "clinically significant upper gastrointestinal events" (CSUGIEs)

- PSM: potential surrogate marker [the term used in the Report of the Surrogate to Final Outcome Working Group to the PBAC [STFOWG]
- STFOWG: Report of the Surrogate to Final Outcome Working Group to the PBAC
- TCO: target clinical outcome [the term used in the STFOWG report]
- UGI: upper gastro-intestinal

Validity of the surrogate in principle

An approach to assess the validity of surrogate outcomes has been developed by the Surrogate to Final Outcome Working Group [STFOWG] in a report to the Pharmaceutical Benefits Advisory Committee. Its value is acknowledged internationally. For example, it is one of only three references in the paper developed by the widely respected GRADE working group on how to assess the validity of surrogate outcomes when rating the quality of indirect evidence [Guyatt et al, 2011].

The issues suggested by the STFOWG and their relationship to the STEPS in PBAC submission Guidelines are outlined in their table [page 4], which is shown below.

Table 5: Framework for assessing a proposed surrogate measure - summary and relation to the 2007 PBAC Guidelines

Part of the Framework	***PBAC Guidelines 2007***	**Summary**
Part One	.	Definition, selection and measurement of the PSM* and TCO**
Part Two	Step 1 (page 108)	Biological reasoning and epidemiological evidence supporting the relationship between the PSM and TCO, independent of any intervention.
Part Three	Step 2 (page 109)	Randomised trial evidence using other drugs to show that there is a basis to conclude that a comparative treatment effect on the PSM has satisfactorily predicted a comparative treatment effect on the TCO.
Part Four	Step 3 (page 109)	Support for why the relationship between the comparative treatment effects on the PSM and TCO with these other drugs is likely to apply to the proposed drug. Information about the comparative treatment effect of the proposed drug on the PSM.
Part Five		Relevant considerations for incorporation of the comparative treatment effect based on the PSM into the economic evaluation.
*PSM- Proposed surrogate measure - A biomarker or clinical outcome that is intended to substitute for a target clinical outcome **TCO = Target clinical outcome. A clinical outcome that is unequivocally patient relevant, but does not necessarily capture both dimensions of quantity and quality of life.		

The most important part of the framework is Part Three, which is concerned most directly with assessing whether the surrogate acts as a reasonable proxy for the outcome of interest in trials of a new drug. Part Two is the next most pertinent part.

Part One of the STFOWG: Definition, selection and measurement of the Proposed Surrogate Measure [PSM] and the Target Clinical Outcome [TCO]

The STFOWG comments that "….a PSM must be responsive and able to be measured with reliability and validity". The pertinent issue for this review is reliability or repeatability.

Extent to which addressed by Sponsor submission

The Sponsors do not present any measures of repeatability but comment that assessment of endoscopic ulcers is standardized in the trials.

Extent to which addressed in recent comments by PES/ PBAC

PBAC suggest poor repeatability on the basis of one small study published only as an abstract.

Reviewer Comment

Ideal information would be a systematic review of repeatability of endoscopic ulcers, which has not been presented by either the Sponsor or PBAC. That information could then be used to estimate the extent to which possible misclassification affects the validity of the PSM. However, if the PSM was poorly repeatable, suggesting misclassification, this would reduce the ability of the PSM to predict clinical endpoints, and this would be ascertainable in the more important Parts Two and Three below.

Conclusion

The 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. This is reflected by the STOFWG comment: "If relevant meta-regression data from multiple randomised trials supporting the link between the comparative treatment effect on the PSM and the comparative treatment effect on the TCO are available for Part Three ….the amount of information needed for 1A.6 is reduced[3]."

Part Two of the STFOWG: Biological reasoning and epidemiological evidence supporting the relationship between the PSM and TCO, independent of any intervention.

The STFOWG identifies cohort studies predicting TCOs by PSMs as the ideal source of information. This direct evidence would involve a cohort study design in which patients with endoscopically-detected ulcers are observed, without intervention or change in treatment, for subsequent clinical events. Studies of this type have not been presented by either the Sponsor or PBAC.

[3] 1.A.6 is " An assessment of the validity, reliability and responsiveness of the method for measuring the PSM."

Extent to which addressed by Sponsor submission

The Sponsor presents indirect evidence, based on a systematic review [Tramer et al, 2000] that shows the effect of NSAIDs on clinically relevant and surrogate outcomes based on different studies to support a claim that *"treatment with NSAIDs resulted in a consistent increased risk for all four levels of harm: endoscopic ulcers, clinically diagnosed ulcers, perforation/bleeding, and deaths."*

The Sponsor also presents evidence, based on a review [Moore et al] to claim that *'Endoscopic ulcers and serious UGI bleeding events are influenced in the same direction and to much the same extent by patient-related variables (including age and previous history'*

Extent to which addressed in recent comments by PES/ PBAC

PBAC comment that not all endoscopic ulcers will progress to clinical ulcers, based on a textbook reference [MacDonald]. In their more detailed comments for the March 2012 PBAC meeting, PES question the value of indirect evidence about the effect of NSAIDS on the surrogate and clinically relevant outcomes and comment that the data are sparse and lack any quantitative analysis.

Reviewer Comment

Progression of all endoscopic ulcers to clinical ulcers is not a necessary criterion to justify the use of a surrogate. Direct evidence, involving a cohort study design in which patients with endoscopically-detected ulcers are observed, without intervention or change in treatment, to detect subsequent clinical events are not presented by the Sponsor or PBAC and it seems unlikely such studies would be done. So, decisions will need to be made on indirect evidence. Progression of all endoscopic ulcers to clinical ulcers is not a necessary criterion to justify the use of a surrogate. The issue is not prediction of clinical ulcers in individuals, but whether the PSM shows the same relationships to other variables as the TCO in population studies. The relationship of surrogate and clinically relevant outcomes to NSAIDS is consistent in direction, though not in apparent magnitude.

Conclusion

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.

Part Three of the STFOWG: Randomised trial evidence using other drugs to show that there is a basis to conclude that a comparative treatment effect on the PSM has satisfactorily predicted a comparative treatment effect on the TCO.

This part is the most relevant criterion. Ideal evidence would be based on studies in which the endoscopic ulcers and clinical endpoints were measured on the same patients randomized to treatment options. [Direct evidence]. STFOWG suggest the following hierarchy, with Level I providing the strongest support for the PSM and Level IV the weakest:

I. multi-trial meta-regression possible
II. single or small number of randomised trials: multi-centre analysis possible - could only be done if participants were randomised by centre and individual patient data are available
III. one randomised trial, no individual patient data or not randomised by centre
IV. no randomised trial data.

Extent to which addressed by Sponsor submission

Direct evidence is not available, so the Sponsor has relied on evidence from PSM and TCO in different trials. Based on a review [Rostom et al, 2010] and extra information from GIDAC documents to FDA [GIDAC, 2010], the Sponsor claims that: *When compared with traditional NSAIDs alone, treatment with NSAIDs plus PPIs or COX-2 inhibitors results in a similar magnitude of risk reduction for endoscopically-detected ulcers and for symptomatic ulcers.*

Because of the importance of this Part, the tables from the 2nd major submission are reproduced below.

Table 6: Extract from AstraZeneca second submission comparing NSAIDs, and Cox2 inhibitors

Table 30 Relative risk of ulcers and events: COX-2 selective inhibitors versus traditional NSAIDs

	RR (95% CI), N trials		
	Endoscopy studies	Clinical outcome studies	
	Ulcers	POBs	PUBs
COX-2 selective NSAIDs vs tNSAIDs	0.26 (0.23, 0.30), N=13	0.43 (0.28, 0.66), N=9	0.43 (0.34, 0.54), N=14
Celecoxib vs tNSAIDs	0.24 (0.17, 0.32), N=3	0.23 (0.07, 0.76), N=3	0.39 (0.21, 0.72), N=4
Rofecoxib vs tNSAIDs	0.26 (0.21, 0.32), N=3	0.42 (0.24, 0.73), N=2	0.42 (0.26, 0.67), N=4
Etoricoxib vs tNSAIDs	0.37 (0.18, 0.77), N=2	0.78 (0.48, 1.27), N=2	0.54 (0.38, 0.77), N=4
Valdecoxib vs tNSAIDs	0.29 (0.21, 0.40), N=3	0.35 (0.14, 0.87), N=1	0.23 (0.15, 0.36), N=1
Lumiracoxib vs tNSAIDs	0.23 (0.16, 0.33), N=2	0.35 (0.23, 0.53), N=1	0.47 (0.36, 0.60), N=1

Source: Modified from Rostom et al (2009)
Abbreviations: CI, confidence interval; COX, cyclooxygenase; GI, gastrointestinal; NSAID, non-steroidal anti-inflammatory drug; POBs, perforations, obstructions and bleeds; PUBs, perforations, ulcerations and bleeds; RR, relative risk

Table 31 Relative risk of ulcers and events: NSAIDs plus PPIs versus NSAIDs alone (GIDAC 2010a)

	RR (95% CI)	Adjusted RR
	Endoscopy studies	Clinical outcome studies
	Ulcers	POBs
Rostom 2009		
NSAID plus PPI vs NSAID	0.39 (0.31, 0.50)	
NSAID plus PPI vs NSAID	0.20 (0.10, 0.39)	
FDA briefing document		
Naproxen plus esomeprazole vs naproxen	**0.2 (0.2, 0.4)[a]**	
Naproxen plus omeprazole vs naproxen		**0.2 (0.1, 0.8)**
NSAID plus lansoprazole 30 mg/day vs NSAID	0.4 (0.2, 0.6)	
NSAID plus lansoprazole 15 mg/day vs NSAID	0.4 (0.3, 0.6)	
NSAID plus esomeprazole 40 mg/day vs NSAID	0.3 (0.2, 0.5)[a]	
NSAID plus esomeprazole 20 mg/day vs NSAID	0.3 (0.2, 0.5)[a]	
Aspirin 100 mg/day plus lansoprazole 30 mg/day vs aspirin 100 mg/day		0.1 (0.0, 0.8)
Aspirin 80 mg/day plus omeprazole 20 mg/day vs aspirin 80 mg/day		0.5 (0.1, 5.4)
Celecoxib 200 mg/day plus esomeprazole 20 mg/day vs celecoxib 200 mg/day		0.0 (0.0, 0.7)

Source: GIDAC Briefing Information Table 5.4 pg 13 and Table 5.5 pg 14.
Abbreviations: CI, confidence interval; NSAID, non-steroidal anti-inflammatory drug; POBs, perforations, obstructions and bleeds; PPI, proton pump inhibitor; PUBs, perforations, ulcers and bleeds; RR, relative risk.
[a] Pooled from the results of the two esomeprazole studies reported in Table 5.4.

Table 7: Extract form AstraZeneca second submission comparing NSAIDs, and NSAIDs plus PPIs

From Table 6 [second major submission report table 30], COX-2 selective NSAIDs reduce the risk of both endoscopic ulcers and clinically relevant outcomes [POBs/PUBs] compared to conventional NSAIDs. There is a suggestion in the data that the relative risk is smaller [i.e. larger relative risk **reduction]** for endoscopic ulcers than for POBs/PUBs. In Table 7 above [second major submission report table 31], for the comparison of naproxen plus esomeprazole vs. naproxen, the adjusted RR for clinically relevant outcomes was 0.2 [CI 0.1, 0.8]. The RR for endoscopy studies was reported as 0.2 [CI 0.2-0.4], based on a meta-analysis of 2 studies. Inspection of the tables on which this meta-analysis was based had a data inconsistency for one of the two studies, which reported 1 endoscopic ulcer in the esomeprazole/naproxen group, out of 218 patients, but gave the incidence as 5%. This has been queried with the Sponsor, and analysis of the correct data shows the RR as 0.23 [CI 0.13, 0.39]. The full explanation is provided in Attachment 4, *Documents used in the review*.

Extent to which addressed in recent comments by PES/ PBAC

The PES commentary for the March 2012 meeting comments on the fact that the RRs for COX-2 selective inhibitors compared with NSAIDS are generally smaller [greater relative risk reduction] for endoscopic ulcers than for clinically relevant outcomes. They suggest that overestimation by using endoscopically detected ulcers may have an impact on establishing non-inferiority. The PES also point out that the CIs are very wide for the study on clinically relevant outcomes in the study of high-risk patients comparing naproxen + esomeprazole vs. naproxen.

Reviewer Comment

This is considered the most important part of the STFOWG. Direct evidence is lacking and unlikely to be obtainable. The indirect evidence points towards endoscopic ulcers showing similar results to clinical endpoints, based on the point estimates, for several drugs which are designed to avoid the UGI complications of conventional NSAIDs. If the effect of these drugs is greater on the PSM than the TCO, it will make for a more stringent test of non-inferiority.

Conclusion

Though not ideal, the evidence is considered acceptable to fulfil this part of the STFOWG.

Part Four of the STFOWG: Support for why the relationship between the comparative treatment effects on the PSM and TCO with these other drugs is likely to apply to the proposed drug. Information about the comparative treatment effect of the proposed drug on the PSM.

In addition to the Part Four requirement stated in the above title, another issue in studies comparing drugs is whether the surrogate is equally good for assessing the drug effects in both arms, i.e. an unbiased 'umpire' of effects [Glasziou et al, 2008]

Extent to which addressed in recent comments by Sponsor submission

The information in Part Three above seems to hold reasonably for drugs such as celecoxib [the major comparator] and there is some evidence that the effect is similar for naproxen plus esomeprazole.

Extent to which addressed in recent comments by PES/ PBAC

No additional major comment

Reviewer Comment

Within the constraints of the information available in Part Three, there are no additional concerns about Part Four.

Conclusion

The requirement for Part Four is reasonably met.

Part Five of the STFOWG: Relevant considerations for incorporation of the comparative treatment effect based on the PSM into the economic evaluation.

According to the STFOWG report "…..economic evaluations presented to PBAC need to capture the full extent of uncertainty associated with having to rely on PSMs to predict comparative treatment effects on the TCOs rather than on a direct measurement of the comparative treatment effect of the TCOs and their 95% confidence intervals in direct randomised trials. Incorporating the full extent of uncertainty more formally into the economic evaluation is particularly important if the uncertainty is to be presented via a probabilistic sensitivity analysis. At the very least, the elements of this uncertainty need to reflect both the uncertainty in the estimation of the comparative treatment effect on the PSM and also the uncertainty of the transformation."

Although non-inferiority is not directly addressed in the STFOWG report, the concept of transformation is relevant to decision-making by the PBAC. Decisions about non-inferiority limits for surrogates is facilitated if there is a quantitative estimate of the relationship between the effect of drugs on the PSM and the TCO, so that a judgement on the non-inferiority limit on the TCO can be back-transformed to the non-inferiority limit for the surrogate. If this quantitative estimate of the PSM:TCO relationship is not available, the judgement still needs to take account of the available information about this relationship.

Extent to which addressed by Sponsor submission

This has not been materially addressed by the Sponsor beyond the information in previous parts.

Extent to which addressed in recent comments by PES/ PBAC

This has not been materially addressed by the PBAC beyond the information in previous parts.

Reviewer Comment

Good quantitative direct evidence on the relative effects of the drugs on the PSM and TCO is lacking. However, the indirect evidence suggests that the effect of drugs will be similar or less on clinically relevant outcomes than on endoscopic ulcers.

Conclusion

The available evidence suggests it would be reasonable to consider Part Five as sufficiently well addressed to allow non-inferiority limits to be set on endoscopic ulcers as a surrogate for clinically relevant outcomes.

Overall Conclusion about the validity of the surrogate in principle.

Although evidence from studies assessing clinically relevant outcomes is clearly always preferable, it seems reasonable to use endoscopic ulcers as a surrogate for clinically

relevant upper gastrointestinal outcomes based especially on Parts Two and Three, the most important parts of the STFOWG report.

However, 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. This judgement needs to take into account that:

- Surrogates are most useful when the clinically relevant outcomes are distant in time. In that case, the use of surrogates can appreciably shorten the duration of studies. If the clinically relevant outcomes occur in a similar timescale to the surrogates, they may still have the advantage of requiring smaller sample sizes in randomised trials.
- Evidence has accumulated, since PBAC decisions were made about celecoxib, to support the use of endoscopic ulcers as a surrogate.
- Getting better [direct] evidence about the value of the surrogate as a predictor of clinically relevant outcomes is unlikely. [STFOWG Part Two]
- Because endoscopic ulcers as a surrogate is becoming more widely accepted, it is difficult now to mount studies to get direct evidence on clinically relevant outcomes. [STFOWG Part Three]

Adequacy of assessment of non-inferiority

If PBAC accept the use of endoscopic ulcers as a surrogate for clinically relevant outcomes, there is still the requirement to assess non-inferiority using the surrogate.

The Sponsor states that the focus of the 2nd submission is on endoscopically-detected ulcer outcome, with one of the points in the overall claim being that Vimovo® is non-inferior to celecoxib. [page 114].

The PBAC Guidelines say that Sponsors are to explain and justify on clinical or other grounds the value of the non-inferiority threshold difference in treatment effect between the proposed drug and its main comparator. Furthermore, there should then be a comparison of the point estimate of the difference between the Sponsor's drug and the comparator with its 95% confidence interval. This allows PBAC to assess whether the confidence interval contains the minimal clinically important difference. This expectation is also reflected in the cost-minimisation checklist. The following cost-minimisation checklist for Vimovo® is copied from the PES commentary for the March 2012 PBAC meeting. Items 4, 5, and 6 are the relevant points for consideration of non-inferiority limits for surrogates.

Table 8: copy of PES Cost Minimisation Checklist March 2012 meeting

COST MINIMISATION CHECKLIST – specifically for the FDC versus celecoxib comparison

1.	Is the comparator acceptable?	Requires consideration.
2.	Is the requested listing the same as that of the comparator?	No. The FDC is requesting listing for patients requiring 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. Celecoxib is listed for the symptomatic treatment of OA and RA.
3.	Are there differences between the two drugs in their approved indications?	Yes
	If yes, are they relevant to the submission? (Consider usage outside restriction.)	No in terms of celecoxib. *However, there may be leakage to patients currently using naproxen or other NSAIDs for chronic arthropathies other than AS, RA and OA.*
4.	Is the clinical evidence a direct head to head RCT or an indirect comparison?	Direct and indirect
5.	Are the clinical outputs of the trial/s surrogate or patient-relevant outcomes?	Patient-relevant (gastrointestinal adverse events) in the direct evidence, but different to those previously considered by the PBAC in their consideration of the relative safety of NSAIDs. Surrogate outcome of "endoscopically detected ulcers" in indirect comparison.
	Are the endpoints similar in all trials?	Yes
6.	What are the non-inferiority limits and what method/s are used to address non-inferiority i.e. lower/upper confidence boundaries or other?	In terms of GI adverse events, neither the trials nor the submission nominate any non-inferiority criteria. Non-inferiority of the naproxen/esomeprazole FDC in terms of WOMAC scales was established if the upper bound of the 2-sided

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Table 8 [continued]: copy of PES Cost Minimisation Checklist March 2012 meeting

		95% CI was less than or equal to a margin of +10mm for the WOMAC pain and function domains and if the lower bound of the 2-sided 95% CI was greater than or equal to a margin of -10mm for PGA-VAS.
	Are non-inferiority limits clinically acceptable?	Yes. As previously accepted by the PBAC in terms of reducing pain, improving function and patient global assessment of disease status (PGADS) *according to WOMAC scales*. Etoricoxib Public Summary Document, July 2008.
	Is there a national/international accepted clinically important difference? If so, provide reference.	Unknown
7.	Are the populations used in the trials comparable in regard to inclusion/exclusion criteria	Yes. However, they are not entirely representative of the population for whom listing is sought.
8.	With respect to toxicities of the two drugs, are there any significant differences both overall and in particular, in specific effects which are serious or could impact on utilisation i.e. compliance?	Yes. Naproxen is less likely to have cardiovascular toxicity compared with celecoxib.
9.	What are the dose relativities?	Naproxen 500mg and esomeprazole 20mg in a fixed dose combination twice daily versus celecoxib 200mg once daily.
	How are the dose relativities determined?	Trial-based doses
	Is there any evidence of a difference in time-dependent alteration of dose?	No
	Is the frequency of dosing different between the two drugs?	Yes. Twice versus once daily.
	If yes, will this be relevant in practice?	Yes. *The submission itself makes a statement regarding the importance of adherence to therapy and the protective effect. Increasing frequency from once daily to twice daily could potentially lead to lower adherence to therapy and therefore an overstated clinical benefit from using the FDC. Also, the dose of esomeprazole in the FDC (20mg bd) is higher than the dose recommended in therapeutic guidelines for maintenance or primary prevention phases of treatment with esomeprazole (down titration to 20mg od).*
10.	Are the modes of administration of the two drugs the same?	Yes
11.	Is the market likely to grow with the introduction of a new agent with the same restriction?	Yes
12.	Should interchangeability rules apply?	No

The checklist above highlights the fact that non-inferiority has been addressed for the pain and joint function outcomes, but that it has not been addressed for the upper gastro-intestinal outcomes. Non-inferiority limits for gastro-intestinal outcomes have not been presented, and therefore the available data on the Vimovo®-celecoxib comparison was not evaluated. However, there is information on the comparison of Vimovo® and celecoxib for gastroduodenal ulcers at 3 months, based on an indirect comparison via Naproxen: the Risk Ratio is 0.85 [CI 0.28 2.56].

Reviewer comment

The upper gastro-intestinal outcomes are of obvious importance for this drug combination, as stated by the Sponsor. However, non-inferiority limits have not been set. The comparison of endoscopic ulcer risk in patients given Vimovo® or celecoxib is based on an indirect comparison, and has wide confidence intervals.

Conclusion

There is inadequate information on which to judge the non-inferiority of Vimovo® vs. the comparator. Therefore, an economic analysis based on cost-minimisation is not well justified.

Non-inferiority limits for upper gastrointestinal outcomes need to be proposed and justified. Using their usual methods and cost-minimisation checklist, PBAC then can consider the quality of the evidence and the confidence limits around the estimated difference in ulcer outcomes between Vimovo® and comparator drugs to decide whether non-inferiority is a reasonable assumption.

A judgement then needs to be made about the appropriate economic evaluation, with sensitivity analyses to reflect the uncertainty about the differences in gastrointestinal outcomes between Vimovo® and comparator drugs. The sensitivity analyses could reflect both the statistical uncertainty of the estimated surrogate outcome, as well as any uncertainty about how the result on the surrogate outcome translates to clinically relevant outcomes.

Recommendations

The following are recommendations for PBAC submissions prompted by consideration of this request for Independent Review.

1. 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.

2. 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.

Annexure 1: Material used in this report

All requests were made though the IRR Convenor.

I enquired whether there have been any updates to the 2009 Report of the Surrogate to Final Outcome Working Group [STFOWG] to the Pharmaceutical Benefits Advisory Committee document, and was told there were none.

I requested more information about the PBACs previous acceptance of directly assessed improvements in patient-relevant outcomes for celecoxib, which is referred to several times in the material initially supplied to me. I received the minutes from PBAC's review of COX2 inhibitors in 2003 and 2004. I have not used this material in my report

Because of an inconsistency between a number and a percentage in table 5.4 of the GIDAC FDA report, on which the Sponsor's meta-analysis of naproxen plus esomeprazole vs. naproxen was based, I requested the Sponsor to confirm exactly what data were used in their meta-analysis, and to provide the results of the meta-analysis to 2 decimal places. The response is attached in full at Attachment 4 and commented on in the body of the report.

Annexure 2: References

All references are referred to in the material supplied to me, except those marked with an *asterisk, which provide conceptual underpinning to my assessment of the material.

GIDAC. Gastrointestinal Drug Advisory Committee Meeting November 4, 2010: Outcome Measures for Claims to Reduce NSAID-Associated Upper Gastrointestinal (UGI) Toxicity Department of Health & Human Services, Food & Drug Administration Center for Drug Evaluation & Research, Office of New Drugs, Division of Gastroenterology Products *

Glasziou P et al. When should a new test become the current reference standard? Annals Intern Med 2008; 149(11): 816-22.

*Guyatt GH et al. for the GRADE [Grading of Recommendations Assessment, Development and Evaluation] working group. Grade Guidelines: 8. Rating the quality of evidence – indirectness. J Clin Epidemiol 2011;64:1303-10

Moore A et al. Evidence for Endoscopic Ulcers as Meaningful Surrogate Endpoint for Clinically significant Upper Gastrointestinal Harm. Clinical Gastroenterology and Hepatology 2009;7:1156-63

Report of the Surrogate to Final Outcome Working Group [STFOWG] to the Pharmaceutical Benefits Advisory Committee: a framework for evaluating proposed surrogate measures and their use in submissions to PBAC. 2009 http://www.health.gov.au/internet/main/publishing.nsf/Content/B11E8EF19B358E39CA25754B000A9C07/$File/STFOWG%20paper%20FINAL.pdf Downloaded 27 March 2013

Rostom A et al. Non steroidal anti-inflammatory drug-induced gastro-duodenal toxicity. In McDonald J et al Evidence Based Gastroeneterology and Hepatology, 3rd ed. Blackwell publishing 2010

Tramer MR et al. Quantitative estimation of rare adverse events which follow a biological progression: a new model applied to chronic NSAID use. Pain 2000:85:169-82

Attachment 3

CONTINUING CONCERN THAT THE LISTING OF VIMOVO COULD RESULT IN INCREASED COSTS TO THE PBS.

Report prepared by | *Names of reviewers redacted*

CONTINUING CONCERN THAT LISTING VIMOVO® COULD RESULT IN INCREASED COSTS TO PBS.

Reviewers

Names of reviewers redacted

Matter detailed in the Independent Review Request

This report addresses the third ground for review:

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" (Ratified minutes of the November 2012 PBAC meeting, page 2, paragraph 4) is unable to be reconciled with any costing analysis available.

There are two specific concerns in relation to the matter:

1. That the Pharmaceutical Benefit Advisory Committee's (PBAC's) conclusion that there is "continuing concern that the listing could result in increased costs to the PBS" (Ratified minutes of the November 2012 PBAC meeting, page 2) is unable to be with any costing analysis available;

2 That the request by the PBAC that it should take into account "ongoing reductions in the PBS prices of some PPIs and NSAID medicines" is inconsistent with the PBAC Guidelines that state that cost estimates should be based on constant prices with no allowance made for inflation and use of a zero discount rate (Part ll Guidelines, page 151).

Reviewer's understanding of the matter to be reviewed

Part II of The Guidelines, Section D (page 115) *Economic Evaluation for the main indication* and Section E (page 143) *Estimated extent of use and financial implications* require the Sponsor to provide information on the economic evaluation, the overall net cost to the PBS and the overall net cost to the government health budget. In each of the three submissions the Sponsor presented information on the projected financial impact of Vimovo® listing to the PBS in accordance with the Guidelines. The following is an excerpt from the records of each of the three meetings.

First Major Submission (considered August 2011)

The net cost (savings) to the PBS is uncertain for the following reasons:

- "There is uncertainty in the proportion of currently listed NSAID +/- gastroprotective combinations that will be substituted following the listing of naproxen/esomeprazole FDC;
- There is likely to be higher uptake than predicted in the population taking NSAID + PPI or other gastroprotective medicines due to the lower costs to the lower costs to patients resulting from fewer co-payments;
- There is also likely to be some uptake in those taking only NSAID's (other than celecoxib) as monotherapy and this has not been considered in the current estimates;
- It is likely that the total cost of substituted therapies has been overstated and that the total reduction in net costs to the PBS also overstated.

(Extract from the Pharmaceutical Evaluation Section Commentary from August 2011 consideration, page 5.7.Com.81)

Second Major Submission (considered March 2012)

- …"the predicted overall and continued decline in the NSAID market is uncertain and an assumption of a stable trend into the future may be more appropriate."

"Further, the DUSC also considered that the assumption that the overall NSAID market will continue to contract may not be valid as it may begin to grow again due to increasing prevalence of obesity and other conditions requiring analgesia which are associated with an ageing population." (Extract from the Pharmaceutical Evaluation Section Commentary from March 2012 consideration, page 7.4.Com.81)

The PES commentary then listed sources of uncertainty in the financial impact estimates, including the proportion of currently listed NSAID +/- gastroprotection combinations that would be substituted with Vimovo®; higher uptake of Vimovo® in the population currently taking NSAID + PPI due to lower costs to patients resulting from fewer co-payments; some uptake of Vimovo® in patients taking NSAIDs as monotherapy; likelihood that the total cost of substituted therapies has been overstated and the total reduction in net costs to the PBS are also overstated. (summarized from the Pharmaceutical Evaluation Section Commentary from March 2012 consideration, page 7.4.Com82 and 83)

The PES Commentary concluded that "Overall, the estimates in the submission are uncertain and a likely overestimate of the stated cost savings to the PBS". (7.4.Com83)

The PBAC stated its concern that the use of Vimovo® would be high and that net savings with listing naproxen/esomeprazole were unlikely.

7.4.21 "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" (Ratified minutes March 2012 PBAC meeting, page 297).

Third Minor Submission (considered November 2012)

…"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 PPI and NSAID medicines. …"(Ratified minutes November 2012 meeting of the PBAC, page 2).

The application for review raises the following questions:

- What were the reasons for PBAC's continuing concern that the listing of Vimovo® on the PBS could result in increased costs to the PBS?
- Was there any information from the Sponsor or used by PBAC that demonstrated the likelihood of increased costs to the PBS?
- Is PBAC required to apply The Guidelines [Part II, Section E page 151 "Costs over five years"] consistently?
- What are the possible sources of concern that Vimovo® listing would increase costs to the PBS?

PBAC's continuing concern that the listing of Vimovo® on the PBS could result in increased costs to the PBS

The grounds for PBAC's continuing concern that the listing of Vimovo® on the PBS could result in increased costs to the PBS relates specifically to factors associated with uncertainty in the Sponsor's assumptions relating to the quantity of the drug consumed in the market and price.

Those factors include:

- growth in the NSAID market itself;
- Vimovo®'s share of the market and the specific assumptions regarding uptake and substitution patterns for Vimovo®;
- price weighting of Vimovo®;
- the proportion of patients currently on celecoxib + PPI or NSAID + PPI who have at least 1 gastrointestinal (GI) risk factor;
- known statutory price reductions for PPIs; and
- further price reductions of NSAIDs.

From the first to the third PBAC submissions for Vimovo® the PES and PBAC consistently expressed concerns about the potential for Vimovo® to increase overall net costs to the PBS.

Information presented to PBAC that demonstrated the likelihood of increased costs to the PBS?

As can be seen below, each successive submission demonstrated greater cost savings to the PBS if Vimovo® were listed. In the 3rd (minor) PBAC submission when the Sponsor included, at the request of PBAC, the known statutory price reductions for rabeprazole and esomeprazole the projected cost saving to the PBS over the forward estimates were maintained. However, despite consideration of each of the issues raised the overall net cost to the PBS does not come close to switching from the negative (cost saving) to the positive (cost inducing).

Overall Net Cost to the PBS and the Government Health Budget

1st submission Base Case

	Dec 11 - Nov 12	Dec 12 - Nov 13	Dec 13 - Nov 14	Dec 14 - Nov 15	Dec 15 - Nov 16
Overall Net Cost to PBS	-$ 1,956,852	-$ 3,291,676	-$ 4,353,784	-$ 4,940,528	-$ 5,051,818
Cost to Government for MBS	$ -	$ -	$ -	$ -	$ -
Overall Net cost to Govt Health Budget	**-$ 1,956,852**	**-$ 3,291,676**	**-$ 4,353,784**	**-$ 4,940,528**	**-$ 5,051,818**

Cumulative cost to Govt over first 5 years of listing	**-$ 19,594,658**

2nd submission Base Case

	April 11 to March 12	April 12 to March 13	April 13 to March 14	April 14 to March 15	April 15 to March 16
Overall Net Cost to PBS	-$ 2,747,263	-$ 4,782,408	-$ 6,527,663	-$ 7,613,402	-$ 7,805,072
Cost to Government for MBS	$ -	$ -	$ -	$ -	$ -
Overall Net cost to Govt Health Budget	**-$ 2,747,263**	**-$ 4,782,408**	**-$ 6,527,663**	**-$ 7,613,402**	**-$ 7,805,072**

Cumulative cost to Govt over first 5 years of listing	**-$ 29,475,808**

Base Case

3rd submission Base Case

	Mar 13- Feb 14	Mar 14-Feb 15	Mar 15-Feb 16	Mar 16-Feb 17	Mar 17-Feb 18
Overall Net Cost to PBS	-$ 3,958,059	-$ 6,559,654	-$ 9,161,248	-$ 10,462,045	-$ 11,762,843
Cost to Government for MBS	$ -	$ -	$ -	$ -	$ -
Overall Net cost to Govt Health Budget	**-$ 3,958,059**	**-$ 6,559,654**	**-$ 9,161,248**	**-$ 10,462,045**	**-$ 11,762,843**

Cumulative cost to Govt over first 5 years of listing	**-$ 41,903,849**

Sensitivity analysis – including known statutory price reductions of rabeprazole and esomeprazole

Cumulative cost to Govt over first 5 years of listing	**-$37,278,855**

The PES and PBAC accepted the Section D and Section E information with just a few minor corrections, the validity of the Sponsor's financial estimates model was not questioned and the Sponsor responded appropriately to PBAC requests for it to model the financial impact using revised assumptions.

Quantitative estimate of uncertainty

The key issue is whether there was any quantitative estimate of uncertainty provided that would support PBAC's continuing concern that the listing could result in increased costs to the PBS.

The Guidelines (Section E, Page 160) specify three aspects for consideration when dealing with uncertainty on the financial impact of a new drug, they are:

- the direction of impact on the estimate (underestimate or overestimate)
- the impact on the magnitude of the estimate (small or large)
- the likelihood that another estimate should replace the base case estimate (probable or improbable).

The Guidelines go on to state: "*although quantitative estimates of uncertainty are preferred, semi-quantitative assessments may need to be given in many instances. Where the effects of some uncertainties are difficult to quantify, this should be noted. As a general principle, the more sensitive the overall financial implications are to a particular source of uncertainty, the more important it is to minimise that uncertainty*" (page 160)

A review of all the documents in the three Vimovo® PBS submissions and minutes of the meetings, focusing in particular on Section D and Section E requirements of the Guidelines, did not reveal any written evidence to support the PBAC claim that listing Vimovo® would increase costs to the PBS.

The Primary Reviewer sought a meeting with the Chair of the PBAC to clarify how PBAC arrived at the conclusion in the minutes of PBAC meeting that Vimovo® would increase the overall net cost to the PBS. That meeting occurred on 23 April 2013.

The Primary Reviewer was advised that the Sponsor lodging a minor submission (as suggested by the Department of Health and Ageing in a pre-submission meeting) meant that the application could not be returned to DUSC for further analysis of utilization against the latest financial impact costings. As a result, the PBAC had to form a view about the utilization figures at the Committee meeting. 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[4].

Conclusion

The claim for Vimovo® being cost saving is robust across all submissions and material before the PBAC. The Sponsor is correct in saying that the PBAC conclusion is unable to be reconciled with any costing analysis available.

The PBAC did not adequately explain and communicate the causes of their concern about Vimovo® listing increasing costs to the PBS.

[4] Quoted from agreed minutes of meeting between the Primary Reviewer and the Chair, PBAC

That the PBAC were concerned about growth in the market was clear in observations in the March and November 2012 PBAC minutes. However, the minutes have not made it clear the Committee holds a strong view that the market for NSAIDs will grow and that this is an expert view of the Committee itself.

The basic principles of just and accountable decision-making generally afford the Sponsor the right to:

- know what criteria they must satisfy;
- be heard – to provide information and argue their case;
- know what information has been considered in making the decision; and
- know the reasons for the decision.

As the minutes did not say clearly that the market was expected to grow by a specified percentage over 5 years this has meant that the Sponsor has been unable to address this issue in the pre-PBAC submissions.

Is PBAC required to apply The Guidelines [Part II, Section E p 151 "Costs over five years"] consistently?

The ratified minutes of the November 2012 PBAC meeting state that "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 resubmission. The analysis and evaluation should take into account the issues raised in previous evaluations and the ongoing reductions in the PBS prices of some PPIs and NSAID medicines." (Ratified minutes of the November 2012 PBAC meeting, page 2).

The Sponsor states that the request by the PBAC that it should take into account "ongoing reductions in the PBS prices of some PPIs and NSAID medicines" is inconsistent with the PBAC Guidelines that state that cost estimates should be based on constant prices with no allowance made for inflation and use of a zero discount rate.

The reviewer agrees that the PBAC request is contrary to the Guidelines. However, as the future price reductions for rabeprazole and esomeprazole were statutory reductions the reviewers consider this to be an entirely justifiable request by PBAC. Beyond that including further price reductions in the financial estimates should have been explained clearly to the Sponsor.

Conclusion

PBAC required further information from the Sponsor that is inconsistent with the Guidelines with the intention of **reducing** the uncertainty about the financial impact of Vimovo® listing. Whilst PBAC has the right to request such information it might consider including information on the reasons for departing from the Guidelines.

Under which scenarios would Vimovo® would increase costs to the PBS?

The reviewers undertook a sensitivity analysis of the projected financial impact of listing Vimovo®, using a range of possible causes for PBAC's ongoing concern about cost increases. The purpose of this analysis is to quantify the magnitude of the impact of the estimate on the net cost to the PBS and the Government health budget and ascertain the likelihood that listing Vimovo® would increase costs to the PBS. The results of the sensitivity analysis are indicative only.

The sensitivity analysis was conducted using the Sponsor's 'Section E' Excel spreadsheet model. The reviewers note that the PBAC did not report on any errors or problems relating to the validity and reliability of the Section E model, nor were any found by the reviewers (over and above the few minor corrections notes by the PES in their commentary).

For each of the potential individual scenarios a range of estimates was made around the base case assumption and the predicted impact on the Overall Net Cost to the PBS (which in this application is equivalent to the Overall Net Cost to Government Health Budget). The results of this modelling are summarized in Table below.

Table 9. Consideration of assumptions in the Vimovo® submissions and price comparison

Assumption	Comment and evidence	Implication of change in assumption
Assumption 1		
Reimbursement market for the treatment of chronic athropathies is mature and well established *Assumption*: Predictions of NSAID (including meloxicam) and celecoxib remain constant over the duration of the model	This is a reasonable assumption and the conclusion that listing Vimovo® will not grow the market (but will take market share from other NSAIDs) is realistic. The introduction of coxibs is likely to have expanded this market to its capacity. Note Sponsor contends that the market is actually declining in volume.	If the market for the treatment of chronic athropathies INCREASES then at some point a Vimovo® listing will INCREASE costs to the PBS If the market for the treatment of chronic athropathies DECREASES then Vimovo® listing will not alter the costs to the PBS but will lead to greater projected savings as it replaced more expensive treatments (celecoxib and celecoxib +PPI)
Economic Analysis *Relax assumption of 'No Growth' in the NSAID market*	*Using Excel GOAL SEEK function, what is the ANNUAL growth of NSAIDs (only) that would switch the financial impact from cost saving to cost inducing? (Celecoxib market held constant, no further cost saving due to substitution – market growth only)*	*9.39% Annual growth in NSAID market is needed to achieve zero cost to government over the next 5 years*
Economic Analysis *Relax assumption of 'No Growth' in the NSAID market*	*Using Excel GOAL SEEK function, what is the ANNUAL growth of Celecoxib (only) that would switch the financial impact from cost saving to cost inducing? (NSAID market held constant, no further cost saving due to substitution – market growth only)*	*23.9% Annual growth in celecoxib market is needed to achieve zero cost to government over the next 5 years*
Assumption 2		
75% of Vimovo®'s market share will come from gastroprotective strategies currently recommended in Australian treatment Guidelines, namely celecoxib ± PPI and NSAID + PPI	This is a reasonable assumption given these are the major current gastroprotective strategies employed in high risk people.	If GREATER than 75% uptake of Vimovo® occurs it would increase net savings to the PBS LESS market share – Vimovo® listing would decrease net savings to the PBS
Economic Analysis	*INCREASE Vimovo®'s market share by 5% across the board*	*BASE CASE: Cumulative cost to Govt over first 5*

Sensitivity analysis on DUSC estimates regarding uptake and substitution patterns for Vimovo®	*(each year), except for NSAID monotherapy*	*years of listing,* -$41,903,849 *Sensitivity Analysis: Cumulative cost to Govt over first 5 years of listing, -$47,762,826*
	DECREASE Vimovo®'s market share by 5% - 15% across the board (each year), except for NSAID monotherapy	*BASE CASE:* Cumulative cost to Govt over first 5 years of listing, -$41,903,849 *Sensitivity Analysis 5% decrease : Cumulative cost to Govt over first 5 years of listing, -$36,044,873* *Sensitivity Analysis 15% decrease: Cumulative cost to Govt over first 5 years of listing -$24,789,344*
Assumption 3		
Uptake from NSAID (incl meloxicam) monotherapy is expected to account for less than 10% of the total therapies that Vimovo® will replace.	Meloxicam monotherapy at a dose of 15 mg daily is not recommended for use in at-risk patients in Australian treatment guidelines. This is reasonable and conservative assumption given that the PBS review of selective NSAIDs concluded similar findings regarding the advantage of celecoxib over meloxicam (*2004 review of the Cox-2 agents, the PBAC considered that meloxicam lies between traditional NSAIDs and Cox-2 specific agents*) The conservative estimate of (slow) uptake of Vimovo® in at risk people with chronic arthropathies is realistic – especially the comments that it is "unlikely to change prescribing behaviour " in a "short time frame".	HIGHER nsNSAID (meloxicam) monotherapy use – Vimovo® listing it would DECREASE net savings to the PBS LOWER nsNSAID (meloxicam) monotherapy use – Vimovo® it would INCREASE net savings to the PBS

Economic Analysis *Sensitivity analysis on DUSC estimates regarding uptake and substitution patterns for Vimovo®*	*INCREASE Vimovo®'s market share by for NSAID monotherapy ONLY*	*BASE CASE: Cumulative cost to Govt over first 5 years of listing,* -$41,903,849 *Sensitivity Analysis: Cumulative cost to Govt over first 5 years of listing , -$36,722,929*
	DECREASE Vimovo®'s market share by for NSAID monotherapy ONLY	*BASE CASE, Cumulative cost to Govt over first 5 years of listing* -$41,903,849 *Sensitivity Analysis Cumulative cost to Govt over first 5 years of listing -$47, 084,769*
Assumption 4		
Price weighting of Vimovo® 73% celecoxib price and 27% meloxicam price	Sponsor contends that this split reflects the likely substitution patterns and further highlights that a 50/50 is not a realistic reflection of the advance of celecoxib over meloxicam My assessment is that these are conservative figures	HIGHER portion of meloxicam price – Vimovo® listing represents BETTER is value for money on the PBS HIGHER portion of celecoxib price – Vimovo® listing represents WORSE value for money on the PBS
Economic Analysis *Sensitivity Analysis on Pricing Split between Celecoxib and Meloxicam*	50:50 Split (celecoxib : meloxicam) 90:10 Split (celecoxib : meloxicam)	*BASE CASE Cumulative cost to Govt over first 5 years of listing* -$41,903,849 *50:50 Split Cumulative cost to Govt over first 5 years of listing -$55,689,339* *90:10 Split Cumulative cost to Govt over first 5 years of listing -$31,925,781*
Assumption 5		

Cost of celecoxib + PPI (separate dispensed dose forms)	A gastroprotective strategy in high risk patients - calculated from Medicare Australia data which estimated the proportion of use accruing to the most frequently dispensed combinations of NSAID + PPI. This is a reasonable assumption – Table suggests lower uptake from celecoxib + PPI than celecoxib monotherapy.	HIGHER use of celecoxib + PPI in high risk people – then Vimovo® listing represents BETER value for money on the PBS LOWER use of celecoxib + PPI in high risk people – then Vimovo® listing represents LESS value for money on the PBS but remain cost neutral
Economic Analysis *Sensitivity analysis*	*Increase the proportion of use of celecoxib +PPI therapy associated with at least 1 GI risk factor from 82% to 100%* *Decrease the proportion of use of celecoxib +PPI therapy associated with at least 1 GI risk factor from 82% to 50%*	*BASE CASE Cumulative cost to Govt over first 5 years of listing* -$41,903,849 *Sensitivity Analysis 100% Cumulative cost to Govt over first 5 years of listing -$44,670,342* *Sensitivity Analysis 50% Cumulative cost to Govt over first 5 years of listing -$37,044,368*
Assumption 6		
Cost of NSAID + PPI (separate dispensed dose forms)	A gastroprotective strategy in high risk patients - calculated from Medicare Australia data which estimated the proportion of use accruing to the most frequently dispensed combinations of NSAID + PPI.	HIGHER use of NSAID + PPI in high risk people – then Vimovo® listing represents BETER value for money on the PBS LOWER use of NSAID + PPI in high risk people – then Vimovo® represents LESS value for money on the PBS but remain cost neutral
Economic Analysis *Sensitivity analysis*	*Increase the proportion of use of NSAID +PPI therapy associated with at least 1 GI risk factor from 82% to 100%* *Decrease the proportion of use of NSAID +PPI therapy associated with at least 1 GI risk factor from 82% to 50%*	*BASE CASE Cumulative cost to Govt over first 5 years of listing* -$41,903,849 *Sensitivity Analysis 100% Cumulative cost to Govt over first 5 years of listing -$51,080,251* *Sensitivity Analysis 50% Cumulative cost to Govt over first 5 years of listing -$25,785,045*
Economic Analysis	*Increase the proportion of use of NSAID monotherapy*	*BASE CASE Cumulative cost to Govt over first 5 years*

Sensitivity analysis	*associated with at least 1 GI risk factor from 62% to 100%*	*of listing* -$41,903,849 *Sensitivity Analysis 100% Cumulative cost to Govt over first 5 years of listing -$17,408,342*
Assumption 7		
Projected statutory price reductions of comparators (including PPIs)	Known statutory price reductions for esomeprazole and rabeprazole have been included over the forward estimates. These assumptions are reasonable in my view and add value the quality of the projections	No variation expected as these changes are statutory price reductions
Sensitivity Analysis provided by Sponsor in their Economic Model	*Known statutory price reductions for esomeprazole and rabeprazole* *What FURTHER price reductions for Celecoxib (+/-PPI) AND NSAID (+/- PPI) would be needed to SWITCH the Cumulative cost to Govt over first 5 years of listing from cost saving to cost INDUCING* *For celecoxib + PPI and NSAID (+/- PPI)*	*BASE CASE Cumulative cost to Govt over first 5 years of listing* -$41,903,849 *Sensitivity Analysis 100% Cumulative cost to Govt over first 5 years of listing -$37.278,855* 18% ADDITIONAL Price reduction, sustained over all five years, would yield a *Cumulative cost to Govt of $53,258* 20% ADDITIONAL Price reduction, sustained over all five years, would yield a *Cumulative cost to Govt of $470,047*
Guidelines recommended either celecoxib or NSAID+PPI in high risk patients Assumptions described in Table 8 of Final Minor Submission	Recommendations derived the TG (Gastrointestinal) 2006 Table includes each of the evidence-based guideline treatment recommendations (celecoxib, celecoxib + PPI and NSAID + PPI) and also NSAID monotherapy (which is	HIGHER use of NSAID + PPI in high risk people – then Vimovo® listing represents BETER value for money on the PBS LOWER use of NSAID + PPI in high risk people – then Vimovo® listing represents LESS value for money on

	not recommended for high risk patients with chronic arthropathies)	the PBS HIGHER use of NSAID monotherapy – then Vimovo® listing represents LESS value for money on the PBS LOWER use of NSAID monotherapy – then Vimovo® listing represents MORE value for money on the PBS
Choice of PPI as the gastroprotection Assumption: all concomitant use of a gastroprotective agent accrues to PPIs.	"both misoprostol and histamine2-receptor antagonists (H2RA) are reimbursed for gastroprotection, neither agent is used to any great degree in clinical practice" Tolerability and lack of comparative efficacy data	HIGHER uptake of H2RA for NSAID gastroprotection – Vimovo® listing represents LESS value for money HIGHER uptake of misoprostol for NSAID gastroprotection – Vimovo® listing represents MORE value for money

*reference: http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2012-03/naproxen-and-esomeprazole

Table 10: Matters or assumptions not included in the estimate of costs to the R/PBS but of relevance

Sponsor Assumption	Comment and evidence	Implication
Combination product (naproxen + PPI) will facilitate adherence to naproxen and gastroprotective strategies with PPI * Poor adherence has been linked to increased risk of upper GI events, hospitalization and increased mortality.	Published studies cited in the application demonstrate that adherence with PPI is reduced over time. This has important implications for the likely continued clinical benefit and the effectiveness comparison with NSAID + PPI trials.	FDC products do provide improvements in adherence and can offer gastro-protection This would suggest there is a higher likelihood of the translation of RCT findings (from the 2 separate dose forms) into practice with the FDC product.
Vimovo® may offer a significant reduction in toxicity over celecoxib in those patients who have cardiovascular risk factors	Naproxen has a more favourable cardiovascular risk profile than celecoxib. This has been established in a range of trials	No effect on main endpoints

Conclusion

Only the assumptions about **market growth** and **price reductions** in celecoxib +/- PPIs and NSAIDs +/- PPI demonstrated the potential to flip the Overall Net Cost to the PBS from negative (cost saving) to positive (cost inducing). The findings can be summarized as follows:

- Changes to the following variables did **not** change the overall net cost to the PBS from negative (cost saving) to positive (cost inducing)
    - *DUSC estimates regarding uptake and substitution patterns for Vimovo®*
    - *uptake of NSAID monotherapy*
    - *pricing split between celecoxib and meloxicam*
    - *cost of NSAID + PPI or celecoxib + PPI (separate dispensed dose forms)*

- Growth of the market required to create a net positive cost to the PBS*
    - *estimated 9.4% annual growth in the NSAID market; OR*
    - *estimated 23.9% annual growth in the celecoxib market*
- Growth in price required to create a cost to the PBS*:
    - *18% pa addition price reduction for celecoxib (+/-PPI) and NSAID (+/-PPI)*

* *Indicate figures only based on the Primary Reviewer's changes to input data in the Financial Impact EXCEL spreadsheet created by the Sponsor.*

It is not within the scope of the Independent review to comment on the growth figures themselves.

Reviewers summary of findings on this aspect of the Review

The Sponsor was not presented with information that would adequately explain the conclusion reached by PBAC. Further analysis by the reviewers of the financial impact of Vimovo® shows that growth in the market is the only reason Vimovo® would generate a net cost to the PBS. The reviewers note that in such circumstances there are a variety of mechanisms that can be used to control the financial impact of a new listing on the PBS, including authority restrictions, a financial cap and risk sharing arrangements.

It is reasonable for PBAC to request that the Sponsor include known statutory price reductions of PPIs in their estimates of the financial impact of Vimovo® listing. However this should have been accompanied by a more detailed explanation of why the request was made.

Annexure 1: Material used in preparing the report

The Primary Reviewer met with Professor Suzanne Hill, Chair of PBAC, to discuss the PBAC conclusion that listing Vimovo® on the PBS would increase the overall net cost to the PBS.

A request was made to the Sponsor for the financial impact spreadsheets in a format that allowed the reviewer to link the separate spreadsheets. The spreadsheets were received but the reviewer was unable to link the files for the purpose of updating results.

Attachment 4

DOCUMENTS USED IN THE REVIEW

All reviewers used the following documents:

TGA

- 2011-04-13 TGA Clinical Evaluation Report
- 2011-04-21 Sponsor request for advice from Advisory Committee on Prescription Medicines (ACPM)
- 2011-06-10 ACPM recommendation (meeting of 2011-06-03)
- 2011-08-15 Ratified minutes of ACPM June 2011 meeting
- 2011-07-07 Letter to Sponsor, re-consideration by ACPM
- 2011-07-26 Sponsor request for advice from ACPM
- 2011-09-09 Ratified minutes of ACPM meeting 2011-09-02
- 2011-10-25 Registration of Vimovo®

First submission (considered at PBAC August 2011 meeting)

- Major submission and attachments
- PES Commentary
- DUSC, ESC and RWG commentary
- Sponsor response
- PBAC ratified minutes of August meeting

Second submission (considered at PBAC March 2012 meeting)

- Major submission and attachments
- PES commentary
- Sponsor response
- ESC commentary
- Sponsor response
- PBAC ratified minutes of March 2012 meeting

Third submission (considered at PBAC November 2012 meeting)

- Minor submission and attachments
- Secretariat overview
- Sponsor response
- PBAC ratified minutes of November 2012 meeting

Sponsor request for Independent Review

- All the above material was attached, as well as material referenced in the submissions but not attached in full to them, viz

- 2010-11-04 Sponsor briefing to FDA Gastrointestinal Drugs Advisory Committee (GIDAC)
- 2010-11-04 Minutes of the FDA GIDAC meeting
- FDA document for November 2010 meeting 'Outcome Measures for Claims to Reduce NSAID-Associated Upper Gastrointestinal (UGI) Toxicity'
- The full text of Moore, Tramer and Rostom references

One reviewer subsequently sought clarification about Table 31 in the second submission:

Query about data for table 31 in the 2nd major submission

Table 31 from the 2nd major submission is reproduced below.
The important grey-shaded area for endoscopy studies shows results from a meta-analysis on 2 unpublished studies from an FDA GIDAC report, table 5.4, which is also reproduced below. The relevant bottom 2 panels show study 1 and study 2. Study 1 shows 1 endoscopic ulcer in the esomeprazole/naproxen group, out of 218 patients, but gives the incidence as 5%. One of those figures appears incorrect.

What data did the Sponsor use for their meta-analysis in table 31?
Please also let me have the meta-analysis result to 2 decimal places.

Table 31 Relative risk of ulcers and events: NSAIDs plus PPIs versus NSAIDs alone (GIDA 2010a)

	RR (95% CI)	Adjusted RR
	Endoscopy studies	Clinical outcome studies
	Ulcers	POBs
Rostom 2009		
NSAID plus PPI vs NSAID	0.39 (0.31, 0.50)	
NSAID plus PPI vs NSAID	0.20 (0.10, 0.39)	
FDA briefing document		
Naproxen plus esomeprazole vs naproxen	**0.2 (0.2, 0.4)[a]**	
Naproxen plus omeprazole vs naproxen		**0.2 (0.1, 0.8)**
NSAID plus lansoprazole 30 mg/day vs NSAID	0.4 (0.2, 0.6)	
NSAID plus lansoprazole 15 mg/day vs NSAID	0.4 (0.3, 0.6)	
NSAID plus esomeprazole 40 mg/day vs NSAID	0.3 (0.2, 0.5)[a]	
NSAID plus esomeprazole 20 mg/day vs NSAID	0.3 (0.2, 0.5)[a]	
Aspirin 100 mg/day plus lansoprazole 30 mg/day vs aspirin 100 mg/day		0.1 (0.0, 0.8)
Aspirin 80 mg/day plus omeprazole 20 mg/day vs aspirin 80 mg/day		0.5 (0.1, 5.4)
Celecoxib 200 mg/day plus esomeprazole 20 mg/day vs celecoxib 200 mg/day		0.0 (0.0, 0.7)

Source: GIDAC Briefing Information Table 5.4 pg 13 and Table 5.5 pg 14.
Abbreviations: CI, confidence interval; NSAID, non-steroidal anti-inflammatory drug; POBs, perforations, obstructions and bleeds; PPI, proton pump inhibitor; PUBs, perforations, ulcers and bleeds; RR, relative risk.
[a] Pooled from the results of the two esomeprazole studies reported in Table 5.4.

Table 5.4: Endoscopically diagnosed GUs and/or DUs in NSAID-treated patients in PPI endoscopy trials[1]

Treatment Groups	Endoscopic ulcers	Incidence of endoscopically diagnosed ulcers	Comparison	RR	95% CI
Lansoprazole Study (12 weeks)[2,3]					
Misoprostol 200 µg QID (n=106)	12	11%	–	–	
Lansoprazole 30 mg/day (n=116)	20	17%	Lansoprazole 30 mg/NSAID vs. NSAID	0.4	0.2, 0.6
Lansoprazole 15 mg/day (n=121)	23	19%	Lansoprazole 15 mg/NSAID vs. NSAID	0.4	0.3, 0.6
Placebo (n=112)	55	49%	–	–	
Esomeprazole Study 1 (6 months)					
Esomeprazole 40 mg/day (n=271)	11	4%	Esomeprazole 40 mg /NSAID vs. NSAID	0.2	0.1, 0.4
Esomeprazole 20 mg/day (n=267)	12	5%	Esomeprazole 20 mg /NSAID vs. NSAID	0.3	0.1, 0.5
Placebo (n=267)	46	17%	–	–	
Esomeprazole Study 2 (6 months)					
Esomeprazole 40 mg/day (n=196)	8	4%	Esomeprazole 40 mg /NSAID vs. NSAID	0.4	0.2, 0.8
Esomeprazole 20 mg/day (n=192)	9	5%	Esomeprazole 20 mg /NSAID vs. NSAID	0.4	0.2, 0.9
Placebo (n=185)	20	11%	–	–	
Esomeprazole/Naproxen Study 1 (6 months)[2,4]					
Esomeprazole/Naproxen (n=218)	1	5%	Esomeprazole 40 mg/ Naproxen vs. Naproxen	0.2	0.1, 0.3
Naproxen (n=216)	60	28%			
Esomeprazole/Naproxen Study 2 (6 months)[2,4]					
Esomeprazole/Naproxen (n=210)	17	8%	Esomeprazole 40 mg/ Naproxen vs. Naproxen	0.3	0.2, 0.5
Naproxen (n=210)	59	28%			

[1] These studies appear in the labels.
[2] The analysis in this table includes both GUs and DUs; however, the primary endpoint for the lansoprazole endoscopy trial and the esomeprazole/naproxen trials only included GUs. Note, the RR of GUs only in these 3 trials is the same as the RR of both GUs and DUs.
[3] The RR (95% CIs) of misoprostol µg QID/NSAID compared to lansoprazole 30 mg/NSAID was 0.7 (0.3, 1.3). The RR (95% CIs) of misoprostol µg QID/NSAID compared to lansoprazole 15 mg/NSAID was 0.6 (0.3, 1.1).
[4] Naproxen was dosed 500 mg BID, esomeprazole was dosed 20 mg BID.

The Sponsor provided the following information.

'Introduction:

On 6 May 2013 the Convenor had forwarded to AstraZeneca a query from one of the Reviewers of the Vimovo® (esomeprazole/naproxen) Independent Review. An extract is below….

Query about data for table 31 in the 2nd major submission

Table 31 from the 2nd major submission is reproduced below. The important grey-shaded area for endoscopy studies shows results from a meta-analysis on 2 unpublished studies from an FDA GIDAC report, table 5.4, which is also reproduced below. The relevant bottom 2 panels show study 1 and study 2. Study 1 shows 1 endoscopic ulcer in the esomeprazole/naproxen group, out of 218 patients, but gives the incidence as 5%. One of those figures appears incorrect.

What data did the Sponsor use for their meta-analysis in table 31? Please also let me have the meta-analysis result to 2 decimal places.

The response to the Reviewer's query is provided below.

Background:

In late 2011, a health economics consultancy undertook a project, on behalf of AstraZeneca, which would inform AstraZeneca's submission to the PBAC for Vimovo®. A report titled "*Assessment of endoscopic ulcers as a surrogate outcome for serious gastrointestinal events and for use as the basis of a non-inferiority claim in the PBAC re-submission for naproxen/esomeprazole (Vimovo®)*" was produced. This report is attached to the email accompanying this response ("a Endoscopic endpoints 311011 FINAL").

The consultant's report made use of data contained in a public FDA briefing document which is attached to the email accompanying this response (attached: "d FDA NSAID-PPI Nov 4 AC briefing background.pdf"). The report was used in the PBAC submission and was the source for Table 31 in the submission dossier.

The Reviewer has identified an inconsistency in the data used in the submission as described in the query. An extract from Table 5.4 of the FDA briefing document is reproduced below, with the relevant data highlighted. As the Reviewer states, it is clear that one of the numbers is incorrect.

Treatment Groups	Endoscopic ulcers	Incidence of endoscopically diagnosed ulcers	Comparison	RR	95% CI
Esomeprazole Study 2 (6 months)					
Esomeprazole 40 mg/day (n=196)	8	4%	Esomeprazole 40 mg /NSAID vs. NSAID	0.4	0.2, 0.8
Esomeprazole 20 mg/day (n=192)	9	5%	Esomeprazole 20 mg /NSAID vs. NSAID	0.4	0.2, 0.9
Placebo (n=185)	20	11%	–	–	
Esomeprazole/Naproxen Study 1 (6 months)[2,4]					
Esomeprazole/Naproxen (n=218)	1	5%	Esomeprazole 40 mg/ Naproxen vs. Naproxen	0.2	0.1, 0.3
Naproxen (n=216)	60	28%			
Esomeprazole/Naproxen Study 2 (6 months)[2,4]					
Esomeprazole/Naproxen (n=210)	17	8%	Esomeprazole 40 mg/ Naproxen vs. Naproxen	0.3	0.2, 0.5
Naproxen (n=210)	59	28%			

Response

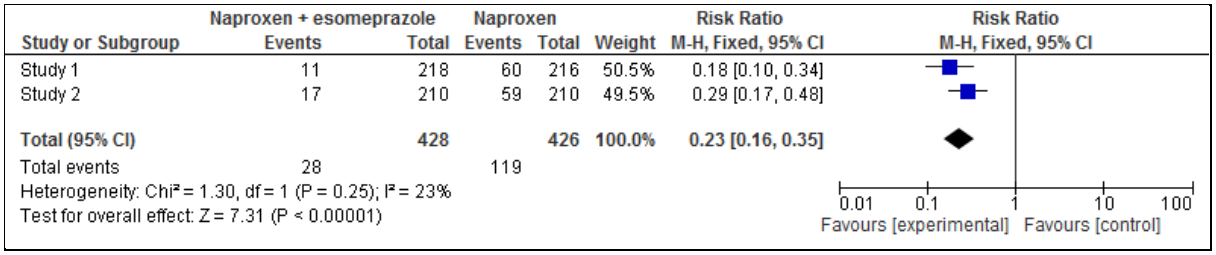
Data:

AstraZeneca global personnel have been alerted and, after examination of the FDA document, confirm that that there is a typographical error in that the number of endoscopic ulcers reported in the table should be 10. The incidence, relative risk and confidence intervals were calculated on the correct data, and are therefore correct.

Methodology:

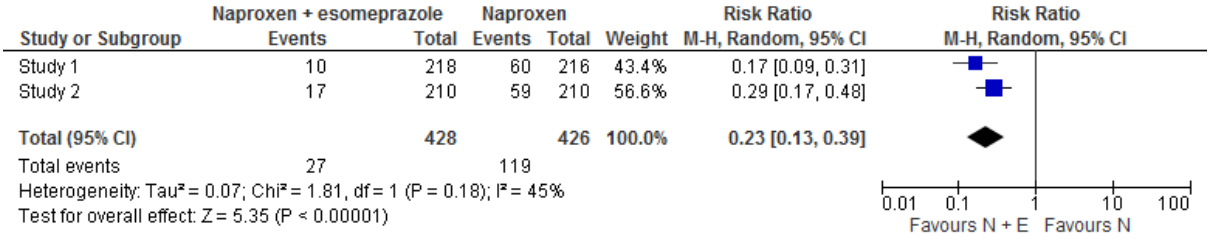
The methodology use to produce the information in the consultant's report is as follows.

The consultant perceived the inconsistency in the FDA document and chose to treat it conservatively. That is, the analysis assumed that the error in the FDA report related to the number of patients experiencing endoscopic ulcers in Study 1 (n=1), as opposed to the percentage (5%). Given that 5% of the study population (N=218) is 11 events, it is likely that the error was due to a missing "1" in the table cell. The analysis presented in the resubmission is reproduced in the Forest plot presented below (to 2 decimal places).



Final note:

As can be seen in the information above, AstraZeneca global has confirmed that the correct number is 10, while the consultant assumed 11 in the original report. The consultant has reproduced the results, to 2 decimal places, using 11 events to examine the impact of this difference.



Conclusion

The typographical error identified by the Reviewer, within the source data imparts no important alteration to the results of the pooled analysis.

We trust this addresses the query satisfactorily.'

Attachment 5

INDEPENDENT REVIEW REQUEST FROM ASTRAZENECA PTY LTD

Consistent with previous Independent Reviews, the submission by AstraZeneca Pty Ltd id re-produced here in full.

"Introduction

Vimovo® is a fixed dose combination of enteric-coated naproxen 500mg, a non-steroidal anti-inflammatory drug and immediate-release esomeprazole 20mg, a proton pump inhibitor.

In August 2011, March 2012, and November 2012, the PBAC recommended rejection of the applications seeking PBS listing for Vimovo®. On each occasion AstraZeneca has sought to understand the reasons for rejection and has discussed ways to address these issues with representatives from the Pharmaceutical Benefits Branch as well as the PBAC Chair. On each occasion AstraZeneca has sought to address these issues in the next submission. However, on each occasion, the PBAC has cited additional reasons for recommending rejection of the listing. As such, AstraZeneca has reluctantly reached the conclusion that an Independent Review is the only avenue remaining to seek clarification on the issues of contention.

Grounds of Review

Following its most recent consideration, the reasons provided by the PBAC for rejection were "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". (Ratified minutes of the November 2012 PBAC meeting, p2, paragraph 4)

AstraZeneca seeks a review of the PBAC's recommendation to reject the application seeking PBS listing for Vimovo® which was considered at the November 2012 meeting. The grounds of review and the issues relating to those grounds are as follows:

PBAC's conclusion "that not all PBAC criteria for combination products are met" (Ratified minutes of the November 2012 PBAC meeting, p2, paragraph 4) inappropriately applies the information requests as outlined on p211-212 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.

This ground of review requires consideration of the appropriateness of the manner in which the combination product criteria have been applied.

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, p2, paragraph 4) is based on insufficiently robust data which has been taken out of context.

This ground of review requires consideration of the rigour of the evidence provided by the Pharmaceutical Evaluation Section (PES) and accepted by the PBAC to refute the validity of the surrogate outcome and whether the evidence cited has been appropriately interpreted.

PBAC's conclusion that there is "continuing concern that the listing could result in increased costs to the PBS" (Ratified minutes of the November 2012 PBAC meeting, p2, paragraph 4) is unable to be reconciled with any costing analysis available.

This ground of review requires an assessment of whether any justification has been provided to support the claim that the PBS listing requested for Vimovo® could result in increased cost to the PBS.

This statement is structured as follows.

First, it provides a brief history of each submission provided for Vimovo® and the reasons provided by the PBAC for rejection of each application.

Second, it discusses the three grounds of review and associated issues outlined above and in doing so refers to each of PBAC's reasons for not recommending listing of Vimovo® following consideration at the November 2012 meeting.

Finally, the statement concludes that the reasons cited for rejection by the PBAC are insufficiently supported, inconsistent with previous decisions made by Committee and inconsistent with the advice provided to Sponsors in the Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (PBAC) (Version 4.3, December 2008).

History of submissions to the PBAC for Vimovo®

The first major submission seeking PBS listing for Vimovo® was considered at the August 2011 Special meeting of the PBAC, with the Committee recommending rejection because the nominated main comparator (Celecoxib) was inappropriate and there were no data presented versus the comparator which the PBAC deemed to be appropriate (Meloxicam) to make a recommendation. (Ratified minutes of the August 2011 Special PBAC meeting, p 8, final paragraph)

The second major submission for Vimovo® was considered at the March 2012 meeting of the PBAC. The resubmission included additional data to address the previously cited reason for rejection as well as other main areas of uncertainty raised with respect to the original submission. The Committee again recommended rejection, this time 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 and an expectation that the listing as requested could result in increased costs both overall and also to the PBS. (Ratified minutes of the March 2012 PBAC meeting, p297, paragraph 7.4.22)

AstraZeneca met with the PBAC Chair and representatives from the PBB for a post-rejection meeting on the 17th of April 2012, where we were advised that the main issues leading to rejection of the second submission related to the comparator, endpoints and price and that a minor resubmission with a revised pricing proposal would be an appropriate way to address these issues. The third minor submission was considered at the November 2012 meeting of the PBAC. The Committee again recommended rejection, for the first time citing failure to meet all PBAC criteria for combination products as a reason for rejection, in addition to two of the three previously cited reasons, namely, 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. (Ratified minutes of the November 2012 PBAC meeting, p2, paragraph 4)
Issues relating to the Grounds of Review

The appropriateness of the manner in which the combination product criteria have been applied

GROUND OF REVIEW: *PBAC's conclusion "that not all PBAC criteria for combination products are met" (Ratified minutes of the November 2012 PBAC meeting, p2) inappropriately applied the information requests as outlined in 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 for PBS listing.*

Points for consideration: *Are the information requests as outlined on p211-212 of Part IV of the Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (PBAC) (version 4.3) "minimum requirements that combination products need to satisfy in order to be eligible for consideration by the PBAC" i.e. do the Guidelines require that all these criteria must be met in order for a combination product to be considered by the PBAC and listed on the PBS and is this interpretation consistent with previous PBAC decisions?*

One of the grounds cited for rejection of the most recent application for Vimovo® (but notably not the first two applications) was that "not all PBAC criteria for combination products are met." (Ratified minutes of the November 2012 PBAC meeting, pg 2, paragraph 4). The ratified minutes (p2, paragraph 3) describe the information requests outlined in Part IV of the Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (PBAC) (Version 4.3, December 2008) as "minimum requirements that combination products need to satisfy in order to be eligible for consideration by the PBAC".

However, the description of these information requests as "minimum requirements" is inappropriate and overstates the standing of these criteria. The PBAC Guidelines (v.4.3, December 2008), Part IV, p211-212, list these criteria as "information requests". There is no indication in the current PBAC Guidelines that all these requirements must be satisfied for a combination product to be eligible for consideration by the PBAC.

Furthermore, these information requests cannot constitute the minimum requirements that a combination product must satisfy to be eligible for consideration by the PBAC because there are combination products currently listed on the PBS which do not meet all these criteria. AstraZeneca cited two such examples (Seretide® and Duodart®) in our responses to the PES Commentary (p3) and ESC advice (p2) from the August 2011 consideration which have been reproduced in Table 1 below. AstraZeneca has included further examples identified for the reference of the reviewer. It is not our intention that this table provide an exhaustive assessment of PBS listed combination products against the combination criteria. However these examples serve to highlight the fact that there combinations products which do not meet all of the combination product criteria yet were recommended by the PBAC and subsequently PBS listed. It is also interesting to note that these examples include products which do not meet the specific criteria which the PBAC raised with respect to Vimovo®. Further consideration should be given to the fact that the criteria which Vimovo® was deemed not to have satisfied has not been consistently stated during the evaluation. (Secretariat Overview from the November 2012 consideration, PBAC SEC OVR 7.10.3 and 7.10.6 and Ratified minutes from the November 2012 PBAC meeting p 2, paragraphs 4 and 5).

Table 1 Combination products recommended by the PBAC which do not meet all of the information requests for combination products

Combination Product	PBS listing of relevance	Information requests not satisfied
Abacavir 300mg with lamivudine 150mg and zidovudine 300mg	HIV	**Criterion g:** The components products require individual titration. The product information states that "If dosage adjustment of individual components is required, do not use this combination formulation."
Alendronate, colecalciferol ± calcium carbonate	Osteoporosis	**Criteria b:** Coleciferol is not listed on the PBS
Dutasteride and tamsulosin)	Lower urinary tract symptoms due to benign prostatic hyperplasia	**Criterion b:** Tamsulosin is not listed on the PBS. It is only listed on the repatriation schedule
Enalapril10/20mg and lercanidipine 10mg	Hypertension	**Criterion g:** Both enalapril and lercanidipine require individual dose titration
Fluticasone/salmeterol)	Chronic obstructive pulmonary disease (COPD)	**Criterion b:** If one applies to logic used in the recent consideration of Vimovo®, this criterion is "partially met" (refer to ratified minutes from the November 2012 consideration, p1, paragraph 5) because although both components are PBS-listed, neither fluticasone nor salmeterol are PBS-subsidised for COPD. AstraZeneca however, does not concur with PBAC's interpretation of this criterion because it confounds criterion b and c. Criterion b considers whether the components are listed on the PBS. Criterion c considers whether the PBS restrictions of the components and the combination product are consistent. **Criterion c:** Fluticasone is listed as a general benefit and as such, is reimbursed for all TGA approved indications; however COPD is not amongst the TGA-approved indications for fluticasone. Salmeterol is not PBS listed for COPD

NOTE: The information requests are presented in this table as they are represented in the Secretariat Overview (PBAC SEC OVR 7.10.3) and ratified minutes from November 2012 consideration of Vimovo® i.e. listed as criterion (a) though (g). This is not consistent with how they are presented in the current PBAC Guidelines; however this nomenclature has been retained in this table for ease of reference between documents

Key: (**a)** The product should be approved or is recommended for approval by the TGA and meets all the clinical criteria required by the TGA; **b)** The component products should preferably be listed on the PBS; **c)** Restrictions for the component products should be consistent with those proposed for the combination; **d)** The doses of the listed component products and the proposed combination should be consistent; **e)** There should be additive (not necessarily synergistic) beneficial effectiveness of the components; **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; **g)** The combination product should not result in inappropriate dosing of either component, nor contain components which require individual dose titration

The reviewer may also wish to consider whether AstraZeneca has been afforded procedural fairness by the PBAC in citing failure to satisfy all the combination product criteria as grounds for rejection of the third submission.

The PBAC was specifically asked by both the PES (PES Commentary 5.7.COM.15 and 5.7.COM.19 from the August 2011 PBAC consideration and PES Commentary 7.4.COM.20 from the March 2012 consideration) and the ESC (ESC advice 5.7.ESC ADV.9 from the August 2011 consideration) whether the combination product criteria applied to the proposed listing for Vimovo®. However the ratified minutes from both the August 2011 and the March 2012 PBAC consideration of Vimovo® contain no reference to the combination product criteria, nor do they cite failure to satisfy all the criteria as grounds for rejection. If the criteria really are to be applied as minimum mandatory requirements for listing, it is not clear why it has taken three applications for the PBAC to cite failure to satisfy all these criteria as grounds for rejection nor why AstraZeneca was not advised of the PBAC's concerns regarding these criteria at the post-rejection meeting. AstraZeneca is cognisant that these meetings are held without prejudice; however, they have a significant impact on the Sponsor's understanding of the main issues with an application from the PBAC's perspective, specifically in the absence of any information in the ratified minutes, as well as providing an opportunity to discuss how best to address the issues raised to the satisfaction of PBAC and work towards PBS listing.

In conclusion, the description and application of the information requests outlined in Part IV of the of the Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (PBAC) (Version 4.3, December 2008) as "minimum requirements that combination products need to satisfy in order to be eligible for consideration by the PBAC" overstates the standing of these criteria, is inconsistent with the way in which these criteria are represented in the current PBAC Guidelines and inconsistent with previous PBAC decisions, whereby combination products which do not meet all the criteria have been not only not only considered by the PBAC but also listed on the PBS. As such, failure to meet all information requests for combination products clearly does not provide an adequate basis for rejection of an application for PBS listing.

2. The rigour of the evidence provided by the Pharmaceutical Evaluation Section (PES) and the PBAC to refute the validity of the surrogate outcome and whether the evidence cited has been appropriately interpreted

GROUND OF REVIEW: *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, p2) is based on insufficiently robust data taken out of context.*

Points for consideration: *Is the evidence cited by the PES and accepted by the PBAC to repudiate the validity of endoscopic ulcers as a valid surrogate endpoint of sufficient rigour and did the PES and therefore the Committee interpret this evidence appropriately?*

"Continued uncertainty regarding the validity of the surrogate outcome for the purposes of demonstrating non-inferiority or more patient-relevant outcomes" was cited as the second reason for rejection following the November 2012 consideration of Vimovo®. (Ratified minutes from the November 2012 PBAC meeting, p 2, paragraph 4). "The PBAC recalled its March 2012 advice, that overall, there is 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." (Ratified minutes from the November 2012 PBAC meeting, p 2). The ratified minutes from the March 2012 consideration provide the following rationale for this conclusion:

"The PBAC noted that there is evidence that 85% of all endoscopically detected ulcers do not progress to clinically significant GI events, and there is also some suggestion that the definition and identification of a case of an endoscopically-detected ulcer may be uncertain." (Ratified minutes from the March 2012 consideration, paragraph 7.4.19, p 296)

This statement provides insight into the two issues which the Committee considers important with respect to determining the validity of endoscopic ulcers as a surrogate for clinically significant GI events (i) The nature of the relationship between endoscopic ulcers and clinically significant GI events (ii) Uncertainty associated with the definition and detection of endoscopic ulcers; both of which were raised by the PES in the PES commentary provided for the March 2012 consideration.

With respect to the first issue regarding the relationship between endoscopic ulcers and clinically significant GI events, the PES commentary states the following:

"MacDonald et al (2004) states that endoscopically detected ulcers are not ideal surrogate outcomes because it is estimated that up to 85% of endoscopic ulcers never become clinically symptomatic. Therefore, it is theoretically possible that treatments that prevent endoscopic ulcers will not prevent clinical ulcers." (PES Commentary March 2012 consideration, 7.4.COM.60)

The evidentiary source cited is an old edition of the textbook entitled "Evidence-based Gastroenterology and Hepatology". Notwithstanding the issues associated with citing an out of date, tertiary source of evidence, of more concern is that the statement as presented in the PES commentary has been taken out of context and the hypothesis formed by the PES

that “it is theoretically possible that treatments that prevent endoscopic ulcers will not prevent clinical ulcers” is inconsistent with the conclusions reached by the authors.

In addition to the statement quoted by the PES above, the authors go on to say the following:

“With the publication of several large randomized controlled trials (RCTs) that used actual clinical endpoints to measure the safety of COX-2 inhibitors and of misoprostol prophylaxis, it became possible to compare the reduction in clinical events with that of the reduction in endoscopic ulcers from the endoscopic studies…The relative risk reduction in endoscopic gastric ulcers with misoprostol prophylaxis and with COX-2 inhibitors is about 80%. In the clinical endpoint studies, the relative risk reductions in NSAID ulcer related perforations, In the clinical endpoint studies, the relative risk reductions in NSAID ulcer related perforations, obstructions and bleeding is about 50% with both these strategies. The consistency suggests that there is a relationship between the endoscopic and clinical endpoints. The relationship does not have to be 1:1. In fact based on our results, prophylactic agents and COX-2 inhibitors are 1.5 – 2.0 times more effective at reducing the risk of endoscopic ulcers than they are at reducing the risk of clinical endpoints. Unfortunately the studies using clinical gastrointestinal events as the primary outcome measure were not designed to look at the relationship of clinical events to endoscopic ulcers, and we used indirect comparisons to arrive at this result. However, with the cautions described above, the reader can estimate what the expected reduction in clinical events would be based on the results of an endoscopic endpoint study, assuming the control groups are average risk arthritic patients requiring long-term NSAID use.”

Thus, the reference cited by the PES, on balance, supports a conclusion that there is a consistent relationship between endoscopically-detected ulcers and incidence of clinically significant GI events and the fact that this relationship is not 1:1, does not diminish the validity of endoscopically-detected ulcers as a surrogate for more patient-relevant outcomes. The consistency of the relationship means that it is possible to estimate the incidence of clinically significant GI events from the incidence of endoscopically-detected ulcers. Furthermore, the reference, by virtue of the cross-study comparison, contradicts the hypothesis formed by the PES, by demonstrating that treatments that prevent endoscopic ulcers also prevent clinical ulcers.

The PBAC, by relying on the advice provided by the PES has been selective in their use of evidence to refute the claim made in the submission that a surrogate relationship exists between the incidence of endoscopically-detected ulcers and the incidence of POBs/CSUGIEs (and that, therefore, the incidence of endoscopically-detected ulcers can be used to predict the rate of perforations, ulcerations and bleeds (POBs)/clinically significant upper GI events

(CSUGIEs). Furthermore, it is clear that by taking the evidence out of context, both the PES and PBAC have interpreted the evidence in a manner which is inconsistent with the ultimate conclusion reached by the authors.

With respect to the second issue regarding the suggestion that the definition and identification of a case of an endoscopically detected ulcer may be uncertain, the PES commentary cites Sung et al (2001) as "evidence that only one third of most common endoscopic ulcers found in clinical trials have been assessed to be actual ulcers" (PES Commentary from the March 2012 consideration, 7.4.COM.60). The evidence cited by the PES refers to an abstract relating to a study which attempted to answer the question of "How Often Are Endoscopic Ulcers in NSAID Trials Diagnosed as Actual Ulcers by Experienced Endoscopists" The method, results and conclusion are reproduced below:

"Method: A pharmaceutical company prepared a training tape to demonstrate the different lesions and standardise the reporting. The tape included typical ulcers, endoscopic ulcers defined as 3 mm or greater in greatest dimension with depth, erosions, and more trivial lesions. The tape was reviewed without the sound (i.e. blinded) by 3 experienced endoscopists."

"Results: The experienced endoscopists agreed 100% with the obvious ulcers and the trivial lesions. Importantly, only one third of the endoscopic ulcers which are by far the most common in clinical trials were considered to be actual ulcers."

"Conclusion: Prospective studies of NSAID induced gastric mucosal damage scores many lesions as ulcers that would not be diagnosed as ulcers in a clinical setting. It is unlikely that the results of such studies are reliable surrogates for actual clinical trials studying healing or prevention of clinical ulcers or ulcer complication. More studies evaluating actual clinical outcomes are needed to answer the question about whether the prospective endoscopic ulcer based trials have clinical relevance."

It is unclear to AstraZeneca exactly what this poorly designed study serves to demonstrate, particularly given the lack of clarity regarding the distinction between what the authors refer to as "endoscopic ulcers" and "actual ulcers". However what is most concerning is that the PES and the PBAC have cited a study with a sample size of 3, conducted using insufficiently robust methodology, as evidence to support the contention that there is "some suggestion that the definition and identification of a case of an endoscopically detected ulcer may be uncertain" and therefore support the position taken by the Committee that endoscopic ulcers lack validity. Clinical trials which employ endoscopic ulcers as clinical endpoints ensure that Investigators are appropriately trained as to the definition and detection of

endoscopic ulcers and as such, this study bears no resemblance to the conduct of the endoscopic studies for Vimovo®.

It is instructive to examine the strength of the evidence relied upon by PES (and therefore PBAC) to repudiate the validity of endoscopic ulcers as a surrogate for clinical significant GI events compared with the level of evidence that Sponsors are required to submit to support such a claim. In contrast to the evidence cited by the PES and accepted by the PBAC, AstraZeneca provided a detailed systematic review of evidence to support its claim that a surrogate relationship exists between endoscopically-confirmed ulcer and clinically significant GI events. The review included a cross-study comparison [analogous to the type of comparison undertaken by McDonald et al (2004) as cited by the PES], which was the primary source of evidence which informed the US Food and Drug Administration's decision to accept endoscopic ulcers as a valid surrogate. (Refer to the Section B.5 of major resubmission for Vimovo® considered at the March 2012 meeting of the PBAC).

AstraZeneca acknowledges that the burden of proof resides with the Sponsor; however, the imbalance between the rigour of evidence that a submission is required to provide to substantiate a claim and the rigour of evidence that can be used by the PBAC to repudiate a claim is inappropriate and not reflective of properly informed decision-making.

3. Justification for the claim that the PBS listing requested for Vimovo® could result in increased cost to the PBS

GROUND OF REVIEW: *PBAC's conclusion that there is "continuing concern that the listing could result in increased costs to the PBS" (Ratified minutes of the November 2012 PBAC meeting, p2) is unable to be reconciled with any costing analysis available.*

Points for consideration: *What justification has the PBAC provided to support the claim that the listing for Vimovo® could result in increased cost to the PBS? Is the treatment of the cost to Government estimates for Vimovo® consistent with the advice provided in the PBAC Guidelines?*

The final reason cited for rejection of the most recent application for Vimovo® was the "continuing concern that the listing could result in increased costs to the PBS" (Ratified minutes of the November 2012 PBAC meeting, pg 2). However, to-date, no analysis has been presented which demonstrates a scenario under which additional costs accrue to the Government.

Over the course of the three submissions, only one analysis has been presented by the Drug Utilisation Sub-Committee (DUSC) for the consideration of the PBAC. The DUSC presented a revised analysis which addressed the main areas of uncertainty with respect to the cost to Government estimates during the evaluation of the first submission, which was considered at the August 2011 Special PBAC meeting. (Pre-PBAC advice from the August 2011 consideration, DUSC ADV 5.7.5) Specifically, the revised analysis included the following assumptions:

Constant growth of the NSAID market (despite current evidence of decline)
Significant uptake by Vimovo® from the NSAID + PPI market, starting at 50% in year 1 and increasing to 90% in year 5
Significant uptake by Vimovo® from the NSAID monotherapy market (which due to significant price erosion due to generic competition and disclosure-related price reductions are lower priced than Vimovo®), starting at 20% in Year 1 and increasing to 40% in year 5

Despite the application of these assumptions, the DUSC analysis still predicted savings to Government (a conclusion which is consistent with the claim made by AstraZeneca in the submission). (Pre-PBAC advice from the August 2011 consideration, DUSC ADV 5.7.5)

Over the course of the three submissions, a number of scenarios have been presented by AstraZeneca which extended the assumptions included in the DUSC analysis to assess the impact of the significant price erosion of the PPIs and meloxicam due to price disclosure, as well as the application of future phased statutory price reductions for the single-branded PPIs (see Table 22 below). Even these extreme scenarios, in which the price of substituted therapies is reduced by more than 50%, support the conclusion that PBS listing of Vimovo® is likely to result in incremental savings to Government. Despite this, the PBAC cited "continuing concern that the listing could result in increased costs to the PBS" as one of the reasons for rejection. (Ratified minutes of the November 2012 PBAC meeting, pg 2).

AstraZeneca contends that no basis is presented for the PBAC's claim of potential increased costs to the PBS and as such, it is inappropriate and unreasonable to cite this unsubstantiated expectation as grounds for rejection.

The ratified minutes go on to state that "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 resubmission. The analysis and evaluation should take into account the issues raised in previous evaluations and the ongoing reductions in the PBS prices of some PPIs and NSAID medicines." (Ratified minutes of the November 2012 PBAC meeting, pg 2).

AstraZeneca takes issue with this statement because the financial impact of the proposed listing has already been subject to extensive analysis and evaluation, which included a re-analysis by the DUSC and which has included a number of scenarios that assessed the impact of potential future price reductions for the PPIs and NSAIDs, none of which have demonstrated incremental costs to Government. It should be noted however that recommendation made by the Committee that the evaluation should take into account "ongoing reductions in the PBS prices of some PPIs and NSAID medicines" is inconsistent with the PBAC Guidelines which provide the following advice to Sponsors:

"Estimate the costs in each year over five years of each of the forms and strengths of each of these drugs substituted, decreased and increased on the basis of each of the estimated utilisation changes. For these calculations use constant prices, make no allowance for inflation and use a zero discount rate." (Pharmaceutical Benefits Advisory Committee (PBAC), Version 4.3, December 2008, Part II, Section E.3, p153)

This advice is provided because assumptions regarding future price reductions are inherently uncertain given that they rely on making predictions about the timing of the entry of second brands to the market as well as attempting to estimate market dynamics and discounting behaviour to inform predictions about disclosure-related reductions. As such, both the timing and magnitude of such reductions is extremely uncertain. The Committee has, in the past, disagreed with the inclusion of even relatively certain future price reductions in cost to Government estimates. It is inappropriate for the Committee to be making decisions based on highly uncertain predictions regarding future price reductions, particularly given that the inclusion of these assumptions is contrary to the advice provided by the PBAC Guidelines.

Conclusion

Following consideration at the November 2012 meeting, the PBAC recommended rejection the third time of Vimovo®, a fixed dose combination of enteric-coated naproxen 500mg, a non-steroidal anti-inflammatory drug and immediate-release esomeprazole 20mg, a proton pump inhibitor. The basis provided for the rejection was "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". (Ratified minutes of the November 2012 PBAC meeting, p2)

AstraZeneca's contends that the information provided in this request for review supports the conclusion that the reasons cited for rejection are insufficiently supported, inconsistent with previous decisions made by Committee and inconsistent with the advice provided to Sponsors in the Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (PBAC) (Version 4.3, December 2008).

Table 2 Cost to Government estimates presented for Vimovo® over the course of the three submissions

Scenario	Estimated net cost to Government				
	Year 1	Year 2	Year 3	Year 4	Year 5
1st submission (Table 86, p202)	-$1,956,852	-$3,291,676	-$4,353,784	-$4,940,528	-$5,051,818
1st submission, PES response, exclude low dose NSAIDs due to revised TGA indication for Vimovo® (revised Section E spreadsheet provided with response)	-$3,500,420	-$6,297,998	-$8,742,045	-$10,155,798	-$10,592,565
1st submission DUSC evaluation (DUSC ADV5.7.5)	-$2,681,691	-$2,965,272	-$3,025,498	-$2,971,834	$2,768,669
2nd submission (Table 104, p193)	-$ 2,747,263	-$ 4,782,408	-$ 6,527,663	-$ 7,613,402	-$ 7,805,072
3rd submission (Table 19, p 34)	-$3,958,059	-$6,559,654	-$9,161,248	-$10,462,045	-$11,762,843
3rd submission, sensitivity analysis, bringing forward remaining statutory price reductions for single-branded PPIs (Table 20, p36)	-$3,840,654	-$5,940,798	-$8,030,391	-$9,165,801	-$10,301,211
3rd submission, pre-PBAC response, bringing forward remaining statutory price reductions and bringing forward estimated price disclosure reduction of almost 40% for single-branded PPIs (Table 1, p3)	-$1,486,437	-$2,340,756	-$3,195,075	-$3,622,235	-$4,049,394

Note that negative net costs to Government indicate incremental savings