

PUBLIC SUMMARY DOCUMENT

Product: Aprepitant, pack containing 1 capsule 125 mg and 2 capsules 80 mg, Emend®

Sponsor: Merck Sharp & Dohme (Australia) Pty Ltd

Date of PBAC Consideration: November 2009

1. Purpose of Application

The submission sought to extend the current authority required listing for aprepitant to include treatment of chemotherapy induced nausea and vomiting (CINV) associated with moderately emetogenic chemotherapy.

2. Background

At the November 2004 meeting, the PBAC recommended an authority required listing for aprepitant capsule, pack of 1 x 125 mg and 2 x 80 mg, on the basis of acceptable cost-effectiveness when used with certain emetogenic cytotoxic chemotherapy agents.

At the March 2006 meeting, the PBAC recommended extending the authority required listing for aprepitant to include use in patients undergoing treatment for breast cancer with cyclophosphamide and an anthracycline on the basis of acceptable cost-effectiveness as compared to placebo.

The PBAC expressed concern, that in time, other cytotoxic regimens are likely to be identified as being highly emetogenic, and foreshadowed the need to develop a mechanism to assess possible future requests to expand PBS access. Variance in inter-patient tolerability of different cytotoxic regimens was also noted to be a potential factor necessitating expanding the clinical role of this drug. The PBAC therefore requested that the sponsor be approached to consider putting forward a future submission to expand PBS access, in line with aprepitant's evolving clinical place in the treatment of nausea and vomiting associated with cancer chemotherapy.

At the March 2007 meeting, the PBAC recommended a change to the listing for aprepitant to allow repeats to be authorised to cover all future cycles of chemotherapy on the basis of efficiency.

At the March 2008 meeting, the PBAC rejected a submission for aprepitant to change the current restriction to expand PBS access in line with evolving clinical practice as no data were provided to demonstrate the cost-effectiveness of treatment in the expanded population.

3. Registration Status

Aprepitant was TGA registered on 21 September 2005 for use in combination with other antiemetic agents, for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy.

Aprepitant is also TGA registered for:

- use in combination with other antiemetic agents, for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy.
- the prevention of postoperative nausea and vomiting.

4. Listing Requested and PBAC's View

(changes to the current restriction are in bold and strikethrough)

Authority Required

Management of nausea and vomiting associated with cytotoxic chemotherapy being used to treat malignancy, in combination with a 5HT₃ antagonist and dexamethasone, where any 1 of the following chemotherapy agents are to be administered:

- (a) altretamine;
- (b) carmustine;
- (c) cisplatin when a single dose constitutes a cycle of chemotherapy;
- (d) ~~intravenous cyclophosphamide at a dose of 1500 mg per square metre per day or greater~~
- (e) dacarbazine;
- (f) procarbazine when a single dose constitutes a cycle of chemotherapy;
- (g) streptozocin;
- (h) oxaliplatin;**
- (i) cytarabine at a dose of greater than 1 g per metre square;**
- (j) carboplatin;**
- (k) ifosfamide;**
- (l) doxorubicin;**
- (m) daunorubicin;**
- (n) epirubicin;**
- (o) idarubicin;**
- (p) irinotecan**

No more than 1 pack containing 1 x 125 mg capsule and 2 x 80 mg capsules will be authorised per cycle of cytotoxic chemotherapy.

~~Management of nausea and vomiting associated with cytotoxic chemotherapy being used to treat breast cancer, in combination with a 5HT₃ antagonist and dexamethasone, where cyclophosphamide and an anthracycline are to be co-administered.~~

~~No more than 1 pack containing 1 x 125 mg capsule and 2 x 80 mg capsules will be authorised per cycle of cytotoxic chemotherapy.~~

NOTE: No applications for increased maximum quantities will be authorised. Prescribers should advise Medicare Australia of the number of cycles planned when requesting approval for repeats.

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

Chemotherapy induced nausea and vomiting (CINV) is the most common side effect of cancer chemotherapy and can significantly affect a patient's quality of life.

Aprepitant would provide an additional option to current CINV preventative treatment for patients treated with moderately emetogenic chemotherapy.

For PBAC's view, see Recommendation and Reasons.

6. Comparator

The submission nominated standard antiemetic regimen including a 5HT₃ antagonist (ondansetron) and a corticosteroid (dexamethasone) as the comparator.

For PBAC's view, see Recommendation and Reasons.

7. Clinical Trials

The submission presented a comparison of the aprepitant CINV regimen and the standard CINV regimen in patients treated with moderately emetogenic intravenous chemotherapy based on one Cycle of a head-to-head trial – Protocol 130. This was a randomised, double-blind, controlled, parallel group, multicentre study conducted under in-house blinding conditions that aimed to determine the efficacy and tolerability of aprepitant for the prevention of chemotherapy-induced nausea and vomiting associated with moderately emetogenic chemotherapy. Protocol 130 assessed a patient population that overlapped with the restriction requested for widening access to aprepitant on the PBS. In the trial population there is a large representation of women (76.9%), and of tumour type, breast cancer makes up approximately 50% of both arms.

Supplementary evidence provided in the submission included the Cycle Two results from Protocol 130 and the per protocol data set from Protocol 130. Details of associated reports presented in the submission are in the table below.

Trial ID / First author	Protocol title / Publication title	Publication citation
Schmoll H et al	Aprepitant for the chemotherapy-induced nausea and vomiting associated with non-anthracycline/cyclophosphamide-based, moderately emetogenic chemotherapies: a randomised, double-blind study.	Poster, Multinational Association for Supportive Care in Cancer (MASCC) Symposium 2009 (accepted)
Rapoport B et al	PN130: Results of aprepitant for the prevention of chemotherapy-induced nausea and vomiting associated with a broad range of moderately emetogenic chemotherapies (MEC) and tumour types.	MASCC 2009 (draft)
Schmoll H et al	Aprepitant for the prevention of chemotherapy-induced nausea and vomiting associated with a broad range of moderately emetogenic chemotherapies and tumour types: a randomised, double-blind study.	Poster, American Society of Oncology (ASCO) 2009 (draft)
Boice J et al	Aprepitant in the prevention of chemotherapy-induced nausea and vomiting associated with moderately or highly emetogenic chemotherapies in patients with gastrointestinal cancer.	Poster, European Society for Medical Oncology World Congress on Gastrointestinal Cancer 2009 (draft)
Rapoport B et al	Aprepitant for the prevention of chemotherapy-induced nausea and vomiting associated with a broad range of moderately emetogenic chemotherapies and tumour types: a randomised, double-blind study.	<i>Support Care Cancer Journal</i> 2009 (draft)

The PBAC noted that the dose of dexamethasone in the CINV regimen + aprepitant arm was lower than in the standard CINV arm (12mg vs. 20mg), and considered that this difference would tend to bias against aprepitant.

Regimens compared in Study 130

	CINV + aprepitant	Standard CINV
Day 1:	Aprepitant 125mg PO od	
	Ondansetron 8mg PO bd	Ondansetron 8mg PO bd
	Dexamethasone 12mg PO od	Dexamethasone <u>20</u> mg PO od
Days 2&3	Aprepitant 80mg PO od	Ondansetron 8mg PO bd

PO = oral; od = once daily; bd = twice daily

8. Results of Trials

The primary and secondary health outcomes reported in Protocol 130 are presented in the table below. All results were from the Overall Phase (Acute Phase and Delayed Phase) of Cycle One for the population of patients fulfilling the requirements for the full analysis set (FAS).

Primary and secondary outcomes from the FAS population of the Overall Phase of Cycle One of Protocol 130

Component	CINV regimen + aprepitant	Standard CINV regimen	Incremental outcome	P value
Primary outcome				
Health Outcome: No Vomiting				
Proportion of patients reaching No Vomiting	76.2%	62.1%	14.1	< 0.0001
Secondary outcomes				
Health Outcome: Complete Response				
Proportion of patients reaching Complete Response	68.7%	56.3%	12.4%	0.0003
Health Outcome: No Use of Rescue Medication				
Proportion of patients with No Use of Rescue Medication	81.4%	75.2%	6.2%	NS
Health Outcome: No Impact of CINV on Daily Life				
Proportion of patients with No Impact of CINV on Daily Life	73.4%	66.3%	7.1%	0.035

CINV=Chemotherapy Induced Nausea and Vomiting; FAS=Full Analysis Set

These outcomes formed the basis of the economic evaluation and ranged from a significant difference in patients reaching the ‘No Vomiting’ and ‘Complete Response’ endpoints (in both acute and delayed phases) to no significant difference in patients reaching the ‘No Use of Rescue Medication’ endpoint between treatment groups.

The PBAC considered a key issue was that the interpretation of these results in terms of the impact that aprepitant may be expected to have on patient quality of life remains unclear. The PBAC was advised it was reasonable to assume that no vomiting would result in an improvement in quality of life. However, the size of the effect was more difficult to assess. The submission did not transform the results to QALYs.

The submission appropriately concluded that there appeared to be no significant difference in comparative toxicity between CINV regimens containing aprepitant and the standard CINV regimen from the results of Protocol 130. The extended assessment of comparative harms did not alter this conclusion.

9. Clinical Claim

The submission described the aprepitant regimen as superior in terms of comparative effectiveness and equivalent in terms of comparative safety over the standard regimen for treating CINV.

For PBAC's view, see Recommendation and Reasons.

10. Economic Analysis

The submission presented a trial based cost-effectiveness analysis using four health outcomes reported in Protocol 130 (No Vomiting, Complete Response, No Use of Rescue Medication and No Impact of CINV on Daily Life) as the basis of the analysis.

The base-case incremental cost-effectiveness ratio (ICER) per extra patient reaching each of the four health outcomes was less than \$15,000.

Additional univariate sensitivity analyses based on estimates of the Australian population (for age, gender, tumour type and chemotherapy type) were also presented in the submission. In the univariate sensitivity analyses each adjustment alone resulted in an increased ICER, but remained below \$15,000.

The PBAC noted that the presentation of a trial-based base case in the submission was intended to allow the PBAC to compare the cost-effectiveness of aprepitant with that of currently reimbursed indications, and the claim that the additional sensitivity analyses based on estimates of the Australian population demonstrated the robustness of the results of the base-case economic evaluation.

The sponsor's Pre-PBAC response provided the results of a univariate analysis for subgroups described by gender, age, tumour type and chemotherapy type based on the trial population for the No Vomiting endpoint and further adjusted to remove cost-offsets due to differences in rescue medication and cumulative effect calculated as a weighted average response. The ICER for the weighted response was further increased but remained below \$15,000.

For PBAC's view, see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications

The submission estimated the likely number of patients per year to be less than 10,000 in Year 5 with an estimated financial cost per year to the PBS of less than \$10 million. The PBAC considered these estimates to be uncertain.

12. Recommendation and Reasons

The PBAC accepted that the treatment algorithm presented in the submission was consistent with evidence-based best practice, and agreed that the comparator is appropriate, noting that aprepitant is added to standard therapy on day one of treatment and substitutes for 5HT₃-antagonist and dexamethasone 8mg on days 2-3. However, to ensure best practice if listed on the PBS, a quality use of medicines program would be needed to ensure appropriate use and adherence to the treatment algorithm so that use of ondansetron and dexamethasone was restricted to day 1.

The PBAC accepted there was a clinical need for aprepitant for patients receiving moderate emetogenic chemotherapy, however noted that the current market, if listed for this indication, would likely double. The PBAC considered that the clinical claim was reasonable and, although not quantified, it was reasonable to assume that there is some quality of life benefit associated with the reduction in CINV.

The PBAC considered the main area of uncertainty in the submission was issues with translation and that the outcomes presented in the submission may not represent the true cost-effectiveness of the CINV regimen that contains aprepitant for the following reasons:

- In particular, the extent of the cost offset per patient generated by aprepitant replacing 5HT₃ antagonist use is unclear and not consistently supported by the relevant clinical CINV guidelines and may not be realised if ondansetron and dexamethasone are continued in clinical practice beyond day 1.
- The extent of the cost offset per patient generated by the assumption that patients receiving aprepitant require fewer days in hospital than those on the standard regimen is unclear and not supported by clinical evidence.
- It is unclear how the health outcomes assessed in the model relate to impact on patient quality of life.
- Uncertain magnitude of benefit in the requested PBS population as the trial outcome is driven by the breast cancer population in the trial (Protocol 130), and the majority of these patients already have access to aprepitant on the PBS.

The PBAC considered that the base case used in the economic analysis was inappropriate, and should have included adjustments for the key applicability issues of gender ratio, age distribution and type of cancer most likely to be treated in the general population. Any future submission should focus on the non-doxorubicin/cyclophosphamide (AC) patients in the trial and then further adjust for the Australian population.

The PBAC noted the sponsor's Pre-PBAC Response provided the results of a univariate analysis for subgroups described by gender, age, tumour type and chemotherapy type based on the trial population and further adjusted to remove cost-offsets due to differences in rescue medication and cumulative effect calculated as a weighted average response. The ICER based on the Australian population (weighted response) was increased from the base-case and remained less than \$15,000.

The PBAC noted that the weighted ICER was within the range of that previously approved for highly emetogenic chemotherapy and AC for breast cancer. However, the PBAC considered the health outcome measure of no vomiting is more likely to be similar to that achieved in the moderate emetogenic breast cancer population receiving AC. Therefore, to achieve a similar ICER to the breast cancer population a price decrease would be needed. Alternatively, the sponsor may wish to consider seeking a secondary prophylaxis listing for moderate emetogenic agents, so that aprepitant could be used in combination with ondansetron and dexamethasone as combination therapy similar to the current listing.

Therefore, the PBAC rejected the submission on the basis of high and uncertain cost-effectiveness in the patient population requested.

The PBAC noted that the submission meets the criteria for an independent review.

13. Context for Decision

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

14. Sponsor's Comment

The sponsor is working with the PBAC to resolve the areas of uncertainty.