PUBLIC SUMMARY DOCUMENT

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

Sponsor: Merck Sharp and Dohme Australia Pty Ltd

Date of PBAC Consideration: March 2010

1. Purpose of Application:

The resubmission sought an extension of the current Authority required listing to include management of nausea and vomiting associated with moderately emetogenic cytotoxic chemotherapy agents where a patient has had a prior episode of chemotherapy induced nausea and vomiting (CINV).

2. Background:

The drug had not previously been considered by the PBAC for use as secondary prophylaxis of CINV associated with moderately emetogenic chemotherapy (MEC) however it was the second submission for the use of aprepitant in CINV associated with MEC. Aprepitant is currently PBS-subsidised for use in the management of nausea and vomiting associated with certain (highly emetogenic) cytotoxic chemotherapy agents.

At the November 2009 meeting, the PBAC rejected a submission for aprepitant to extend the current Authority required listing to include CINV associated with MEC on the basis of high and uncertain cost-effectiveness in the patient population requested.

3. Registration Status:

Aprepitant was registered by the Therapeutic Goods Administration (TGA) on 23 April 2004. Aprepitant is 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.
- moderately emetogenic cancer chemotherapy.

4. Listing Requested and PBAC's View:

<u>Authority required</u>

Management of nausea and vomiting associated with cytotoxic chemotherapy where the patient has had a prior episode of chemotherapy induced nausea or vomiting and whose chemotherapy regimen includes one or more of the following agents:

(a) intravenous cyclophosphamide at a dose of less than 1500mg per square metre per day
(b) oxaliplatin
(c) cytarabine at a dose of greater than 1g per square meter per day
(d) carboplatin
(e) ifosphamide
(f) doxorubicin
(g) danorubicin
(h) epirubicin
(i) idarubicin
(j) irinotecan

No more than one pack containing 1 x 125mg capsule and 2 x 80mg capsules will be authorised per cycle of cytotoxic chemotherapy. Concomitant use of a 5HT3 antagonist or

dexamethasone should not occur with aprepitant on days 2 and 3 of any chemotherapy cycle.

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:

CINV is the most common side effect of cancer chemotherapy and can significantly affect a patient's quality of life. Aprepitant will provide an additional option to current CINV preventative treatment for patients treated with MEC agents.

6. Comparator:

Standard antiemetic regimen consisting of the combined use of a 5-hydroxytryptamine-3 receptor (5HT3) antagonist and a corticosteroid (dexamethasone) was nominated as the main comparator.

7. Clinical Trials:

The submission presented an updated discussion of the areas of uncertainty identified by the PBAC at the November 2009 meeting including clinical benefit in patients with prior CINV associated with MEC, incremental cost effectiveness ratios (ICERs) in patients with prior CINV associated with MEC, and 5HT3 antagonist use in Australia. In addition, the submission proposed a quality use of medicines program to support the use of aprepitant, and a price reduction.

The submission relied on six (6) observation single arm studies. All six studies were published at the time of submission, as follows:

Trial ID / First author	Protocol title / Publication title	Publication citation
Bokemeyer C et al 2005	Aprepitant as salvage therapy in patients with chemotherapy-induced nausea and emesis refractory to prophylaxis with 5-HT3-antagonists and dexamethasone.	Bokemeyer C, Oechsle K, Mueller MR, Hartmann JT, Kanz L, Journal of Clinical Oncology, 2005 ASCO Annual Meeting Proceedings, Vol 23, No 16S (June 1 Supplement), 2005: 8166
Hesketh PJ et al 2008	Aprepitant as salvage antiemetic therapy in breast cancer patients receiving doxorubicin and cyclophosphamide.	Hesketh PJ, Younger J et al, Support Care Cancer, 2008, Early Online - Dec 6 2008
Smith AR et al 2005	Aprepitant for the control of chemotherapy induced nausea and vomiting in adolescents.	Smith AR, Repka TL, Weigel BJ, Pediatr Blood Cancer, 45(6): 857-860, Nov 2005.
Chua W et al 2006	Aprepitant as salvage anti-emetic in women receiving anthracycline-containing chemotherapy for early breast cancer.	Chua W, Sullivan A, Beale P et al, Internal Med J., 2006;36(4): A154

Oechsle K et al 2006	Aprepitant as salvage therapy in patients with chemotherapy-induced nausea and emesis refractory to prophylaxis with 5-HT3 antagonists and dexamethasone.	Oechsle K, Muller MR, Hartmann JT, Kanz L, Bokemeyer C, Onkologie 29(12): 557-561, 2006
Abbrederis K et al 2009	Chemotherapy-Induced Nausea and Vomiting in the Treatment of Gastrointestinal Tumors and Secondary Prophylaxis with Aprepitant.	Abbrederis K, Rothling N et al, Onkologie 32(1-2): 30-34 2009

8. Results of Trials

Clinical benefit in patients with prior CINV

The PBAC noted that all the submitted studies are observational, single arm studies of patients not restricted to MEC prophylaxis, and provided a low level of evidence in the requested population.

5HT3 antagonist use in Australia

The submission claimed from the EMEND Clinical Survey and the Australian Tandem Oncology Monitor survey sources that 100% and 98.2% respectively, of patients on intravenous MEC are treated with a 5HT3 antagonist, and that aprepitant will substitute for the current use of 5HT3-antagonists in the delayed phase of emesis. All clinicians in the EMEND Clinical Study reported the use of 5HT3 antagonists in both the acute and delayed phase of emesis with the majority prescribing 5HT3 antagonists in combination with dexamethasone.

9. Clinical Claim

The submission claimed that aprepitant would provide an additional PBS-subsidised option to current CINV preventative treatment for patients receiving moderately emetogenic chemotherapy.

10. Economic Analysis

The submission presented an updated evaluation of the ICERs for aprepitant in the requested patient population (patients prior to CINV). The submission estimated an ICER of less than $15,000 for each additional patient experiencing "no vomiting" comparable to the ICER previously accepted by the PBAC for aprepitant and claimed this was for use in patients with highly emetogenic chemotherapy (HEC), and in anthracycline cyclophosphamide (AC) treated breast cancer patients.

The submission derived a logistic regression model based on the outcome of "no-vomiting" using individual patient data from Protocol 130. This was presented to address one of "the key issues" that the economic analysis did not include multiple adjustments for the key applicability issues of gender, age and type of cancer. The submission used a backward selection procedure looking at five (5) variables.

- treatment regimen (aprepitant or standard care);
- age (less than 55 years or greater than or equal to 55 years);
- gender
- tumour type (gastrointestinal, breast, lung, other) and;
- chemotherapy regimen (AC or non-AC)

The submission claimed the estimated ICERs were all significantly lower than the ICERs of less than $15,000 previously accepted by the PBAC to gain a "no vomiting' response in patients treated with AC chemotherapy for breast cancer.

11. Estimated PBS Usage and Financial Implications:

The submission estimated that the net cost to the PBS of the requested listing for aprepitant for the management of MEC would be less than $10 million per year, with a reduction in the use of PBS-subsidised 5HT3 antagonists and dexamethasone. The likely number of patients and packs dispensed/prescriptions per year for aprepitant for the management of MEC was estimated to be between 10,000 and 50,000 in Year 5.

12. Recommendation and Reasons:

The PBAC recommended extending the listing of aprepitant to include the management of nausea and vomiting associated with moderately emetogenic chemotherapy (MEC) on a cost minimisation basis with standard antiemetic therapy including a $5HT_3$ antagonist and a corticosteroid (dexamethasone).

The submission presented a logistic regression model based on the outcome of 'no vomiting' using individual patient data from Protocol 130 to address the issue PBAC had with the previous economic model not including multiple adjustments for key applicability issues such as gender, age and type of cancer. The results from the model were used to calculate the incremental difference in proportion of patients not vomiting and the incremental cost per responder. The PBAC was concerned that a logistic regression model was presented in a minor application and as such was not subject to the full evaluation process. The PBAC considered that the submission should have been a major submission and not a minor.

From six observational, single arm studies the submission calculated updated ICERs incorporating a price reduction for aprepitant in patients with prior CINV per "no vomiting greater than 2 days" to "complete control" responder of less than $15,000. The PBAC accepted it was reasonable to assume that the treatment effect on standard prophylaxis in cycle 2 would be the same as the observed effect in cycle 1.

The PBAC noted that with the offered price reduction, the estimated ICER for MEC of less than $15,000 for each additional patient experiencing no vomiting compared with the ICERs previously accepted by the PBAC for aprepitant for use in patients with highly emetogenic chemotherapy (HEC), and in anthracycline cyclophosphamide (AC) treated patients, respectively. The PBAC noted there would be cost offsets associated with decreased prescribing of $5HT_3$ antagonists on days 2-3 for the management of delayed emesis and that prescriber education was needed to realise any decreased use of $5HT_3$ antagonists. The PBAC requested that the National Prescribing Service provide education to prescribers with regards to the treatment of delayed emesis and the importance of using $5HT_3$ antagonists prior to chemotherapy but not on an ongoing basis following chemotherapy.

The PBAC requested that the utilisation of the current listing and the MEC listing for aprepitant be monitored over time.

The PBAC considered that the list of moderately emetogenic chemotherapy agents included be consistent with the National Comprehensive Cancer Network (NCCN), as recommended by the PBAC in July 2008, and the eviQ Cancer Treatments Online Guidelines.

The Committee indicated that the sponsor be requested to market a pack size to enable the use of aprepitant, without wastage, for patients undergoing chemotherapy treatment over multiple days.

Recommendation:
APREPITANT, pack containing 1 capsule 125 mg and 2 capsules 80 mg

Add the following indication to the current restriction:

NOTE:
Aprepitant is not PBS-subsidised for nausea and vomiting associated with radiotherapy being used to treat malignancy.

Authority required
Management of nausea and vomiting associated with moderately emetogenic cytotoxic chemotherapy being used to treat malignancy, in combination with a 5HT3 antagonist and dexamethasone on day 1, where the patient has had a prior episode of chemotherapy induced nausea or vomiting where any 1 of the following intravenous chemotherapy agents is to be administered:

(a) arsenic trioxide
(b) azacitidine
(c) carboplatin
(d) cyclophosphamide at a dose of less than 1500 mg per square metre per day.
(e) cytarabine at a dose of greater than 1g per square meter per day
(f) dactinomycin
(g) daunorubicin
(h) doxorubicin
(i) epirubicin
(j) fotemustine
(k) idarubicin
(l) ifosfamide
(m) irinotecan
(n) melphalan
(o) methotrexate at a dose of 250 mg to 1 g per square metre
(p) oxaliplatin
(q) raltitrexed

No more than one pack containing 1 x 125 mg capsule and 2 capsules will be authorised per cycle of cytotoxic chemotherapy. Concomitant use of a 5HT3 antagonist should not occur with aprepitant on days 2 and 3 of any chemotherapy cycle.

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.

Maximum quantity: 1
Repeats: 0

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 pleased with the PBAC decision to make aprepitant available to patients who have suffered nausea or vomiting while treated with moderately emetogenic chemotherapy.