Public Summary Document

Product:	Aprepitant, capsule, 1 x125 mg and 2 x 80 mg Tri - pack, Emend®
Sponsor:	Merck Sharp and Dohme (Australia) Pty Ltd
Date of PBAC Consideration:	March 2006

1. Purpose of Application

To extend the current authority required listing for aprepitant to include use in patients undergoing treatment for breast cancer with cyclophosphamide-based chemotherapy.

2. Background

At the November 2004 meeting, the PBAC recommended an authority required listing for aprepitant for the management of nausea and vomiting associated with cytotoxic chemotherapy, being used to treat malignancy, in combination with a 5HT3 antagonist and dexamethasone, on the basis of acceptable cost-effectiveness, where any one 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) cyclophosphamide at a dose of 1500 mg/m^2 per day or greater;
e) dacarbazine;
f) procarbazine when a single dose constitutes a cycle of chemotherapy;
g) streptozocin.

3. Registration Status

Aprepitant tri-pack capsule blister pack 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 moderately emetogenic cancer chemotherapy; and of highly emetogenic cancer chemotherapy.

4. Listing Requested and PBAC's View

Authority required

The application sought to extend the current PBS listing by adding: Patients undergoing treatment for breast cancer with a chemotherapy regimen containing either an anthracycline (i.e doxorubicin or epirubicin) plus cyclophosphamide (i.e AC, EC, FEC, or FAC) or cyclophosphamide plus methotrexate plus 5-fluorouracil (ie. CMF).

The PBAC noted that the 2005 update of the *MASCC Antiemetic Guidelines* do not mention the emetogenicity of the CMF combination regimen and this combination contributes little to the evidentiary basis in the submission for including this combination in any PBS restriction.

5. Clinical Place for the Proposed Therapy

The majority of breast cancer patients being treated with chemotherapy will be treated with a regimen containing cyclophosphamide plus one or more chemotherapy agents. Even with the use of current antiemetic therapy (i.e. 5HT3 antagonists), 40-60% of these patients will still suffer from chemotherapy-induced emesis at some stage during their breast cancer treatment.

Aprepitant provides an additional option to reduce the burden of chemotherapy induced nausea and vomiting during cancer treatment.

6. Comparator

The submission appropriately nominated placebo plus higher doses of the current antiemetic regimen (ondansetron and dexamethasone) as the main comparator.

7. Clinical Trials

The submission presented a multicentre, randomised, double-blind, parallel group, controlled trial (Protocol 071) to assess the safety and efficacy of aprepitant in the prevention of chemotherapy induced nausea and vomiting (CINV) in patients undergoing treatment for breast cancer with a chemotherapy regimen containing cyclophosphamide and an anthracycline. A small number of patients (1.2%) in the trial received a chemotherapy combination which included cyclophosphamide, methotrexate and 5-fluorouracil (CMF). The protocol had two components. The first component focused on the initial cycle of chemotherapy. The second component consisted of a multiple cycle extension for up to 3 subsequent cycles of chemotherapy.

This study has been published as follows:

Trial/First author	Protocol/Publication title	Publication citation
Protocol 071/ Warr, DG	Efficacy and tolerability of aprepitant for the prevention of chemotherapy-induced nausea and vomiting in patients with breast cancer after moderately emetogenic chemotherapy.	J Clin Oncol. 2005; 23(12):2822-30. Erratum in: J Clin Oncol. 2005; 23(24):5851.
Protocol 071/ Herrstedt,	Efficacy and tolerability of aprepitant for the prevention of chemotherapy-induced nausea and emesis over multiple cycles of moderately emetogenic chemotherapy.	Cancer 2005; 104(7):1548-55.

In addition seven published papers were provided as supportive evidence concerning interaction/safety data for aprepitant.

8. Results of Trials

In the overall phase analysis of Cycle 1 (the primary analysis) in the key trial, the aprepitant plus standard antiemetic treatment group reported a statistically significantly greater percentage of patients with complete response (no vomiting and no rescue medicine) than the placebo plus standard antiemetic treatment group (50.8% vs 42.5%, p=0.015). Overall, a statistically significantly greater percentage of patients in the aprepitant treatment group than in the placebo treatment group reported having no vomiting throughout the overall phase in Cycle 1 (75.7% vs 58.7%), and likewise reported no vomiting in both the acute and delayed phases (acute phase: 87.5% vs 77.3%; delayed phase: 80.8% vs 69.1%). For all three phases, a greater percentage of patients in the aprepitant treatment group than in the placebo treatment group reported no rescue on any of the 5 days post-chemotherapy, although this difference was not statistically significant (58.7% vs 56.2%).

The absolute difference in complete response in Protocol 071 was 8.3% which was smaller than in the two trials in the November 2004 submission where it was 19.9%. The absolute

difference in no vomiting was similar across all trials. There was greater use of rescue medication in Protocol 071, which may be due to the greater effect on vomiting than nausea of aprepitant. Overall, the effectiveness results favour the aprepitant treatment regimen for most outcomes.
For PBAC's view, see Recommendations and Reasons.

9. Clinical Claim

The submission claimed that a regimen containing aprepitant has significant clinical advantages over standard therapy (corticosteroid and 5HT3 antagonist). It is significantly more effective than standard therapy, and has similar toxicity. This claim was accepted by the PBAC for the group of women receiving treatment for breast cancer with the combination of an anthracycline and cyclophosphamide, although it was noted that the clinical benefit was inferior to that demonstrated in the November 2004 PBAC submission.

10. Economic Analysis

A preliminary (trial-based) economic evaluation was presented. The resources included were drug costs and associated therapy costs. The trial-based incremental cost per extra patient free of emesis or use of rescue therapy for 120 hours in Cycle 1 of therapy was < $15,000.

A modelled economic evaluation was not presented.
For PBAC's view, see Recommendations and Reasons.

11. Estimated PBS Usage and Financial Implications

The submission estimated the likely number of packs dispensed per year to be 10,000 – 50,000 per year in Year 4 at an estimated cost to the PBS of < $10 million per year.

12. Recommendation and Reasons

The PBAC recommended listing on the basis of acceptable cost-effectiveness as compared to placebo for the management of nausea and vomiting associated with cytotoxic chemotherapy, comprising cyclophosphamide and an anthracycline, being used to treat breast cancer. The PBAC noted that the price requested was the same as in the November 2004 submission despite an inferior clinical benefit demonstrated in the current submission. However, based on the increase in estimated cost-offsets, the cost-effectiveness in this patient group was considered to be acceptable.

The PBAC recalled that one of the bases of its November 2004 recommendation to initially list aprepitant on the PBS, was for the treatment of nausea and vomiting associated with highly emetogenic cytotoxic agents as endorsed by the *MASCC Antiemetic Guidelines* from the 2004 Perugia International Cancer Conference. The PBAC noted that the 2005 updated MASCC guidelines states that women receiving a combination of anthracycline plus cyclophosphamide represent a group at particular great risk of nausea and vomiting, and that a three-drug regimen including single dose of a 5HT3 antagonist, dexamethasone and aprepitant given before chemotherapy is recommended. The PBAC also noted the updated MASCC guidelines do not mention the emetogenicity of the CMF (cyclophosphamide and methotrexate and 5-fluorouracil) combination regimen and this combination contributes little to the evidentiary basis in the submission for including this combination in any PBS restriction. The PBAC therefore recommended that this combination be excluded from the restriction.

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 to 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.

Recommendation

Amend the current restriction to read:

Aprepitant, capsule, 1 x125 mg and 2 x 80 mg

Restriction	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 one 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) 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. **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 and/or repeats will be authorised.
Maximum Quantity	1 Pack containing 1 capsule 125 mg and 2 capsules 80 mg
Repeats	Nil

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

No comment.