

7.14 FOSAPREPITANT

Powder for I.V. infusion 150 mg

Emend[®] IV,

Merck Sharp & Dohme (Australia) Pty Ltd.

1 Purpose of Application

- 1.1 The minor submission requested an Authority Required (Streamlined) listing of an intravenous (IV) formulation of fosaprepitant for the management of nausea and vomiting associated with cytotoxic chemotherapy.

2 Requested listing

- 2.1 The submission sought the same restrictions and price as aprepitant. Aprepitant has General Schedule and Section 100 (Efficient Funding of Chemotherapy – Related Benefits; s100 CT) Authority Required (Streamlined) listings for use as:
- Primary prophylaxis prior to highly emetogenic chemotherapy (HEC) or prior to breast cancer chemotherapy with cyclophosphamide and an anthracycline.
 - Secondary prophylaxis prior to moderately emetogenic chemotherapy (MEC).
 - Primary prophylaxis prior to administration of carboplatin/oxaliplatin regimens.

For more detail on PBAC's view, see section 7 "PBAC outcome"

3 Background

- 3.1 Fosaprepitant is 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, or moderately emetogenic cancer chemotherapy.
- 3.2 Fosaprepitant was previously recommended by the PBAC in March 2011, on a cost-minimisation basis against aprepitant oral three-day regimen (125 mg on day 1, 80 mg on days 2 and 3). The PBAC recommended that a cost offset should apply for the IV formulation to account for additional nursing resources and chair time.
- 3.3 The sponsor did not accept the PBAC's pricing recommendation in relation to this listing, and it did not proceed. At the March 2016 meeting, the previous recommendation was rescinded on the basis that PBAC recommendations that have not been implemented and are more than five years old are no longer considered reliable by the Committee due to the passage of time.
- 3.4 Other relevant PBAC considerations in the past five years:
- July 2011: Fosaprepitant – Request for PBAC advice regarding an appropriate cost for the nursing time associated with the administration of fosaprepitant. The PBAC remained of the opinion that nursing resources need to be offset in the

determination of fosaprepitant's price and that there would also be extra costs incurred for "chair" time for some patients, but was uncertain of the value that should be applied.

- July 2012: Aprepitant – The PBAC recommended Authority Required (Streamlined) listing of a higher strength, single dose oral presentation with the same indications as the current PBS listing for the three day dose pack. The PBAC subsequently advised that it had no concerns with the deletion of the three-dose regimen from the PBS in November 2013.
- November 2015: Aprepitant – The PBAC rejected the request for an extension to the listing to include use with carboplatin/oxaliplatin regimens from the first chemotherapy cycle without having a prior episode of chemotherapy induced nausea and vomiting (CINV) on the basis that the cost-effectiveness in this setting was not adequately demonstrated.
- March 2016: Aprepitant – Re-submission relating to the November 2015 request. Extension of the listing was recommended on the basis of cost-minimisation to the price of aprepitant use in MEC, with an RSA applied.

4 Clinical place for the proposed therapy

- 4.1 An IV infusion formulation provides an alternative [to oral aprepitant] for children, patients with difficulty swallowing, or patients with difficulty absorbing the drug from an oral formulation.

5 Comparator

- 5.1 The previous major submission considered by the PBAC in March 2011 nominated the aprepitant three-day regimen. This submission nominated the aprepitant one-day regimen (165 mg). The PBAC noted that the aprepitant one-day regimen was listed on a cost-minimisation basis to the three-day regimen.

For more detail on PBAC's view, see section 7 "PBAC outcome"

6 Consideration of the evidence

Sponsor hearing

- 6.1 There was no hearing for this item as it was a minor submission.

Consumer comments

- 6.2 The PBAC noted that no consumer comments were received for this item.

Clinical trials

- 6.3 As a minor submission, no new clinical trials were presented in the submission. The minor submission noted the following clinical trials. Protocol 031 was not included in the 2011 fosaprepitant submission.

Table 1: Trials and associated reports noted in the re-submission

Trial ID	Protocol title/ Publication title	Publication citation
Direct randomised trials		
Protocol 165	A Single-Dose Bioequivalence and Food Effect Study with Aprepitant and Fosaprepitant Dimeglumine in Healthy Young Adult Subjects	8 March 2010
Protocol 031	A Phase III, Randomized, Double-Blind, Active Comparator-Controlled Parallel-Group Study, Conducted Under In-House Blinding Conditions, to Examine the Efficacy and Safety of a Single 150 mg Dose of Intravenous Fosaprepitant Dimeglumine for the Prevention of Chemotherapy-Induced Nausea and Vomiting (CINV) Associated With Moderately Emetogenic Chemotherapy	23 June 2015

Source: Compiled during the minor overview

- 6.4 The minor submission also included synopses of two Clinical Study Reports. These studies were not noted in the minor submission, and no context was provided for their inclusion.

Table 2: Reports provided with the submission

Trial ID	Protocol title/ Publication title	Publication citation
Direct randomised trials		
Protocol 017	A Phase III, Randomized, Double-Blind, Active-Controlled, Parallel-Group Study, Conducted Under In-House Blinding Conditions, to Examine the Safety, Tolerability, and Efficacy of a Single Dose of Intravenous MK-0517 for the Prevention of Chemotherapy-Induced Nausea and Vomiting (CINV) Associated with Cisplatin Chemotherapy	28 September 2009
Protocol 018	An Open-Label, 2-Part, Randomized, 2-Period, Crossover, Single-Centre Study to Evaluate the Effect of a Single 150-mg Intravenous Dose of Fosaprepitant Dimeglumine (MK-0517) on the Pharmacokinetics of Oral Dexamethasone in Part 1, and on the Pharmacokinetics of Oral Midazolam in Part 2, in Healthy Young Adult Subjects.	24 September 2008

Source: Compiled during the minor overview

Comparative effectiveness

- 6.5 The PBAC previously considered Protocol 017 as the pivotal study for the fosaprepitant submission in March 2011, where it was viewed as supportive of the claim that fosaprepitant was comparable to the aprepitant three-day regimen in efficacy in the acute phase (0-24 hours post chemotherapy).
- 6.6 The PBAC previously considered Protocol 165 in the July 2012 submission for the higher strength 165 mg aprepitant. It was presented as evidence of bioequivalence between aprepitant 165 mg capsules and 150 mg fosaprepitant IV. The submission stated that the bioavailability of these two formulations was found to be similar in study P165. On the basis of this study, in combination with P017, the PBAC accepted the submission's claim that the single dose aprepitant 165 mg regimen has non-inferior efficacy and safety to the aprepitant three-day dose regimen.
- 6.7 The PBAC previously considered Protocol 031 in the November 2015 submission for aprepitant use with carboplatin/oxaliplatin without the requirement for a prior episode of CINV.

- 6.8 The PBAC recalled that at the March 2011 meeting, it considered that fosaprepitant had comparable efficacy to the aprepitant three-day regimen. The PBAC also recalled that it had previously accepted clinical equivalence between the oral three-day and single dose regimens of aprepitant. On this basis, the PBAC considered that the evidence considered in the original submission in which it recommended fosaprepitant to have non-inferior safety and efficacy to aprepitant three-day regimen, could also be applied to the single dose oral regimen.

Clinical claim

- 6.9 The submission reiterated the March 2011 claim that fosaprepitant compared with aprepitant has non-inferior comparative effectiveness and non-inferior safety. The PBAC previously accepted this claim for the three-day regimen.
- 6.10 The PBAC considered that the claim of non-inferior comparative effectiveness and safety was reasonable when compared with aprepitant one-day regimen.

Economic analysis

- 6.11 The submission noted that the PBAC had previously recommended fosaprepitant on a cost-minimisation basis against aprepitant three-day regimen. The PBAC previously considered that the price should take into account the increased nursing time to administer the drug. The current submission claimed that these cost offsets should not apply since fosaprepitant requires a 'shorter pre-medication time' – that is, fosaprepitant is administered 30 minutes prior to chemotherapy, while aprepitant is administered 60 minutes prior to chemotherapy. The PI states that the IV infusion is administered over a period of 20 – 30 minutes.
- 6.12 The PBAC recalled its previous advice that the oral formulation would be the preferred option for patients. It also noted that there was a clinical need for fosaprepitant as an alternative option for those patients who could not use the oral form. The PBAC considered that uptake of fosaprepitant will not be large, and that the impact of any additional chair time will be negligible, and therefore agreed that no cost offset is needed.

Estimated PBS usage & financial implications

- 6.13 The minor submission estimated there to be no financial implications to the PBS as the submission expects fosaprepitant to only substitute for aprepitant, at the same cost to the Commonwealth. The minor submission also claimed that fosaprepitant will not change the use of other anti-emetic drugs such as ondansetron and dexamethasone. Estimates of patient or prescription numbers were not provided.

Financial Management including Risk Sharing Arrangements

- 6.14 In the March 2016 consideration to extend the aprepitant listing to include use with carboplatin/oxaliplatin regimens from the first chemotherapy cycle, without having a prior episode of CINV, the PBAC recommended a Risk Sharing Arrangement to manage the risk for potential use beyond the estimated patient numbers. The PBAC considered that fosaprepitant should also be included in this RSA, with no change to the existing caps, under the same rebate arrangements as currently in place for

aprepitant.

- 6.15 The sponsor requested the same AEMP as aprepitant. This current price of aprepitant is weighted between prices for the highly emetogenic/anthracycline plus cyclophosphamide (breast cancer) indications, and the moderately emetogenic chemotherapy indication. As fosaprepitant will be listed with the same indications as for aprepitant, the PBAC considered that this was reasonable.

Table 3: Aprepitant weighted price – effective 1 October 2016

HEC/AC regimens	\$		%	\$
MEC regimens	\$		%	

Source: Compiled during the minor overview

For more detail on PBAC’s view, see section 7 “PBAC outcome”

7 PBAC Outcome

- 7.1 The PBAC recommended the Authority Required (Streamlined) General Schedule and Section 100 (Efficient Funding of Chemotherapy – Related Benefits) listing of fosaprepitant for the management of nausea and vomiting associated with cytotoxic chemotherapy, on a cost-minimisation basis against aprepitant (one-day regimen). The PBAC considered that the equi-effective doses were 150 mg fosaprepitant and 165 mg aprepitant.
- 7.2 The PBAC recommended that the same restrictions apply to fosaprepitant listings as currently apply to aprepitant listings:
- Primary prophylaxis prior to highly emetogenic chemotherapy (HEC) or prior to breast cancer chemotherapy with cyclophosphamide and an anthracycline.
 - Secondary prophylaxis prior to moderately emetogenic chemotherapy (MEC).
 - Primary prophylaxis prior to administration of carboplatin/oxaliplatin regimens.
- 7.3 The PBAC recommended that the listings should provide a maximum quantity of 1 vial (150 mg), with 5 repeats, and that the aprepitant Prescribing Instruction should be amended for the fosaprepitant listings as follows: “No more than 1 vial of fosaprepitant 150 mg will be authorised per cycle of cytotoxic chemotherapy.”
- 7.4 The PBAC agreed with the submission that the appropriate comparator was aprepitant one-day regimen (165 mg tablet).
- 7.5 The PBAC considered that evidence presented in the submission, and previously considered by the PBAC in consideration of fosaprepitant and aprepitant, was supportive of the claim that fosaprepitant has non-inferior comparative effectiveness and non-inferior safety compared with aprepitant.
- 7.6 The PBAC considered that PBS listing of fosaprepitant was unlikely to grow the market for anti-emetic therapy. Rather, it would likely be prescribed as a substitute for PBS-listed aprepitant. The PBAC also considered that the intravenous formulation has a clinical place, particularly for patients with swallowing difficulties, or difficulties absorbing the drug from the oral form, and some children.
- 7.7 The PBAC recommended that the fosaprepitant listing for use with

carboplatin/oxaliplatin regimens from the first chemotherapy cycle, without having a prior episode of CINV, should also be included in the existing aprepitant RSA.

- 7.8 The PBAC recommended that under Section 101(3BA) of the *National Health Act 1953*, fosaprepitant should be treated as interchangeable on an individual patient basis with aprepitant.
- 7.9 The PBAC advised that fosaprepitant is suitable for inclusion in the PBS medicines for prescribing by nurse practitioners under the General Schedule, but not under s100 CT.
- 7.10 The PBAC recommended that the Early Supply Rule should not apply, as it does not currently apply to s100 CT listings and does not apply to the current aprepitant listings.
- 7.11 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:

Recommended

8 Recommended listing

8.1 Add new item:

Name, Restriction, Manner of administration and form	Max. Qty (units)	Max. Qty (packs)	No. of Rpts	Proprietary Name and Manufacturer	
FOSAPREPITANT Fosaprepitant 150 mg injection, 1 vial	1	1	5	Emend IV®	Merck Sharp & Dohme (Australia) Pty Ltd

Category / Program:	GENERAL – General Schedule (Code GE) Section 100 – Efficient Funding of Chemotherapy – Related Benefits
Prescriber type:	<input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners (GE listings only)
PBS Indication:	Nausea and vomiting
Restriction Level / Method:	<input checked="" type="checkbox"/> Authority Required (STREAMLINED)

Clinical criteria:	The condition must be associated with cytotoxic chemotherapy being used to treat malignancy, AND The treatment must be in combination with a 5-hydroxytryptamine receptor (5HT3) antagonist and dexamethasone, AND Patient must be scheduled to be administered a chemotherapy regimen that includes any 1 of the following agents: altretamine; carmustine; cisplatin when a single dose constitutes a cycle of chemotherapy; cyclophosphamide at a dose of 1500 mg per square metre per day or greater; dacarbazine; procarbazine when a single dose constitutes a cycle of chemotherapy; streptozocin.
Prescribing Instructions	No more than 1 vial of fosaprepitant 150 mg will be authorised per cycle of cytotoxic chemotherapy.

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Administrative Advice	This drug is not PBS-subsidised for nausea and vomiting associated with radiotherapy being used to treat malignancy. No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised.
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Clinical criteria:	The condition must be associated with cytotoxic chemotherapy being used to treat breast cancer, AND The treatment must be in combination with a 5-hydroxytryptamine receptor (5HT3) antagonist and dexamethasone, AND Patient must be scheduled to be co-administered cyclophosphamide and an anthracycline.
Prescribing Instructions	No more than 1 vial of fosaprepitant 150 mg will be authorised per cycle of cytotoxic chemotherapy.
Administrative Advice	This drug is not PBS-subsidised for nausea and vomiting associated with radiotherapy being used to treat malignancy. No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised.

Clinical criteria:	The condition must be associated with moderately emetogenic cytotoxic chemotherapy being used to treat malignancy, AND The treatment must be in combination with a 5-hydroxytryptamine receptor (5HT3) antagonist and dexamethasone, AND Patient must have had a prior episode of chemotherapy induced nausea or vomiting, AND Patient must be scheduled to be administered a chemotherapy regimen that includes any 1 of the following intravenous chemotherapy agents: arsenic trioxide; azacitidine; cyclophosphamide at a dose of less than 1500 mg per square metre per day; cytarabine at a dose of greater than 1 g per square metre per day; dactinomycin; daunorubicin; doxorubicin; epirubicin; fotemustine; idarubicin; ifosfamide; irinotecan; melphalan; methotrexate at a dose of 250 mg to 1 g per square metre; raltitrexed.
Prescribing Instructions	No more than 1 vial of fosaprepitant 150 mg will be authorised per cycle of cytotoxic chemotherapy. Concomitant use of a 5HT3 antagonist should not occur with fosaprepitant on days 2 and 3 of any chemotherapy cycle.
Administrative Advice	This drug is not PBS-subsidised for nausea and vomiting associated with radiotherapy being used to treat malignancy. No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised.

Clinical criteria:	The condition must be associated with cytotoxic chemotherapy being used to treat malignancy, AND The treatment must be in combination with a 5-hydroxytryptamine receptor (5HT3) antagonist and dexamethasone on day 1 of a chemotherapy cycle, AND Patient must be scheduled to be administered a chemotherapy regimen that includes either carboplatin or oxaliplatin.
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Prescribing Instructions	No more than 1 vial of fosaprepitant 150 mg will be authorised per cycle of cytotoxic chemotherapy. Concomitant use of a 5HT3 antagonist should not occur with fosaprepitant on days 2 and 3 of any chemotherapy cycle.
Administrative Advice	This drug is not PBS-subsidised for nausea and vomiting associated with radiotherapy being used to treat malignancy. No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised.

9 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.

10 Sponsor's Comment

The sponsor had no comment.