7.12 APREPITANT
165 mg capsule, 1,
Emend®, Merck Sharp and Dohme (Australia) Pty Limited

1 Purpose of Application

1.1 The minor re-submission requested an extension to the current Section 100 (Chemotherapy – Related Benefits) and General Schedule PBS listing of aprepitant to include use with carboplatin/oxaliplatin regimens from the first chemotherapy cycle, without having a prior episode of chemotherapy induced nausea and vomiting (CINV).

2 Requested listing

2.1 The submission requested the Authority Required (STREAMLINED) listing below. Suggestions and additions proposed by the Secretariat to the requested listing are added in italics and suggested deletions are crossed out with strikethrough.

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty*	Proprietary Name and Manufacturer
APREPITANT 165 mg capsule, 1	1	5	$[redacted] (CT) $[redacted] (GE)	Emend® MK

**weighted by revised estimates of PBS utilisation of moderately emetogenic chemotherapy (MEC) regimens/ non-MEC regimens, see 'Economic analysis' section for more detail.*

Category / Program	GENERAL – General Schedule (Code GE) Section 100 – Chemotherapy – related benefits (CT)
Prescriber type:	☐Dental ☒Medical Practitioners ☒Nurse practitioners ☐Optometrists ☐Midwives
Episodicity:	-
Severity:	-
Condition:	Nausea and vomiting
PBS Indication:	Nausea and vomiting
Treatment phase:	-
Restriction Level / Method:	☐Restricted benefit ☐Authority Required - In Writing ☐Authority Required - Telephone ☐Authority Required – Emergency ☐Authority Required - Electronic ☒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 ($5HT_3$) 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.
Prescriber Instructions	No more than 1 capsule of aprepitant 165 mg 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.*
Administrative Advice	Aprepitant 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.

2.2 The sponsor has requested a separate streamlined listing for this indication, rather than incorporation into the existing restrictions, as proposed in the original submission. This is for the purposes of data collection under the proposed Risk Sharing Agreement.

3 Background

3.1 Aprepitant 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 emetogenic cancer chemotherapy
- moderately emetogenic cancer chemotherapy

Aprepitant is also indicated for the prevention of postoperative nausea and vomiting.

3.2 Aprepitant for the requested indication (i.e. first-line therapy for nausea and vomiting associated with carboplatin/oxaliplatin regimens) was previously considered by the PBAC in November 2015.

3.3 The PBAC rejected the previous submission on the basis that the cost-effectiveness of aprepitant in the proposed population had not been adequately demonstrated by the submission.

3.4 Aprepitant is currently listed for use:

- as secondary prophylaxis for CINV associated with moderately emetogenic cytotoxic chemotherapy (MEC regimens)
- as primary prophylaxis for CINV associated with highly emetogenic cytotoxic chemotherapy, including anthracycline use for the treatment of breast cancer. (HEC regimens).

3.5 The current effective price of aprepitant is higher for use in HEC regimens than MEC regimens, and the published price reflects a weighted value of 67% and 33% respectively across these indications.

3.6 The previous major submission requested that the new listing of aprepitant be priced consistent with use in HEC regimens (resulting in a revised weighting of 8% and 92% across indications). In the pre-PBAC response, the sponsor proposed that the aprepitant price be maintained at its current levels and not re-weighted. This re-submission proposed that the new listing of aprepitant be priced consistent with use in MEC regimens, and re-weighted at [redacted]% and [redacted]% respectively across HEC and MEC regimens. This submission also applied the statutory 5% price reduction expected on 1 April 2016.

3.7 The following table provides a summary of the previous submission and the current re-submission.

Summary of the previous submission and current re-submission

	Aprepitant, November 2015	Current re-submission
Requested PBS listing	General schedule and Section 100 (CT), Authority Required (STREAMLINED) listing for aprepitant for the prevention of acute and delayed chemotherapy induced nausea and vomiting (CINV) associated with carboplatin/oxaliplatin based chemotherapy regimens. **PBAC Comment:** None	Same as previously, although requested as a separate item code rather than included under current listings, for the purposes of monitoring the proposed Risk Share Agreement.
Requested Ex-manufacturer price	$[redacted]	$[redacted] proposed for the extension to indication; and $[redacted] proposed as a weighted price for all aprepitant use. This includes a 5% statutory price reduction from 1 April 2016.
Main comparator	Standard treatment, comprising of dexamethasone plus ondansetron, **PBAC Comment:** The appropriate comparator would be secondary prophylaxis, i.e. aprepitant after experiencing CINV, as this is the therapy that would most likely be replaced. [Para 7.2]	Not stated, although the submission requests a consistent aprepitant price for use as primary or secondary prophylaxis of CINV associated with MEC regimens.
Clinical evidence	A series of meta-analyses of four head-to-head trials comparing a regimen containing aprepitant or fosaprepitant, to one not containing these drugs. **PBAC Comment:** None	No new evidence.
Key effectiveness data	A statistically significantly higher proportion of patients treated with aprepitant compared with those receiving the control: reported complete response across all time phases; reported no vomiting consistently across all times phases; and did not require rescue medication in the overall phase. Time to first vomiting was statistically significantly longer in patients treated with aprepitant than with the control regimen, and the impact of chemotherapy on daily life was also reduced in aprepitant patients compared to the control regimen.	No new data presented.

	Aprepitant, November 2015	Current re-submission
	PBAC Comment: See Clinical claim	
Key safety data	The meta-analyses showed that there were no statistically significant differences between the aprepitant and control regimen with respect to any of the safety outcomes, and the types of adverse events reported across the RCTs were similar between treatment groups and were comparable to the types of adverse events observed in subjects with cancer receiving emetogenic chemotherapy. **PBAC Comment:** See Clinical claim	No new data presented.
Clinical claim	The submission described aprepitant plus standard antiemetic therapy as superior in terms of comparative effectiveness and similar in terms of comparative safety over standard therapy alone. **PBAC Comment:** The claim was considered reasonable, however the magnitude of the benefit was uncertain in the specific subgroup of patients treated with carboplatin and oxaliplatin based chemotherapy regimens. [Para 6.11]	Same as previously.
Economic evaluation	The submission did not provide a formal economic evaluation, but claimed that since the PBAC had previously determined aprepitant to be cost-effective for management of CINV associated with cyclophosphamide plus an anthracycline being used to treat breast cancer, aprepitant for the proposed population could be considered at least as cost-effective, as the risk difference for management of CINV in the proposed population is greater than that shown for the cyclophosphamide plus an anthracycline regimen. **PBAC Comment:** In the absence of an economic analysis, the cost-effectiveness of aprepitant in the broader population requested could not be determined. If the submission, wished to pursue the requested price increase for aprepitant when used as primary prophylaxis with oxaliplatin or carboplatin compared to the current secondary prophylaxis listing, a major re-submission with an appropriate economic evaluation to support a claim of cost-effectiveness would be required. Alternatively, the PBAC considered that a pragmatic way forward would be to cost-minimise the price of aprepitant in the proposed population to the price of aprepitant when used with moderately emetogenic chemotherapy. [Para 7.4 & 7.7]	Requests the same aprepitant price in the proposed population (i.e. for primary prophylaxis) as when used with moderately emetogenic chemotherapy for secondary prophylaxis of CINV.
Number of chemotherapy journeys	10,000 – 50,000 in Year 1 increasing to 10,000 – 50,000 in Year 5. **PBAC Comment:** None.	Same as previously.
Estimated cost to PBS	Less than $10 million in Year 1 increasing to less than $10 million in Year 5 for a total of $10 - $20 million over the first 5 years of listing. In the Pre-PBAC Response, this was revised to less than $10 million in Year 1 increasing to less than $10 million in	Less than $10 million in Year 1 increasing to less than $10 million in Year 5 for a total of $10 - $20 million over the first 5 years of listing.

	Aprepitant, November 2015	Current re-submission
	Year 5 for a total of $10 - $20 million over the first 5 years of listing. **PBAC Comment:** The requested listing would make aprepitant available to a substantially broader population of patients and the financial implications of such an extension to listing were uncertain. The PBAC considered that if the listing was extended in the future, there should be a risk sharing mechanism to manage for potential use beyond the estimated patient numbers. [Para 7.6]	
PBAC decision	Rejected. In making its recommendation, the PBAC considered that the cost-effectiveness of aprepitant in the proposed population had not been adequately demonstrated by the submission. [Para 7.1]	-

Source: Compiled during the Minor Overview

4 Clinical place for the proposed therapy

4.1 The clinical place in therapy was unchanged from the November 2015 major submission.

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

5 Comparator

5.1 The previous major submission considered by the PBAC in November 2015 nominated standard treatment, comprising of dexamethasone plus ondansetron, as the comparator. As noted above, the PBAC considered that the appropriate comparator would be secondary prophylaxis, i.e. aprepitant after experiencing CINV, as this is the therapy that would most likely be replaced.

5.2 This resubmission proposed that the price of aprepitant in the requested population be cost-minimised to the price of aprepitant when used with moderately emetogenic chemotherapy.

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.

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 re-submission.

6.4 The basis of the minor submission's request was to propose:
   a. a new (lower) price for aprepitant when used in the proposed population which is consistent with the current price of aprepitant when used with moderately emetogenic chemotherapy (MEC); and
   b. that the risks of potential use beyond the estimated patient numbers be shared between the sponsor and the Commonwealth through a Risk Sharing Agreement (RSA)

Comparative effectiveness

6.5 The trial results remain unchanged from the previous major submission considered in November 2015.

Comparative harms

6.6 The trial results remain unchanged from the previous major submission considered in November 2015.

Clinical claim

6.7 The clinical claim remains unchanged from the previous major submission considered in November 2015. As noted above, the previous submission claimed aprepitant plus standard antiemetic therapy was superior in terms of comparative effectiveness and similar in terms of comparative safety when compared with standard therapy alone. The PBAC considered that this claim may be reasonable, however noted that the magnitude of the benefit was uncertain in the specific subgroup of patients treated with carboplatin and oxaliplatin based chemotherapy regimens.

6.8 The PBAC consideration of the clinical claim remained unchanged from its November 2015 meeting.

Economic analysis

6.9 In the previous major submission considered by PBAC in November 2015, the submission did not present a formal economic evaluation. The PBAC considered that in the absence of an economic evaluation, the cost-effectiveness of aprepitant in the broader population requested could not be determined. The PBAC considered that a pragmatic way forward would be to cost-minimise the price of aprepitant in the proposed population to the price of aprepitant when used with moderately emetogenic chemotherapy.

6.10 The re-submission proposed a new lower price for this listing consistent with the price of aprepitant when used with moderately emetogenic chemotherapy, re-weighted at [redacted]% and [redacted]% respectively across use in MEC and HEC regimens. The submission also applied a statutory 5% price reduction expected from 1 April 2016.

6.11 The table below shows the current and proposed pricing of aprepitant as calculated in the re-submission. In the calculation of costs to the PBS, a "weighted across s85/s100" (79%/21%) price was applied. The submission proposed an ex-man price of $[redacted] for the extension to indication, and proposed a weighted ex-man price of $[redacted].

Table 1: Current and proposed pricing, minor re-submission

	HEC effective price	MEC effective price	Weighted published price	
			Current (33%/67%)	Proposed ([redacted]%/[redacted]%)
Ex-man (updated for 5% statutory price reduction Apr 16)	$[redacted]	$[redacted]	$105.53	$[redacted]

Source: EMEND Financial Estimates.xlsx, March 2016 minor re-submission

6.12 The PBAC noted that price of aprepitant in the proposed population was the same as when used with moderately emetogenic chemotherapy. The PBAC considered this approach consistent with its previous advice in November 2015.

Drug cost/ chemotherapy 'journey' with oxaliplatin/carboplatin: $[redacted]/ $[redacted]

6.13 The estimate was based on 4.35 cycles and 7.28 cycles per chemotherapy journey with carboplatin and oxaliplatin, 93.7% of chemotherapy cycles where aprepitant is used, assuming that one script of aprepitant is administered per cycle (EMEND Financial Estimates.xls), and a cost per script of $[redacted] (including co-payments).

Estimated PBS usage & financial implications

6.14 The minor submission estimated a net cost to the PBS of less than $10 million in Year 5 of listing, with a total net cost to the PBS of $10 - $20 million over the first 5 years of listing. This is summarised in the table below, with comparison to the previous submission financial estimates, as well as the revised estimates proposed by the sponsor in the pre-PBAC Response. The expected number of chemotherapy journeys and prescription numbers are also presented below, and remained unchanged from the previous submission.

Table 2: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated extent of use with a change to the PBS listing					
Total chemotherapy journeys	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of chemotherapy journeys with aprepitant	41.4%	50.2%	53.8%	56.3%	57.2%
Scripts of aprepitant*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated net cost to PBS/RPBS/MBS					
Net cost to PBS/RPBS (excluding co-payments)	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net cost to MBS	-	-	-	-	-
Estimated total net cost					
Net cost to PBS/RPBS/MBS (this submission)	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net cost to PBS/RPBS/MBS (Pre-PBAC Response, Nov 2015)	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net cost to PBS/RPBS/MBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]

	Year 1	Year 2	Year 3	Year 4	Year 5
(Nov 2015 submission)					

** Based on 4.35 cycles and 7.28 cycles per chemotherapy journey with carboplatin and oxaliplatin, 93.7% of chemotherapy cycles where aprepitant is used, assuming that one script of aprepitant is administered per cycle (Section E Spreadsheet.xls),*
Source: EMEND Financial Estimates.xlsx; 6.02 aprepitant Pre-PBAC Response, November 2015.

6.15 In Table 5 of the minor re-submission (p.8), the projected 'HEC use' without listing was over 200,000 (Row C), the predicted impact of listing on HEC use was zero (Row D), but the projected HEC use following the proposed PBS listing increased to over 200,000 (Row E). At the same time, in the spreadsheet provided, projected HEC use with listing was shown as over 200,000, which was consistent with the nil impact predicted on HEC usage in the re-submission .

Financial Management – Risk Sharing Arrangements

6.16 As noted above, the PBAC previously considered that the requested listing would make aprepitant available to a substantially broader population of patients and the financial implications of such an extension to listing were uncertain. The PBAC considered that if the listing was extended in the future, there should be a risk sharing mechanism to manage for potential use beyond the estimated patient numbers.

6.17 In accordance with the PBAC recommendation, the minor re-submission proposed RSA parameters which would be acceptable to the sponsor (Minor resubmission, pp. 9-10), including:

- yearly caps (up to five years) based on the financial estimates provided in the re-submission; and
- rebates for any incremental sales over the caps of [redacted]%.

6.18 In line with its previous advice, the PBAC recommended an RSA to manage the risk for potential use beyond the estimated patient numbers. The PBAC noted that resubmission proposed yearly caps (up to five years) based on the financial estimates provided and rebates for any incremental sales over the caps of [redacted]%.

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

7 PBAC Outcome

7.1 The PBAC recommended listing aprepitant as an Authority Required (Streamlined) benefit on the General Schedule and under the Section 100 program Efficient Funding of Chemotherapy – Related Benefits, for use with carboplatin/oxaliplatin regimens from the first chemotherapy cycle, without having a prior episode of chemotherapy induced nausea and vomiting (CINV).

7.2 In making its recommendation, the PBAC noted that the resubmission proposed a price for aprepitant for this indication that was cost-minimised to the price of aprepitant when used with moderately emetogenic chemotherapy, as per the PBAC's advice from November 2015.

7.3 The PBAC agreed with the Secretariat's suggested changes to the proposed restriction, consistent with the current listing for second-line therapy for nausea and vomiting associated with moderately emetogenic cytotoxic chemotherapy including:

- specifying that treatment must be in combination with a 5-hydroxytryptamine receptor (5HT3) antagonist and dexamethasone on day 1 of a chemotherapy cycle; and
- adding a Prescriber Instruction: "Concomitant use of a 5HT3 antagonist should not occur with aprepitant on days 2 and 3 of any chemotherapy cycle".

7.4 The PBAC noted that no new clinical data was presented in the resubmission, and that the PBAC's consideration of the clinical claim remained unchanged from November 2015.

7.5 The PBAC noted that the re-submission estimated a total net cost to the PBS of $10 $20 million over the first 5 years of listing compared with the original submission, which estimated a total net cost to the PBS of $10 - $20 million over the first 5 years of listing.

7.6 Under section 101 (3BA) of the *National Health Act*, the PBAC advised that aprepitant should be not treated as interchangeable with any other drugs. The PBAC recalled its previous advice in November 2015 that therapeutically, netupitant + palonosetron FDC could be considered interchangeable with the free combination of aprepitant with a 5-HT_3 RA. (netupitant + palonosetron PSD, Nov 2015).

7.7 The PBAC advised that aprepitant is suitable for prescribing by nurse practitioners on the General Schedule. The PBAC noted that currently, nurse practitioners are able to prescribe aprepitant under the General Schedule but not under Section 100 (CT).

7.8 The PBAC recommended that the Early Supply Rule should not apply.

7.9 The PBAC noted that as a result of the recommended amendment to the aprepitant listing, flow-on restriction changes would be required for the current aprepitant listing for nausea and vomiting associated with moderately emetogenic cytotoxic chemotherapy to remove carboplatin and oxaliplatin.

Outcome:
Recommended

8 Recommended listing

8.1 Amend existing/recommended listing as follows:

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer
APREPITANT			Emend® MK
165 mg capsule, 1	1	5	

Category / Program	GENERAL – General Schedule (Code GE) Section 100 – Chemotherapy – related benefits (CT)

Prescriber type:	☐Dental ☒Medical Practitioners ☒Nurse practitioners ☐Optometrists ☐Midwives
Episodicity:	-
Severity:	-
Condition:	Nausea and vomiting
PBS Indication:	Nausea and vomiting
Treatment phase:	-
Restriction Level / Method:	☐Restricted benefit ☐Authority Required - In Writing ☐Authority Required - Telephone ☐Authority Required – Emergency ☐Authority Required - Electronic ☒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 ($5HT_3$) 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.
Prescriber Instructions	No more than 1 capsule of aprepitant 165 mg 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.
Administrative Advice	Aprepitant 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

MSD is pleased that the PBAC has recommended aprepitant for patients receiving carboplatin or oxaliplatin chemotherapy regimens without requiring the patient to

experience an episode of chemotherapy induced nausea or vomiting first. This will mean that patients on these regimens will have access to aprepitant before their first chemotherapy dose, which will enable them to reduce one of the debilitating side effects of chemotherapy, and therefore improve their quality of life.