7.07 NETUPITANT/PALONOSETRON capsule, 300 mg/500 mcg, Akynzeo®, Specialised Therapeutics Australia Pty Ltd

1 Purpose of Application

1.1 The minor re-submission requested an Authority Required (streamlined) listing for netupitant/palonosetron (NEPA) fixed dose combination for the prevention of acute and delayed chemotherapy-induced nausea and vomiting:

- in patients treated with highly emetogenic chemotherapy used for treatment of malignancy; and
- in breast cancer patients treated with anthracycline plus cyclophosphamide based regimens.

1.2 The re-submission no longer sought reimbursement for patients scheduled to receive moderately emetogenic chemotherapy with a prior episode of chemotherapy-induced nausea and vomiting.

1.3 No new data or analyses were presented in the minor re-submission for NEPA.

2 Requested listing

2.1 The re-submission sought the following new proposed listing for NEPA. The price is unchanged and the wording is as suggested by the PBAC Secretariat in the March 2015 public summary document (PSD).

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer	
GENERAL SCHEDULE NETUPITANT WITH PALONOSETRON Capsule 300 mg + 0.5 mg, 1	1	5	$[redacted]	Akynzeo®	Specialised Therapeutics
SECTION 100 (CHEMOTHERAPY) NETUPITANT WITH PALONOSETRON Capsule 300 mg + 0.5 mg, 1	1	5	$[redacted]	Akynzeo®	Specialised Therapeutics

Category / Program:	GENERAL – General Schedule* (Code GE) SECTION 100 – Chemotherapy related benefits
Prescriber type:	☐Dental ☒Medical Practitioners ☒Nurse practitioners* ☐Optometrists ☐Midwives
Condition:	Nausea and vomiting
PBS Indication:	Nausea and vomiting
Restriction Level / Method:	☒Streamlined

Clinical criteria:	The condition must be associated with cytotoxic chemotherapy being used to treat malignancy; **AND** The treatment must be in combination with 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.
Prescriber Instructions:	No more than 1 capsule of 300mg netupitant/0.5mg palonosetron fixed dose combination will be authorised per cycle of cytotoxic chemotherapy.
Administrative Advice:	No increase in the maximum quantity or number of units may be authorised. No Increase in the maximum number of repeats may be authorised. This medicine is not PBS-subsidised for nausea and vomiting associated with radiotherapy being used to treat malignancy.

Category / Program:	GENERAL – General Schedule* (Code GE) SECTION 100 – Chemotherapy related benefits
Prescriber type:	☐Dental ☒Medical Practitioners ☒Nurse practitioners* ☐Optometrists ☐Midwives
Condition:	Nausea and vomiting
PBS Indication:	Nausea and vomiting
Restriction Level / Method:	☒Streamlined
Clinical criteria:	The condition must be associated with cytotoxic chemotherapy being used to treat breast cancer; **AND** The treatment must be in combination with dexamethasone; **AND** Patient must be scheduled to be co-administered cyclophosphamide and an anthracycline;
Prescriber Instructions:	No more than 1 capsule of 300mg netupitant/0.5mg palonosetron fixed dose combination will be authorised per cycle of cytotoxic chemotherapy.
Administrative Advice:	No increase in the maximum quantity or number of units may be authorised. No Increase in the maximum number of repeats may be authorised. This medicine is not PBS-subsidised for nausea and vomiting associated with radiotherapy being used to treat malignancy.

2.2 The Economic Sub-Committee (ESC) considered that it may be appropriate for a note to be added to each restriction preventing the concomitant use of another serotonin receptor antagonist (5-HT_3 RA) (paragraph 2.2 of the March 2015 PBAC minutes).

2.3 The re-submission requested listing for the treatment of patients receiving highly emetogenic chemotherapy (HEC) and for breast cancer patients receiving an anthracycline-based chemotherapy (AC) regimen only. This is consistent with the PBAC's consideration in March 2015, and the proposed restrictions incorporated the Secretariat's previous suggestions regarding the Administrative Advice.

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

3 Background

3.1 NEPA was registered with the Therapeutic Goods Administration (TGA) in May 2015. NEPA is indicated in adult patients for:

- prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy; and
- prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy.

3.2 NEPA was previously considered by the PBAC at the March 2015 meeting. The major submission for NEPA was rejected by the PBAC as there was no recognised unmet clinical need for this population of patients and the clinical place for NEPA was not established in the major submission (paragraph 7.1 of the March 2015 PSD). Further, the PBAC was concerned that the fixed dose combination guidelines were not addressed in the submission. The PBAC Guidelines express the preference for components to be individually listed on the Pharmaceutical Benefits Schedule (PBS), as well as avoiding unnecessary proliferation of products or dose forms (paragraph 7.4 of the March 2015 PSD).

Table 1 provides a summary of the previous submission and current re-submission.

Table 1: Summary of the previous submission and current re-submission

	NEPA March 2015	Current re-submission
Requested PBS listing	1. HEC 2. Breast cancer - AC based regimen 3. MEC with CINV **PBAC Comment:** noted that guidelines for managing emesis risk have changed, meaning that any restriction for antiemetic therapy based on the emesis risk of specific chemotherapy agents, such as that proposed for NEPA, may become outdated. The clinical claim of non-inferiority with aprepitant + 5-HT3 RA was poorly supported for the patients due to receive MEC as no clinical evidence was provided in patients who had experienced a previous event of chemotherapy induced nausea/vomiting. The PBAC remained concerned about potential for use in patients undergoing MEC who do not have refractory CINV.	1. HEC 2. Breast cancer - AC based regimen The re-submission removed third restriction (MEC with CINV)
Requested price	Effective DPMQ Section 85: $[redacted] Section 100: $[redacted]	No change
Main comparator	Main comparator: aprepitant + 5-HT_3 RA **PBAC Comment:** considered that aprepitant plus a 5-HT_3 RA is the appropriate main comparator for patients due to receive highly emetogenic chemotherapy and patients with breast cancer who are due to receive anthracycline plus cyclophosphamide.	No change
Clinical evidence	Direct evidence of two head to head trials for patients who received HEC and MEC: • NETU-07-07 (N=270) • NETU-10-29 (N = 412) Indirect comparison for patients with breast cancer who received AC: • NETU-08-18; (N=1455) • Trial 071 (N=866)	No new data or analyses.
Key effectiveness data	**HEC: Complete Response – direct evidence** Acute (0-24 hr), RD (95% CI): 0.01 (-0.07, 0.09) Delayed (25-120 hr), RD (95% CI): 0.12 (-0.13, 0.36) Overall (0-120 hr), RD (95% CI): 0.10 (-0.08, 0.28) **Breast cancer - AC: Complete Response – indirect evidence** Acute (0-24 hr), RR (95% CI): 0.95 (0.87, 1.04) Delayed (25-120 hr), RR (95% CI): 0.98 (0.18, 5.21) Overall (0-120 hr), RR (95% CI): 0.93 (0.80, 1.09) **PBAC Comment:** considered that despite the wide CIs, the clinical claim that NEPA is non-inferior to aprepitant + 5-HT_3 RA is reasonably supported for patients due to receive HEC and in breast cancer patients due to receive AC.	No new data or analyses.

	NEPA March 2015	Current re-submission
Key safety data	**HEC: direct evidence** **Breast cancer – AC: indirect evidence** No statistically significant differences in treatment related AE, SAE and adverse events leading to discontinuation. **PBAC Comment:** considered that the claim of non-inferior comparative safety was reasonable.	No new data or analyses.
Clinical claim	NEPA was therapeutically equivalent to aprepitant in combination with a 5-HT_3 RA. **PBAC Comment:** Claims accepted for patients due to receive HEC and patients with breast cancer due to receive AC.	No change of clinical claim.
Economic evaluation	Cost-minimisation, with the equi-effective doses calculated during the submission. **PBAC Comment:** The economic evaluation presented was not a cost-minimisation analysis but rather a cost comparison. The PBAC noted the equi-effective doses as proposed in the evaluation. The PBAC considered in the absence of the single components of the FDC being available on the PBS, the pricing of the FDC would be difficult to establish. The clinical evidence was not sufficiently robust to be used as the basis for a cost-minimisation analysis, particularly for the patients due to receive moderately emetogenic chemotherapy.	No change in economic evaluation.
Number of patients	A total of less than 10,000 prescriptions in Year 1, increasing to 50,000 to 100,000 prescriptions in Year 5.	A total of less than 10,000 prescriptions in Year 1 increasing to 10,000 to 50,000 prescriptions in Year 5. Reduction due to removal of request for listing in patients with MEC with CINV
Estimated cost to PBS	A net save of less than $10 million in Year 1 increasing to less than $10 million in Year 5, for a total net save of less than $10 million over the first 5 years of listing. **PBAC Comment:** Agreed with ESC that there was a risk of leakage into populations where combination therapy may not be required, and therefore any savings calculated by the submission may not be realised.	A net save of less than $10 million in Year 1 increasing to less than $10 million in Year 5, for a total of less than $10 million over the first 5 years of listing.
PBAC decision	• Reject Paragraph 7.1 of the March 2015 PSD. In making its recommendation, the PBAC considered there was no unmet clinical need for this population of patients and the clinical place for FDC was not established in the submission.	

Source: Compiled for the Minor Overview

AC = anthracycline plus cyclophosphamide; AE = adverse event; CI = confidence interval; CINV = chemotherapy-induced nausea and vomiting; DPMQ = dispensed price for maximum quantity; ESC = Economic Sub-Committee; FDC = fixed dose combination; HEC = highly emetogenic chemotherapy; hr = hour; MEC = moderately emetogenic chemotherapy; NEPA = netupitant/palonosetron; PBAC = Pharmaceutical Benefits Advisory Committee; PBS = Pharmaceutical Benefits Schedule; RD = risk difference; RR = relative risk; SAE = serious adverse event; 5-HT_3 RA = serotonin receptor antagonist

4 Clinical place for the proposed therapy

4.1 The re-submission stated that one of the major international guidelines for antiemetic treatments, the National Comprehensive Cancer Network (NCCN) guidelines (2015), was recently updated to specifically include NEPA given with dexamethasone for the prevention of chemotherapy-induced nausea and vomiting following highly emetogenic chemotherapy. These guidelines recommend a triple-drug regimen starting on day one including a neurokinin-1 receptor antagonist (e.g. aprepitant or netupitant), a 5-HT_3 RA and a corticosteroid (dexamethasone) for the prevention of chemotherapy-induced nausea and vomiting in patients scheduled to receive highly emetogenic chemotherapy. Within these guidelines anthracycline plus cyclophosphamide based regimens have been reclassified as highly emetogenic chemotherapy.

4.2 The re-submission suggested the availability of a fixed dose combination (FDC) regimen on the PBS will improve adherence to treatment guidelines at time of HEC administration, improve patient compliance in the home, and impact on resource use.

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

5 Comparator

5.1 The PBAC considered that aprepitant plus a 5-HT_3 RA was the appropriate comparator for patients scheduled to receive highly emetogenic chemotherapy and patients with breast cancer who were scheduled to receive anthracycline plus cyclophosphamide based regimens.

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 and welcomed the input from health care professionals (8) via the Consumer Comments facility on the PBS website. The comments described some of the perceived benefits of netupitant and palonosetron, including its potential compliance advantage over injectable treatment options.

Clinical trials

6.3 No new clinical data was presented in the re-submission for NEPA.

Comparative effectiveness and harms

6.4 In March 2015, the PBAC considered that despite the wide confidence intervals, the clinical claim that NEPA was non-inferior to aprepitant plus a 5-HT_3 RA was reasonably well supported for patients scheduled to receive highly emetogenic

chemotherapy and in patients with breast cancer scheduled to receive anthracycline plus cyclophosphamide based regimens (paragraph 7.6 of the March 2015 minutes).

6.5 In March 2015, the PBAC considered that the claim of non-inferior comparative safety was reasonable (paragraph 6.18 of the March 2015 minutes).

Economic analysis

6.6 The major submission for NEPA considered by the PBAC in March 2015, presented a cost-minimisation analysis against aprepitant plus a 5-HT_3 RA. The PBAC considered the economic evaluation presented to be a cost comparison, rather than a cost-minimisation analysis (paragraph 7.7 of the March 2015 PSD).

6.7 The PBAC was concerned that the fixed dose combination guidelines were not addressed in the major submission for NEPA. The PBAC guidelines for listing fixed dose combination products express a preference for components to be individually listed on the PBS, as well as avoiding unnecessary proliferation of products or dose forms (paragraph 7.4 of the March 2015 PSD). The re-submission acknowledged this remained unresolved due to the fact that neither of the component products are registered with the TGA or listed on the PBS. The re-submission for NEPA reiterated that this was not a mandatory requirement and provided evidence of examples where fixed dose products were listed on the PBS, despite one or more of the components not being listed individually on the PBS.

6.8 In March 2015, the PBAC considered that the pricing of NEPA would be difficult to quantify in the absence of the single components of NEPA being listed on the PBS. The PBAC also stated that the clinical evidence was not sufficiently robust to be used as the basis for a cost-minimisation analysis, particularly for patients scheduled to receive moderately emetogenic chemotherapy (paragraph 7.8 of the March 2015 PSD). The re-submission stated that NEPA was priced on the basis of equivalence with aprepitant, with no cost assigned to the 5-HT_3 RA. As the individual components were not listed on the PBS the pricing of NEPA was argued to be similar to the pricing for a new chemical entity on the F1 formulary, rather than as a composite price of its components. The re-submission considered the cost-minimisation technique was valid with the removal of the requested listing of patients scheduled to receive moderately emetogenic chemotherapy with a prior chemotherapy-induced nausea and vomiting event.

Estimated PBS usage & financial implications

6.9 The minor re-submission for NEPA updated the financial estimates from the major submission for NEPA, to reflect the new restriction where NEPA is for patients scheduled to receive highly emetogenic chemotherapy and for patients with breast cancer scheduled to receive anthracycline plus cyclophosphamide based regimens (see Table 2).

Table 2: Estimated financial impact to the PBS for listing NEPA

	Year 1 2016	Year 2 2017	Year 3 2018	Year 4 2019	Year 5 2020
Estimated extent of use					
Number NEPA scripts	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number NEPA scripts – March 2015	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Uptake rate	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Uptake rate – March 2015	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Net change in scripts	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net change in scripts– March 2015	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated net cost to PBS					
Net cost to PBS	**–$[redacted]**	**–$[redacted]**	**–$[redacted]**	**–$[redacted]**	**–$[redacted]**
Net cost to PBS – March 2015	–$[redacted]	–$[redacted]	–$[redacted]	–$[redacted]	–$[redacted]

Source: Compiled during the evaluation

NEPA = netupitant/palonosetron; PBS = Pharmaceutical Benefits Schedule

6.10 As presented in the redacted table above, the minor re-submission for NEPA estimated that there would be 10,000 to 50,000 prescriptions in Year 5, totalling 100,000 to 200,000 prescriptions of NEPA over the first five years of listing. The previous submission estimated 50,000 to 100,000 prescriptions in Year 5, totalling 100,000 to 200,000 prescriptions over the first five years of listing. The difference was due to the exclusion of patients on moderately emetogenic chemotherapy.

6.11 Also as precented in the redacted table above, the minor re-submission for NEPA estimated that the total net save to the PBS would be less than $10 million in Year 5 of listing, with a total net save to the PBS of less than $10 million over the first five years, compared to less than $10 million in Year 5 of listing, with a total net save to the PBS of less than $10 million over the first five years of listing estimated in the previous submission.

6.12 At the March 2015 meeting, the PBAC noted the Pre-PBAC response with regard to potential leakage, given the proposed TGA indication was broader than the proposed PBS restriction. The sponsor had suggested that the leakage with NEPA was unlikely to be significantly greater than it is with aprepitant and therefore the market share approach for the financial estimates would capture potential leakage. The PBAC agreed with the ESC that there was a risk of leakage into populations where combination therapy may not be required, and therefore any savings calculated by the submission may not be realised (paragraph 7.9 of the March 2015 PSD).

6.13 The current re-submission suggested limiting the indication to patients receiving HEC and patients with breast cancer receiving AC chemotherapy would limit the risk of leakage into populations where combination therapy is not recommended in any guidelines.

Quality Use of Medicines

6.14 The re-submission considered the fixed dose combination would improve adherence to treatment guidelines. The re-submission suggested the lack of adherence to antiemetic clinical guidelines was a result of the complexity of administrating multiple drugs in a short time period at the time of the highly emetogenic chemotherapy infusion. Evidence to support this claim was anecdotal evidence from health practitioners.

6.15 The re-submission made a claim of improved compliance with NEPA for delayed chemotherapy-induced nausea and vomiting. This was based on a study by Chan *et al* (2012) that examined the association between non-compliance and delayed phase patients with breast cancer who received anthracycline plus cyclophosphamide based regimens.

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

7 PBAC Outcome

7.1 The PBAC decided not to recommend that netupitant with palonosetron (NEPA) fixed dose combination tablet be made available on the PBS for chemotherapy induced nausea and vomiting. In making its recommendation, the PBAC considered that there was still an uncertain clinical need for this population of patients, and that a number of concerns raised in its previous consideration in March 2015 had not been adequately addressed in the re-submission.

7.2 The PBAC noted the updated NCCN guidelines but considered the clinical need for the FDC in Australia was not established by the re-submission.

7.3 The PBAC remained concerned that the Fixed Dose Combination guidelines were not addressed in the submission. The guidelines express the preference for components to be individually listed on the PBS, as well as avoiding unnecessary proliferation of products or dose forms.

7.4 The PBAC did not accept the claims proposed by the submission that the availability of a FDC regimen on the PBS will improve adherence and patient compliance. The PBAC did acknowledge however, that the simplified dosing may be useful for some patients.

7.5 The PBAC noted that the updated proposed restriction for NEPA, which removed the indication for the population of patients scheduled to receive moderately emetogenic chemotherapy, was consistent with the PBAC's recommendation from March 2015. The PBAC considered however, that despite the restriction, leakage was likely to occur into the population of patients scheduled to receive moderately emetogenic chemotherapy and also to patients who would usually only receive the 5-HT_3 RA component because of the dose form being one tablet.

7.6 The PBAC had previously accepted aprepitant with a 5-HT_3 RA as the appropriate comparator.

7.7 The PBAC considered that the clinical claim that NEPA is non-inferior to aprepitant with a 5-HT_3 RA is reasonable. The PBAC had previously considered that the clinical claim had been poorly supported in patients due to receive moderately emetogenic chemotherapy and noted that the previously requested indication for this population had appropriately been removed in the re-submission.

7.8 The PBAC noted that the economic evaluation remained the same as that from March 2015, which was a cost comparison rather than a cost-minimisation. As

previously noted in March 2015, the PBAC considered in the absence of the single components of the FDC being available on the PBS, the pricing of the FDC would be difficult to establish.

7.9 The PBAC noted that the financial estimates had been updated from the previous submission to reflect the removal of the indication associated with moderately emetogenic cancer chemotherapy. The PBAC considered that there was still risk of leakage into populations where combination therapy may not be required.

7.10 Considering the uncertain clinical need for NEPA FDC, and potential for leakage, especially to patients who would usually only require the 5-HT_3 RA component and in the absence of a robust risk sharing arrangement to address this financial risk, the PBAC considered that a pragmatic approach forward would be to price NEPA FDC similar to that of a 5-HT_3 RA.

7.11 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:
Rejected

8 Context for Decision

8.1 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.

9 Sponsor's Comment

The sponsor had no comment.