

**5.16 NETUPITANT/PALONOSETRON**

**netupitant 300 mg + palonosetron 500 mcg capsule, 1; Akynzeo®; Specialised Therapeutics**

**1 Purpose of Application**

- 1.1 The submission requested Authority Required (STREAMLINED) listing for netupitant/palonosetron (NEPA) fixed dose combination for the prevention of acute and delayed chemotherapy induced nausea and vomiting (1-5 days after initiating chemotherapy) associated with patients scheduled to receive:
- Highly emetogenic chemotherapy
  - Anthracycline plus cyclophosphamide chemotherapy for patients with breast cancer, or
  - Moderately emetogenic chemotherapy with a prior episode of chemotherapy induced nausea and vomiting.

**2 Requested listing**

- 2.1 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
NETUPITANT WITH PALONOSETRON Netupitant 300mg + palonosetron 500 microgram capsule, 1	1	5	\$ [REDACTED]	Akynzeo® Specialised Therapeutics

<b>Category / Program</b>	Section 100 – Chemotherapy related benefits GENERAL – General Schedule
<b>Prescriber type:</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Condition:</b>	Nausea and vomiting
<b>PBS Indication:</b>	Nausea and vomiting
<b>Restriction Level / Method:</b>	<input checked="" type="checkbox"/> Streamlined
<b>Clinical criteria:</b>	The condition must be associated with cytotoxic chemotherapy being used to treat malignancy;  AND  The treatment must be in combination with dexamethasone;  AND

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

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

<b>Category / Program</b>	Section 100 – Chemotherapy related benefits GENERAL – General Schedule
<b>Prescriber type:</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives

Condition:	Nausea and vomiting
PBS Indication:	Nausea and vomiting
Restriction Level / Method:	<input checked="" type="checkbox"/> Streamlined
Clinical criteria:	<p>The condition must be associated with moderately emetogenic cytotoxic chemotherapy being used to treat malignancy;</p> <p><b>AND</b></p> <p>The treatment must be in combination with dexamethasone on day 1 of a chemotherapy cycle;</p> <p><b>AND</b></p> <p>Patient must have had a prior episode of chemotherapy induced nausea or vomiting;</p> <p><b>AND</b></p> <p>Patient must be scheduled to be administered a chemotherapy regimen that includes any 1 of the following intravenous chemotherapy agents: arsenic trioxide; azacitidine; carboplatin; 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; oxaliplatin; raltitrexed.</p>
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	<p><i>No increase in the maximum quantity or number of units may be authorised.</i></p> <p><i>No Increase in the maximum number of repeats may be authorised.</i></p> <p><i>This medicine is not PBS-subsidised for nausea and vomiting associated with radiotherapy being used to treat malignancy.</i></p>

- 2.2 The 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<sub>3</sub> RA).
- 2.3 The ESC noted that the proposed restrictions mirrored the existing restrictions for aprepitant. This was confirmed in the Pre-Sub-Committee Response (PSCR, p2).
- 2.4 The submission presented a cost minimisation analysis based on clinical evidence presented in Section B. The submission concluded that NEPA was therapeutically equivalent to aprepitant in combination with a 5-HT<sub>3</sub> RA.

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

### **3 Background**

- 3.1 **TGA status:** The TGA Delegate's Overview was received after the ESC consideration. The draft TGA indication was:  
NEPA is indicated in adults for prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly or moderately emetogenic cancer chemotherapy.
- 3.2 The Delegate was unable to make a recommendation as to whether NEPA should be approved for registration.
- 3.3 NEPA has not been considered by PBAC previously. At the time of the evaluation, the individual component netupitant was not TGA registered nor PBS listed, and palonosetron was only listed in intravenous form. The submission stated and the PSCR (p1) confirmed that the sponsor did not intend to request registration of the individual NEPA components as netupitant was developed as an oral fixed dosage form in combination with palonosetron and has not been developed as a single agent.

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

### **4 Clinical place for the proposed therapy**

- 4.1 The submission proposed NEPA for the prevention and control of chemotherapy-induced nausea and vomiting. The submission did not provide a diagram outlining the proposed clinical treatment algorithm for the use of NEPA, and only described the treatment algorithm for patients treated with highly emetogenic chemotherapy. The table below, constructed during the evaluation, describes the current and proposed treatments for the prevention of chemotherapy-induced nausea and vomiting associated with emetogenic chemotherapy.

Current treatment and proposed treatment of the prevention of chemotherapy-induced nausea and vomiting associated with emetogenic chemotherapy

Patient group	Current guidelines	Proposed
Highly emetogenic chemotherapy – all	Aprepitant + 5-HT <sub>3</sub> RA <sup>a</sup> + Dex	OR NEPA + Dex
Combined AC regimens – breast cancer	Aprepitant + 5-HT <sub>3</sub> RA <sup>a</sup> + Dex	OR NEPA + Dex
Moderate emetogenic chemotherapy		
No previous chem-ind nausea and vomiting	5-HT <sub>3</sub> RA <sup>b</sup> + Dex	Not requested
Previous chem-ind nausea and vomiting	5-HT <sub>3</sub> RA <sup>b</sup> + Dex OR aprepitant + 5-HT <sub>3</sub> RA <sup>b</sup> + Dex	OR NEPA + Dex

Source: Constructed for ESC, using Figures 3-4, p14 of the submission

5-HT<sub>3</sub> RA = serotonin receptor antagonist; AC = anthracycline plus cyclophosphamide regimens; chem-ind = chemotherapy induced; Dex = dexamethasone; HEC = highly emetogenic chemotherapy; MEC = moderately emetogenic chemotherapy; NEPA = netupitant/palonosetron fixed dose combination.

<sup>a</sup> palonosetron is preferred 5-HT<sub>3</sub> RA (NCCN guidelines, evidence 2B); <sup>b</sup> palonosetron is preferred 5-HT<sub>3</sub> RA (ASCO guidelines 2011)

- 4.2 Current clinical guidelines from the American Society of Clinical Oncology (ASCO, 2011) recommend aprepitant plus a 5-HT<sub>3</sub> RA for patients treated with highly emetogenic chemotherapy and a 5-HT<sub>3</sub> RA for patients treated with moderately emetogenic chemotherapy. The submission considered anthracycline plus cyclophosphamide based regimens to be moderately emetogenic, however, the consensus guidelines from ASCO classified combined anthracycline and cyclophosphamide regimens as highly emetogenic chemotherapy.
- 4.3 The submission classified patients scheduled to receive moderately emetogenic chemotherapy with a prior episode of chemotherapy induced nausea and/or vomiting as “refractory”, which implies failure of, or lack of response to, other agents that have been used for chemotherapy-induced nausea and vomiting. Although the requested listing replicates the current PBS listings for aprepitant, there remains a lack of clarity around the definition of refractory chemotherapy induced nausea and vomiting for patients receiving moderately emetogenic chemotherapy. The ESC therefore considered that the clinical place of NEPA is unclear.

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

## 5 Comparator

- 5.1 Aprepitant plus a 5-HT<sub>3</sub> RA. The ESC considered this was the appropriate comparator for patients who received highly emetogenic chemotherapy and patients with breast cancer who received anthracycline plus cyclophosphamide treatment regimens.
- 5.2 The ESC considered the appropriate comparator for patients who received moderately emetogenic chemotherapy with prior chemotherapy induced nausea and or vomiting could be aprepitant plus a 5HT<sub>3</sub>-RA or 5-HT<sub>3</sub> RA monotherapy. The PBAC did not agree that this was the only appropriate comparator and instead considered that aprepitant with dexamethasone may also be an appropriate comparator in this population.

*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 The submission was based on two head-to-head trials in chemotherapy naïve populations:

- NETU-07-07 compared oral netupitant (3 different doses) plus oral palonosetron, provided as two capsules, to aprepitant plus a 5-HT<sub>3</sub> RA (IV ondansetron) for patients who received highly emetogenic cisplatin-based chemotherapy; and
- NETU-10-29 compared fixed dose NEPA to aprepitant plus a 5-HT<sub>3</sub> RA (oral palonosetron) for patients who received highly or moderately emetogenic chemotherapy.

6.4 The submission included an indirect comparison for breast cancer patients who received anthracycline plus cyclophosphamide treatment regimens. The NEPA trial (NETU-08-18) included patients with solid malignant tumours (>97% breast cancer), while the aprepitant plus 5HT<sub>3</sub>-RA trial (Trial 071) included only patients with breast cancer.

6.5 Details of the trials presented in the submission are provided in the table below.

**Trials and associated reports presented in the submission**

Trial ID	Protocol title/ Publication title	Publication citation
<b>Direct randomised trials</b>		
NETU-07-07	<p>Helsinn Healthcare SA. A Randomized, Double-Blind, Parallel Group, Dose-Ranging, Multicenter Study Assessing the Effect of Different Doses of Netupitant or Placebo Administered with Palonosetron and Dexamethasone on the Prevention of Highly Emetic Chemotherapy-Induced Nausea and vomiting in Cancer Patients.</p> <p>Hesketh PJ, Rossi G, Rizzi G, et al. Efficacy and safety of NEPA, an oral combination of netupitant and palonosetron, for prevention of chemotherapy-induced nausea and vomiting following highly emetic chemotherapy: a randomized dose-ranging pivotal study.</p>	<p>Clinical Study Report. 16 February 2010</p> <p>Ann Oncol 2014; 25(7):1340-1346.</p>
NETU-10-29	<p>Helsinn Healthcare SA. A phase III, multicentre, randomized, double-blind, unbalanced (3:1) active control study to assess the safety and describe the efficacy of netupitant and palonosetron for the prevention of chemotherapy-induced nausea and vomiting in repeated chemotherapy cycles.</p> <p>Gralla RJ, Bosnjak SM, Hontsa A, et al. A phase III study evaluating the safety and efficacy of NEPA, a fixed-dose combination of netupitant and palonosetron, for prevention of chemotherapy-induced nausea and vomiting over repeated cycles of chemotherapy.</p>	<p>Clinical Study Report. 5 June 2013</p> <p>Ann Oncol 2014; 25(7):1333-1339.</p>
<b>Trials included for the indirect comparison</b>		
NETU-08-18	<p>Helsinn Healthcare SA. A phase III multicentre, randomized, double-blind, double-dummy, active-controlled, parallel group study of the efficacy and safety of oral netupitant administered in combination with palonosetron and dexamethasone compared to oral palonosetron and dexamethasone for the prevention of nausea and vomiting in cancer patients receiving moderately emetic chemotherapy.</p> <p>Aapro M, Rugo H, Rossi G, et al. A randomized phase III study evaluating the efficacy and safety of NEPA, a fixed-dose combination of netupitant and palonosetron, for prevention of chemotherapy-induced nausea and vomiting following moderately emetic chemotherapy.</p>	<p>Clinical Study Report. 12 June 2013</p> <p>Ann Oncol 2014; 25(7):1328-1333.</p>
071	<p>Warr DG, Hesketh PJ, Gralla RJ, et al. Efficacy and tolerability of aprepitant for the prevention of chemotherapy-induced nausea and vomiting in patients with breast cancer after moderately emetic chemotherapy.[Erratum appears in Journal Clinical Oncology. 2005 Aug 20;23(24):5851 Note: Dosage error in published abstract; MEDLINE/PubMed abstract corrected].</p>	<p>J Clin Oncol 2005; 23(12):2822-2830.</p>
Yeo (2009)	<p>Yeo W, Mo FK, Suen JJ, et al. A randomized study of aprepitant, ondansetron and dexamethasone for chemotherapy-induced nausea and vomiting in Chinese breast cancer patients receiving moderately emetic chemotherapy.</p>	<p>Breast Cancer Res Treat 2009; 113(3):529-535.</p>

Source: Table 7, pp30-33 of the submission

NEPA = netupitant/palonosetron

- 6.6 In the commentary, data from Yeo (2009) were not presented, because most of the patients in Yeo (2009) were also included in Trial 071. The ESC considered this was appropriate.
- 6.7 The key features of the direct randomised trials are summarised in the table below.

Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Key outcomes
<b>NEPA vs. aprepitant plus 5-HT<sub>3</sub> RA</b>					
NETU-07-07	270 <sup>a</sup>	R, MC, DB 22 days	Low	HEC	CR,CP,TC,NSN,NN,NRM,NE
NETU-10-29	412	R, MC, DB 2-5 weeks	Low	HEC (n=100) and MEC (n=312)	CR, NSN, NRM
<b>NEPA vs. 5-HT<sub>3</sub> RA</b>					
NETU-08-18	1,455	R, DB Max. 37 days	Low	AC	CR,CP,TC, NSN, NN, NRM,NE
<b>Aprepitant plus 5-HT<sub>3</sub> RA vs. 5-HT<sub>3</sub> RA</b>					
071	866	R, DB 5 days	Low	AC	CR, NSN, NRM, NE

Source: compiled during the evaluation

5-HT<sub>3</sub> RA = serotonin receptor antagonist; AC = anthracycline plus cyclophosphamide based regimens; CR = complete response; CP = complete protection; DB = double blind; HEC = highly emetogenic chemotherapy; MEC = moderately emetogenic chemotherapy; MC = multi-centre; NE = no emesis; NEPA = netupitant/palonosetron; NN = no nausea; NSN = no significant nausea; NRM = no rescue medication; R = randomised; TC = total control

<sup>a</sup> only included patients for 300 mg NEPA dose and appropriate comparator arms

- 6.8 Patient characteristics were largely comparable in all trials. The table below presents the dosing regimen in the four included trials.

Dosing regimens in the included clinical trials

Trial	NEPA	5HT <sub>3</sub> RA	Apre + 5HT <sub>3</sub> RA
NETU-07-07	NE 300 mg oral + PA oral 0.5 mg + Dexam <sup>a</sup>	PA oral 0.5 mg + Dexam <sup>b</sup>	Apre 3-day dosing <sup>c</sup> + Ond i.v. 32 mg + Dexam <sup>a</sup>
NETU-10-29	NEPA 300 mg/0.5 mg oral + Dexam <sup>d</sup>	-	Apre 3-day dosing <sup>c</sup> + PA 0.5 mg oral + Dexam <sup>d</sup>
NETU-08-18	NEPA 300 mg/0.5 mg oral + Dexam 12 mg <sup>e</sup>	PA 0.5 mg oral + Dexam 20 mg <sup>e</sup>	-
Trial 071	-	Day 1-3: Ond 8 mg BiD oral + Dexam 20 mg <sup>e</sup>	Apre 3-day dosing <sup>c</sup> + Day 1: Ond 8 mg BiD oral + Dexam 12 mg <sup>e</sup>

Source: Table 26, p68-69 of the submission

5-HT<sub>3</sub> RA = serotonin receptor antagonist; Apre = aprepitant; BiD = twice daily; Dexam = dexamethasone; i.v. = intravenous; NE = netupitant; NEPA = netupitant/palonosetron; Ond = ondansetron; PA = palonosetron

<sup>a</sup> Dexamethasone schedule: day 1: 12 mg; day 2-4: 8 mg once daily

<sup>b</sup> Dexamethasone schedule: day 1: 20 mg; day 2-4: 8 mg twice daily

<sup>c</sup> Apre 3-day dosing schedule was 125 mg oral aprepitant on day 1 and 80 mg oral aprepitant on days 2 and 3

<sup>d</sup> Dexamethasone schedule: Day 1: 12 mg; Day 2-4: 8 mg daily (only for those patients on highly emetic chemotherapy).

<sup>e</sup> Dexamethasone provided on day 1 only

- 6.9 Ondansetron was administered in trial NETU-07-07 at a higher dose (32 mg intravenously) than recommended in Australian practice (8 mg – 16 mg) limiting the generalisability of the outcomes of study NETU-07-07 to the Australian setting. For the indirect comparison the common comparator (5-HT<sub>3</sub> RA) was different, i.e. palonosetron (oral, 0.5mg daily) in NETU-08-18 and ondansetron (oral, 8mg BD) in Trial 071. Whether palonosetron (oral 0.5mg) and ondansetron (oral 8mg BD) are equivalent has not been addressed in the submission.

- 6.10 The comparison between NEPA vs. aprepitant plus a 5-HT<sub>3</sub> RA was an exploratory analysis in the two direct trials, as the main analysis in NETU-07-07 was between NE+PA vs. oral palonosetron monotherapy while NETU-10-29 was a safety study of NEPA in initial and repeated cycles with efficacy as a secondary outcome. In this latter trial, the aprepitant plus 5-HT<sub>3</sub> RA group was included to help interpret

unexpected safety findings in the experimental arm. The ESC noted that prior use of NK1 inhibitors (i.e. aprepitant) varied across the clinical trial populations.

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

### Comparative effectiveness

- 6.11 The submission reported ‘complete response’, defined as no emesis (acute, delayed or overall) and ‘no use of rescue medication’, as the main primary outcomes.

Results for complete response across the direct randomised trials <sup>a</sup>

Trial ID	NEPA <sup>a</sup> n/N (%)	PA n/N (%)	Apré + 5-HT <sub>3</sub> RA n/N (%)	RD (95% CI) vs. PA	RD (95% CI) vs. Apré + 5-HT <sub>3</sub> RA
<b>Highly emetogenic chemotherapy</b>					
<b>Acute (0-24 hr.)</b>					
NETU-07-07	133/135 (98.5%)	122/136 (89.7%)	127/134 (94.8%)	<b>0.09 (0.03, 0.14)</b>	0.04 (-0.01, 0.08)
NETU-10-29	68/74 (91.9%)	-	25/26 (96.2%)	N/A	-0.04 (-0.14, 0.05)
Meta-analysis, I <sup>2</sup> = 55.0%					0.01 (-0.07, 0.09)
<b>Delayed (25-120 hr.)</b>					
NETU-07-07	122/135 (90.4%)	109/136 (80.1%)	119/134 (88.8%)	<b>0.10 (0.02, 0.19)</b>	0.02 (-0.01, 0.08)
NETU-10-29	65/74 (87.8%)	-	15/26 (57.7%)	N/A	<b>0.30 (0.13, 0.52)</b>
Meta-analysis, I <sup>2</sup> = 79.9%					0.12 (-0.13, 0.36)
<b>Overall (0-120 hr.)</b>					
NETU-07-07	121/135 (89.6%)	104/136 (76.5%)	116/134 (86.6%)	<b>0.13 (0.04, 0.22)</b>	0.03 (-0.05, 0.11)
NETU-10-29	62/74 (83.8%)	-	15/26 (57.7%)	N/A	<b>0.26 (0.05, 0.47)</b>
Meta-analysis I <sup>2</sup> = 63.5%					0.10 (-0.08, 0.28)
<b>Moderately emetogenic chemotherapy: NETU-10-29</b>					
Acute (0-24 hr.)	219/235 (93.2%)	-	72/77 (93.5%)	N/A	0.00 (-0.07, 0.06)
Delay (25-120 hr.)	192/235 (81.7%)	-	65/77 (84.4%)	N/A	-0.03 (-0.12, 0.07)
Overall (0-120 hr.)	187/235 (79.6%)	-	63/77 (81.8%)	N/A	-0.02 (-0.12, 0.08)

Source: Table 33, pp89-90 of the submission

5-HT<sub>3</sub> RA = serotonin receptor antagonist; Apré = aprepitant; CI = confidence interval; hr. = hour; n = number with event; N = number in group; NEPA = netupitant/palonosetron; N/A = not applicable; PA = palonosetron; RD = risk difference; Bold = significant result

<sup>a</sup> In both trials the results were presented for the full analysis set, rather than the ITT population.

<sup>b</sup> Results presented for 300 mg netupitant plus 0.5mg palonosetron

- 6.12 NEPA administered as individual components in treatment naïve patients due to receive highly emetogenic chemotherapy was associated with statistically significantly more patients reporting a complete response compared to palonosetron monotherapy. The submission claimed there was no significant difference between NEPA and aprepitant + 5HT<sub>3</sub> RA in complete response for both head to head randomised trials. The submission did not define a minimum clinically important difference and the trials were not designed as non-inferiority trials. No studies included patients with prior chemotherapy treatment. The ESC considered this problematic given the requested restriction required patients due to receive moderately emetogenic chemotherapy to have had a prior episode of CINV.

- 6.13 The ESC noted that the comparative effectiveness is difficult to interpret as the direct evidence in patients due to receive either highly emetogenic or moderately emetogenic chemotherapy are based on exploratory analyses.
- 6.14 Based on the results of the indirect comparison in patients with anthracycline plus cyclophosphamide based regimens, there were no statistically significant differences between NEPA and aprepitant plus 5-HT<sub>3</sub> RA, using 5-HT<sub>3</sub> RA as common comparator. The submission concluded that there is equivalent efficacy for NEPA and aprepitant plus 5-HT<sub>3</sub> RA in breast cancer patients treated with anthracycline plus cyclophosphamide based regimens. This might not be reasonable as:
- The 5-HT<sub>3</sub> RA arm in the two trials did not result in comparable complete response rate, which could be due to differences in treatment (5-HT<sub>3</sub> RA) or patient characteristics.
  - The confidence intervals around the risk difference for the indirect comparisons were wide, especially for complete response in the delayed phase (25-120 hour) which could indicate that NEPA may be five times better or worse than aprepitant plus ondansetron.
- 6.15 The ESC noted that comparative effectiveness is difficult to interpret in the indirect analysis as it relies on assumed equivalence across multiple comparisons, which have not been supported.

### Comparative harms

- 6.16 The submission compared adverse events recorded in first and multiple cycles of scheduled cytotoxic chemotherapy. No deaths were reported related to study drugs. The submission concluded that the type, frequency, and severity of treatment-emergent adverse events were comparable across treatment groups. Overall, the majority of adverse events were similar between NEPA and aprepitant plus 5-HT<sub>3</sub> RA and of mild to moderate intensity.

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

### Clinical claim

- 6.17 The overall claim of the submission was that NEPA was therapeutically equivalent to aprepitant in combination with a 5-HT<sub>3</sub> RA. However the following limitations were noted by ESC:

#### Highly emetogenic population

- In NETU-07-07, for the comparison arm, ondansetron (intravenous, 32 mg) was prescribed at a higher dose than recommended in Australian practice.
- The clinical trials were not designed as non-inferiority trials and the submission did not provide non-inferiority limits.

#### Anthracycline plus cyclophosphamide based regimens in patients with breast cancer

- This claim of equivalent efficacy and safety was based on an indirect comparison without the same common comparator (5-HT<sub>3</sub> RA) in both trials.
- The clinical evidence was based on exploratory post-hoc analysis.

**Moderately emetogenic chemotherapy**

With known previous event of chemotherapy induced nausea and vomiting

- No clinical evidence was provided for the efficacy and safety in patients on moderately emetogenic chemotherapy who had experienced a previous chemotherapy induced nausea and/or vomiting event.

- 6.18 The PBAC considered that the claim of non-inferior comparative effectiveness was reasonable for patients due to receive highly emetogenic chemotherapy and in breast cancer patients due to receive anthracycline with cyclophosphamide. However, the clinical claim is poorly supported for the patients due to receive moderately emetogenic chemotherapy.
- 6.19 The PBAC considered that the claim of non-inferior comparative safety was reasonable.

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

**Economic analysis**

- 6.20 The submission presented a cost-minimisation analysis of NEPA. The submission did not estimate the equi-effective doses, but these were proposed during the evaluation and presented in the table below. The PSCR (p2) agreed with the equi-effective doses presented below.

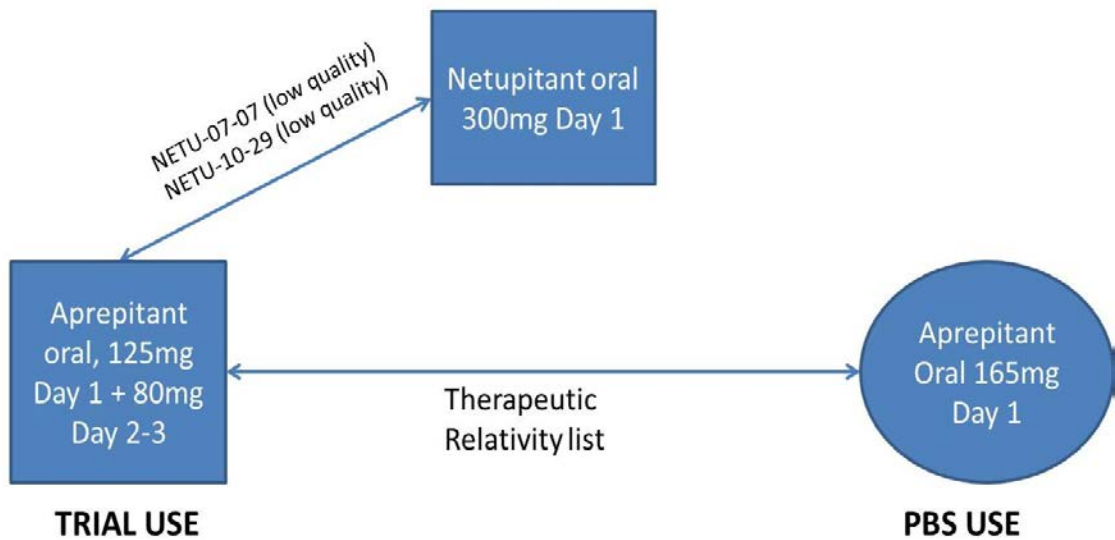
Equi-effective dosing for NEPA and aprepitant + 5-HT<sub>3</sub> RA

Medication	Dosing schedule		Source
	Substance P inhibitor	5-HT <sub>3</sub> RA	
NEPA, FDC	NE: Day 1: 300 mg oral	PA: 0.5 mg oral day 1	Clinical trials, proposed
<b>Comparator</b>			
Use in clinical trials	Apré: Day 1: 125 mg oral Day 2 and 3: 80 mg oral	Ond: 32 mg iv day 1; OR PA: 0.5 mg oral day 1; OR Ond: 16 mg oral day 1-3	NETU-07-07 NETU-10-29 Trial 071
PBS listed dosing	Apré: Day 1: 165 mg oral	PA 0.25 mg iv on day 1; OR Ond 8-32 mg iv on day 1	PBS Schedule

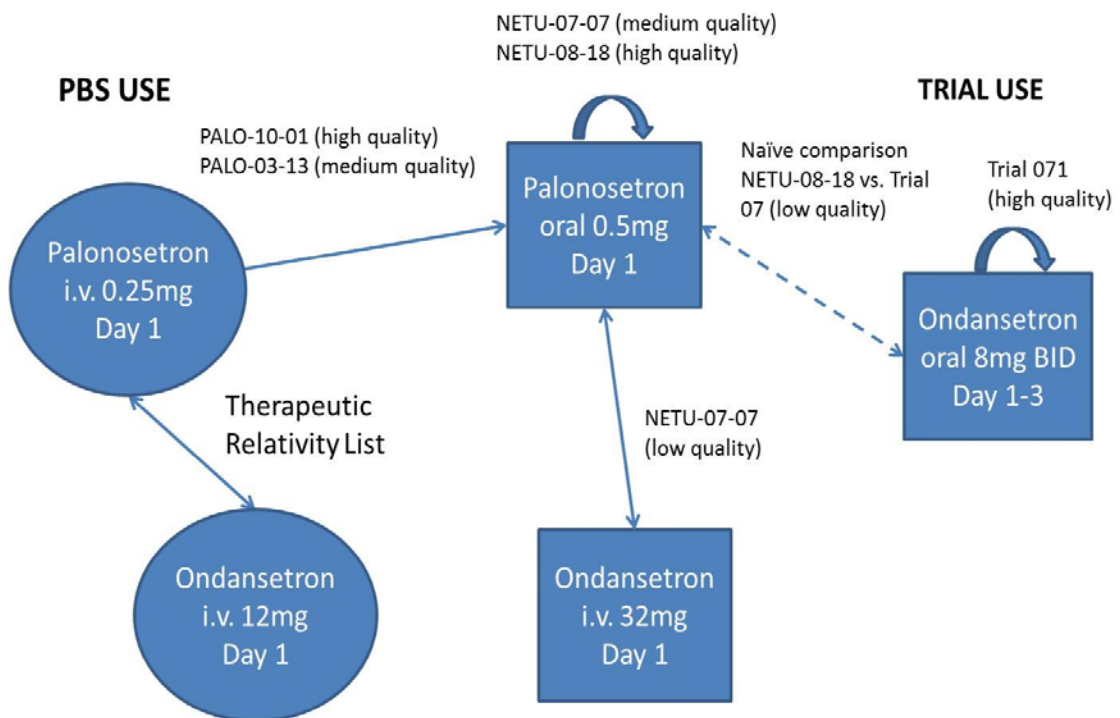
Source: Constructed during evaluation

5-HT<sub>3</sub> RA = serotonin receptor antagonist; Apré = aprepitant; iv = intravenous; FDC = fixed dose combination; mg = milligrams; NE = netupitant; NEPA = netupitant/palonosetron; Ond = ondansetron; PA = palonosetron; PBS = Pharmaceutical Benefits Scheme

- 6.21 The PBAC had previously considered the two dosing schedules of aprepitant (1 and 3 day dosing) to be non-inferior. According to the Therapeutic Relatively List, the equi-effective doses for the 5-HT<sub>3</sub> RAs are palonosetron 0.25 mg and ondansetron 12 mg (both intravenously). Further, the submission considered that the oral palonosetron dosing schedule was non-inferior to the intravenous dosing schedule. If the PBAC accepts the non-inferiority claim, the PBS listed dosing of aprepitant and 5-HT<sub>3</sub> RA (palonosetron or ondansetron) might be equi-effective to NEPA.
- 6.22 The figures below demonstrate the currently accepted dose relativities or available trial-based relativities for both NK1 antagonists (aprepitant and netupitant) and 5-HT<sub>3</sub> RAs (ondansetron and palonosetron).



Dose-relativities of aprepitant and netupitant



Dose-relativities of ondansetron and palonosetron

6.23 The cost-minimisation analysis is presented in the table below.

Economic evaluation provided by submission

Drug name	% Co- Prescribed with Apre <sup>a</sup>	General Schedule DPMQ		Section 100 (CT) DPMQ	
		NEPA	Apre + 5-HT <sub>3</sub> RA	NEPA	Apre + 5-HT <sub>3</sub> RA
NEPA	NA	\$ [REDACTED]	-	\$ [REDACTED]	-
Aprepitant	100%	-	\$138.13	-	\$111.08
Granisetron (3 mg/3mL injection)	10.3%	-	\$11.68	-	\$3.98
Ondansetron (4 and 8 mg tablet, 4)	12.2%	-	\$19.82	-	\$10.56
Palonosetron	44.2%	-	\$48.20	-	\$34.36
Tropisetron	5.9%	-	\$18.84	-	\$9.77
Total weighted cost	-	\$ [REDACTED]	\$164.19	\$ [REDACTED]	\$128.56
<b>Weighted cost, 67% general schedule, 33% Section 100 (CT)<sup>b</sup></b>					
NEPA	-	-	-	-	\$ [REDACTED]
Apre + 5-HT <sub>3</sub> RA	-	-	-	-	\$152.51
Apre + 5-HT <sub>3</sub> RA (80%) <sup>c</sup>					\$ [REDACTED]
5-HT <sub>3</sub> RA (20%)					\$126.66

Source: Table 89, pp179 of the submission, and calculated using Akynzeo\_PBAC\_SectionD.xlsx,

5-HT<sub>3</sub> RA = serotonin receptor antagonist; Apre = aprepitant; CT = Chemotherapy; DPMQ = dispensed price maximum quantity; NEPA = netupitant/palonosetron

<sup>a</sup> 2013 estimates from HI Connections 2014

<sup>b</sup> This estimate was derived from the weighted average of general schedule and section 100 for PBS data recorded between 2009-13

<sup>c</sup> Assuming that 80% of patients would receive aprepitant. The split for the 5-HT<sub>3</sub> RA was unchanged

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

**Drug cost/patient/cycle: \$ [REDACTED]**

6.24 The submission estimated that the proposed price would be \$ [REDACTED] per cycle compared to \$152.51 for aprepitant plus 5-HT<sub>3</sub> RA. The submission did not provide details of how the proposed price was derived.

6.25 The ESC noted that the weighted cost of 5HT<sub>3</sub> RA does not account for other dosage forms of ondansetron (intravenous or wafers), which appear to be used to the same, if not higher, extent than 5HT<sub>3</sub> RAs such as granisetron.

**Estimated PBS usage & financial implications**

6.26 This submission was not considered by DUSC. The submission used a market share approach to estimate the utilisation and cost of NEPA over a five year time horizon.

Estimated use and financial implications of listing NEPA

	Year 1 (2016)	Year 2 (2017)	Year 3 (2018)	Year 4 (2019)	Year 5 (2020)
<b>Estimated extent of use of NEPA</b>					
Number treated	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Market share	[REDACTED] %	[REDACTED] %	[REDACTED] %	[REDACTED] %	[REDACTED] %
Net change in Scripts	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
<b>Estimated total net cost</b>					
Net cost to PBS/RPBS/MBS	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]

Source: Table 96-98, pp188-189 of the submission

AC-MEC = anthracycline-based moderately emetogenic chemotherapy; HEC = highly emetogenic chemotherapy; MBS = Medicare Benefits Schedule; MEC = moderately emetogenic chemotherapy; NEPA = netupitant/palonosetron; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme

- 6.27 The redacted table above estimates that less than 10,000 patients will be treated in year one, increasing to 50,000 to 100,000 in year 5.
- 6.28 The submission estimated that listing NEPA on the PBS could result in a cost saving of up to less than \$10 million per year in the fifth year of listing. The accuracy of the financial estimates could not be established. The main assumptions that were poorly supported were:
- Whether the uptake of NEPA can be reliably based on the historical data for palonosetron market uptake, which may be a different patient population, i.e. this patient population also included patients on moderate emetogenic chemotherapy who may have not had a previous event. The PSCR (p2) considered that this provides the best estimate for the likely uptake of NEPA in the absence of other data;
  - The co-prescription analysis may have underestimated co-administration of aprepitant with 5-HT<sub>3</sub> RA, due to assumption that the dispensing needed to be on the same day. This would impact the estimated changes in use of other drugs; and
  - Potential patient leakage if the TGA approves a broader indication for NEPA than the proposed PBS restriction. Patients scheduled to receive moderately emetogenic chemotherapy should receive 5-HT<sub>3</sub> RA as first-line therapy, and only change treatment to include NEPA if they have an emetogenic event.
- 6.29 Depending on the proportion of current 5-HT<sub>3</sub> RA monotherapy scripts that could be replaced, the cost-savings may be less or there may be an additional cost, as 5-HT<sub>3</sub> RA monotherapy is less expensive than NEPA.

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

### **Quality use of medicines**

- 6.30 The ESC considered a relevant QUM concern to be the potential for co-administered 5-HT<sub>3</sub> RA with NEPA. This would be inappropriate and could be addressed through a note in the restriction.

## **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 no unmet clinical need for this population of patients and the clinical place for the FDC was not established in the submission.
- 7.2 The PBAC considered that the proposed restriction for NEPA that mirrors the restriction of aprepitant was not necessarily inappropriate. However, the PBAC 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.

- 7.3 The PBAC noted that the TGA Delegate was unable to make a recommendation as to whether NEPA should be approved for registration due to a lack of evidence for patients scheduled to receive moderately emetogenic chemotherapy and an unknown benefit/risk balance.
- 7.4 The PBAC was concerned that the Fixed Dose Combination guidelines were not addressed in the submission. The clinical need for a combination product was unclear. 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.
- 7.5 The PBAC considered that aprepitant with a 5-HT<sub>3</sub> RA is the appropriate comparator for patients due to receive highly emetogenic chemotherapy and patients with breast cancer who are due to receive anthracycline plus cyclophosphamide. However, the PBAC considered that the same comparator may not be appropriate in the population of patients scheduled to receive moderately emetogenic chemotherapy as it was considered that the majority of these patients may be effectively treated with aprepitant with dexamethasone.
- 7.6 The PBAC considered that despite the wide confidence intervals, the clinical claim that NEPA is non-inferior to aprepitant in combination with a 5-HT<sub>3</sub> receptor antagonist is reasonably well supported for patients due to receive highly emetogenic chemotherapy and in breast cancer patients due to receive anthracycline with cyclophosphamide. However, the clinical claim was poorly supported for the patients due to receive moderately emetogenic chemotherapy 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.
- 7.7 The PBAC noted that the economic evaluation presented is not a cost-minimisation analysis but rather a cost comparison.
- 7.8 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.
- 7.9 The PBAC noted the Pre-PBAC response with regard to the market share approach for the financial estimates but 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.
- 7.10 The PBAC noted that this submission is eligible for an Independent Review.

**Outcome:**  
Rejected

**8 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.

**9 Sponsor's Comment**

The Sponsor had no comment.