6.18 NETUPITANT WITH PALONOSETRON, Capsule containing netupitant 300 mg with palonosetron 500 microgram (as hydrochloride), Akynzeo®, Juniper Biologics Pty Ltd

1 Purpose of Submission

1.1 The Category 4 submission requested an amendment to the current clinical criteria of the fixed dose combination, netupitant with palonosetron (hereafter referred to as NEPA), to reference international and national guidelines such as the National Comprehensive Cancer Network (NCCN) or eviQ's database rather than naming specific chemotherapy drugs.

1.2 Table 1 below outlines the guidelines for NCCN and eviQ.

Table 4: eviQ and NCCN Guidelines: Recommendation for Guideline use

	Preferred Prophylaxis	Details	Dosing Administration
eviQ			
Multi-day Cancer Therapy	For patients receiving multi-day anti-cancer drugs, prophylaxis is more difficult; this may be due to anticipatory emesis on the subsequent treatment days and/or to the compounding of acute and delayed effects of treatment. It is recommended that antiemetics appropriate for the emetic risk of the anti-cancer drug be given on each day of the chemotherapy and for 2 days after completion of the anti-cancer regimen (Hesketh, Kris et al. 2020). Patients treated with a 5-day cisplatin protocol should be offered a three-drug combination of an NK1 RA, a 5HT3 RA and dexamethasone,1 with the scheduling of the NK1 RA and the 5HT3 RA dependent on half-life of the individual drugs. Dexamethasone should be administered once daily over the days of treatment (4 to 8 mg in the morning depending on individual prescriber preference) and continued for up to 2 days after chemotherapy.		
HEC with blood or marrow transplantation	The prevention of emesis associated with high doses of cytotoxic chemotherapy (+/- total body irradiation), and stem cell or bone marrow transplantation remains challenging, as current guidelines address primarily single-day therapies. In 2017, ASCO suggested a three-drug combination of an NK1 RA, a 5HT3 RA, and dexamethasone. However, the recent update now recommends that olanzapine be added (Hesketh, Kris et al. 2020).		
HEC and MEC	Follows both the NCCN and ASCO Guidelines.		
Oral anti-cancer drugs	As emetic risk information for oral anti-cancer drugs is limited and varies, eviQ has now aligned with both ASCO and NCCN to display two categories of emetogenicity for oral anti-cancer drugs: minimal to low and moderate to high. Changes across eviQ single oral anti-cancer drug protocols to be addressed.		
NCCN			
HEC	Treatment option A (preferred), use the following combination b	1. Olanzapine 5–10 mg oral (PO) once [a] 2. NK1 receptor antagonist (RA) (choose one): ◊ Aprepitant 125 mg PO once	• Olanzapine 5–10 mg PO daily on days 2, 3, 4 [a] • Aprepitant 80 mg PO daily on days 2, 3 (if

	Preferred Prophylaxis	Details	Dosing Administration
		◊ Aprepitant injectable emulsion 130 mg intravenous (IV) once [c] ◊ Fosaprepitant 150 mg IV once ◊ Netupitant 300 mg / palonosetron 0.5 mg (available as fixed combination product only) PO once. [d] ◊ Fosnetupitant 235 mg / palonosetron 0.25 mg (available as fixed combination product only) IV once[d] ◊ Rolapitant 180 mg PO once[o] 3. 5HT3 RA (choose one)[f,g]: ◊ Dolasetron 100 mg PO once ◊ Granisetron 10 mg subcutaneous (SQ) once,[h] or 2 mg PO once, or 0.01 mg/kg (max 1 mg) IV once, or 3.1 mg/24-h transdermal patch applied 24–48 h prior to first dose of anticancer therapy: ◊ Ondansetron 16–24 mg PO once, or 8–16 mg IV once, ◊ Palonosetron 0.25 mg IV once 4. Dexamethasone 12 mg PO/IV onces,[i,j]	aprepitant PO is used on day 1), • Dexamethasone 8 mgs,[j] PO/IV daily on days 2, 3, 4.
MEC	DAY 1: Select treatment option D, E, or F. All treatment options are category 1 and should be started before anticancer therapy.	Treatment option F, use the following combination: 1. NK1 RA (choose one): ◊ Aprepitant 125 mg PO once ◊ Aprepitant injectable emulsion 130 mg IV once[c] ◊ Fosaprepitant 150 mg IV once[d] ◊ Netupitant 300 mg/palonosetron 0.5 mg (available as fixed combination product only) PO once[d] ◊ Fosnetupitant 235 mg / palonosetron 0.25 mg (available as fixed combination product only) IV once[d] ◊ Rolapitant 180 mg PO once[e] 2. 5HT3 RA (choose one)[f,g]: ◊ Dolasetron 100 mg PO once ◊ Granisetron 10 mg SQ once,[h] or 2 mg PO once, or 0.01 mg/kg (max 1 mg) IV once, or 3.1 mg/24-h transdermal patch applied 24–48 h prior to first dose of anticancer therapy. ◊ Ondansetron 16–24 mg PO once, or 8–16 mg IV once ◊ Palonosetron 0.25 mg IV once 3. Dexamethasone 12 mg PO/IV once [i,j]	Treatment option F: • Aprepitant 80 mg PO daily on days 2, 3 (if aprepitant PO used on day 1) • ± Dexamethasone

a Data suggest that a 5-mg dose of olanzapine is efficacious. Consider this dose especially for elderly or over sedated patients. (Hashimoto, Abe et al. 2020, Mukhopadhyay, Dutta et al. 2021) See Pharmacologic Considerations for Antiemetic Prescribing (AE-B).

b If not used previously, consider escalating to a 4-drug regimen (option A) if emesis occurred during a previous cycle of anticancer therapy with a 3-drug regimen (olanzapine-containing regimen B or E or NK1 RA-containing regimen C or F). Olanzapine-containing regimens may be useful for patients with severe nausea. See Principles for Managing Breakthrough Emesis (AE-C).
c Aprepitant injectable emulsion is a unique formulation of aprepitant and is NOT interchangeable with the IV formulation of fosaprepitant.
d Available as a fixed combination product only.
e Rolapitant has an extended half-life and should not be administered at less than 2-week intervals.
f If netupitant/palonosetron or fosnetupitant/palonosetron fixed combination product is used, no further 5HT3 RA is required.
g When used in combination with an NK1 RA, there is no preferred 5HT3 RA. See Principles of Managing Multiday Emetogenic Chemotherapy Regimens (AE-A).
h Granisetron extended-release injection is a unique formulation of granisetron using a polymer-based drug delivery system. This formulation is specifically intended for subcutaneous administration and is NOT interchangeable with the intravenous formulation. Granisetron extended-release injection has an extended half-life and should not be administered at less than 1-week intervals.
i Emerging data and clinical practice suggest dexamethasone doses may be individualized. Higher doses may be considered, especially when an NK1 RA is not given concomitantly. Lower doses, given for shorter durations, or even elimination of dexamethasone on subsequent days (for delayed nausea and emesis prevention) may be acceptable based on patient characteristics. If dexamethasone is eliminated on subsequent days for delayed nausea and emesis prevention, consider other alternative antiemetics (e.g., olanzapine).
j Use of corticosteroid premedications should be avoided with cellular therapies. See Pharmacologic Considerations for Antiemetic Prescribing (AE-B).
Source: (NCCN 2014, Cancer Institute NSW 2021). Table provided in the submission.

2 Background

2.1 NEPA is currently on the PBS as an Authority Required (STREAMLINED) listing for prophylaxis of nausea and vomiting associated with the use of highly emetogenic chemotherapy (HEC) and moderately emetogenic chemotherapy (MEC).

2.2 The submission stated that, due to changes in clinical practice, the list of chemotherapy agents included in the NEPA clinical criteria is out of date: some of the named agents are no longer utilised, and some recently introduced agents are not included.

2.3 The submission stated that referring to widely-used guidelines rather than specific agents will reflect best clinical practice and avoid the need for future updates.

2.4 Table 2 outlines the updated NCCN guidelines in comparison to the current clinical criteria for NEPA on the PBS.

Table 2: Oral and IV anti-cancer agents identified as HEC or MEC in the NCCN Guidelines® and their alignment with the PBS clinical criteria for FDC NEPA

	IV chemotherapies		Oral chemotherapies	
			C Used in combination in a cycle	D Used continuously
	A HIGH (>90% frequency of emesis)	B MODERATE (>30% - 90% frequency of emesis)	MODERATE to HIGH (≥30% frequency of emesis)	
Category 1 TGA Approved.	azacitidine	cyclophosphamide<1500 mg/m^2	procarbazine	altretamine#
	carboplatin[a]		cyclophosphamide ≥100 mg/m^2/day*	

	IV chemotherapies		Oral chemotherapies	
			C **Used in combination in a cycle**	**D** **Used continuously**
	A **HIGH** **(>90% frequency of emesis)**	**B** **MODERATE** **(>30% - 90% frequency of emesis)**	**MODERATE to HIGH** **(≥30% frequency of emesis)**	
PBS Listed as HEC/ MEC. **In NCCN Guidelines®.**	carmustine >250 mg/m^2 [d]	cytarabine >1g mg/m^2[e]		
	cisplatin	dactinomycin		
	cyclophosphamide>1500 mg/m^2	doxorubicin <60 mg/m^2[b]		
	Cyclophosphamide with anthracycline	daunorubicin		
	dacarbazine	epirubicin ≤90 mg/m^2[c]		
	oxaliplatin	idarubicin		
	streptozocin	ifosfamide[i] <2 g/m^{2}per dose		
		irinotecan		
		melphalan <140 mg/m^2		
		methotrexate at a dose ≥ 250 mg [d]		
		raltitrexed		
Category 2 **TGA Approved.** **PBS Listed as HEC/ MEC.** **Not in NCCN Guidelines®.**		arsenic trioxide		
		fotemustine		
Category 3 Incremental Group of Interest. **TGA Approved.** **Not PBS Listed as HEC/ MEC.**	doxorubicin ≥60 mg/m^2 [b*]	bendamustine*	encorafenib*	binimetinib
	epirubicin >90 mg/m^2 [c*]	busulfan*	imatinib > 400 mg/m^2*	busulfan ≥4 mg/day
	ifosfamide ≥2 g/m^2 per dose*	carmustine ≤250 mg/m^2[d]*	lenvatinib*	dabrafenib
	melphalan > 140 mg/m^2 [j*]	cytarabine >200 mg/m^2[e]*	lomustine	cabozantinib
	sacituzumab govitecan-hziy*	clofarabine	midostaurin*	ceritinib
		dinutuximab**	mitotane	crizotinib

	IV chemotherapies		Oral chemotherapies	
			C Used in combination in a cycle	D Used continuously
	A HIGH (>90% frequency of emesis)	B MODERATE (>30% - 90% frequency of emesis)	MODERATE to HIGH (≥30% frequency of emesis)	
Included in NCCN Guidelines®.		fam-trastuzumab deruxtecan-nxki	temozolomide >75 mg/m^2/day*	enasidenib
		lurbinectedin		etoposide
		romidepsin		niraparib
		trabectedin		Selinexor
Category 4 **Not registered in Australia.** **Not PBS Listed as HEC/ MEC.** **Included in NCCN Guidelines®.**		aldesleukin	avapritinib	bosutinib
		amifostine		estramustine
		amivantamab-vmjw	fedratinib	mobocertinib
		dual-drug liposomal encapsulation of cytarabine and daunorubicin	lomustine	
		irinotecan liposomal injection	olaparib	
		naxitamab-gqgk	rucaparib	
		temozolomide		

[a] Carboplatin is PBS listed as MEC, while NCCN defined carboplatin as HEC when used at target dose of AUC ≥4 mg/mL/min.
[b] Doxorubicin is PBS listed without restriction as MEC, though if used at dose ≥60 mg/m^2, NCCN defines as HEC.
[c] Epirubicin is PBS listed without restriction as MEC, though if used at dose >90 mg/m^2, NCCN defines as HEC.
[d] Carmustine is mentioned in the HEC restriction but does not specify whether it is the implant or the iv form; only the implant is PBS listed; there is a differentiation in that the NCCN list Carmustine as MEC if used at dose ≤250 mg/m^2.
[e] Cytarabine is PBS listed as MEC at a dose > 1000 mg/m^2, while NCCN defined cytarabine as MEC when used at a dose > 200 mg/m^2.
[f] Daunorubicin is listed on the PBS as a MEC, while daunorubicin plus cytarabine liposome is not listed.
[g] Irinotecan is currently listed on the PBS as a MEC, while Irinotecan liposomal injection is not listed. Based on NCCN, ASCO and ESMO guidelines, it is assumed that irinotecan liposomal injection has moderate emetic risk, same as irinotecan.
[h] currently restricted to methotrexate at a dose of 250 mg to 1 g per square metre
[I] Ifosfamide is PBS listed without restriction as MEC, though if used at dose ≥2g/m^2, NCCN defines as HEC.
[j] melphalan is PBS listed without restriction as MEC, though if used at dose ≥ 140 mg/m^2 NCCN defines as HEC.
*PBS listed.
**Listed under National Health Reform Agreement Addendum.
No longer registered by the TGA.
Source: Australian PIs (Merck Sharp & Dohme 2012, Juniper Biologics 2022, Merck Sharp & Dohme 2022), eviQ (eviQ 2021) and as an example for orals used in a protocol in combination with other anti-cancer drugs within a cycle cyclophosphamide (eviQ 1654 2020), encorafenib (eviQ 4111 2022), imatinib (eviQ 1291 2020), lenvatinib (eviQ 4163 2022), lomustine (eviQ 2044 2021), midostaurin (eviQ 3509 2022). Table provided in the submission.

Registration status

2.5 NEPA was registered in the Australian Register of Therapeutic Goods (ARTG) on 6 May 2015 for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of HEC and MEC.

Previous PBAC consideration

2.6 The PBAC considered submissions for NEPA at its March 2015 and July 2015 meetings. On both occasions, the submission was rejected due to uncertainties regarding the clinical need and clinical place for NEPA (paragraph 7.1 of the March 2015 Public Summary Document (PSD); paragraph 7.1 and 7.3 of the July 2015 PSD).

2.7 At both the March and July 2015 PBAC meetings, the PBAC noted the changes in the guidelines for the management of emesis as well as the updated NCCN guidelines, respectively. The PBAC acknowledged that any restriction for antiemetic therapy based on the emesis risk of specific chemotherapy agents, such as that proposed for NEPA, may become outdated (paragraph 7.2 of the March and July 2015 PSD).

2.8 The PBAC recommended the listing NEPA at its November 2015 meeting as an Authority Required STREAMLINED benefit on the General Schedule and under the Section 100 program Efficient Funding of Chemotherapy – Related Benefits, for the prevention of nausea and vomiting associated with initial and repeat courses of HEC and anthracycline plus cyclophosphamide based regimens in patients with breast cancer (paragraph 7.1 of the November 2015 PSD).

2.9 At its November 2016 PBAC meeting, the PBAC recommended listing NEPA on the PBS for the secondary prophylaxis of chemotherapy induced nausea and vomiting associated with MEC and for primary prophylaxis of chemotherapy induced nausea and vomiting associated with carboplatin or oxaliplatin chemotherapy regimens (paragraph 7.1 of the November 2016 PSD).

For more detail on PBAC's view, see section 5 PBAC outcome.

3 Requested listing

3.1 The submission requested the following changes to the existing listing. Suggested additions are in *italics* and deletions are in strikethrough.

3.2 The PBAC noted that the requested amendment would also be relevant to the other chemotherapy-induced nausea and vomiting (CINV) prophylactic treatments listed on the PBS: fosaprepitant (Emend® IV) and aprepitant oral (Aprepitant SCP® and Aprepitant Apotex®).

3.3 The PBAC noted that, as an alternative to referring to NCCN or EviQ guidelines, the restrictions for NK1 inhibitors (single-agent and combination products with 5-HT3 antagonists, i.e., Akynzeo) could be aligned with the TGA indication: 'Prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly and moderately emetogenic cancer chemotherapy'. The PBAC noted that this would avoid linking to an overseas list (NCCN) or eviQ and would allow patients who receive non-PBS-subsidised MEC or HEC to access PBS-subsidised NEPA.

3.4 The PBAC noted that the Secretariat had received feedback that the NEPA restrictions are unaligned with current clinical practice with regard to multi-day chemotherapy

regimens and had suggested relevant changes to the Prescribing Instruction to manage this.

Committee-In-Confidence information

3.5 [redacted]

3.6 [redacted]

3.7 [redacted]

End Committee-In-Confidence information

Category / Program: Section 100 Chemotherapy Related Benefits (Code CT)						
MEDICINAL PRODUCT medicinal product pack		**PBS item code**	**Max. qty packs**	**Max. qty units**	**№.of Rpts**	**Available brands**
NETUPITANT + PALONOSETRON						
netupitant 300 mg + palonosetron 500 microgram capsule, 1		10714X MP	1	1	5	Akynzeo
	Administrative Advice: No increase in the maximum number of repeats may be authorised.					
	Administrative Advice: No increase in the maximum quantity or number of units may be authorised.					
	Administrative Advice: This medicine is not PBS-subsidised for nausea and vomiting associated with radiotherapy being used to treat malignancy.					
Restriction Summary 5991 / Treatment of Concept: 5991: Authority Required: Streamlined						
	Indication: Nausea and vomiting					
	Clinical criteria:					
	The condition must be associated with cytotoxic chemotherapy being used to treat malignancy					
	AND					
	Clinical criteria:					
	The treatment must be in combination with dexamethasone					
	AND					
	Clinical criteria:					
(Remove)	~~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~~					

	Patient must be scheduled to be administered a chemotherapy regimen that includes anti-cancer agents listed as having high emetic risk in the current National Comprehensive Cancer Network (NCCN) Guidelines or eviQ guidance.
	Prescribing Instructions: No more than 1 capsule of 300 mg netupitant/0.5 mg palonosetron fixed dose combination will be authorised per cycle of cytotoxic chemotherapy.
Add	*For emetogenic chemotherapy regimens that contain multiple days of administration of the emetogenic agent within one cycle, second/subsequent nausea/vomiting days are to be addressed with one of the repeat prescriptions.*
Restriction Summary 5994 / ToC: 5994: Authority Required: Streamlined	
	Indication: Nausea and vomiting
	Clinical criteria:
	The condition must be associated with cytotoxic chemotherapy being used to treat breast cancer
	AND
	Clinical criteria:
	The treatment must be in combination with dexamethasone
	AND
	Clinical criteria:
	Patient must be scheduled to be co-administered cyclophosphamide and an anthracycline
	Prescribing Instructions: No more than 1 capsule of 300 mg netupitant/0.5 mg palonosetron fixed dose combination will be authorised per cycle of cytotoxic chemotherapy.
Restriction Summary 6937 / ToC: 6937: Authority Required: Streamlined	
	Indication: Nausea and vomiting
	Clinical criteria:
	The condition must be associated with moderately emetogenic cytotoxic chemotherapy being used to treat malignancy
	AND
	Clinical criteria:
	The treatment must be in combination with dexamethasone on day 1 of a chemotherapy cycle
	AND
	Clinical criteria:
	Patient must have had a prior episode of chemotherapy induced nausea or vomiting
	AND
	Clinical criteria:
(Remove)	~~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~~
	Patient must be scheduled to be administered a chemotherapy regimen that includes anti-cancer agents listed as having moderate emetic risk in the current National Comprehensive Cancer Network (NCCN) Guidelines or eviQ guidance.
	Prescribing Instructions: No more than 1 capsule of 300 mg netupitant/0.5 mg palonosetron fixed dose combination will be authorised per cycle of cytotoxic chemotherapy.
Add	*For emetogenic chemotherapy regimens that contain multiple days of administration of the emetogenic agent within one cycle, second/subsequent nausea/vomiting days are to be addressed with one of the repeat prescriptions.*
Restriction Summary 6879 / ToC: 6879: Authority Required: Streamlined	
	Indication: Nausea and vomiting
	Clinical criteria:
	The condition must be associated with moderately emetogenic cytotoxic chemotherapy being used to treat malignancy
	AND
	Clinical criteria:
	The treatment must be in combination with dexamethasone on day 1 of a chemotherapy cycle
	AND
	Clinical criteria:
	Patient must be scheduled to be administered a chemotherapy regimen that includes either carboplatin or oxaliplatin
	Prescribing Instructions: No more than 1 capsule of 300 mg netupitant/0.5 mg palonosetron fixed dose combination will be authorised per cycle of cytotoxic chemotherapy.

Category / Program: General Schedule (Code GE)

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
NETUPITANT + PALONOSETRON					
netupitant 300 mg + palonosetron 500 microgram capsule, 1	10731T MP NP	1	1	5	Akynzeo
Restriction summaries as above					

For more detail on PBAC's view, see section 5 PBAC outcome.

4 Consideration of the evidence

Sponsor hearing

4.1 There was no hearing for this item.

Consumer comments

4.2 The PBAC noted and welcomed the input from individuals (1), health care professionals (1) and organisations (2) via the Consumer Comments facility on the PBS website. The comment from the individual described the negative impact of CINV on quality of life, and the financial difficulty experienced by individuals who self-fund NEPA due to the limitations of the current clinical criteria. The input from the health professional noted the limits of the current clinical criteria for the treatment of CINV and stated that expanding and updating the criteria would provide both clinical and financial benefits to patients receiving new anti-cancer treatments.

4.3 The PBAC noted input received from Antengene AUS Pty Ltd (Antengene) in support of NEPA submission. The input emphasised that CINV remains one of the most common adverse events suffered by patients and that it negatively impacts treatment outcomes and health related quality of life as well as increasing healthcare resource utilisation. Antengene further highlighted that there is critical unmet clinical need for additional PBS-listed anti-emetics for patients receiving MEC and HEC.

4.4 The PBAC also noted the input received from the Society of Hospital Pharmacists of Australia (SHPA) in support of NEPA submission. The comments from SHPA advocated for the amendment of the clinical criteria for NEPA to enable more patients access to NEPA on the PBS to increase cancer treatment tolerability, adherence and success.

4.5 The PBAC noted that the Medical Oncology Group of Australia (MOGA) had also expressed its support for the submission.

Clinical trials

4.6 The submission presented no new clinical evidence.

Estimated PBS utilisation and financial implications

4.7 Table 3 lists the potential additional anti-cancer drugs, or detailed dosing of existing drugs, that were identified by the submission as potentially impacting on the total PBS cost.

4.8 The submission incorporated the following assumptions to make its forward projections:

- incremental additional PBS use of NEPA will increase in the first year of listing to accommodate the additional treatments identified in the NCCN Guidelines
- Use of additional treatments (i.e. those not already listed in the criteria) is expected to increase over time as they are largely newer therapies

- 100% use of anti-emetic therapies for all chemotherapies available via the NCCN Guidelines and not already listed in the PBS anti-emetic criteria
- PBS/RPBS split assumed to mirror that of anti-cancer medications not already listed in the PBS anti-emetic criteria
- Average co-payment (based on the projected use of the anti-cancer medications expected to be eligible for PBS funded anti-emetics) is $18.38
- 60% of patients using MEC experience CINV and go on to receive secondary prophylaxis
- No change in MBS costs or in use of other medicines
- 10% of patients using chemotherapies in Group 2 will use higher doses, which are classified as HEC, and will therefore be able to access primary prophylaxis rather than secondary prophylaxis. Market share of NEPA (based on the PBS/Medicare statistics) is 33% (s.100) and 67% (s.85). Therefore, NEPA (General Listing "GE") is the most commonly used prophylactic anti-emetic PBS indication.

Table 3: Potential additional chemotherapies

Anti-cancer Agent	IV or PO	% experiencing CINV*	TGA Registered	PBS Listed	Current PBS Anti-Emetic Criteria	NCCN Guidelines® 2022	Which NCCN dosing is MEC	Which NCCN dosing is HEC	Section 4 Costed
Group 1	**Increase in FDC NEPA use for chemotherapies that are currently not recognised as HEC/MEC by the PBS.**								
Sacituzumab govitecan-hziy	IV	40-67%	Yes	Yes	No	HEC		Any	Yes
Bendamustine	IV	15%	Yes	Yes	No	MEC	Any		Yes
Busulfan	IV	40-77%	Yes	Yes	No	MEC	Any		Yes
Temozolomide	IV	36–43%	Yes	Yes	No	MEC	Any		Yes
Group 2	**Change in FDC NEPA use for chemotherapies that are currently recognised as HEC/MEC by the PBS but their NCCN classification depends on dose.**								
Doxorubicin	IV	≥10%	Yes	Yes	Yes MEC – no dose restriction	HEC/MEC	<60 mg/m^2	≥60 mg/m^2	Yes
Epirubicin	IV	>5%	Yes	Yes	Yes MEC – no dose restriction	HEC/MEC	<90 mg/m^2	>90 mg/m^2	Yes
Ifosfamide	IV	>10%	Yes	Yes	Yes MEC – no dose restriction	HEC/MEC	<2 g/m^2 per dose	≥2 g/m^2 per dose	Yes
Melphalan	IV	≥10%	Yes	Yes	Yes MEC– no dose restriction	HEC/MEC	≤ 140 mg/m^2	> 140 mg/m^2	Yes
Carmustine	IV	≥10%	Yes	Yes	Yes HEC – no dose restriction	HEC/MEC	≤250 mg/m^2	>250 mg/m^2	No
Cytarabine	IV	>10%	Yes	Yes	Yes MEC – no dose restriction	MEC	>200 mg/m^2		No
Group 3	**Oral Agents that are not included because the NCCN Guidelines® recommend other anti-emetic options before NK1 class drugs so there is no change in FDC NEPA use.**								
Encorafenib	PO	27-39%	Yes	Yes	No	HEC/MEC	Any	Any	No
Imatinib	PO	58-73%	Yes	Yes	No	HEC/MEC	> 400 mg/m^2		No
Lenvatinib	PO	36-47%	Yes	Yes	No	HEC/MEC	Any	Any	No
Midostaurin	PO	68-83%	Yes	Yes	No	HEC/MEC	Any	Any	No
Selinexor	PO	41-72%	Yes	Yes	No	HEC/MEC	Any	Any	No
Temozolomide	PO	29-49%	Yes	Yes	No	HEC/MEC	>75 mg/m^2/day		No
Group 4	**Change in FDC NEPA use unquantifiable – because these anti-cancer agents that cannot be costed as they are not PBS Listed.**								
Clofarabine	IV	39-61%	Yes	No	No	MEC	Any	Any	No
Cam-trastuzumab deruxtecan-nxki	IV	49-80%	Yes	No	No	MEC	Any	Any	No
Dinutuximab	IV	>10%	Yes	No	No	MEC	Any		No
Lurbinectedin	IV	22-37%	Yes	No	No	MEC	Any	Any	No
Romidepsin	IV	39-59%	Yes	No	No	MEC	Any	Any	No
Trabectedin	IV	46-75%	Yes	No	No	MEC	Any	Any	No
Lomustine	PO	45-100%	Yes	No	No	HEC/MEC	Any	Any	No
Mitotane	PO	>10%	Yes	No	No	HEC/MEC	Any	Any	No

Abbreviations: qd: once a day; bid; twice a day.

*Derived from Product Information. Table provided in the submission.

4.9 The submission estimated that there will be a financial cost to the government from the proposed changes of NEPA over six years, from approximately $0 to < $10 million in Year 1, increasing to approximately $0 to < $10 million in Year 6. No change in MBS costs was anticipated (see Table 4).

4.10 Table 4 shows the submission's estimated net cost to Government using the published price of NEPA.

Table 4: Financial Summary – incremental increase in anti-emetic use (published price)

	Year 1 2023	Year 2 2024	Year 3 2025	Year 4 2026	Year 5 2027	Year 6 2028
Number of PBS/RPBS Rx	[redacted][1]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]
Net Cost to PBS/RPBS	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Net Cost to MBS	nil	nil	nil	nil	nil	nil
Net Cost to Government	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]

Table provided in the submission

The redacted values correspond to the following ranges:

[1] 20,000 to <30,000

[2] $0 to <$10 million

[3] 30,000 to <40,000

4.11 The submission did not incorporate current utilisation patterns of palonosetron and ondansetron for treatment of nausea and vomiting associated with cytotoxic chemotherapy. Table 5 shows the estimated net impact of patients switching from ondansetron or palonosetron to a broader listing of NEPA, aprepitant or fosaprepitant. Patients who were historically using three or more repeats for palonosetron or ondansetron were used to estimate prescriptions in line with PBS guidelines. Restricting the analysis to patients who used three or more prescriptions reduced the incident patient count from 300,000 to < 400,000per year to 20,000 to < 30,000 which was assumed to more accurately capture the target population. Linear extrapolation using prescription data from 2016-2022 was used to estimate prescription utilisation going forward. It was assumed that all of these patients would be eligible for a broader restriction of NEPA and consequently aprepitant and fosaprepitant. Of these patients, [redacted]% were assumed to take up these medications. Patients were distributed between the three medications according to the PBS distribution for 2022, i.e. 1%, 96% and 3% for aprepitant, NEPA and fosaprepitant respectively.

4.12 These inputs and assumptions resulted in a higher estimated net cost to Government compared to that presented in the submission: approximately $10 million to < $20 million to $10 million to < $20 million per year across the 6 years.

Table 5: Estimated PBS/RPBS cost of patients switching from palonosetron and ondansetron

	Year 1 2023	Year 2 2024	Year 3 2025	Year 4 2026	Year 5 2027	Year 6 2028
Projected PBS/RPBS Scripts						
Palonosetron 250mcg/5mL[a]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Ondansetron Syrup	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Ondansetron 4mg	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Ondansetron 8mg	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Proportion applicable to indication	100%	100%	100%	100%	100%	100%
Proportion uptake	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
PBS/RPBS Scripts affected						
Palonosetron 250mcg/5mL	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Ondansetron Syrup	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Ondansetron 4mg	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Ondansetron 8mg	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
PBS/RPBS Script distribution						
Aprepitant	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
NEPA	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]
Fosaprepitant	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
PBS/RPBS Potential cost						
Aprepitant	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]
NEPA	$[redacted][5]	$[redacted][5]	$[redacted][5]	$[redacted][5]	$[redacted][5]	$[redacted][5]
Fosaprepitant	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]
Net cost minus copayments PBS/RPBS	**$**[redacted][5]	**$**[redacted][5]	**$**[redacted][5]	**$**[redacted][5]	**$**[redacted][5]	**$**[redacted][5]

Source: DUSC Secretariat analysis

[a] The DUSC Secretariat noted that there has been a considerable decline in palonosetron utilisation with approx. 180,000 prescriptions in 2016 reducing to 100,000 in 2022.

The redacted values correspond to the following ranges:

[1] *<500*

[2] *500 <5,000*

[3] *100,000 to < 200,000*

[4] *$0 to <$10 million*

[5] *$10 million to <$20 million*

Sensitivity analysis

4.13 The submission noted that the main source of uncertainty in the forward estimates is the number of patients who will utilise NEPA as part of their chemotherapies following the proposed change. The utilisation and financial estimates presented above were limited to PBS-listed chemotherapies because their usage data was readily available.

4.14 As a sensitivity analysis, the submission estimated the potential usage and financial implications of the requested change if non-PBS listed chemotherapies were also taken into account.

4.15 The Sponsor assumed the number of scripts for anti-emetics would double (Table 6). This resulted in a doubling of the anticipated cost in the forward estimates.

4.16 As a Category 4 submission, the financial estimates have not been independently evaluated.

Table 6: Summary of Sensitivity Analysis

	2023	2024	2025	2026	2027	2028
Base Case						
Number of PBS/RPBS Rx	[redacted][1]	[redacted][5]	[redacted][5]	[redacted][5]	[redacted][5]	[redacted][5]
Net Cost of FDC NEPA	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]
Net Savings to PBS/RPBS from displaced medications	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]
Net Cost to PBS/RPBS	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]
Net Cost to MBS	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]
Net Cost to Government	**$[redacted][2]**	**$[redacted][2]**	**$[redacted][2]**	**$[redacted][2]**	**$[redacted][2]**	**$[redacted][2]**
SS1: Incorporation of non-PBS listed chemotherapies						
Number of PBS/RPBS Rx	[redacted][4]	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][7]
Net Cost of FDC NEPA	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]
Net Savings to PBS/RPBS from displaced medications	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]
Net Cost to PBS/RPBS	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]
Net Cost to MBS	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]
Net Cost to Government	**$[redacted][2]**	**$[redacted][2]**	**$[redacted][2]**	**$[redacted][2]**	**$[redacted][2]**	**$[redacted][2]**

Table provided in the submission

The redacted values correspond to the following ranges:

[1] *20,000 to <30,000*

[2] *$0 to <$10 million*

[3] *Net cost saving*

[4] *50,000 to < 60,000*

[5] *30,000 to <40,000*

[6] *60,000 to <70,000*

[7] *70,000 to <80,000*

For more detail on PBAC's view, see section 5 PBAC outcome.

5 PBAC Outcome

5.1 The PBAC recommended the amendment to the restriction criteria of NEPA to align with the TGA indication: 'Prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly and moderately emetogenic cancer chemotherapy' rather than referencing specific chemotherapy drugs. The PBAC considered that the extension to the restriction criteria would be acceptably cost-effective with a price reduction.

5.2 The PBAC also recommended that this amendment should be applied to other NK1 inhibitors on the PBS: [fosaprepitant (fosaprepitant 150 mg injection, 1 vial), with a price reduction to achieve an equivalent price as required for NEPA; and aprepitant capsule (aprepitant 165 mg capsule, 1)].

5.3 The PBAC considered that the change in NEPA restrictions would address unmet clinical need and inequities for patients receiving new chemotherapy regimens that are not covered by the existing clinical criteria.

5.4 The PBAC noted that the submission had estimated that there would be a cost to the government of $0 to < $10 million in the first year of listing, increasing to $0 to < $10 million by the sixth year following the proposed change in the restriction criteria.

5.5 The PBAC noted the following uncertainties associated with the recommended restriction change:

- the extent of NEPA prescribing that may occur for patients treated with MEC agents, not all of which require NK1 inhibitors
- the impact of the restriction changes on the overall utilisation of NEPA and associated costs to Government
- the number and type of new chemotherapy agents that may enter the market in future and whether these will require NK1 inhibitors

5.6 The PBAC noted that the recommended restriction change would have the effect of lowering the cost-effectiveness of the NEPA PBS listing, as it would broaden the restriction and allow more first line use. The PBAC considered a % price reduction would be required for NEPA to be acceptably cost-effective in the expanded population. The PBAC noted that uncertainties in the utilisation and financial impact would also be partly mitigated by a price reduction.

5.7 The PBAC noted that the Secretariat had received feedback that some health professionals believe the NEPA restrictions are unaligned with current clinical practice with regard to multi-day chemotherapy regimens. The PBAC considered that the relevant prescribing instruction could be removed, as it created confusion due to differing definitions of a 'cycle' of chemotherapy and was unnecessary as clinicians are familiar with prescribing NK1s for primary and secondary prophylaxis of CINV.

5.8 The PBAC recommended that the Drug Utilisation Sub-Committee review the utilisation of NEPA when 12-24 months of data are available post the restriction change.

5.9 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:
Recommended

6 Recommended listing

6.1 Amend listings as follows:

Category / Program: Section 100 Chemotherapy Related Benefits (Code CT)					
MEDICINAL PRODUCT medicinal product pack	**PBS item code**	**Max. qty packs**	**Max. qty units**	**№.of Rpts**	**Available brands**
NETUPITANT + PALONOSETRON					
netupitant 300 mg + palonosetron 500 microgram capsule, 1	10714X MP	1	1	5	Akynzeo

	Administrative Advice: No increase in the maximum number of repeats may be authorised.
	Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
	Administrative Advice: This medicine is not PBS-subsidised for nausea and vomiting associated with radiotherapy being used to treat malignancy.
Restriction Summary 5991 / Treatment of Concept: 5991: Authority Required: Streamlined	
	Indication: Nausea and vomiting
	~~**Clinical criteria:**~~
	~~The condition must be associated with cytotoxic chemotherapy being used to treat malignancy~~
	~~**AND**~~
	~~**Clinical criteria:**~~
	The treatment must be in combination with dexamethasone, unless contraindicated
	~~**AND**~~
	~~**Clinical criteria:**~~
	~~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~~
	Clinical criteria:
	Treatment must be for prevention of nausea and vomiting associated with moderate to highly emetogenic anti-cancer therapy
	Prescribing Instructions: ~~No more than 1 capsule of 300 mg netupitant/0.5 mg palonosetron fixed dose combination will be authorised per cycle of cytotoxic chemotherapy.~~
	Administrative advice: *Various sources of information outline the emetic risk associated with cancer treatment. Examples include the National Comprehensive Cancer Network guidelines (USA), eviQ guidelines and approved Product Information of individual drugs. These examples are not a comprehensive list of which anti-cancer drugs that have moderate to high emesis risk.*
~~**Restriction Summary 5994 / ToC: 5994: Authority Required: Streamlined**~~	
	~~**Indication:** Nausea and vomiting~~
	~~**Clinical criteria:**~~
	~~The condition must be associated with cytotoxic chemotherapy being used to treat breast cancer~~
	~~**AND**~~

	Clinical criteria:
	The treatment must be in combination with dexamethasone
	AND
	Clinical criteria:
	Patient must be scheduled to be co-administered cyclophosphamide and an anthracycline
	Prescribing Instructions: No more than 1 capsule of 300 mg netupitant/0.5 mg palonosetron fixed dose combination will be authorised per cycle of cytotoxic chemotherapy.
Restriction Summary 6937 / ToC: 6937: Authority Required: Streamlined	
	Indication: Nausea and vomiting
	Clinical criteria:
	The condition must be associated with moderately emetogenic cytotoxic chemotherapy being used to treat malignancy
	AND
	Clinical criteria:
	The treatment must be in combination with dexamethasone on day 1 of a chemotherapy cycle
	AND
	Clinical criteria
	Patient must have had a prior episode of chemotherapy induced nausea or vomiting
	AND
	Clinical criteria:
	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
	Prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly and moderately emetogenic cancer chemotherapy
	Prescribing Instructions: No more than 1 capsule of 300 mg netupitant/0.5 mg palonosetron fixed dose combination will be authorised per cycle of cytotoxic chemotherapy.
Restriction Summary 6879 / ToC: 6879: Authority Required: Streamlined	
	Indication: Nausea and vomiting
	Clinical criteria:
	The condition must be associated with moderately emetogenic cytotoxic chemotherapy being used to treat malignancy
	AND
	Clinical criteria:

	~~The treatment must be in combination with dexamethasone on day 1 of a chemotherapy cycle~~
	~~**AND**~~
	~~**Clinical criteria:**~~
	~~Patient must be scheduled to be administered a chemotherapy regimen that includes either carboplatin or oxaliplatin~~
	~~**Prescribing Instructions:**~~ ~~No more than 1 capsule of 300 mg netupitant/0.5 mg palonosetron fixed dose combination will be authorised per cycle of cytotoxic chemotherapy.~~

Category / Program: General Schedule (Code GE)					
MEDICINAL PRODUCT **medicinal product pack**	**PBS item code**	**Max. qty packs**	**Max. qty units**	**№.of Rpts**	**Available brands**
NETUPITANT + PALONOSETRON					
netupitant 300 mg + palonosetron 500 microgram capsule, 1	10731T MP NP	1	1	5	Akynzeo
As above					

Flow on changes:

6.2 Amend the fosaprepitant, fosaprepitant 150 mg injection, 1 vial (11103J, 11107N) listings as follows:

Flow on changes required to align clinical criteria with the TGA indication: 'Prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly and moderately emetogenic cancer chemotherapy' rather than referencing specific chemotherapy drugs.

	~~**Clinical criteria:**~~
	~~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~~
	Clinical criteria:
	Treatment must be for prevention of nausea and vomiting associated with moderate to highly emetogenic anti-cancer therapy
	Prescribing Instructions: ~~No more than 1 vial of fosaprepitant 150 mg injection will be authorised per cycle of cytotoxic chemotherapy.~~

6.3 Amend the aprepitant capsule, aprepitant 165 mg capsule, 1 (2518M, 2550F) listings as follows:

Flow on changes required to align clinical criteria with the TGA indication: 'Prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly and moderately emetogenic cancer chemotherapy' rather than referencing specific chemotherapy drugs.

	~~**Clinical criteria:**~~
	~~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~~
	Clinical criteria:
	Treatment must be for prevention of nausea and vomiting associated with moderate to highly emetogenic anti-cancer therapy
	Prescribing Instructions: ~~No more than 1 capsule of aprepitant 165 mg will be authorised per cycle of cytotoxic chemotherapy.~~

These restrictions may be subject to further review. Should there be any changes made to the restriction the sponsor will be informed.

7 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

8 Sponsor's Comment

The sponsor had no comment.