

**5.06 FOSNETUPITANT (AS CHLORIDE
HYDROCHLORIDE)/PALONOSETRON (AS
HYDROCHLORIDE),
Solution concentrate for I.V. infusion containing
fosnetupitant 235 mg and palonosetron 0.25 mg in
20 mL vial,
Akynzeo® IV,
Juniper Biologics Pty Ltd**

1 Purpose of submission

- 1.1 The Category 2 submission requested a Section 100 (Efficient Funding of Chemotherapy – Related Benefits (Code CT)) Authority Required (STREAMLINED) listing and a General Schedule Authority Required (STREAMLINED) listing for Akynzeo IV® for the treatment of nausea and vomiting in patients receiving highly or moderately emetogenic chemotherapy (HEC and MEC, respectively).
- 1.2 Akynzeo IV® is an intravenous (IV) fixed-dose combination (FDC) of fosnetupitant (FosNTP) 235 mg (a neurokinin 1 receptor antagonist (NK1 RA)) plus palonosetron (PALO) 250 mcg (a 5-hydroxytryptamine-3 receptor antagonist (5-HT3 RA)). Akynzeo IV® is henceforth referred to as NEPA IV.
- 1.3 Listing was requested on the basis of a cost-minimisation approach (CMA) versus the currently PBS listed IV formulation of another NK1 RA, fosaprepitant (FosAPR) 150 mg (henceforth referred to as Emend IV), used with a 5-HT3 RA. The 5-HT3 RA specified in the submission was PALO. The submission considered Emend IV plus PALO to be the least expensive PBS combination of a NK1 RA and 5-HT3 RA, with an IV manner of administration. Both NEPA IV and Emend IV + a 5-HT3 RA are used in conjunction with dexamethasone (DEX).
- 1.4 The key components of the clinical issue addressed by the submission are summarised in Table 1.

Table 1: Key components of the clinical issue as stated in the submission

Component	Description
Population	Prophylactic treatment of patients treated with highly or moderately emetogenic chemotherapy.
Intervention	Akynzeo IV: fixed dose combination of fosnetupitant 235 mg plus palonosetron 250 mcg powder for intravenous infusion, 20 mL glass vial.
Comparator	Fosaprepitant 150 mg injection (Emend IV) plus 5-hydroxytryptamine-3 receptor antagonist (5-HT3 RA)
Outcomes	Treatment-related adverse events: injection site reactions and injection site pain Effectiveness: complete response rate (<i>i.e.</i> , no emetic episodes and no use of rescue medication) in the acute (0-24 hours), delayed (>24-120 hours) and total (0-120 hours) phases.
Clinical claim	In patients likely to have chemotherapy-induced nausea and vomiting (CINV) with moderately or highly emetogenic chemotherapy, Akynzeo IV (fixed dose combination fosnetupitant/palonosetron) + dexamethasone is non-inferior in terms of effectiveness and superior in terms of safety compared with the comparator Emend IV + 5HT3 RA + dexamethasone.

Source: Table 1-2, p14 of the submission.

mg = milligrams; mcg = micrograms; mL = millilitres

2 Background

Registration status

2.1 NEPA IV was registered on the Australian Register of Therapeutic Goods (ARTG) on 13 March 2020 for the same indications as the oral form NEPA. Akynzeo IV 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.
- Prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy.

Previous PBAC consideration

2.2 Table 2 summarises key characteristics of the previous and current submissions for NEPA and NEPA IV.

Table 2: Summary of key characteristics of the previous NEPA and NEPA IV submissions and the current NEPA IV submission

	November 2016 NEPA (oral capsule) netupitant 300 mg with palonosetron 0.5 mg	July 2020 NEPA IV fosnetupitant 235 mg with palonosetron 0.25 mg	Current submission March 2023 NEPA IV fosnetupitant 235 mg with palonosetron 0.25 mg
Requested PBS listing	1. Primary prophylaxis of CINV for carboplatin/oxaliplatin regimens 2. Secondary prophylaxis of CINV for MEC	Four restrictions with specified chemotherapy regimens for each including AC for breast cancer, secondary prophylaxis for MEC, and carboplatin or oxaliplatin.	The specified chemotherapy agents were similar to those specified in the July 2020 submission and are consistent with current Emend IV listings (with relevant differences noting Emend IV requires concomitant use of a 5-HT3 RA).

Public Summary Document – March 2023 PBAC Meeting

	November 2016 NEPA (oral capsule) netupitant 300 mg with palonosetron 0.5 mg	July 2020 NEPA IV fosnetupitant 235 mg with palonosetron 0.25 mg	Current submission March 2023 NEPA IV fosnetupitant 235 mg with palonosetron 0.25 mg
Requested AEMP	\$103.01 per capsule	The minor submission proposed the same AEMP for NEPA IV as NEPA (\$97.16 per vial). The proposed AEMP was equivalent to that of Emend IV (fosaprepitant 150 mg)	\$█ per vial
Main comparator	Aprepitant + 5-HT3 RA	NEPA	Emend IV + 5-HT3 RA (specified as palonosetron)
Clinical evidence	Direct evidence (one trial NETU-10-29 HEC and MEC). Additional subgroup analysis of MEC patients treated with and without carboplatin/oxaliplatin	Direct evidence (four trials (HEC/AC) to demonstrate that NEPA IV and NEPA were equivalent.	Direct evidence (two trials): CONSOLE (primarily lung cancer patients on cisplatin chemotherapy). CONSOLE-BC (breast cancer patients on AC chemotherapy).
Clinical claim	NEPA is non-inferior to aprepitant + a 5-HT3 RA.	NEPA IV is non-inferior to NEPA	NEPA IV is non-inferior in effectiveness and superior in safety compared to Emend IV + 5-HT3 RA.
Economic evaluation	Cost-minimisation vs. aprepitant + a 5-HT3 RA, and a cost-minimisation vs. aprepitant alone.	Cost-minimisation vs. NEPA (oral)	Cost-minimisation vs. Emend IV + a 5-HT3 RA (nominated as palonosetron).
Number of scripts dispensed	A total of █ ¹ NEPA scripts in Year 1 increasing to █ ² scripts in Year 5	A total of █ ³ NEPA IV scripts in Year 1 increasing to █ ¹ scripts in Year 6.	A total of █ ³ NEPA IV scripts in Year 1 increasing to █ ¹ scripts in Year 6.
Estimated net cost to PBS/RPBS	A net saving of \$█ ⁴ in Year 1, increasing to \$█ ⁴ in Year 5, for a total net saving of \$█ ⁴ over the first 5 years of listing.	A net cost of \$█ ⁴ in Year 1, increasing to \$█ ⁴ in Year 6, for a total net cost of \$█ ⁴ over the first 6 years of listing.	A net cost of \$█ ⁴ in Year 1, increasing to \$█ ⁴ in Year 6, for a total net cost of \$█ ⁴ over the first 6 years of listing.

Source: Compiled during the evaluation from the current submission and the PSDs and evaluation commentaries (where available) for the previous submissions.

AC=anthracycline plus cyclophosphamide; AEMP=approved ex-manufacturer price; AEs=adverse events; CINV=chemotherapy induced nausea and vomiting; DPMQ=dispensed price for maximum quantity; DPMA=dispensed price for maximum amount; FDC=fixed dose combination; HEC=highly emetogenic chemotherapy; 5-HT3 RA=5-hydroxytryptamine 3 receptor antagonist; ISRs=injection site reactions; IV=intravenous; MEC=moderately emetogenic chemotherapy; NK1=neurokinin 1; PO=per oral; PP=primary prophylaxis; PSD=Public Summary Document; RD=risk difference; SP=secondary prophylaxis; TGA=Therapeutic Goods Administration; TRAE=treatment related adverse event.

Note: For response outcomes, Acute: 0-24 hr; Delayed: 24-120 hr; Overall: 0-120 hr

^a Defined as no emetic event, no rescue medication.

^b As noted in the netupitant with palonosetron PSD, November 2016 PBAC Meeting.

The redacted values correspond to the following ranges:

¹ 10,000 to < 20,000

² 50,000 to < 60,000

³ 500 to < 5,000

⁴ \$0 to < \$10 million

2.3 Table 3 summarises the key matters from the previous PBAC consideration of NEPA IV and how the submission addressed those concerns.

Table 3: NEPA IV PBAC summary of recommendations (July 2020 consideration)

PBAC outcomes (Fosnetupitant/palonosetron, PSD, July 2020)	Issues addressed by the current submission
<p>The PBAC recommended listing NEPA IV as an Authority Required STREAMLINED benefit under both the General Schedule and Section 100 (Efficient Funding of Chemotherapy – Related Benefits (Code CT)) under the same conditions as the currently PBS listed capsule form, NEPA, and among other matters on the basis that NEPA IV would be acceptable on a cost-minimisation basis to the lowest cost combination of a NK1 RA with a 5-HT3 RA (paragraph 6.1).</p> <p>The PBAC considered that the clinical claim that NEPA IV was non-inferior in terms of effectiveness and safety to NEPA to be reasonable. However, it recalled its November 2015 recommendation where it considered NEPA to be non-inferior to aprepitant with a 5-HT3 RA. It therefore considered NEPA IV was also likely to be non-inferior to any NK1 RA (aprepitant or Emend IV) with any 5-HT3 RA (paragraph 6.2).</p>	<p>It was stated in the submission that due to the individual cost components of the cheapest oral alternatives, it was not feasible to list the IV formulation on the PBS.</p> <p>This submission noted that the patient population that requires the IV formulation is different to the oral population. For example, patients may have difficulty swallowing, such as patients with head and neck cancer and other types of cancers or where IV treatment represents the best clinical management, and the use of oral treatments would be contraindicated.</p>
<p>The PBAC recalled that NEPA was cost-minimised to aprepitant alone and that despite NEPA being considered non-inferior to aprepitant with a 5-HT3 RA, no cost was given to the 5-HT3 RA component due to high risk of leakage into populations that would otherwise use only a 5-HT3 RA (paragraph 4.3). It also noted the pre-PBAC response which argued that aprepitant alone is not equivalent or non-inferior effectiveness to NEPA IV, citing clinical guidelines supporting the use of both a NK1 RA with a 5-HT3 RA for highly emetogenic chemotherapies. The PBAC however noted that no further evidence has been presented since the PBS listing of NEPA around the likelihood of treatment escalation to combination therapy for patients that might otherwise receive a single agent (paragraph 6.3).</p>	<p>Not reproduced in the submission</p>
<p>The PBAC considered that NEPA IV should be cost-minimised to the lowest cost combination of a NK1 RA and a 5HT3 RA at equi-effective doses. The PBAC noted that it could only recommend listing NEPA IV at a higher price than the alternative therapy or therapies if it was satisfied that it would provide, for some patients, a significant improvement in efficacy or reduction of toxicity over the alternative therapy or therapies (the Act, Section 101(3B)). Based on the evidence presented in the submission, the PBAC considered that it could not be satisfied that NEPA IV provides a significant improvement in efficacy or reduction of toxicity over the alternative therapies (paragraph 6.4).</p>	<p>This submission presents additional evidence providing significant improvement in the reduction of toxicity over the alternative therapies (Emend IV plus palonosetron).</p>

Source: Compiled from Table 1-7, p33 of the submission and the Fosnetupitant/palonosetron, PSD, July 2020
 5-HT3 RA=5-hydroxytryptamine-3 receptor antagonist; NEPA=oral fixed dose combination of netupitant 300 mg with palonosetron 500 mcg; NEPA IV= intravenous fixed dose combination of fosnetupitant 235 mg plus palonosetron 250 mcg; NK1 RA= neurokinin 1 receptor antagonist; PSD=Public Summary Document.

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

3 Requested listing

Name, Restriction, Manner of administration and form	Max. Qty (units)	Dispensed Price Max Qty	№.of Rpts	Proprietary Name and Manufacturer
General Pharmaceutical Benefit Authority Required (STREAMLINED) FOSNETUPITANT + PALONOSETRON	1	\$ [REDACTED]	5	Akynteo IV Juniper Biologics Pty Ltd

Public Summary Document – March 2023 PBAC Meeting

fosnetupitant 235 mg + palonosetron 250 microgram injection, 1 vial				
Section 100 related pharmaceutical Authority Required (STREAMLINED) FOSNETUPITANT + PALONOSETRON fosnetupitant 235 mg + palonosetron 250 microgram injection, 1 vial	1	\$ [REDACTED]	5	

- 3.1 The submission noted that identical restrictions that apply to Emend IV are proposed for NEPA IV. There is a concurrent submission for Akynzeo (NEPA) (item 6.18) which proposes that chemotherapies defined as HEC or MEC need to be updated and National Comprehensive Cancer Network (NCCN) guidelines or eviQ guidance be referred to (instead of listing specific agents as is the current case). The PBAC considered changes to the restriction for oral netupitant/palonosetron (item 6.18, March 2023 PBAC meeting) should be flowed on to the listing of NEPA IV.
- 3.2 As substantial changes were proposed to the restrictions as a whole, the listing requested in the submission are presented below (see Section 8 ‘Recommended listing’ for the PBAC recommended listing).

Proposed Restriction 1 - Use in emetogenic chemotherapy

Category / Program:	Section 100 – Efficient Funding of Chemotherapy – Related Benefits GENERAL – General Schedule (Code GE)
Prescriber type:	<input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners
PBS Indication:	Nausea and vomiting
Restriction Level / Method:	<input checked="" type="checkbox"/> Authority Required (STREAMLINED)
Clinical criteria:	The condition must be associated with cytotoxic chemotherapy being used to treat malignancy, AND The treatment must be in combination with dexamethasone, AND Patient must be scheduled to be administered a chemotherapy regimen that includes any 1 of the following agents: altretamine; carmustine; cisplatin when a single dose constitutes a cycle of chemotherapy; cyclophosphamide at a dose of 1500 mg per square metre per day or greater; dacarbazine; procarbazine when a single dose constitutes a cycle of chemotherapy; streptozocin.
Prescribing Instructions	No more than 1 vial of fosnetupitant 235 mg plus palonosetron 250 microgram injection will be authorised per cycle of cytotoxic chemotherapy.

Public Summary Document – March 2023 PBAC Meeting

Proposed Restriction 2 – Use in breast cancer with cyclophosphamide and an anthracycline

Category / Program:	Section 100 – Efficient Funding of Chemotherapy – Related Benefits GENERAL – General Schedule (Code GE)
Prescriber type:	<input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners
PBS Indication:	Nausea and vomiting
Restriction Level / Method:	<input checked="" type="checkbox"/> Authority Required (STREAMLINED)
Clinical criteria:	The condition must be associated with cytotoxic chemotherapy being used to treat breast cancer, AND The treatment must be in combination with dexamethasone, AND Patient must be scheduled to be co-administered cyclophosphamide and an anthracycline.
Prescribing Instructions	No more than 1 vial of fosnetupitant 235 mg plus palonosetron 250 microgram injection will be authorised per cycle of cytotoxic chemotherapy.

Proposed Restriction 3 – Use in emetogenic chemotherapy

Category / Program:	Section 100 – Efficient Funding of Chemotherapy – Related Benefits GENERAL – General Schedule (Code GE)
Prescriber type:	<input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners
PBS Indication:	Nausea and vomiting
Restriction Level / Method:	<input checked="" type="checkbox"/> Authority Required (STREAMLINED)
Clinical criteria:	The condition must be associated with emetogenic cytotoxic chemotherapy being used to treat malignancy, AND The treatment must be in combination with dexamethasone, AND Patient must have had a prior episode of chemotherapy induced nausea or vomiting, AND Patient must be scheduled to be administered a chemotherapy regimen that includes any 1 of the following intravenous chemotherapy agents: arsenic trioxide; azacitidine; cyclophosphamide at a dose of less than 1500 mg per square metre per day; cytarabine at a dose of greater than 1 g per square metre per day; dactinomycin; daunorubicin; doxorubicin; epirubicin; fotemustine; idarubicin; ifosfamide; irinotecan; melphalan; methotrexate at a dose of 250 mg to 1 g per square metre per day; raltitrexed.
Prescribing Instructions	No more than 1 vial of fosnetupitant 235 mg plus palonosetron 250 microgram injection will be authorised per cycle of cytotoxic chemotherapy.

Proposed Restriction 4 – Use in emetogenic chemotherapy

Category / Program:	Section 100 – Efficient Funding of Chemotherapy – Related Benefits GENERAL – General Schedule (Code GE)
Prescriber type:	<input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners
PBS Indication:	Nausea and vomiting
Restriction Level / Method:	<input checked="" type="checkbox"/> Authority Required (STREAMLINED)
Clinical criteria:	The condition must be associated with cytotoxic chemotherapy being used to treat malignancy, AND The treatment must be in combination with dexamethasone, AND Patient must be scheduled to be administered a chemotherapy regimen that includes either carboplatin or oxaliplatin.
Prescribing Instructions	No more than 1 vial of fosnetupitant 235 mg plus palonosetron 250 microgram injection will be authorised per cycle of cytotoxic chemotherapy.

- 3.3 The proposed restrictions are similar to those proposed in the July 2020 NEPA IV submission except that:
- For Restrictions 3 and 4, there was no specification that the chemotherapy regimens should be moderately emetogenic; and
 - Removal of administrative advice which recommends that i) the drug should not be PBS-subsidised for nausea and vomiting associated with radiotherapy being used to treat malignancy, and ii) no increase in the maximum quantity/number of units and the maximum number of repeats will be authorised.
- 3.4 The maximum quantity and number of repeats, as well as the prescribing instruction limiting quantities to 1 vial per chemotherapy cycle, are consistent with those in the previous NEPA IV submission and the current restriction for Emend IV.
- 3.5 The requested price is higher than i) that proposed in the previous July 2020 PBAC consideration of NEPA IV, and ii) that proposed in the November 2016 PBAC consideration of NEPA. Refer to Table 2.
- 3.6 The Pre-Sub-Committee Response (PSCR) and pre-PBAC response advised the sponsor was amenable to changes to the requested listing to restrict NEPA IV to patients who are unsuitable for oral anti-emetics.

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

4 Population and disease

- 4.1 Chemotherapy-induced nausea and vomiting (CINV)¹ can significantly affect a patient's quality of life (QoL), leading to poor compliance with further chemotherapy treatment.
- 4.2 Acute-onset nausea and/or vomiting usually occurs within a few minutes to several hours after drug administration and commonly resolves within the first 24 hours. Delayed-onset nausea and/or vomiting develops in patients more than 24 hours after chemotherapy is administered and commonly occurs when cisplatin, carboplatin, cyclophosphamide, and/or doxorubicin are used.
- 4.3 Primary prophylaxis refers to not having had a prior episode of CINV and secondary prophylaxis refers to having had a prior episode of CINV (also referred to as refractory CINV). Breakthrough CINV refers to CINV which occurs despite prophylaxis.
- 4.4 Australian eviQ guidelines² categorise the emetogenic potential of chemotherapy as follows:
- High risk: 90% or more of patients experience acute emesis.
 - Moderate risk: 30% to 90% of patients experience acute emesis.
 - Low risk: 10% to 30% of patients experience acute emesis.
 - Minimal risk: fewer than 10% of patients experience acute emesis.
- 4.5 For single IV chemotherapy use, eviQ guidelines³ classify (non-exhaustive) anthracycline/cyclophosphamide (AC) combination (breast cancer protocols), cisplatin, and cyclophosphamide ≥ 1500 mg/m² as highly emetogenic, and cyclophosphamide < 1500 mg/m², epirubicin, doxorubicin, and irinotecan (higher end of moderate risk) as moderately emetogenic. However, eviQ guidelines note that oxaliplatin, epirubicin, and irinotecan may be highly emetogenic in clinical practice for some patients.
- 4.6 The submission stated NEPA IV has a clinical place, particularly for patients with swallowing difficulties who cannot use the oral form (NEPA), or difficulties absorbing the drug from the oral form. Patients with swallowing difficulties include patients with head and neck cancer or patients with other types of cancer associated with dysphagia and mouth ulcers. The submission also noted that some patients who do not have swallowing difficulties are treated with a NK1 IV formulation mainly because of a faster mode of action, ease of administration, and patient choice.

¹ "AINV" (Antineoplastic drug induced nausea and vomiting) is the updated term in the literature but "CINV" is consistent with the product information terminology for NEPA IV.

²<https://www.eviq.org.au/clinical-resources/side-effect-and-toxicity-management/gastrointestinal/7-prevention-of-anti-cancer-therapy-induced-nausea#classification-of-emetogenic-potential-of-anti-can>

³<https://www.eviq.org.au/clinical-resources/side-effect-and-toxicity-management/gastrointestinal/7-prevention-of-anti-cancer-therapy-induced-nausea#classification-of-emetogenic-potential-of-anti-can>

- 4.7 Fosnetupitant (netupitant is the active moiety of fosnetupitant) is a high-affinity NK1 RA and PALO is a 5-HT3 RA. NK1 RA and 5-HT3 RA drugs are used in combination for the treatment of nausea and vomiting associated with emetogenic chemotherapy⁴. Treatment is in combination with DEX. The recommended dosing regimen for NEPA IV in the Product Information (PI) is one vial (including fosnetupitant 235 mg plus PALO 250 mcg (0.25 mg)) administered as an IV infusion over 30 minutes, initiated approximately 30 minutes prior to the start of each chemotherapy cycle.

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

5 Comparator

- 5.1 The submission nominated Emend IV + a 5-HT3 RA as the main comparator, whilst also specifying PALO IV as the specific 5-HT3 RA partner to Emend IV. The main arguments provided to support this nomination include:

- the comparator contains the same pharmacological therapies as NEPA IV. Both fosnetupitant and fosaprepitant are pro-drugs for oral netupitant and aprepitant;
- Emend IV + a 5-HT3 RA is the treatment most likely to be replaced in clinical practice; and
- Emend IV + PALO IV is the least expensive PBS combination of a NK1 RA and a 5-HT3 RA.

- 5.2 Emend IV plus a 5-HT3 RA is an appropriate comparator. However, NEPA IV may substitute for other therapies:

- NEPA: The proposed restriction does not specifically exclude patients without swallowing difficulties. NEPA contains the same therapies as NEPA IV but in an oral form. Part of the submission's rationale for the proposed listing of NEPA IV is that the IV formulation is preferred over oral options as it has a faster mode of action. Recognising the low response rate of a survey of medical oncologists and haematology nurses⁵, expert advice received by the sponsor indicated that a main reason for using IV combinations in patients who did not have swallowing difficulties was the clinical superiority of IV anti-emetics over oral options (e.g. quicker, more effective, better responses, and ensures more absorption). Given this view, NEPA IV is also expected to replace NEPA although the extent of substitution is difficult to quantify.
- Single use of a 5-HT3 RA: There is a high risk that NEPA IV will substitute for single use of a 5-HT3 RA. This concern was raised by the PBAC in the July 2020

⁴ <https://www.evig.org.au/clinical-resources/side-effect-and-toxicity-management/gastrointestinal/7-prevention-of-antineoplastic-induced-nausea-and>

⁵ The response rate of total medical oncologists (MOs) approached was 5.1% and that of "willing" MOs (oncologists who indicated they were willing to participate) was 37%. The response rate of total nurses approached was 1.7% and that of willing nurses was 37.9%.

consideration of NEPA IV (paragraph 4.3, Fosnetupitant/palonosetron Public Summary Document (PSD), July 2020 PBAC Meeting). Refer to Table 3 for details.

- 5.3 Overall, NEPA IV may replace IV forms of NK1 and 5-HT3 RAs (for those who have swallowing difficulties), NEPA and other oral forms of NK1 RAs used with 5-HT3 RAs. Emend IV + PALO is currently not the lowest cost combination of a NK1 and 5-HT3 RA, with NEPA and combinations of aprepitant with other 5-HT3 RAs having lower costs. The PBAC cannot make a positive recommendation for a medicine that is substantially more costly than an alternative medicine unless it is satisfied that the proposed medicine also provides a significant improvement in health (PBAC Guidelines, version 5.0 reference to *National Health Act 1953*, Section 101(3B)). The PSCR (pg. 1) stated the use of Emend IV in practice is low (approximately 5% of relevant prescribing) based on PBS prescribing data, with most of the dispensing being for oral anti-emetics. On that basis, the PSCR argued it is clear clinicians do not use IV anti-emetics at the same rate as oral therapies and the IV formulations would appear to have a specific place in therapy. In addition, the sponsor noted a survey of clinical practice was undertaken, which indicated IV formulations are used in specific populations, such as for patients unable to swallow, or for whom an oral medication is contraindicated.
- 5.4 The ESC considered IV anti-emetics could be more convenient than oral therapies for some patients and hence NEPA IV would likely replace oral therapies in practice to some extent, particularly as the 5-HT3 RA component was also included in NEPA IV. Furthermore, the ESC noted the survey referred to by the sponsor indicated that 47% of patients are receiving IV anti-emetics despite not having swallowing difficulties. To that end, the ESC advised all oral therapies should be considered alternative therapies, unless NEPA IV could be specifically restricted to patients unsuitable for oral therapies. The ESC noted the PSCR indicated the sponsor was amenable to such a restriction. The Pre-PBAC Response noted the advice of the ESC and proposed additional restriction text to restrict the listing of NEPA IV to use only in patients who are unable to swallow or are otherwise contraindicated to oral anti-emetics. The Pre-PBAC Response argued this could be monitored at the proposed restriction level (streamlined authority).

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 the input from Antengene (AUS) Pty Ltd (the sponsor of the PBS-listed drug selinexor), which discussed the impact of chemotherapy-induced nausea and vomiting and highlighted the need for additional treatment options and for broader review of the structure of the listings of anti-emetic agents for this purpose.

Clinical trials

- 6.3 The submission was based on two head-to-head, double-blinded, randomised trials (CONSOLE and CONSOLE-BC) which compared the administration of a premixed infusion⁶ of FosNTP + PALO + DEX (henceforth referred to as FosNTP+PALO with use of DEX assumed), with FosAPR + PALO + DEX injection (henceforth referred to as FosAPR+PALO with use of DEX assumed), in patients receiving two types of HEC (platinum-based therapy, >85% for lung cancer in CONSOLE and AC combination for breast cancer in CONSOLE-BC). The submission assumed that premixed FosNTP+PALO, as administered in the trials, was a reasonable proxy for NEPA IV. The CONSOLE and CONSOLE-BC trials have not been previously considered by the PBAC (refer to Table 2 for details on previous submissions for NEPA and NEPA IV).
- 6.4 The CONSOLE trial was comprised of two phases: a single chemotherapy cycle (S-cycle; Course 1); and a multiple chemotherapy cycles phase (M-cycles; Courses 2-4). The S-cycle evaluated the non-inferiority of FosNTP to FosAPR when administered once in combination with PALO 0.75 mg and DEX to patients receiving cisplatin-based chemotherapy. The M-cycles evaluated the safety of administering multiple (up to three) courses of FosNTP to patients who had completed the S-cycle and consented to participate. Thus, the S-cycle represents the blinded randomised control phase and the key evidence for comparative effectiveness and safety. The M-cycles phase represents the open-label single arm phase.
- 6.5 A PALO dose of 0.75 mg was administered in the CONSOLE and CONSOLE-BC trials. This dose is higher than the PALO component dose (0.25 mg) in NEPA IV. The submission presented evidence to support that both doses have equivalent efficacy and safety.
- 6.6 A claim of superior safety in terms of a reduced risk of injection site reactions (ISRs) was made based on a meta-analysis of the CONSOLE and CONSOLE-BC trials conducted for the submission.
- 6.7 Details of the trials presented in the submission are provided in Table 4.

⁶ In the fosnetupitant arm, fosnetupitant 235 mg, PALO 0.75 mg, and DEX 9.9 mg were mixed together and infused for 30 min, starting 1 hour before the start of cisplatin administration.

Table 4: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
CONSOLE	Hata A, Okamoto I, et al. Randomized, Double-Blind, Phase III Study of Fosnetupitant Versus Fosaprepitant for Prevention of Highly Emetogenic Chemotherapy-Induced Nausea and Vomiting: CONSOLE.	<i>Journal of Clinical Oncology</i> 2022; 40(2): 180-188.
	Hata A, Shiraishi Y, et al. Exploratory Analysis Comparing Fosnetupitant Versus Fosaprepitant for Prevention of Highly Emetogenic Chemotherapy-Induced Nausea and Vomiting (CINV): A Randomized, Double-Blind, Phase 3 Study (CONSOLE).	<i>Oncology and Therapy</i> 2022; 10(1): 253-262.
CONSOLE-BC	Matsuura K, et al. A phase 3 safety study of fosnetupitant as an antiemetic in patients receiving anthracycline and cyclophosphamide: CONSOLE-BC.)	<i>Cancer</i> 2022; 128(8): 1692-1698.
	Tsurutani J, et al. A randomized, double-blind, multicenter, phase III study of fosnetupitant for the prevention of chemotherapy-induced nausea and vomiting (CINV) in patients receiving doxorubicin-cyclophosphamide/epirubicin-cyclophosphamide (AC/EC) based highly emetogenic chemotherapy: CONSOLE-BC.	<i>Journal of Clinical Oncology</i> 2021; 39 (SUPPL.15)

Source: Table 2-5, p46 of the submission.

6.8 The key features of the direct randomised trials are summarised in Table 5.

Table 5: Key features of the included trials comparing FosNTP + PALO with FosAPR + PALO

Trial	N	Design/ outcome/ duration post-administration of chemo	Risk of bias	Patient population	Outcome(s)
CONSOLE (S-Cycle)	785	R, DB	Low	Adults receiving HEC containing cisplatin primarily for lung cancer (>85%)	CR Overall: 0-120 hr Acute: 0-24 hr Delayed: 24-120 hr 0-168 hr 120-168 hr
CONSOLE-BC	102	R, DB	Low	Adults receiving AC for breast cancer.	CR Overall: 0-120 hr
Meta-analysis (CONSOLE and CONSOLE-BC)	887	Outcome: TRAEs- ISRs Clinical heterogeneity arising from differences in patient/disease characteristics and chemo regimens.			

Source: Compiled during the evaluation based on Sections 2.3-2.6 of the submission.

AC=anthracycline plus cyclophosphamide; AEs=adverse events; chemo=chemotherapy; CR=complete response (overall CR was the primary outcome in both CONSOLE and CONSOLE-BC. It is defined as no emetic event and no rescue medication); DB=double blind; HEC=highly emetogenic chemotherapy; ISRs=injection site reactions; R=randomised; S-Cycle=single course of chemotherapy (randomised phase); TRAEs=treatment-related adverse events

6.9 A non-inferiority (NI) margin of 10% for overall complete response (CR) was pre-specified for the CONSOLE trial. If the lower margin of the confidence interval (CI) was higher than -10%, non-inferiority was considered to be confirmed, and if it was higher than 0%, superiority was considered to be confirmed. The clinical rationale for the proposed minimum clinically important difference (MCID) was not clear from the trial publications or the submission. The primary objective of the CONSOLE-BC trial was to descriptively assess safety. Thus, no NI margins for efficacy or safety were pre-specified in CONSOLE-BC.

6.10 For the meta-analysis of safety outcomes (ISRs), the submission proposed a risk reduction of >25% (i.e., a risk ratio (RR) < 0.75) as clinically meaningful for treatment related adverse events (TRAEs) related ISRs. The submission noted that no MCID was identified in the published domain for this disease area and that the 25% risk reduction was based on Grading of Recommendations, Assessment, Development and Evaluations (GRADE)⁷.

Comparative effectiveness

6.11 The results of key efficacy outcomes in CONSOLE are summarised in Table 6.

Table 6: Efficacy outcomes in CONSOLE

Outcome (time post- chemotherapy)	Definition of outcome	CONSOLE (S phase, 1 st chemotherapy treatment cycle)			
		FosNTP+PALO IV N=392	FosAPR+PALO IV N=393	Comparative effectiveness (95% CI) ^a FosNTP+PALO vs. FosAPR+PALO	
		n (%)	n (%)	Risk difference	Risk ratio
Complete Response (CR)					
Overall ^b : 0-120 hr	No emetic event, no rescue medication	295 (75.2%) ^a	279 (71.0%) ^a	4.1% (-2.1%, 10.3%) ^a	1.06 (0.97, 1.15)
Acute: 0-24 hr		368 (93.9%)	364 (92.6%)	1.3% (-2.3%, 4.8%)	1.01 (0.98, 1.05)
Delayed: 24-120 hr		301 (76.8%)	286 (72.8%)	4.0% (-2.1%, 10.1%)	1.06 (0.97, 1.14)
0-168 hr		287 (73.2%)	263 (66.9%)	6.3% (-0.0%, 12.7%)	1.10 (1.00, 1.12)
120-168 hr		339 (86.5%)	320 (81.4%)	5.1% (-0.0%, 10.2%)	1.06 (1.00, 1.13)
Total control rate					
Overall: 0-120 hr	No emetic event, no rescue medication, no nausea ^c	196 (50.0%)	185 (47.1%)	0.9% (-6.1%, 8.9%)	1.02 (0.88, 1.17)
Acute: 0-24 hr		296 (75.5%)	314 (79.9%)	-4.6% (-10.4%, 1.2%)	0.94 (0.87, 1.02)
Delayed: 24-120 hr		205 (52.3%)	193 (49.1%)	3.1% (-3.9%, 10.1%)	1.06 (0.93, 1.22)
0-168 hr		181 (46.2%)	177 (45.0%)	1.0% (-6.0%, 8.0%)	1.02 (0.88, 1.19)
120-168 hr		273 (69.6%)	260 (66.2%)	3.3% (-3.2%, 9.8%)	1.05 (0.95, 1.16)

Source: Modified from Table 2-16, pp72-73 of the submission.

CI=confidence interval; FosNTP=fosnetupitant; FosAPR=fosaprepitant; n=number of participants with event; N=total participants in group; PALO=palonosetron;

^a The CONSOLE primary outcome (i.e., Overall CR) treatment difference was reported in the publication. All other risk differences and risk ratios were calculated using RevMan 5.3 for the submission

^b The Overall CR rate was stratified by sex and age category.

^c Nausea was assessed by patients on a 4-point Likert scale (none, mild, moderate or severe).

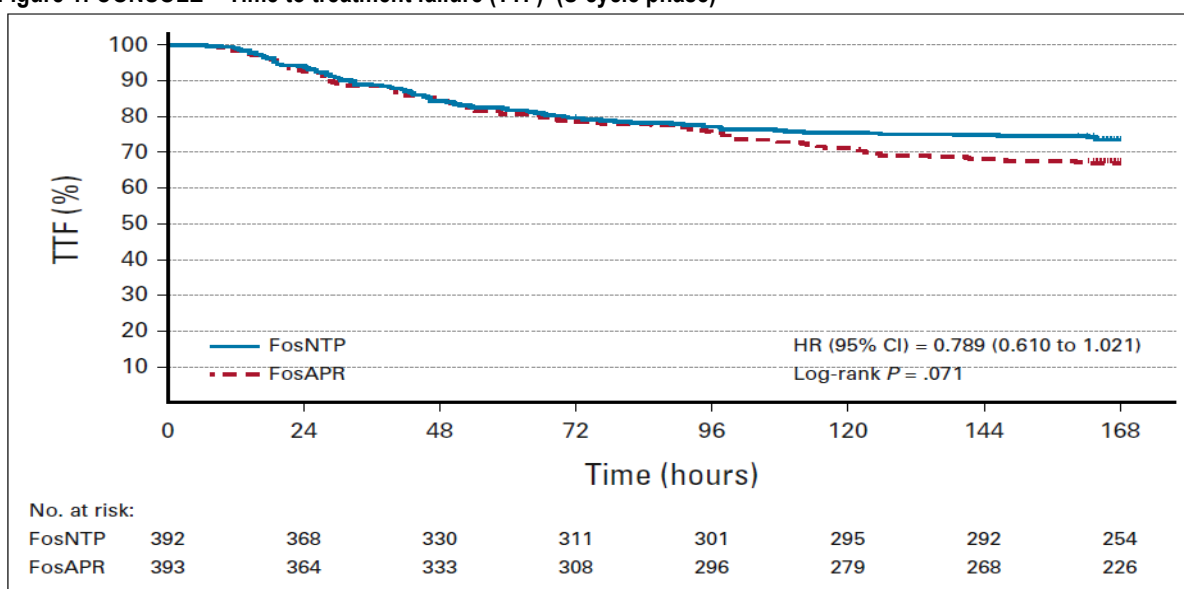
6.12 In the randomised double-blind S-cycle phase, the primary endpoint of overall CR (defined as “No emetic event and no rescue medication”) was 75.2% versus 71.0% with FosNTP+PALO versus FosAPR+PALO, respectively. The between group difference was 4.1% (95% CI: -2.1%, 10.3%), demonstrating non-inferiority of FosNTP compared to FosAPR (lower margin of the 95% CI for the absolute difference of -2.1% was above the NI margin of -10%). Superiority was not demonstrated from the data.

⁷ Guyatt GH, Oxman AD, Kunz R, Brozek J, Alonso-Coello P, Rind D, et al. GRADE guidelines 6. Rating the quality of evidence—imprecision. *Journal of clinical epidemiology*. 2011;64(12):1283-93.

6.13 Other secondary CR outcomes were generally similar between the FosNTP+PALO IV and the FosAPR+ PALO IV treatment arms, with no statistically significant differences over the acute, delayed or overall durations.

6.14 The time to treatment failure (TTF) (time to first emetic event or use of rescue medication) Kaplan-Meier (KM) curves in CONSOLE are presented in Figure 1.

Figure 1: CONSOLE – Time to treatment failure (TTF)^a (S-cycle phase)



Source: Figure 2-4, p71 of the submission.

CI=confidence interval; FosAPR=fosaprepitant; FosNTP=fosnetupitant; HR=hazard ratio; S-cycle= single chemotherapy cycle

^a Time to first emetic event or use of rescue medication.

6.15 The reduction in the hazard of first emetic event or use of rescue medication favoured the FosNTP+PALO IV treatment arm over the FosAPR+PALO IV treatment arm, but was not statistically significant (hazard ratio (HR): 0.79; 95% CI: 0.61, 1.02; p=0.071).

6.16 The primary objective of the CONSOLE-BC trial was the assessment of safety. Safety results are presented further below. Results of exploratory secondary efficacy outcomes are summarised in Table 7.

Table 7: CONSOLE-BC – Secondary efficacy outcomes

Outcome (including timeframe)	Definition	FosNTP+PALO IV N=51 n (%)	FosAPR+PALO IV N=49 n (%)	Comparative treatment effect (95% CI) ^a FosNTP+PALO vs. FosAPR+PALO	
				Risk difference ^a	Risk ratio ^a
Complete Response (CR)					
Overall ^b : 0-120 hr	No emetic event, no rescue medication	23 (45.9%)	25 (51.3%)	-5.9% (-25.5%, 13.6%)	0.88 (0.59, 1.33)
Complete protection					
Overall: 0-120 hr	No emetic event, no rescue medication, no more than mild nausea	21 (41.2%)	23 (46.9%)	-5.8% (-25.2%, 13.7%)	0.88 (0.56, 1.37)
Total control rate					
Overall 0-120 hr	No emetic event, no rescue medication, no nausea	14 (27.5%)	12 (24.5%)	3.0% (-14.2%, 20.1%)	1.12 (0.58, 2.18)

Source: Modified from Table 2-16, pp72-73 of the submission.

CI=confidence interval; FosAPR=fosaprepitant; FosNTP=fosnetupitant; IV=intravenous

^a Calculated for the submission - CONSOLE-BC was a safety study (descriptive) and no formal statistical analysis of efficacy or safety was pre-specified.

^b The overall CR rate was stratified by age category

- 6.17 There was a difference in the overall CR rate favouring the comparator FosAPR treatment arm. However, the number of patients per treatment arm was small and the trial was not powered to detect meaningful differences in efficacy. The overall CR rate standardised by age category was 45.9% (23/51 patients; 95% CI: 33.2%, 58.6%) in the FosNTP+PALO IV treatment arm and 51.3% (25/49 patients; 95% CI: 37.3%, 65.2%) in the FosAPR+PALO IV treatment arm.
- 6.18 The submission presented a meta-analysis on the comparative efficacy between the PALO dose used in the included trials (0.75 mg) and the registered PALO dose in NEPA IV (0.25 mg). Table 8 summarises the results.

Table 8: Meta-analysis comparing PALO 0.25 mg and 0.75 mg doses in HEC and MEC

Methods	Random effects meta-analysis of directly comparative studies		
Included trials	8 RCTs with N=1,926 patients from all randomised, double-blind studies with the two PALO doses. Included: n=4 HEC studies, n=4 MEC studies.		
Outcomes			
Results	All studies	HEC studies	MEC studies
Number of studies (number of patients)	8 (N=1,926)	4 (N=720)	4 (N=1,206)
RR (95% CI) for 5-day CR	1.00 (0.91,1.10) p=0.97	1.10(0.93,1.31)	0.96 (0.86,1.07)
RR (95% CI) for acute CR	1.00 (0.91,1.10) p=0.96	1.08 (0.88,1.32) p=0.49	0.99 (0.89,1.09) p=0.77
RR (95% CI) for delayed emesis	1.00 (0.92,1.09)	1.07 (0.91,1.25)	0.98 (0.88,1.08)
RR for incidence of Grade 3-4 TEAEs	No significant differences found (<i>Results not provided in the submission</i>)		

Source: Table 2-12, p60 of the submission.

CR=complete response; HEC=highly emetogenic chemotherapy; MEC=moderately emetogenic chemotherapy; PALO=palonosetron; RR=relative risk; TEAEs=treatment emergent adverse events.

Note: Results rounded to 2 decimal places

6.19 The submission concluded from the meta-analysis that there was similar efficacy and safety associated with both doses in terms of 5-day CR, acute CR, delayed emesis, and Grade 3-4 adverse events (AEs). Results from other reviews^{8,9} assessing the comparative effectiveness of these two PALO doses appear consistent with these results.

Comparative harms

6.20 Table 9 summarises overall AEs in the included trials.

⁸ Bria E, Lesser M, Raftopoulos H. Using two meta-analysis methods to determine whether common dose differences affect efficacy with the serotonin antagonist (5-HT) palonosetron: an individual patient data (IPD) meta-analysis and an abstracted data (AD) meta-analysis of 1947 patients entered into the 8 double-blinded randomized clinical trials (RCTs). *Support Care Cancer*. 2009;17(872):02-007

⁹ Likun Z, Xiang J, Yi B, Xin D, Tao ZL. A systematic review and meta-analysis of intravenous palonosetron in the prevention of chemotherapy-induced nausea and vomiting in adults. *The Oncologist*. 2011;16(2):207-16

Table 9: Adverse events in CONSOLE and CONSOLE-BC

	CONSOLE (S cycle)		CONSOLE-BC	
	FosNTP+PALO IV N=392	FosAPR+PALO IV N=393	FosNTP+PALO IV N=52	FosAPR+PALO IV N=50
	n (%)	n ^a (%)	n (%)	n (%)
AEs (all cause)	390 (99.5)	389 (99.0)	52 (100)	49 (98.0)
Grade ≥3 AEs (all cause)	254 (64.8)	231 (58.8)	43 (82.7)	36 (72.0)
TRAEs	87 (22.2)	100 (25.4)	11 (21.2)	11 (22.0)
Grade ≥3 TRAEs	10 (2.6)	12 (3.1)	5 (9.6)	0 (0.0)
Serious AEs	46 (11.7)	37 (9.4)	2 (3.8)	0 (0.0)
Serious TRAEs	0 (0.0)	2 (0.5)	1 (1.9)	0 (0.0)
AEs leading to discontinuation	0 (0.0)	3 (0.8)	0 (0.0)	1 (2.0)
AEs leading to death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
TRAEs leading to discontinuation	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)
TRAE leading to death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: Modified from Table 2-16, pp72-73 of the submission

AE=adverse event; FosAPR=fosaprepitant; FosNTP=fosnetupitant; IV=intravenous; PALO=palonosetron; TRAE=treatment-related AE.

^a For CONSOLE, n values were derived from percentages of reported AEs and TRAEs

6.21 The incidence of Grade ≥3 AEs was higher in the FosNTP+PALO IV treatment arm compared to the FosAPR+PALO IV treatment arm in both the CONSOLE (64.8% vs. 58.8%) and CONSOLE-BC (82.7% vs. 72.0%) trials. The incidence of Grade ≥3 TRAEs was also higher with FosNTP+PALO IV compared to FosAPR+PALO IV in CONSOLE-BC (9.6% vs. 0.0%), although similar between the treatment arms in CONSOLE. The PSCR argued that Grade ≥3 AEs and Grade ≥3 TRAEs should not be compared as the clinical trials involved a single dose, and this does not reflect clinical practice where patients would receive ongoing doses, and therefore may have fears of subsequent AEs. However, ESC noted that any severe AEs could impact on the fear of subsequent treatments and not just ISRs.

6.22 Table 10 summarises the incidence of ISRs in the included trials.

Table 10: AEs and TRAEs relevant to ISRs in CONSOLE and CONSOLE-BC

	CONSOLE (S cycle)			CONSOLE-BC		
	FosNTP+PALO IV N=392 n, (%)	FosAPR+PALO IV N=393 n, (%)	p-value ^a	FosNTP+PALO IV N=52 n, (%)	FosAPR+PALO IV N=50 n, (%)	p-value ^b
AEs relevant to ISRs						
Total ISR	43 (11.0)	81 (20.6)	<0.001	3 (5.8)	13 (26.0)	0.004
Injection site pain	22 (5.6)	52 (13.2)	<0.001	1 (1.9)	8 (16.0)	0.011
Injection site erythema	10 (2.6)	19 (4.8)	0.129	2 (3.8)	2 (4.0)	0.967
Injection site induration	4 (1.0)	11 (2.8)	0.115	0 (0.0)	2 (4.0)	0.225
Injection site swelling	6 (1.5)	5 (1.3)	0.773	0 (0.0)	1 (2.0)	0.461
Injection site vasculitis	5 (1.3)	5 (1.3)	1	0 (0.0)	3 (6.0)	0.112
Infusion site pain	0 (0.0)	2 (0.5)	0.499	NR	NR	-
Injection site phlebitis	2 (0.5)	1 (0.3)	0.624	0 (0.0)	2 (4.0)	0.225
Injection site thrombosis	1 (0.3)	1 (0.3)	1	NR	NR	-
Infusion site phlebitis	0 (0.0)	1 (0.3)	1	NR	NR	-
TRAEs relevant to ISRs^c						
Total ISR	1 (0.3)	14 (3.6)	<0.001	0 (0)	5 (10.0)	0.027
Injection site pain	1 (0.3)	11 (2.8)	0.006	0 (0)	4 (8.0)	0.056
Injection site erythema	0 (0.0)	3 (0.8)	0.249	0 (0.0)	0 (0)	-
Injection site induration	0 (0.0)	2 (0.5)	0.499	0 (0.0)	0 (0)	-
Injection site swelling	0 (0.0)	0 (0.0)	-	0 (0.0)	0 (0.0)	-
Injection site vasculitis	0 (0.0)	1 (0.3)	1	0 (0.0)	1 (2.0)	0.461

Source: Table 2-18, pp75-76 of the submission and the published reports for CONSOLE and CONSOLE-BC.

AE=adverse event; FosAPR=fosaprepitant; FosNTP=fosnetupitant; ISR= injection site reaction; IV=intravenous; NR=not reported; PALO=palonosetron; TRAE=treatment-related AE

^a Fisher's exact test

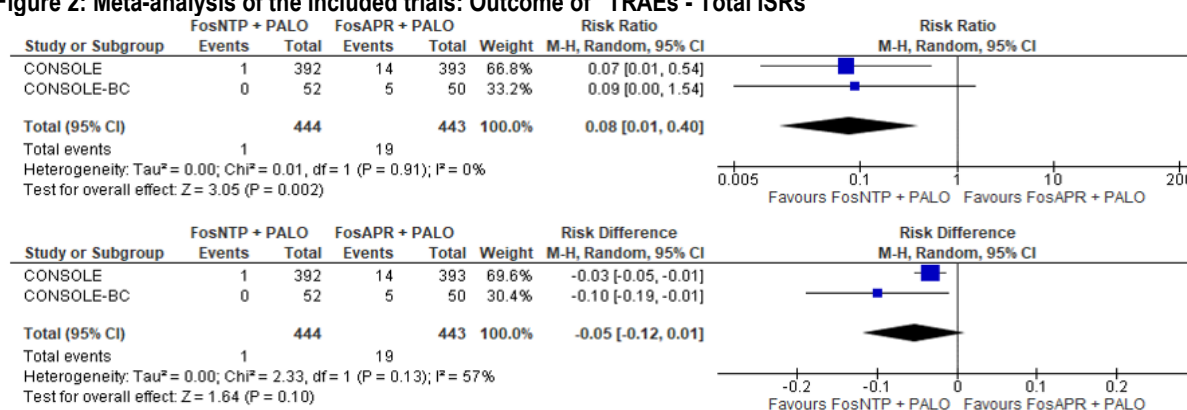
^b Not reported in CONSOLE-BC. p values for risk difference calculated for the submission using RevMan 5.3

^c There were no events recorded for pain, phlebitis, and thrombosis.

- 6.23 In CONSOLE, the incidence of total ISRs was lower in the FosNTP+PALO IV treatment arm compared with the FosAPR+PALO IV treatment arm (11.0% vs. 20.6%). Injection site pain also occurred at a lower frequency with FosNTP+PALO IV (5.6%) versus FosAPR+PALO IV (13.2%). The incidence of treatment-related total ISRs and injection site pain was also lower with FosNTP+PALO IV versus FosAPR+PALO IV (TRAE total ISRs: 0.3% vs. 3.6%; TRAE injection site pain: 0.3% vs. 2.8%).
- 6.24 The submission presented p-values for differences in the frequency of AEs between the treatment arms in the CONSOLE and CONSOLE-BC trials. There was no indication from the trial reports or submission that i) formal statistical analyses were pre-specified for safety in the CONSOLE and CONSOLE-BC trial protocols, and ii) adjustment for multiplicity was carried out in order to control the false positive rate. The presented p-values may lead to misinterpretation and inadequate conclusions about comparative safety. In the case of AEs, p-values can be of limited value; the clinical importance of differences in AEs between treatment arms depends on the seriousness or severity of the safety outcomes, irrespective of the derived p-values.

- 6.25 In CONSOLE, for FosNTP+PALO IV versus FosAPR+PALO IV, TRAEs (excluding ISRs) that were observed in $\geq 5\%$ of patients in either treatment arm were constipation (11.2% vs. 13.7%) and hiccups (4.8% vs. 7.1%).
- 6.26 Extended safety in single arm M-cycles phase of CONSOLE: 126 patients out of a total of 785 patients (16.1%) received open label FosNTP+PALO IV during cycles 2-4 (n=65 from the randomised FosNTP+PALO IV arm and n=61 from the randomised FosAPR+PALO IV arm). One patient (0.8%) reported a Grade ≥ 3 TRAE during chemotherapy Cycle 3. The only TRAE seen in $\geq 5\%$ of patients was hiccups (5.9% in Cycle 3). Overall, the incidence of AEs appeared lower in the extended phase compared to the randomised S-Cycle phase.
- 6.27 In CONSOLE-BC, in the FosNTP+PALO IV treatment arm, TRAEs (excluding ISRs) reported in $\geq 5\%$ of patients were headache, diarrhoea, urticaria, malaise, and decreased appetite (5.8% (3 out of 52 patients each)). One serious TRAE (urticaria) was reported in the FosNTP+PALO IV treatment arm which was resolved 6 days after its onset with treatment. In the FosAPR+PALO IV treatment arm, the TRAE reported in $\geq 5\%$ of patients was constipation (6.0% (3 of 50 patients)).
- 6.28 No AEs leading to death or discontinuation were reported in the trials.
- 6.29 The submission conducted a meta-analysis of ISR-related outcomes in CONSOLE and CONSOLE-BC using a random effects model. The forest plots for the outcomes of “TRAEs Total ISRs”, “TRAEs Injection site pain”, “AEs Total ISRs”, and “AEs Injection site pain” are presented in Figure 2, Figure 3, Figure 4, and Figure 5, respectively.

Figure 2: Meta-analysis of the included trials: Outcome of “TRAEs - Total ISRs”

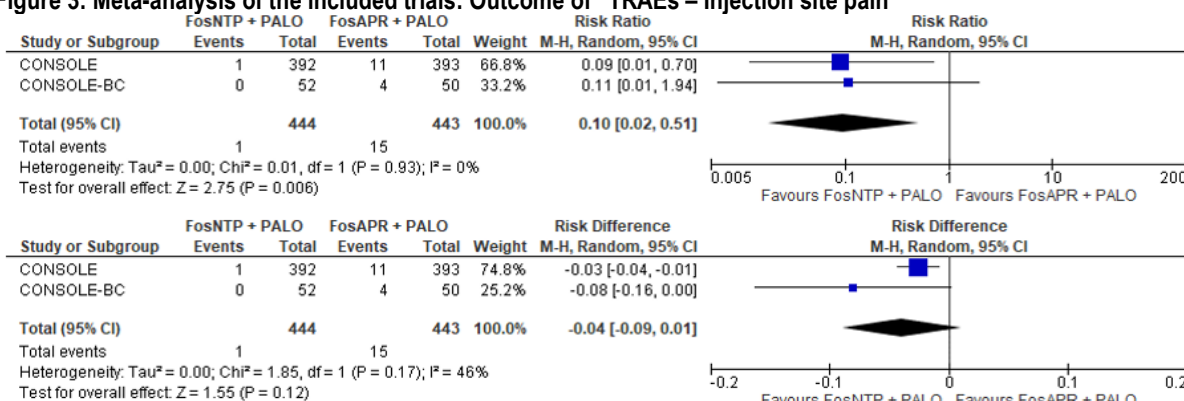


ISR: injection-site reactions; RD: risk difference; RR: risk ratio; TRAE: treatment-related adverse event.¶

Source: Table 2-21, p80, and Figure ES-2 of the Executive Summary of the submission.

CI=confidence interval; FosAPR=fosaprepitant; FosNTP=fosnetupitant; ISRs=injection site reactions; PALO=palonosetron; TRAEs=treatment-related adverse events.

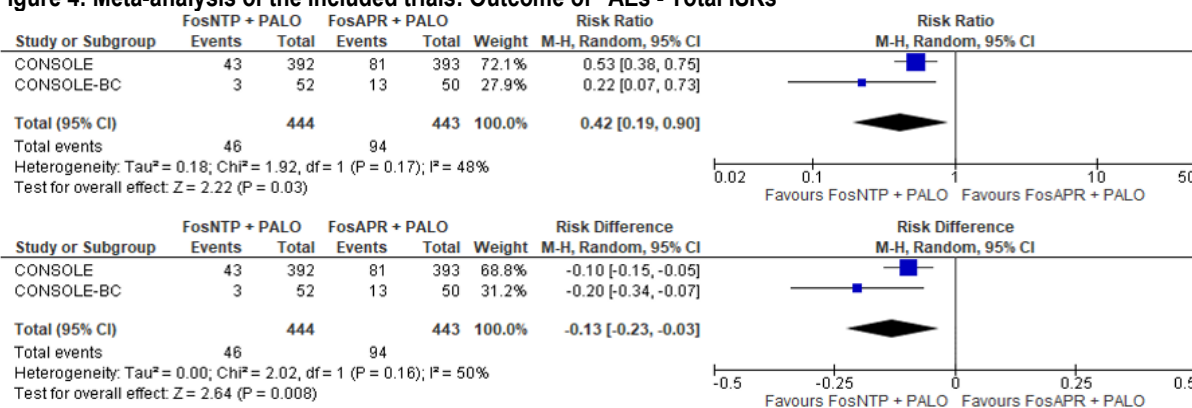
Figure 3: Meta-analysis of the included trials: Outcome of “TRAEs – Injection site pain”



ISR: injection-site reactions; RD: risk difference; RR: risk ratio; TRAE: treatment-related adverse event.

Source: Table 2-21, p80, and Figure ES-3 of the Executive Summary of the submission. CI=confidence interval; FosAPR=fosaprepitant; FosNTP=fosnetupitant; PALO=palonosetron; TRAEs=treatment-related adverse events

Figure 4: Meta-analysis of the included trials: Outcome of “AEs - Total ISRs”

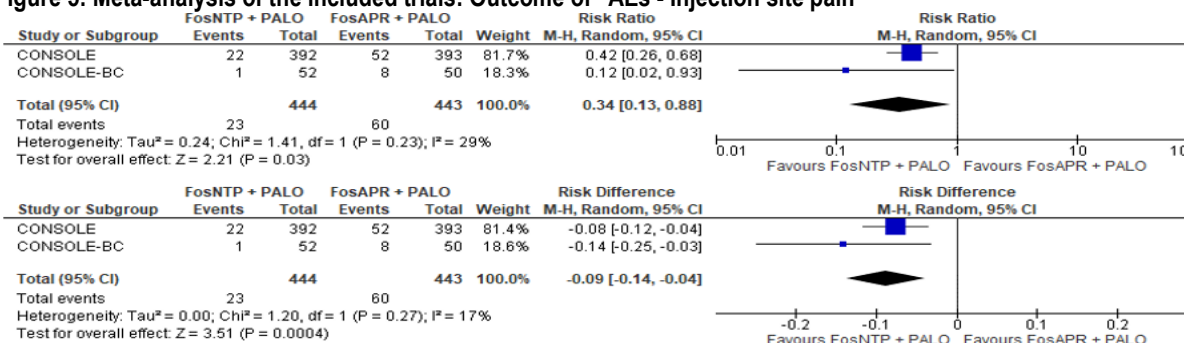


ISR: injection-site reactions; RD: risk difference; RR: risk ratio; TRAE: treatment-related adverse event.

Source: Table 2-21, p80, and Figure ES-4 of the Executive Summary of the submission.

AEs=adverse events; CI=confidence interval; FosAPR=fosaprepitant; FosNTP=fosnetupitant; ISRs=injection site reactions; PALO=palonosetron

Figure 5: Meta-analysis of the included trials: Outcome of “AEs - Injection site pain”



ISR: injection-site reactions; RD: risk difference; RR: risk ratio; TRAE: treatment-related adverse event.

Source: Table 2-21, p80, and Figure ES-5 of the Executive Summary of the submission.

AEs=adverse events; CI=confidence interval; FosAPR=fosaprepitant; FosNTP=fosnetupitant; PALO=palonosetron

- 6.30 The overall pooled treatment effects are not reliable given the clinical heterogeneity between the CONSOLE and CONSOLE-BC trials in terms of malignant tumour type (lung vs. breast), gender (female: 23% vs. 100%), age (≥ 55 years: 87% vs. 56%), regular drinking history (yes: 45% vs. 11%), smoking status (non-smoking: 17% vs. 71%), history of motion sickness (yes: 9% vs. 44-54%), and concurrent chemotherapy regimens (cisplatin-based chemotherapy vs. AC chemotherapy).
- 6.31 The submission concluded that:
- there was an approximate 90% statistically significant reduction in risk of TRAEs-total ISRs (RR: 0.08; 95% CI: 0.01, 0.40) and TRAEs-injection site pain (RR: 0.10; 95% CI: 0.02, 0.51) favouring FosNTP+PALO IV over FosAPR+PALO IV;
 - there was an approximate 60% reduction in risk of AEs-total ISRs (RR: 0.42; 95% CI: 0.19, 0.90) and an approximate 65% reduction in risk of AEs-injection site pain (RR: 0.34; 95% CI: 0.13, 0.88) favouring FosNTP+PALO IV over FosAPR+PALO IV which were statistically significant; and
 - The observed levels of risk reduction (and corresponding 95% CIs) were much greater than the 25% risk reduction proposed as the MCID based on GRADE recommendations.
- 6.32 The Pre-PBAC Response reiterated the meta-analysis results showed a clinically and statistically significant reduction in ISRs, particularly ISRs compared to other TEAEs and argued these results demonstrated that in terms of ISR adverse events, NEPA IV is superior to Emend IV. The Response also noted no MCID was found in published literature and argued the nominated MCID of a risk reduction of $>25\%$ was based on the GRADE (Grading of Recommendations, Assessment, Development and Evaluations) criteria.

Benefits/harms

- 6.33 A benefits and harms table is not presented as the submission made a claim of non-inferior comparative effectiveness (however did make a claim of superior comparative safety based on ISRs). Based on the meta-analysis, the submission concluded that in terms of number needed to treat (NNT) with FosNTP+PALO IV, treating 20-25 patients (based on the RD¹⁰ and RR¹¹, respectively) is required to avoid one TRAE ISR. The NNT to avoid one AE total ISR is 8 patients and to avoid one AE injection site pain is 11 patients.

¹⁰ Using the formula $NNT = 1/RD$, see https://training.cochrane.org/handbook/current/chapter-15#_Ref529393759

¹¹ Using the formula $NNT = 1/(ACR \times (1-RR))$ with ACR = assumed comparator risk, which is the weighted risk of TREA ISR in the comparator arms of CONSOLE and CONSOLE-BC, see https://training.cochrane.org/handbook/current/chapter-15#_Ref529393759

Clinical claim

- 6.34 The submission described NEPA IV as non-inferior in terms of effectiveness and superior in terms of safety compared to Emend IV plus a 5-HT3 RA for the prevention of nausea and vomiting in patients undergoing treatment with MEC and HEC. Both therapies are administered as a single dose per cycle prior to the administration of chemotherapy.
- 6.35 The therapeutic conclusion presented in the submission regarding effectiveness appeared to have been adequately supported by the direct evidence from the CONSOLE and CONSOLE-BC trials, noting that the assessment of efficacy was a secondary objective in CONSOLE-BC.
- 6.36 The evaluation considered the claim of superior comparative safety to be uncertain. The incidence of Grade ≥ 3 AEs was numerically higher in the FosNTP+PALO IV treatment arm compared to the FosAPR+PALO IV treatment arm in both the CONSOLE (64.8% vs. 58.8%) and CONSOLE-BC (82.7% vs. 72.0%) trials. The incidence of Grade ≥ 3 TRAEs was also numerically higher with FosNTP+PALO IV compared to FosAPR+PALO IV in CONSOLE-BC (9.6% vs. 0.0%), although similar between treatment arms in CONSOLE. Importantly, there were no differences between the treatment arms in terms of TRAEs leading to discontinuation of treatment (no events in CONSOLE and only one event with FosAPR+PALO IV in CONSOLE-BC) indicating that the observed TRAEs in the trials were well tolerated, and unlikely to have been severe enough to warrant changes in treatment/management.
- 6.37 ISR data from the individual trials, and from the meta-analysis of safety (recognising the clinical heterogeneity between the CONSOLE and CONSOLE-BC trials), showed a reduction in risk of ISRs associated with FosNTP+PALO IV over FosAPR+PALO IV. Notwithstanding the low response rate in a survey of clinical experts conducted by the sponsor, responding medical oncologists estimated that, for nearly all of the patients (98.7%), the ISR associated with the use of Emend IV was not severe enough to require some form of medical treatment. The Pre-PBAC Response noted that based on responses from both oncology nurses and oncologists, 20% of ISRs were severe enough to require treatment and argued that in practice, the source of the AE report (oncology nurse or oncologist) should have no bearing on how reports are interpreted.
- 6.38 The PSCR reiterated that the ISRs are clinically relevant, and further argued there is additional evidence supporting Emend IV having a high rate of ISRs that may lead to changes in the administration of treatment, particularly for AC chemotherapy (doxorubicin/cyclophosphamide) administered for breast cancer. The PSCR stated that a 2014 study (Sato, Kondo et al 2014¹²) found the ISR rate per patient and per

¹² Sato, Y., M. Kondo, A. Inagaki, H. Komatsu, C. Okada, K. Naruse, T. Sahashi, J. Kuroda, H. Ogura, S. Uegaki, T. Yoshida, Y. Mori, H. Sawada, S. Watanabe, H. Sugiura, Y. Endo, N. Yoshimoto, T. Toyama, S. Iida, K. Yamada, K. Kimura and A. Wakita (2014). "Highly Frequent and Enhanced Injection Site Reaction Induced by Peripheral Venous Injection of Fosaprepitant in Anthracycline-Treated Patients." *Journal of Cancer* 5(5): 390-397.

injection was higher in the Emend IV group than the control group. The ESC considered the focus on ISRs was overall poorly justified and further considered that while the statistical analyses may indicate NEPA IV is associated with fewer ISRs, the clinical significance of this difference remained uncertain. In the broader context of a claim of superior comparative safety, the ESC was of the view that this one statistical difference did not adequately support a claim of superior comparative safety.

- 6.39 The PBAC considered that the claim of non-inferior comparative effectiveness was reasonable.
- 6.40 The PBAC considered that the claim of superior comparative safety, based on a reduction in the number and severity of ISRs was not adequately justified, as the focus on ISRs and its clinical significance was highly uncertain. Based on the available evidence, the PBAC considered a claim of non-inferior comparative safety to be reasonable.

Economic analysis

- 6.41 The submission presented a cost-minimisation approach (CMA) comparing NEPA IV with Emend IV + a 5-HT3 RA (PALO IV was nominated as the 5-HT3 RA). While the claim of superior safety may be uncertain, the presentation of a CMA is reasonable. However, the comparator applied in the cost-minimisation may not be the least costly amongst the relevant alternative therapies, as NEPA IV may also substitute for other combinations of a NK1 RA + a 5-HT3 RA, including NEPA. The PBAC previously considered that NEPA IV be cost-minimised to the lowest cost combination of a NK1 RA and a 5-HT3 RA. Emend IV + PALO IV is not the lowest cost combination of a NK1 RA and a 5-HT3 RA, as NEPA and combinations of aprepitant with other 5-HT3 RAs are associated with lower costs. The table below summarises the costs of all possible NK1 and 5-HT3 RAs.

Table 11: Costs per course of relevant alternative therapies

Component	Dose per patient per course of acute therapy ^a	AEMP cost per course ^b
FDC NK1 RA and 5-HT3 RA		
NEPA IV (netupitant + palonosetron)	235 mg + 0.25 mg on Day 1	\$█
NEPA oral (netupitant + palonosetron)	300 mg + 0.25 mg on Day 1	\$97.16
NK1 inhibitors and 5-HT3 RAs (used in combination)		
5-HT3 RAs^c		
• Palonosetron IV	0.25 mg on Day 1	\$22.04
• Ondansetron oral	16-24 mg on Day 1	\$4.33
• Granisetron IV	3 mg on Day 1	\$2.50
• Tropisetron IV	5 mg on Day 1	\$4.57
NK1 inhibitors^d		
• Emend IV	150 mg	\$97.16
• Aprepitant oral	165 mg on Day 1	\$62.30
5-HT3 RAs (used alone for MEC)		
• Palonosetron IV	0.25 mg on Day 1	\$22.04
• Ondansetron oral ^e	16-32 mg on Days 1-5, (flexible dosing)	\$12.99 - \$21.65
• Granisetron IV	3 mg on Day 1, 2 mg oral tablet on Days 2-3	\$19.08

Source: Constructed during the evaluation.

^a As per NCCN Guidelines (**Error! Reference source not found.**, Attachment 1)

^b per chemotherapy cycle

^c 5-HT3 RAs are given alone for MEC and in combination with NK1 inhibitors for HEC

^d NK1 RAs are only given in combination with a 5-HT3 RA for HEC/FDC=Fixed dose combination; NK1=neurokinin 1; 5-HT3 RA=5-hydroxytryptamine receptor antagonist; AEMP=approved ex-manufacturer price; IV=intravenous; MEC=moderately emetogenic chemotherapy; HEC=highly emetogenic chemotherapy

^e Ondansetron regimen updated based on advice of the ESC that a full 5 day course was likely to be used in practice.

6.42 The key assumptions and components of the cost-minimisation approach are summarised below.

Table 12: Key components and assumptions of the cost-minimisation approach

Component	Claim or assumption
Treatments	NEPA IV vs Emend IV + 5-HT3 RA (nominated to be palonosetron). NEPA IV may also replace NEPA oral or other combinations of a NK1 RA + a 5-HT3 RA.
Therapeutic claim: effectiveness	Based on evidence presented effectiveness is assumed to be non-inferior. This is reasonable
Therapeutic claim: safety	Based on evidence presented, safety is assumed to be superior. This is not reasonable as the reduction in risk of ISRs associated with NEPA IV may not be clinically meaningful (also discussed in 'other costs' below).
Evidence base	Meta-analysis of direct randomised controlled trials (CONSOLE and CONSOLE-BC).
Equi-effective doses	1 dose of NEPA IV (containing a FDC of 235 mg FosNTP and 0.25 mg PALO IV) administered on Day 1 of each chemotherapy cycle is equivalent to 1 dose of Emend IV (150 mg FosAPR) given concurrently with a 5-HT3 RA such as palonosetron (0.25 mg) administered on Day 1 of each chemotherapy cycle.
Direct medicine costs	Costs per patient per course of acute therapy, one vial NEPA IV compared to one vial of Emend IV and one vial of PALO IV.
Other costs or cost offsets	No difference in monitoring costs and administration costs were assumed. Consistent with the claim of superior safety, the cost of treating injection site pain was included. This is not reasonable as it is unclear which adverse events, if any, would require additional medical attendance.

Source: Adapted from Table 3-1, p88 of the submission

FDC=Fixed dose combination; NK1=neurokinin 1; 5-HT3 RA=5-hydroxytryptamine receptor antagonist; IV=intravenous; NEPA=fixed dose combination netupitant/palonosetron; IV=intravenous

- 6.43 The submission, based on the meta-analysis of the CONSOLE and CONSOLE-BC trials, established the equi-effective doses as follows: FDC fosnetupitant (235 mg)/palonosetron (0.25 mg) IV administered on Day 1 of each chemotherapy cycle is equi-effective to the combination of Emend IV (150 mg) + palonosetron IV (0.25 mg) administered on Day 1 of each chemotherapy cycle. The PALO dose administered in the trials (0.75 mg) was different from that available as part of the FDC of NEPA IV (0.25 mg). Results from a meta-analysis presented in the submission indicated these two PALO doses had similar efficacy and safety profiles. Overall, the evaluation considered that the equi-effective doses established in the submission appear reasonable.
- 6.44 In addition to direct medicine costs, the submission included, consistent with the claim of superior safety, an incremental cost saving of \$0.79 per patient associated with managing/monitoring of ISRs associated with the comparator. These cost savings were based on the risk difference in injection site pain observed from the CONSOLE study. The purpose of the meta-analysis of safety remains unclear as the submission did not utilise the meta-analysed results for risk differences in ISRs. Further, it is difficult to discern which AEs, if any, would require an additional attendance. As such, the cost savings claimed per patient are uncertain and may not be realised.
- 6.45 The results of the CMA are presented below.

Table 13: Cost-minimisation of NEPA IV against Emend IV + PALO IV

	NEPA IV	Emend IV + PALO IV
Direct medicines costs		
Proposed NEPA IV AEMP	\$	-
Emend IV AEMP	-	\$97.16
Palonosetron AEMP	-	\$22.04
Costs associated with managing AEs		
Incidence of injection site pain [A]	5.6%	13.2%
Paracetamol, two tablets [B]	\$0.195	\$0.195
Nurse attendance [C]	\$	\$10.15
Management of ISR pain $A \times (B + C)$	\$	\$1.37
Total cost (Direct medicines cost + Management of ISR pain)	\$	\$120.57
Difference		\$0.00

Source: Compiled during evaluation.

AEs= adverse events; ISR=injection site reaction; FDC=fixed dose combination; AEMP=approved ex-manufacturer price

- 6.46 Based on Table 11, the lowest cost combination would be aprepitant oral and granisetron (based on an assumption of a single dose of granisetron). At the price proposed in the submission, NEPA IV is associated with additional costs.
- 6.47 The ESC considered that, as the claim of superior comparative safety over Emend IV (plus a 5-HT3 RA) was not adequately justified, excluding alternative therapies on the basis of safety differences was not reasonable. However, if restricted to patients who are unsuitable for an oral alternative, the ESC considered it may be reasonable to exclude oral agents as alternative therapies.

- 6.48 The ESC noted there was variation in the duration of effectiveness of doses of some agents, and considered it may be reasonable for the cost-minimisation approach to reflect the cost of additional doses. To that end, the ESC noted the argument raised in the PSCR that granisetron administration was complex and may require additional administrations (incurring additional costs) and concomitant corticosteroid administration. The submission stated that granisetron only provides 24 hours of anti-emetic coverage and included clinical advice that when granisetron is used, patients are then given 4-5 tablets to be taken daily, thereafter. The pre-PBAC Response similarly noted that the recommended dosing of tropisetron IV includes oral administration on days 2-6.
- 6.49 The Pre-PBAC Response disagreed the observed outcomes for ISRs were not clinically significant, however accepted the removal of the offset from the CMA. The Response also noted the advice of the ESC that the CMA should account for the need for additional doses of granisetron and tropisetron and argued the inclusion of these in the approach was appropriate as palonosetron achieves the same outcomes with a single dose. The Response also noted tropisetron was unsuitable for patients who were CYP2D6 ultrarapid metabolisers.

Drug cost/patient/cycle

- 6.50 Under Section 100 listings, the drug cost/patient/cycle of chemotherapy was \$ [REDACTED] for NEPA IV, \$97.16 for Emend IV and \$22.04 for PALO IV. These costs were assumed to apply on day 1 of a chemotherapy cycle.

Estimated PBS usage & financial implications

- 6.51 This submission was not considered by DUSC. The submission used a market share approach to estimate the extent of use of NEPA IV and the financial impact of listing it on the PBS. The key inputs for the financial analysis are summarised in Table 14.

Table 14: Data sources and parameter values applied in the utilisation and financial estimates

Data	Value	Source	Comment
Eligible population			
Size of the market, 2022	█ ¹ GE scripts, █ ¹ CT scripts	The number of Emend IV scripts (PBS items 11107N and 11103J), 2021	May be reasonable, if restricted to patients ineligible for oral anti-emetics.
Growth rate	█%	Based on Emend IV scripts dispensed between 2019 and 2021.	This growth rate may be optimistic as the rate of cancer incidence over the last 5 years was around 3% ¹ . The pre-PBAC Response noted the AIHW report also reported that population growth was not consistent across age groups and cancer is more commonly diagnosed in older populations where growth is projected to be greatest.
Treatment utilisation			
Uptake rate	Yr 1: █% Yr 2: █% Yr 3: █% Yr 4: █% Yr 5-6: █%	Assumption	Uptake rates may be underestimated owing to the convenience of administering NEPA IV (single injection) over the combination of Emend IV and palonosetron IV, which have to be administered sequentially.
Costs			
Proposed medicine	GE: \$█ CT: \$█	Proposed DPMQ	The proposed price of NEPA IV was requested on a cost-minimisation basis against the combination of Emend IV and PALO IV.
Comparator – Emend IV	GE: \$116.83 CT: \$97.16	PBS item numbers: 11107N, 11103J	This was reasonable
Comparator - palonosetron	CE: \$35.84 CT: \$22.04	PBS item numbers: 5295Q, 5853C	This was reasonable
Patient co-payment	\$18.84 \$6.87	Services Australia PBS item statistics PBS item numbers: 11107N, 11103J	This was reasonable.
PBS/RPBS split	GE: 98.05%/1.95% CT: 99.7%/0.3%	Services Australia PBS Item statistics PBS item numbers: 11107N, 11103J	This was reasonable
Nurse practitioner attendance	\$8.12 per service	MBS Item 82200 (80% rebate)	While the source may be reasonable, a reduction in nurse practitioner attendances as claimed may not be realised. Additionally, offsets for general practice items should not be included in financial estimations as these costs/savings to Government will not be realised in clinical practice.

Source: Table 4-1, p93 of the submission.

5-HT3 RA=5-hydroxytryptamine 3 receptor antagonist; CT=chemotherapy; DPMQ=dispensed price for maximum quantity, GE=General Schedule; MBS=Medicare benefits schedule; NK1 RA=neurokinin 1 receptor antagonist; PBS=pharmaceutical benefits scheme; PSD=public summary document; RPBS=repatriation pharmaceutical benefits scheme.

^a Australian Institute of Health Welfare. Cancer data in Australia. Canberra: AIHW 2022

The redacted values correspond to the following ranges:

¹ 500 to < 5,000

- 6.52 The submission used a market share approach that assumed NEPA IV would only be used in the market that currently uses Emend IV for the prevention of CINV. However, as NEPA IV may also replace NEPA and other combinations of NK1 + 5-HT3 RAs, the approach used may not adequately capture the extent of use and financial impact of listing NEPA IV on the PBS.
- 6.53 The submission assumed the size of the market for IV therapies for the prevention of CINV would grow based on the average annual growth in use of Emend IV 2019-2021 (1%). This may not be reasonable as cancer incidence over the last 5 years has grown at an average annual rate of 3.0%¹³, which was comparable to the increase in use of PBS-listed emetogenic chemotherapy services in the last 5 years (average annual growth rate of 3.4%).
- 6.54 The submission assumed the market share of NEPA IV would grow from 0% in Year 1 up to 10% by Year 6. There is some uncertainty around the lower and upper estimates of the uptakes rates utilised in the submission. The uptake rates may be an underestimate owing to the convenience of administering a NK1 RA and 5-HT3 RA (the components of NEPA IV) as a single injection as well as clinicians' familiarity with the oral form of NEPA.
- 6.55 The submission estimated a net cost of \$0 to < \$10 million to the PBS/RPBS in Year 6. Additional costs to the PBS/RPBS are a result of a reduction in patient co-payments – where one is applied per script or original script for NEPA IV compared to two co-payments per script or original script for Emend IV + PALO IV. It is also important to note that if NEPA IV were to replace other combinations of NK1 + 5-HT3 RAs, and in those who would otherwise have received in 5-HT3 RAs alone, there may be a further increase in the net cost to the PBS/RPBS.
- 6.56 A summary of the net financial implications for PBS/RPBS is provided in the table below.

¹³ Australian Institute of Health Welfare. Cancer data in Australia. Canberra: AIHW2022.

Table 15: Estimated reduction in the net cost to the PBS/RPBS

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Size of market	1	5	5	5	5	6
Market share taken by NEPA IV	%	%	%	%	%	%
NEPA IV scripts	2	1	1	5	5	5
- GE scripts	2	2	1	1	5	5
- CT scripts	3	2	2	2	2	2
Cost of NEPA IV ^a	\$ 4	\$ 4	\$ 4	\$ 4	\$ 4	\$ 4
Patient co-payments ^b	\$ 4	\$ 4	\$ 4	\$ 4	\$ 4	\$ 4
Cost of NEPA IV to the PBS/RPBS less copays	\$ 4	\$ 4	\$ 4	\$ 4	\$ 4	\$ 4
Reduction in Emend IV scripts	2	1	1	5	5	5
Reduction in palonosetron scripts	2	1	1	5	5	5
Reduction in cost of Emend IV ^c and palonosetron ^d	\$ 4	\$ 4	\$ 4	\$ 4	\$ 4	\$ 4
Reduction in patient co-payments ^e	\$ 4	\$ 4	\$ 4	\$ 4	\$ 4	\$ 4
Reduction in cost to the PBS/RPBS less copays	\$ 4	\$ 4	\$ 4	\$ 4	\$ 4	\$ 4
Net cost to the PBS/RPBS	\$ 4	\$ 4	\$ 4	\$ 4	\$ 4	\$ 4

Source: Tabulated during evaluation from sheets “3b. Impact -proposed (pub), 4b. Impact – affected (pub) and 6. Net changes (SA)” of the “FosNTP – Akynzeo IV – Section 4 – Base Case (Final)” workbook included in the submission.

^a \$ 4 per GE script and \$ 4 per CT script

^b \$18.84 per PBS script and \$6.87 per RPBS script. These are applied for each GE script or each original CT script (assumed to be 1/6th of total CT scripts)

^c \$116.83 per GE script and \$97.16 per CT script

^d \$35.84 per GE script and \$22.04 per CT script

^e 18.84 per PBS script and \$6.87 per RPBS script. These are applied for each GE or each original CT Emend IV script (assumed to be 1/6th of total CT scripts) and for each palonosetron script.

CT=chemotherapy; GE=general schedule; IV=intravenous; NEPA=fixed dose combination netupitant/palonosetron; PBS=pharmaceuticals benefits scheme; RPBS=repatriation pharmaceuticals benefits scheme

The redacted values correspond to the following ranges:

¹ 5,000 to < 10,000

² 500 <5,000

³ <500

⁴ \$0 to < \$10 million

⁵ 10,000 to <20,000

⁶ 20,000 to <30,000

6.57 The financial estimates also included a reduction in the use and MBS cost of nurse practitioner attendance due to a reduction in injection site pain. None of the TRAEs in CONSOLE and CONSOLE-BC led to discontinuation and so it may not be reasonable to assume a reduction in these costs to the MBS. Additionally, offsets for general practice items should not be included in financial estimations as these costs/savings to Government will not be realised in clinical practice.

6.58 The ESC considered that if NEPA IV were restricted only to patients who cannot swallow, the utilisation was likely to be lower than estimated, as the population of eligible chemotherapy patients who genuinely cannot use an oral alternative was likely to be small.

Quality Use of Medicines

6.59 The submission noted that NEPA IV contains both an NK1 RA as well as a 5-HT3 RA and thereby circumvents the need for concurrent use of these agents – as is the case with

administration of Emend IV. The sponsor claimed that the listing of NEPA IV would improve access to anti-emetics/anti-nauseants in patients who would otherwise be unable to take the oral forms of these drugs.

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

7 PBAC Outcome

- 7.1 The PBAC recommended the General Schedule and Section 100 (Efficient Funding of Chemotherapy – Related Benefits) listing of fosnetupitant (FosNTP) with palonosetron (herein referred to as NEPA IV) for the prophylaxis of nausea and vomiting in patients receiving highly or moderately emetogenic chemotherapy (HEC and MEC, respectively), who are unable to swallow or are contraindicated to an oral anti-emetic regimen. The PBAC's recommendation for listing was based on, among other matters, its assessment, as described above, that the cost-effectiveness of NEPA IV would be acceptable if it were cost-minimised to IV fosaprepitant (FosAPR) and IV palonosetron.
- 7.2 The PBAC advised the equi-effective doses were as follows:
- For the NK1 antagonist component:**
- Fosnetupitant 235 mg IV (as part of NEPA IV) = fosaprepitant 150 mg IV, both given once per chemotherapy cycle.
- For the 5-HT3 RA component:**
- Palonosetron 0.25 mg IV (as part of NEPA IV) = palonosetron 0.25 mg IV (given concomitantly with an IV NK1 antagonist), both given once per chemotherapy cycle.
- 7.3 The PBAC considered there was a low-to-moderate clinical need for additional anti-emetic options for patients receiving HEC or MEC who cannot use oral therapies, noting that a combination of IV FosAPR with an IV 5-HT3 RA and dexamethasone was the standard option for these patients.
- 7.4 The PBAC noted the sponsor was willing to accept a listing for NEPA IV only for patients who cannot swallow or are contraindicated to oral alternatives, and the PBAC considered this would be reasonable. However, the PBAC considered the risk of use by patients who are able to take an oral therapy was high, as many patients may find a single IV administration at time of chemotherapy more convenient than daily oral therapy (paragraph 5.4 refers). On that basis, the PBAC considered an Authority Required (telephone/electronic) level of authority was appropriate for the listing of NEPA IV. The PBAC also considered changes to the restriction for oral netupitant/palonosetron (item 6.18, March 2023 PBAC meeting) should be flowed on to the listing of NEPA IV.
- 7.5 The PBAC considered the nominated comparator of FosAPR plus an 5-HT3 RA was reasonable. The Committee advised, noting that use is to be restricted to patients who cannot use oral anti-emetics, that oral 5-HT3 RA therapies should not be considered

alternatives. Similarly, the PBAC noted that the IV forms of granisetron and tropisetron require, at least for a proportion of patients, subsequent oral therapy and therefore considered they should not be considered alternative therapies, and further noted that in the population who are unable to use oral therapies, additional doses would need to be IV based and would incur further additional costs, including for administration. The IV form of palonosetron does not require subsequent therapy. The PBAC therefore considered the comparator to be IV FosAPR plus IV palonosetron given the restricted listing for NEPA IV for patients who cannot swallow or are contraindicated to oral treatments.

- 7.6 The PBAC noted two randomised, head-to-head clinical trials comparing NEPA IV to a regimen of IV FosAPR + palonosetron (both arms also received dexamethasone), with primary outcomes of effectiveness for one study (CONSOLE) and safety for the other (CONSOLE-BC). The PBAC noted CONSOLE demonstrated non-inferiority of FosNTP + palonosetron and FosAPR + palonosetron based on the outcome of overall complete response (defined as “no emetic event and no rescue medication”) with the lower 95% CI for the absolute difference (-2.1%) being greater than the non-inferiority margin (-10%). The PBAC noted the dose of palonosetron used in CONSOLE and CONSOLE-BC was 0.75 mg whereas the registered dose is 0.25 mg but considered the presented meta-analysis of eight randomised trials comparing the two doses adequately supported similar efficacy and safety. Based on the evidence presented, the PBAC was satisfied that NEPA IV was of non-inferior comparative effectiveness to IV FosAPR and IV palonosetron.
- 7.7 The PBAC noted the submission made a claim of superior comparative safety to a FosAPR-based regimen, based on a reduction in total injection site reactions (ISRs) and injection site pain. The PBAC considered the focus on these outcomes was not adequately supported in the context of the sponsor’s survey indicating that the most common ISR perceived by physicians was phlebitis (30% versus 14% for injection site pain), and the higher rate of grade 3 or above treatment related adverse events with NEPA IV compared with FosAPR plus palonosetron (9.6% vs 0%). The PBAC further considered that the clinical significance of a reduction in ISRs (and their severity) was highly uncertain, particularly as they appeared to only require medical intervention infrequently and did not appear to have an impact on treatment discontinuation (paragraphs 6.36 and 6.37 refer). The PBAC also noted a substantial number of patients receiving HEC or MEC would likely have a central IV line in place, further reducing the risk of localised ISRs in the proposed population. The PBAC considered the claim of superior safety was not adequately supported however, a claim of non-inferior comparative safety would be reasonable.
- 7.8 The PBAC considered the methodology for the cost minimisation approach used in the submission was reasonable, however agreed with the ESC that offsets for the management of ISRs were not justified as noted in the above paragraph. The PBAC therefore considered the cost minimisation approach should be based on direct drug costs, using the equi-effective doses described in paragraph 7.2.

- 7.9 The PBAC noted the submission estimated the financial implications using a market share approach that assumed NEPA IV would only replace IV FosAPR for the prevention of CINV. The PBAC considered this reasonable on the basis of a restricted listing for NEPA IV for patients who cannot swallow or are contraindicated to oral alternatives. However, the PBAC considered that the annual market growth of 1% was overestimated, noting this increased the market by nearly 3-fold over the 6 year period of the estimates, and the uptake was potentially underestimated in the context of the additional convenience of a single infusion but likely overestimated in the context of a restricted listing for patients unable to use oral therapies. Overall given the cost-minimisation approach, the PBAC noted the net cost to the PBS/RPBS would be small and due to a reduction in patient co-payments with one per script for NEPA IV compared to two co-payments per script for FosAPR and palonosetron. The PBAC considered the assumed reduction in MBS costs for nurse practitioner attendance due to a reduction in injection site pain was unreliable and should be removed from the estimates.
- 7.10 The PBAC requested the Drug Utilisation Sub-Committee (DUSC) undertake a review of the uptake and use of NEPA IV to assess whether the utilisation is consistent with estimates of the population who cannot use oral therapies 24 months following its listing on the PBS.
- 7.11 The PBAC advised that the combination drug FosNTP with palonosetron should be treated as interchangeable on an individual patient basis with FosAPR plus a 5-HT3 RA.
- 7.12 The PBAC advised that nurse practitioner prescribing arrangements for NEPA IV should be consistent with the listings of FosAPR, i.e., permitted for the General Schedule listings, but not for the Section 100 (CT) listings.
- 7.13 The PBAC recommended that the Early Supply Rule should not apply, similar to current listings for FosAPR.
- 7.14 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because NEPA IV is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over an alternative IV NK1 antagonist + IV 5-HT3 RA, or not expected to address a high and urgent unmet clinical need given the presence of an alternative therapy, the criteria prescribed by the National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022 for Pricing Pathway A were not met.
- 7.15 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:

Recommended

8 Recommended listing

8.1 Add new item/s as follows:

Name, Restriction, Manner of administration and form	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Proprietary Manufacturer	Name and
FOSNETUPITANT with PALONOSETRON Fosnetupitant 235 mg plus palonosetron 250 microgram powder for IV infusion, vial	NEW	1	1	5	Akynzeo IV®	Juniper Biologics Pty Ltd

Restriction Summary: variant of 6886 / Treatment of Concept: variant of 6886

Concept ID	Category / Program: GENERAL – General Schedule (Code GE) Section 100 – Efficient Funding of Chemotherapy {Related Benefits}
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners (GE listings only)
	Restriction Level / Method: <input type="checkbox"/> Unrestricted benefit <input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required – In Writing <input checked="" type="checkbox"/> Authority Required – Telephone/Electronic/Emergency <input type="checkbox"/> Authority Required – Streamlined
	Condition: Nausea and vomiting
	Indication: Nausea and vomiting
	Clinical Criteria
	Treatment must be for prevention of nausea and vomiting associated with moderate to highly emetogenic anti-cancer therapy
	AND
	Clinical criteria: The treatment must be in combination with dexamethasone, unless contraindicated
	AND
	Clinical criteria: Patient must be unable to swallow; or
	Patient must be contraindicated to oral anti-emetics.
	Prescribing Instructions: No more than 1 vial of fosnetupitant 235 mg plus palonosetron 250 microgram injection will be authorised per cycle of cytotoxic chemotherapy.
	Administrative Advice: This medicine is not PBS-subsidised for nausea and vomiting associated with radiotherapy being used to treat malignancy.
	Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
	Administrative Advice: No increase in the maximum number of repeats may be authorised.
	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.

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

9 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.

10 Sponsor's Comment

The sponsor had no comment.