

5.19 FOSNETUPITANT with PALONOSETRON, Powder for Injection containing fosnetupitant 235 mg with palonosetron 250 microgram, Akynzeo IV[®], Mundipharma Pty Ltd

1 Purpose of application

- 1.1 The minor submission sought a General Schedule and Section 100 (Efficient Funding of Chemotherapy – Related benefits (Code CT)) Authority Required (STREAMLINED) listing of an intravenous (IV) form of fosnetupitant 235 mg with palonosetron 250 mcg (Akynzeo IV[®]) fixed-dose combination (FDC) (henceforth referred to as NEPA IV), under the same conditions as the currently PBS listed capsule form, netupitant 300 mg with palonosetron 500 mcg capsule (Akynzeo[®]) (henceforth referred to as NEPA oral).

2 Background

- 2.1 Fosnetupitant is a neurokinin-1 receptor antagonist (henceforth referred to as NK1 RA) and palonosetron is a 5-hydroxytryptamine (serotonin) receptor antagonist (henceforth referred to as 5HT3 RA). NK1 RA and 5HT3 RA drugs are used in combination for the treatment of nausea and vomiting associated with emetogenic chemotherapy¹.

Registration status

- 2.2 NEPA IV was registered on the ARTG on 13 March 2020 for the same indications as NEPA oral.

Previous PBAC consideration

- 2.3 NEPA oral was recommended by the PBAC at its November 2015 meeting and listed in April 2016 for the indications ‘patients treated with highly emetogenic chemotherapy’ and ‘in breast cancer patients treated with anthracycline plus cyclophosphamide-based regimens’ with initial and repeat courses.
- 2.4 At its November 2016 meeting, the PBAC recommended extending the indications for NEPA capsule to include ‘secondary prophylaxis for chemotherapy induced nausea and vomiting associated with moderately emetogenic chemotherapy’ and ‘primary

¹ <https://www.eviq.org.au/clinical-resources/side-effect-and-toxicity-management/gastrointestinal/7-prevention-of-antineoplastic-induced-nausea-and>

Public Summary Document – July 2020 PBAC Meeting

prophylaxis for chemotherapy induced nausea and vomiting associated with carboplatin or oxaliplatin chemotherapy regimens’.

2.5 NEPA IV had not been previously considered by the PBAC.

For more detail on PBAC’s view, see section 6 PBAC outcome.

3 Requested listing

3.1 The submission requested the following new listing. Secretariat suggestions are in italics and deletions in strikethrough

Name, Restriction, Manner of administration and form	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
FOSNETUPITANT + PALONOSETRON fosnetupitant 235 mg + palonosetron 250 microgram injection, 1 vial	NEW	1	1	5	Akynzeo IV

Category / Program: GENERAL – General Schedule (Code GE)
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners

Category / Program: Section 100 – Efficient Funding of Chemotherapy – Related benefits (Code CT)
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners

Identical restriction to netupitant 300 mg + palonosetron 500 microgram capsule: PBS Items 10714X (s100 CT) and 10731T (GE), with the following difference:

Prescribing Instructions: No more than 1 capsule of 300 mg netupitant/0.5 mg palonosetron 1 vial will be authorised per cycle of cytotoxic chemotherapy.

For more detail on PBAC’s view, see section 6 PBAC outcome.

4 Comparator

4.1 The minor submission nominated NEPA oral as the main comparator, as NEPA oral contains the same therapies as NEPA IV (noting that fosnetupitant is the pro-drug for oral netupitant, suitable for IV administration) and claimed that NEPA IV was most likely to replace NEPA oral in practice.

4.2 At its November 2015 meeting, the PBAC originally recommended NEPA oral for listing on the PBS at a price that was lower than the price of aprepitant alone, however noted that the clinical claim that NEPA oral is non-inferior to aprepitant plus a 5HT3 RA was likely reasonable. At the time, the PBAC considered that the clinical need for the NEPA oral FDC remained low, noting the very high potential for leakage.

4.3 At its November 2016 meeting, the PBAC further recommended listing NEPA oral on a cost-minimisation basis to aprepitant, at a price based on aprepitant, with no cost assigned to the 5HT3 RA. At the time the PBAC accepted that aprepitant plus a 5HT3

RA was an appropriate comparator, however the PBAC considered that there may be leakage into populations where a 5HT3 RA alone would otherwise be used.

- 4.4 At its November 2016 meeting, the PBAC recommended the listing of fosaprepitant on a cost-minimisation basis against aprepitant alone. At its March 2010 meeting, it also recommended palonosetron, and considered that a single IV dose of palonosetron was non-inferior to other 5HT3 RA drugs administered as a single IV dose (paragraph 12.4, palonosetron Public Summary Document March 2010).
- 4.5 The pre-PBAC response argued that aprepitant oral alone was not a reasonable comparator for NEPA IV, since patients prescribed the IV form were unlikely to be tolerant of oral forms, aprepitant oral did not include a 5HT3 RA component, and guidelines such as eviQ and the US National Comprehensive Cancer Network (NCCN) recommend the use of a combination of a NK1 RA with a 5HT3 RA for the treatment of nausea and vomiting in highly emetogenic chemotherapy.

For more detail on PBAC's view, see section 6 PBAC outcome.

5 Consideration of evidence

Sponsor hearing

- 5.1 There was no hearing for this item as it was a minor submission.

Consumer comments

- 5.2 The PBAC noted that no consumer comments were received for this item.

Clinical trials

- 5.3 The minor submission presented four clinical trials to demonstrate that NEPA IV and NEPA oral were equivalent, and to demonstrate that NEPA IV given over a 30 minute infusion is equivalent to that of a 30-second bolus to support the clinical claims.
- 5.4 A summary of the studies presented in the submission are provided in Table 1.

Public Summary Document – July 2020 PBAC Meeting

Table 1: Trials and associated reports presented in the submission.

Trial ID/First Author	Protocol title/ Publication title	Publication citation
Direct randomised trials		
Helsin Healthcare SA 2015 (PNET-12-23)	A Phase I, double-blind, controlled, parallel groups, unbalanced single ascending dose study to assess the safety of intravenously administered pronetupitant combined with crossover study extensions to estimate the dose of intravenous pro-netupitant yielding equivalent drug exposure as oral netupitant 300 mg/palonosetron 0.5 mg fixed dose combination in healthy male and female volunteers.	-
Helsin Healthcare SA 2017 (PALO-15-17)	A phase 3, single-dose, multicentre, randomized, double-blind, parallel group study to assess the efficacy and safety of palonosetron 0.25 mg administered as a 30-minute IV infusion compared to palonosetron 0.25 mg administered as a 30-second IV bolus for the prevention of chemotherapy-induced nausea and vomiting in cancer patients receiving highly emetogenic chemotherapy.	Karthaus, M., C. Tibor, V. Lorusso, et al. (2015). "Efficacy and safety of oral palonosetron compared with IV palonosetron administered with dexamethasone for the prevention of chemotherapy-induced nausea and vomiting (CINV) in patients with solid tumors receiving cisplatin-based highly emetogenic chemotherapy (HEC)." Support Care Cancer 23(10): 2917-2923. (Karthaus, Tibor et al. 2015)
Helsin Healthcare SA 2017 (NEPA-15-18)	A phase 3, multicentre, randomized, double-blind, active control study to evaluate the safety and efficacy of IV pro-netupitant/palonosetron (260 mg/0.25 mg) combination for the prevention of chemotherapy-induced nausea and vomiting in repeated chemotherapy cycles in patients receiving highly emetogenic chemotherapy (Eudra CT: 2015-001800- 74), Helsinn Healthcare SA,.	Schwartzberg, L., E. Roeland, Z. Andric, D. Kowalski, J. Radic, D. Voisin, G. Rizzi, R. Navari, R. J. Gralla and M. Karthaus (2018). "Phase III safety study of intravenous NEPA: a novel fixed antiemetic combination of fosnetupitant and palonosetron in patients receiving highly emetogenic chemotherapy." Annals of oncology: official journal of the European Society for Medical Oncology 29(7): 1535-1540. (Schwartzberg, Roeland et al. 2018)
Helsin Healthcare SA 2017 (NEPA-17-05)	A multicentre, randomized, double-blind, double-dummy, active-controlled, parallel group phase 3b study to assess the safety and to describe the efficacy of IV fosnetupitant/palonosetron (260 mg/0.25 mg) combination (NEPA IV FDC) compared to oral netupitant/palonosetron (300 mg/0.5 mg) combination (Akynzeo®) for the prevention of chemotherapy-induced nausea and vomiting in initial and repeated cycles of anthracycline/cyclophosphamide (AC) chemotherapy in women with breast cancer	Schwartzberg, L., R. Navari, R. Clark-Snow, E. Arkania, I. Radyukova, K. Patel, D. Voisin, G. Rizzi, R. Wickham, R. J. Gralla, M. Aapro and E. Roeland (2020). "Phase IIIb Safety and Efficacy of Intravenous NEPA for Prevention of Chemotherapy-Induced Nausea and Vomiting (CINV) in Patients with Breast Cancer Receiving Initial and Repeat Cycles of Anthracycline and Cyclophosphamide (AC) Chemotherapy." The oncologist 25(3): e589-e597. (Schwartzberg, Navari et al. 2020)

Source: Minor Submission, Table 7 (pp23).

Comparative effectiveness and harms

- 5.5 The treatment safety and effectiveness of NEPA IV was evaluated by the TGA based on the trials presented in Table 1. The TGA Delegate’s overview concluded ‘the safety profile of AKYNZEO IV has been adequately characterised and is similar to the safety profile of oral AKYNZEO’. It also found the bioavailability of netupitant and palonosetron in NEPA IV was equivalent to that of NEPA oral, and that a 30 second bolus of NEPA IV was equi-effective to a 30 minute infusion. Overall, it concluded that the ‘quality, efficacy and safety of AKYNZEO IV have been satisfactorily established’.

Clinical claim

- 5.6 The minor submission claimed that NEPA IV is non-inferior in efficacy and safety compared to NEPA oral for the prevention of nausea and vomiting in patients undergoing treatment with moderately and highly emetogenic chemotherapy.
- 5.7 This claim was accepted by the PBAC since both forms were found to have comparable effectiveness and safety, and the TGA Delegate considered that both forms had the same exposure.

Economic analysis

- 5.8 The minor submission presented a cost-minimisation analysis of NEPA IV compared with NEPA oral, based on 1 vial of NEPA IV being equi-effective to 1 capsule of NEPA oral; and proposed the same approved ex-manufacturer price (AEMP) for NEPA IV as NEPA oral (\$97.16). It also noted the proposed AEMP is equivalent to that of fosaprepitant IV.
- 5.9 The price of aprepitant with a 5HT3 RA is currently lower than NEPA oral (and fosaprepitant). Should the PBAC consider aprepitant with a 5HT3 RA a relevant comparator for NEPA IV, it may be appropriate for the cost-minimisation to be conducted against aprepitant with a 5HT3 RA. The PBAC could only recommend listing NEPA IV at a higher price than the alternative therapy or therapies if it was satisfied that it provides, for some patients, a significant improvement in efficacy or reduction of toxicity over the alternative therapy or therapies (*National Health Act 1953* (‘the Act’), Section 101(3B)).

Estimated PBS usage & financial implications

- 5.10 The submission used a market share approach and assumed no market growth as a consequence of the proposed listing and that NEPA IV would only replace NEPA oral, fosaprepitant IV and aprepitant oral, at the same price, and therefore the proposed listing would be cost-neutral to government.
- 5.11 The sponsor based its market share estimate on PBS data for fosaprepitant IV since listing, and assumed NEPA IV would displace NEPA oral and aprepitant oral at a rate of █████% in Year 1, █████% in Year 2, and then █████% each year thereafter. The sponsor

Public Summary Document – July 2020 PBAC Meeting

assumed NEPA IV would displace fosaprepitant at a linear rate from █% to █% for Years 1 to 5 then remain at █%.

5.12 The minor submission estimated the anti-emetics/anti-nauseants market to grow by █% per year based on the average annual growth rate over the last year.

Table 2: Financial impact of NEPA IV over six years

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated number of PBS/RPBS scripts for NEPA IV						
Total number of GE PBS/RPBS services	█	█	█	█	█	█
Total number of CT PBS/RPBS services	█	█	█	█	█	█
Total number of PBS/RPBS services	█	█	█	█	█	█
Estimated net cost to PBS/RPBS (DPMQ less co-payments)						
Net PBS/RPBS cost for NEPA IV	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
Net PBS/RPBS saving for NEPA IV	-\$ █	-\$ █	-\$ █	-\$ █	-\$ █	-\$ █
Net cost to Government	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █

GE: General Schedule; CT: Efficient Funding of Chemotherapy – Related benefits
Source: Minor Submission, Table 22 (pp 52).

The redacted table shows that at Year 6, the estimated number of patients was less than 10,000 per year and the net cost to the PBS would be less than \$10 million.

5.13 The Sponsor noted the minor net-cost to government amounts in Table 2 were due to rounding errors in the financials spreadsheet.

5.14 The Secretariat noted the price for aprepitant oral used by the sponsor was not current. When updating the AEMP to \$62.30, in place of the \$97.16 applied by the sponsor, the net cost to government increased: less than \$10 million in Year 1 to less than \$10 million in Year 6, with a total cost of less than \$10 million over six years.

Quality Use of Medicines (QUM)

5.15 The minor submission argued that listing of NEPA IV would allow patients who are intolerant of oral anti-emetics to be treated, reducing the side-effect profile of the associated chemotherapies and allowing more patients to maintain their anti-tumour regimes. The sponsor noted in the pre-PBAC response that this would constitute approximately █% of all patients using anti-emetics for chemotherapy.

For more detail on PBAC’s view, see section 6 PBAC outcome.

6 PBAC Outcome

6.1 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

Public Summary Document – July 2020 PBAC Meeting

currently PBS listed capsule form, NEPA oral, 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 5HT3 RA.

- 6.2 The PBAC considered that the clinical claim that NEPA IV was non-inferior in terms of effectiveness and safety to the nominated comparator NEPA oral to be reasonable. However, it recalled its November 2015 recommendation for NEPA oral where it considered NEPA oral to be non-inferior to aprepitant with a 5HT3 RA. It therefore considered NEPA IV was also likely to be non-inferior to any NK1 RA (aprepitant or fosaprepitant) with any 5HT3 RA.
- 6.3 The PBAC recalled that NEPA oral was cost minimised to aprepitant alone and that despite NEPA oral being considered non-inferior to aprepitant with a 5HT3 RA, no cost was given to the 5HT3 RA component due to high risk of leakage into populations that would otherwise use only a 5HT3 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 5HT3 RA for highly emetogenic chemotherapies. The PBAC however noted that no further evidence has been presented since the PBS listing of NEPA oral around the likelihood of treatment escalation to combination therapy for patients that might otherwise receive a single agent.
- 6.4 On balance, 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.
- 6.5 The PBAC advised under Section 101(3BA) of the Act that NEPA IV should not be treated as interchangeable with any other drugs on an individual patient basis.
- 6.6 The PBAC noted the only difference in the restriction between NEPA IV and NEPA oral was the revised prescribing instructions 'no more than 1 vial will be authorised per cycle of cytotoxic chemotherapy', to suit the IV form, and considered this appropriate.
- 6.7 The PBAC advised that NEPA IV is suitable for prescribing by nurse practitioners under the General Schedule listing.
- 6.8 The PBAC advised that the Early Supply Rule should not apply to NEPA IV.
- 6.9 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 the lowest cost

Public Summary Document – July 2020 PBAC Meeting

combination of a NK1 RA and a 5HT3 RA at equi-effective doses, 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 2009 for Pricing Pathway A were not met.

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

Outcome:

Recommended

7 Recommended listing

7.1 Add new medicinal product:

Name, strength, manner of administration and form	PBS item codes	Max. qty packs	Max. qty units	No. of Rpts	Available brands
FOSNETUPITANT + PALONOSETRON fosnetupitant 235 mg + palonosetron 250 microgram injection, 1 vial	NEW (several)	1	1	5	Akynzeo IV

Category / Program: GENERAL – General Schedule (Code GE)
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners
Category / Program: Section 100 – Efficient Funding of Chemotherapy (Code CT)
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners

Restriction Summary 5991 edited:

Restriction Type / Method: <input checked="" type="checkbox"/> Authority Required – Streamlined (new 4 or 5 digit code)
Indication: Nausea and vomiting
Clinical criteria: <ul style="list-style-type: none"> ▪ The condition must be associated with cytotoxic chemotherapy being used to treat malignancy <p style="text-align: center;">AND</p> <ul style="list-style-type: none"> ▪ The treatment must be in combination with dexamethasone
Prescribing Instructions: No more than 1 vial will be authorised per cycle of cytotoxic chemotherapy, This product is also not subsidised for use with another receptor antagonist drug within the same pharmacological classes as the component drugs.
Administrative Advice: No increase in the maximum number of repeats may be authorised. No increase in the maximum quantity or number of units may be authorised. This medicine is not PBS-subsidised for nausea and vomiting associated with radiotherapy being used to treat malignancy.

Public Summary Document – July 2020 PBAC Meeting

Restriction Summary 5994 edited:

Restriction Type / Method: <input checked="" type="checkbox"/> Authority Required – Streamlined (new 4 or 5 digit code)
Indication: Nausea and vomiting
Clinical criteria: <ul style="list-style-type: none">▪ 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 will be authorised per cycle of cytotoxic chemotherapy. This product is also not subsidised for use with another drug within the same pharmacological classes as the component drugs.
Administrative Advice: <p>No increase in the maximum number of repeats may be authorised. No increase in the maximum quantity or number of units may be authorised. This medicine is not PBS-subsidised for nausea and vomiting associated with radiotherapy being used to treat malignancy.</p>

Restriction Summary 6937 edited:

Restriction Type / Method: <input checked="" type="checkbox"/> Authority Required – Streamlined (new 4 or 5 digit code)
Indication: Nausea and vomiting
Clinical criteria: <ul style="list-style-type: none">▪ The condition must be associated with moderately emetogenic cytotoxic chemotherapy being used to treat malignancy AND▪ The treatment must be in combination with dexamethasone on day 1 of a chemotherapy cycle 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; raltitrexed
Prescribing Instructions: No more than 1 vial will be authorised per cycle of cytotoxic chemotherapy. This product is also not subsidised for use with another drug within the same pharmacological classes as the component drugs.
Administrative Advice: <p>No increase in the maximum number of repeats may be authorised. No increase in the maximum quantity or number of units may be authorised. This medicine is not PBS-subsidised for nausea and vomiting associated with radiotherapy being used to treat malignancy.</p>

Public Summary Document – July 2020 PBAC Meeting

Restriction Summary 6879 edited:

Restriction Type / Method: <input checked="" type="checkbox"/> Authority Required – Streamlined (new 4 or 5 digit code)
Indication: Nausea and vomiting
Clinical criteria: <ul style="list-style-type: none"> ▪ The condition must be associated with moderately emetogenic cytotoxic chemotherapy being used to treat malignancy AND ▪ The treatment must be in combination with dexamethasone on day 1 of a chemotherapy cycle AND ▪ Patient must be scheduled to be administered a chemotherapy regimen that includes either carboplatin or oxaliplatin
Prescribing Instructions: No more than 1 vial will be authorised per cycle of cytotoxic chemotherapy. This product is also not subsidised for use with another drug within the same pharmacological classes as the component drugs.
Administrative Advice: No increase in the maximum number of repeats may be authorised. No increase in the maximum quantity or number of units may be authorised. This medicine is not PBS-subsidised for nausea and vomiting associated with radiotherapy being used to treat malignancy.

7.2 Flow-on changes

Apply the following changes to fosaprepitant 150 mg injection, 1 vial (PBS item codes: 11103J & 11107N) to prevent the simultaneous subsidy of multiple anti-nauseant, injectable drugs:

Edit 20391	Prescriber Instructions: No more than 1 vial of fosaprepitant 150 mg injection will be authorised per cycle of cytotoxic chemotherapy. This product is also not subsidised for use with another drug within the same pharmacological class.
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The restrictions may be subject to further review. Should there be any changes made to the restriction the Sponsor will be informed.

8 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.

9 Sponsor’s Comment

Mundipharma welcomes the PBAC’s decision.