

7.05 NETUPITANT WITH PALONOSETRON
Capsule containing netupitant 300mg with palonosetron 500
microgram (as hydrochloride),
Akynzeo®,
Mundipharma Pty Ltd.

1 Purpose of Application

- 1.1 The resubmission requested General Schedule and Section 100 (CT), Authority Required (STREAMLINED) listing for netupitant with palonosetron FDC
- secondary prophylaxis for chemotherapy induced nausea and vomiting associated with MEC (previously rejected at the March 2015 PBAC meeting); and
 - primary prophylaxis for chemotherapy induced nausea and vomiting associated with carboplatin or oxaliplatin chemotherapy regimens (new proposed listing).

2 Requested listing

- 2.1 The listing was requested on a cost-minimisation basis to aprepitant + 5HT₃ antagonist.

| Name, Restriction, Manner of administration and form | Max. Qty | No. of Rpts | Dispensed Price for Max. Qty | Proprietary Manufacturer | Name and |
|--|----------|-------------|------------------------------|--------------------------|---------------------|
| GENERAL SCHEDULE | | | | | |
| NETUPITANT + PALONOSETRON netupitant 300 mg + palonosetron 500 microgram capsule, 1 | 1 | 5 | \$121.18 | Akynzeo® | Mundipharma Pty Ltd |

| | | | | | |
|--|---|---|----------|--|--|
| SECTION 100 (CT) | | | | | |
| NETUPITANT + PALONOSETRON netupitant 300 mg + palonosetron 500 microgram capsule, 1 | 1 | 5 | \$103.01 | | |

| | |
|------------------------------------|--|
| Category / Program | GENERAL – General Schedule (GE)* Section 100 – Efficient funding of Chemotherapy (CT) |
| Prescriber type: | <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners* <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives |
| Condition: | Nausea and vomiting |
| PBS Indication: | Nausea and vomiting |
| Restriction Level / Method: | <input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required - Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined |

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

| | |
|------------------------------------|---|
| Category / Program | GENERAL – General Schedule (GE)* Section 100 – Efficient funding of Chemotherapy (CT) |
| Prescriber type: | <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners* <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives |
| Condition: | Nausea and vomiting |
| PBS Indication: | Nausea and vomiting |
| Restriction Level / Method: | <input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required - Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined |
| Clinical criteria: | The condition must be associated with moderately emetogenic cytotoxic chemotherapy being used to treat malignancy; AND The treatment must be in combination with dexamethasone <i>on day 1 of a chemotherapy cycle</i> ; AND Patient must be scheduled to be administered a chemotherapy regimen that includes either carboplatin or oxaliplatin. |
| Prescriber Instructions | No more than 1 capsule of 300mg netupitant/0.5mg palonosetron fixed dose combination will be authorised per cycle of cytotoxic chemotherapy. |
| Administrative Advice | No increase in the maximum quantity or number of units may be authorised. No Increase in the maximum number of repeats may be authorised. This medicine is not PBS-subsidised for nausea and vomiting associated with radiotherapy being used to treat malignancy. |

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

3 Background

- 3.1 Netupitant with palonosetron FDC was registered by the TGA in May 2015 for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderately and highly emetogenic cancer chemotherapy in adult patients.
- 3.2 At the March 2015 meeting, the PBAC considered an Authority required listing for netupitant with palonosetron FDC when used in combination with dexamethasone for the prevention of chemotherapy induced nausea and vomiting, as:
- primary prophylaxis in highly emetogenic chemotherapy regimens;
 - primary prophylaxis in anthracycline plus cyclophosphamide chemotherapy regimens (breast cancer); and
 - secondary prophylaxis in MEC regimens.
- 3.3 The PBAC rejected the submission on the basis that there was no unmet clinical need in the target population, and that the clinical place for the fixed dose combination was not established in the submission.

- 3.4 Minor resubmissions for netupitant with palonosetron FDC for use as primary prophylaxis for highly emetogenic chemotherapy regimens, and for anthracycline plus cyclophosphamide (breast cancer) indications were considered at the July 2015 and November 2015 PBAC meetings. Netupitant with palonosetron FDC received a positive recommendation for these indications at the November 2015 meeting, on a cost comparison basis versus aprepitant.
- 3.5 Table 1 summarises the outstanding matters of concern from the March 2015 rejection for nausea and vomiting associated with MEC and how they were addressed in the current submission.

Table 1: Outstanding matters of concern to the PBAC

| Matters of concern | How the resubmission addresses it |
|---|---|
| PBAC considered that the appropriate comparator for patients who received moderately emetogenic chemotherapy with prior chemotherapy induced nausea and/or vomiting could be aprepitant plus a 5HT ₃ antagonist, 5HT ₃ antagonist monotherapy, or aprepitant with dexamethasone. | Nominated aprepitant in combination with a 5HT ₃ antagonist as the main comparator. There was no consideration of alternative comparators. |
| The submission did not define a minimum clinically important difference. | Nominated a non-inferiority margin of -15%. |
| The claim of non-inferiority of netupitant with palonosetron FDC versus aprepitant + 5HT ₃ antagonist in secondary prophylaxis was poorly supported, as no clinical evidence was provided in patients who had experienced a previous event of chemotherapy induced nausea/vomiting. | No additional evidence presented for netupitant with palonosetron FDC in the secondary prophylaxis setting. The submission argued that the comparator (aprepitant in combination with a 5HT ₃ antagonist) was listed for use in the secondary prophylaxis setting primarily on the basis of evidence of efficacy in a primary prophylaxis setting. |
| The submission did not estimate equi-effective doses. The PBAC noted the equi-effective doses as proposed in the evaluation, and the PSCR agreed with the equi-effective doses presented in the evaluation. The PBAC considered in the absence of the single components of the FDC being available on the PBS, the pricing of the FDC would be difficult to establish. The clinical evidence was not sufficiently robust to be used as the basis for a cost-minimisation analysis, particularly for the patients due to receive moderately emetogenic chemotherapy. | Clinical evidence (NETU-10-29) based on netupitant with palonosetron FDC 300mg/0.5mg versus aprepitant 125mg/80mg/80mg (3-day regimen) + palonosetron 0.5mg. The submission proposed that 300mg of netupitant with 0.5mg palonosetron was equivalent to 165mg of aprepitant in combination with a 5HT ₃ antagonist. The submission proposed equi-effective doses for 5HT ₃ antagonists based on the eviQ chemotherapy induced nausea and vomiting guidelines. |
| The weighted cost of the 5HT ₃ antagonist component did not account for other dosage forms of ondansetron (intravenous or wafers), which appear to be used to the same, if not higher, extent than 5HT ₃ antagonists such as granisetron. | The weighted cost for the 5HT ₃ antagonist component excluded oral forms of ondansetron and granisetron. |
| The PBAC remained concerned that there was a risk of leakage into populations where combination therapy may not be required, and therefore any savings calculated by the submission may not be realised. | The submission requested a restriction that was in line with aprepitant, and argued that as a result, there would be no additional market growth. An extension of the current moderately emetogenic chemotherapy risk share arrangement was proposed. |

Source: Compiled during the evaluation

Abbreviations: 5HT₃, 5-hydroxytryptamine type 3; FDC, fixed dose combination.

3.6 Table 2 provides a comparison of information relevant to the MEC indication from the previous and current submissions.

Table 2: Summary of the information relevant to MEC from the previous submission and current resubmission

| | March 2015 submission | Current submission |
|------------------------|---|--|
| Requested PBS listing | <ol style="list-style-type: none"> 1. Primary prophylaxis of CINV for HEC (listed) 2. Primary prophylaxis of CINV for AC based breast cancer treatment (listed) 3. Secondary prophylaxis of CINV for MEC | <ol style="list-style-type: none"> 1. Primary prophylaxis of CINV for carboplatin/oxaliplatin regimens 2. Secondary prophylaxis of CINV for MEC |
| Requested price | - | Proposed DPMQ/DPMA Section 85: \$121.18 Section 100: \$103.01 |
| Main comparator | Aprepitant + 5HT ₃ antagonist | Aprepitant + 5HT ₃ antagonist |
| Clinical evidence | Direct evidence from two head to head trials: <ul style="list-style-type: none"> • NETU-10-29 (HEC N=103, MEC N=309) | Direct evidence from one head to head trial: <ul style="list-style-type: none"> • NETU-10-29 (HEC N=103, MEC N=309) Additional post hoc subgroup analysis of MEC patients treated with and without carboplatin/oxaliplatin |
| Key effectiveness data | MEC: complete response, cycle 1 (primary prophylaxis) Acute, RD (95% CI): 0.00 (-0.07, 0.06) Delayed, RD (95% CI): -0.03 (-0.12, 0.07) Overall, RD (95% CI): -0.02 (-0.12, 0.08) | MEC: complete response, cycle 1 (primary prophylaxis)¹ Acute, RD (95% CI): 0.00 (-0.07, 0.06) Delayed, RD (95% CI): -0.03 (-0.12, 0.07) Overall, RD (95% CI): -0.02 (-0.12, 0.08) Carboplatin/oxaliplatin: complete response, cycle 1 (primary prophylaxis) [REDACTED] Non-carboplatin/oxaliplatin: complete response, cycle 1 (primary prophylaxis) [REDACTED] |
| Key safety data | No statistically significant differences in adverse events between treatments. | No statistically significant differences in adverse events between treatments. |
| Clinical claim | Netupitant with palonosetron was therapeutically equivalent to aprepitant in combination with a 5HT ₃ antagonist. | Netupitant with palonosetron was non-inferior to aprepitant in combination with a 5HT ₃ antagonist. |

| | March 2015 submission | Current submission |
|-----------------------|--|---|
| Economic evaluation | Cost-comparison. The submission did not estimate equi-effective doses. The following doses were proposed during the evaluation: <u>NK₁ antagonist:</u> Netupitant 300mg PO day 1 Aprepitant 125mg/80mg/80mg PO day 1-3 Aprepitant 165mg PO day 1 <u>5HT₃ antagonist:</u> Palonosetron 0.5mg PO (day 1) Ondansetron 8mg-32mg IV (day 1) Ondansetron 16mg oral (day 1-3) Palonosetron 0.25mg IV (day 1) | Presented a cost-minimisation versus aprepitant in combination with a 5HT ₃ antagonist, and a cost-minimisation versus aprepitant alone. Proposed equi-effective doses: <u>NK₁ antagonist:</u> Netupitant 300mg PO (day 1) Aprepitant 125mg/80mg/80mg PO (day 1-3) Aprepitant 165mg PO (day 1) <u>5HT₃ antagonist (as per eviQ):</u> Palonosetron 0.25mg IV or 0.5mg PO Granisetron 3mg IV or 2mg PO Ondansetron 8mg IV or 16mg PO (in divided doses) Tropisetron 5mg IV |
| Number of patients | - | MEC SP and MEC PP (carboplatin/oxaliplatin): A total of ██████ prescriptions in Year 1 increasing to ██████ prescriptions in Year 5 |
| Estimated cost to PBS | - | A net saving of \$ ██████ in Year 1, increasing to \$ ██████ in Year 5, for a total net saving of \$ ██████ over the first 5 years of listing. |

Source: Compiled during the evaluation.

Abbreviations: CINV, chemotherapy induced nausea and vomiting; HEC, highly emetogenic chemotherapy; AC, anthracycline plus cyclophosphamide; MEC, moderately emetogenic chemotherapy; DPMQ, dispensed price for maximum quantity; DPMA, dispensed price for maximum amount; 5HT₃, 5-hydroxytryptamine 3; RD, risk difference; NK₁, neurokinin 1; PO, per oral; IV, intravenous; SP, secondary prophylaxis; PP, primary prophylaxis.

¹ The submission presented two sets of confidence intervals for the MEC subgroup risk difference: one based on the external statistical analysis (Table B-17, p. B39 of the submission, which was consistent with the original submission results and is reproduced here), and one based on the clinical study report results (Table B-16, p. B39 of the submission). The small differences in the confidence intervals did not affect interpretation of non-inferiority.

4 Clinical place for the proposed therapy

- 4.1 Netupitant with palonosetron FDC is a fixed dose combination of an NK₁ antagonist and a 5HT₃ antagonist, and is used in combination with dexamethasone for the prevention of nausea and vomiting associated with chemotherapy treatment.

5 Comparator

- 5.1 The submission nominated aprepitant in combination with a 5HT₃ antagonist as the main comparator in both the primary prophylaxis and secondary prophylaxis settings. The ESC agreed that this was the appropriate comparator.
- 5.2 The PBAC has previously suggested that aprepitant in combination with a 5HT₃ antagonist, 5HT₃ antagonist monotherapy, and aprepitant with dexamethasone may be potential comparators in the secondary prophylaxis setting (netupitant with palonosetron PSD March 2015). The submission did not consider any comparators other than aprepitant in combination with a 5HT₃ antagonist.
- 5.3 The PBAC has not previously considered appropriate comparators for primary prophylaxis of nausea and vomiting associated with carboplatin/oxaliplatin regimens.

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 and welcomed the input from health care professionals (2) via the Consumer Comments facility on the PBS website. The comments described some of the perceived benefits of treatment with netupitant with palonosetron, including improvement in convenience and quality of life for patients and decreased PBS co-payments.

Clinical trials

6.3 The submission was based on one head-to-head randomised trial (NETU-10-29) comparing netupitant with palonosetron FDC to aprepitant in combination with oral palonosetron. The results of NETU-10-29 were considered previously by the PBAC as part of the March 2015 submission. The current submission supplemented the trial results with post hoc carboplatin/oxaliplatin and non-carboplatin/oxaliplatin subgroup analyses.

6.4 Details of the included trial (NETU-10-29) are provided in Table 3.

Table 3: Trials and associated reports presented in the resubmission

| Trial ID | Protocol title/ Publication title | Publication citation |
|------------|--|------------------------------------|
| NETU-10-29 | Helsinn Healthcare SA. A phase III, multicentre, randomized, double-blind, unbalanced (3:1) active control study to assess the safety and describe the efficacy of netupitant and palonosetron for the prevention of chemotherapy-induced nausea and vomiting in repeated chemotherapy cycles. | Clinical Study Report, 5 June 2013 |
| | Gralla RJ, Bosnjak SM, Hontsa A et al. A phase III study evaluating the safety and efficacy of NEPA, a fixed-dose combination of netupitant and palonosetron, for prevention of chemotherapy-induced nausea and vomiting over repeated cycles of chemotherapy. | Ann Oncol 2014; 25(7):1333-1339. |

Source: Table B-2, p.B.11 of the submission.

6.5 The key features of NETU-10-29 are summarised in Table 4.

Table 4: Key features of the included evidence

| Trial | N | Design/ duration | Risk of bias | Patient population | Outcomes |
|------------|-----|------------------|--------------|--|-------------------------|
| NETU-10-29 | 412 | R, DB, MC, PG | Low | Adults, naïve to cytotoxic chemotherapy, scheduled to receive moderately (N=309) or highly (N=103) emetogenic chemotherapy | Safety and tolerability |

Source: Table B-4, p.B13 of the submission.

Abbreviations: R, randomised; DB, double blind; MC, multi-centre; PG, parallel group.

- 6.6 Overall, the risk of bias for trial NETU-10-29 was considered low. However, the risk of bias for the post hoc subgroup analyses for the carboplatin/oxaliplatin and non-carboplatin/oxaliplatin subgroups was considered high.

Comparative effectiveness

- 6.7 Table 5 summarises the results for the proportion of patients with a complete response (CR) across the total and subgroup populations for cycle 1.

Table 5: Summary of cycle 1 results for the proportion of patients with a complete response (CR) across the total and subgroup populations

| Trial ID | Netupitant/ palonosetron FDC n/N (%) | Aprepitant + palonosetron n/N (%) | Risk difference (95% CI) | Relative risk (95% CI) |
|---|--|---|----------------------------------|---------------------------|
| Overall trial population (combined HEC/MEC) | | | | |
| Overall (0-120 hr) | 249/309 (80.6) | 78/103 (75.7) | 0.049 (-0.038, 0.148) | 1.06 (0.94, 1.20) |
| Acute (0-24 hr) | 287/309 (92.9) | 97/103 (94.2) | -0.013 (-0.059, 0.054) | 0.99 (0.93, 1.04) |
| Delayed (25-120 hr) | 257/309 (83.2) | 80/103 (77.7) | 0.055 (-0.028, 0.152) | 1.07 (0.95, 1.20) |
| MEC subgroup | | | | |
| Overall (0-120 hr) | 187/235 (79.6) | 63/77 (81.8) | -0.02 (-0.12, 0.08) ¹ | 0.97 (0.86, 1.10) |
| Acute (0-24 hr) | 219/235 (93.2) | 72/77 (93.5) | 0.00 (-0.07, 0.06) ¹ | 1.00 (0.93, 1.07) |
| Delayed (25-120 hr) | 192/235 (81.7) | 65/77 (84.4) | -0.03 (-0.12, 0.07) ¹ | 0.97 (0.86, 1.08) |
| Carboplatin/oxaliplatin MEC subgroup² | | | | |
| Overall (0-120 hr) | ██████████ | ██████████ | ██████████ | ██████████ |
| Acute (0-24 hr) | ██████████ | ██████████ | ██████████ | ██████████ |
| Delayed (25-120 hr) | ██████████ | ██████████ | ██████████ | ██████████ |
| Non-carboplatin/oxaliplatin MEC subgroup² | | | | |
| Overall (0-120 hr) | ██████████ | ██████████ | ██████████ | ██████████ |
| Acute (0-24 hr) | ██████████ | ██████████ | ██████████ | ██████████ |
| Delayed (25-120 hr) | ██████████ | ██████████ | ██████████ | ██████████ |

Source: Table B-16, p.B39; Table B-17, p.B39; Table B-22, p.B43; Table B-23, p.B43 of the submission; Table 14.2.1.1, p. 448 of the NETU-10-29 clinical study report; italicised results calculated during the evaluation.

Abbreviations: FDC, fixed dose combination; CI, confidence interval; HEC, highly emetogenic chemotherapy; MEC, moderately emetogenic chemotherapy; hr, hour.

¹ The submission presented two sets of confidence intervals for the MEC subgroup risk difference: one based on the external statistical analysis (Table B-17, p. B39 of the submission, which was consistent with the original submission results and is reproduced here), and one based on the clinical study report results (Table B-16, p. B39 of the submission). The small differences in the confidence intervals did not affect interpretation of non-inferiority.

² Discrepancy noted during the evaluation – carboplatin/oxaliplatin and non-carboplatin/oxaliplatin post hoc subgroup patients totalled 78, which was greater than the number in the MEC subgroup (77).

- 6.8 There were no statistically significant differences between netupitant with palonosetron FDC and aprepitant + palonosetron in the proportion of patients with a complete response for the overall trial population (combined HEC/MEC) or the MEC subgroup in cycle 1. The difference met the nominated non-inferiority margin of -15%, as the lower limit of the 95% confidence interval was greater than -0.15.

- 6.9 There were no statistically significant differences between treatment arms for the post hoc carboplatin/oxaliplatin and non-carboplatin/oxaliplatin subgroups during cycle 1. However, while the difference between treatment groups for the carboplatin/oxaliplatin subgroup met the nominated non-inferiority margin of -15% (-0.15), the non-carboplatin/oxaliplatin subgroup failed to meet the nominated non-

inferiority margin for the overall, acute, and delayed phases. The ESC noted that the number of patients in the non-carboplatin/oxaliplatin subgroup was small.

Comparative harms

6.10 A summary of the reported adverse events for NETU-10-29 is presented in Table 6.

Table 6: Summary of reported adverse events in NETU-10-29

| Trial treatment arm | Any adverse event n (%) | Treatment-related adverse events n (%) | Treatment-related AE leading to discontinuation n (%) | Serious treatment-related adverse events n (%) | Severe treatment-related adverse events n (%) |
|--|----------------------------|---|--|---|--|
| Overall trial population (combined HEC/MEC) | | | | | |
| Netupitant/palonosetron (N=308) | 265 (86.0) | 31 (10.1) | 1 (0.3) | 2 (0.6) | 1 (0.3) |
| Aprepitant + palonosetron (N=104) | 95 (91.3) | 6 (5.8) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| MEC subgroup | | | | | |
| Netupitant/palonosetron (N=233) | 201 (86.3) | 21 (9.0) | 1 (0.4) | 2 (0.9) | 1 (0.4) |
| Aprepitant + palonosetron (N=79) | 73 (92.4) | 3 (3.8) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Carboplatin/oxaliplatin MEC subgroup | | | | | |
| Netupitant/palonosetron (N=192) | ████████ | ████████ | ██ | ██ | ██ |
| Aprepitant + palonosetron (N=71) | ████████ | ████████ | ██ | ██ | ██ |
| Non-carboplatin/oxaliplatin MEC subgroup | | | | | |
| Netupitant/palonosetron (N=41) | ████████ | ████ | ██ | ██ | ██ |
| Aprepitant + palonosetron (N=8) | ████████ | ████ | ██ | ██ | ██ |

Source: Table B-20, p. B42; Tables B-22, B-23 p.B43; Table B-24, p. B-44, of the submission; Table 14.3.1.1.1.1, p. 701 of the NETU-10-29 clinical study report.

Abbreviations: AE, adverse event; MEC, moderately emetogenic chemotherapy; HEC, highly emetogenic chemotherapy; NR, not reported.

6.11 There were numerically greater treatment-related adverse events in the netupitant with palonosetron FDC group. The most common treatment related adverse event was constipation, which was observed in 3.6% of patients overall in the netupitant with palonosetron FDC group, and 1% of the aprepitant with palonosetron group.

6.12 There were two serious adverse events in the netupitant with palonosetron FDC group: an episode of cardiac arrhythmia (ventricular extrasystoles), and an episode of acute psychosis (also listed as a severe adverse event). There were no treatment-related deaths. The Pre-PBAC Response (p.3) noted that the differences observed in treatment related AEs were judged by the investigators not to be clinically relevant.

Clinical claim

6.13 Primary prophylaxis:

The submission described netupitant with palonosetron FDC as non-inferior in terms of comparative efficacy and safety to aprepitant with a 5HT₃ antagonist, when used for primary prophylaxis of nausea and vomiting associated with MEC.

- 6.14 This claim may be adequately supported for carboplatin/oxaliplatin regimens when used as primary prophylaxis, given that the majority of patients in the MEC subgroup of NETU-10-29 received treatment with carboplatin or oxaliplatin. However, NETU-10-29 was not designed as a non-inferiority trial. The carboplatin/oxaliplatin and non-carboplatin/oxaliplatin subgroup analyses were constructed post hoc, and were therefore subject to high risk of bias.
- 6.15 Secondary prophylaxis:
The submission described netupitant with palonosetron FDC as non-inferior in terms of comparative efficacy and safety to aprepitant with a 5HT₃ antagonist, when used for secondary prophylaxis of nausea and vomiting associated with moderately emetogenic chemotherapy.
- 6.16 This claim was not adequately supported. There was insufficient available data on the use of netupitant with palonosetron FDC in non-carboplatin/oxaliplatin based regimens. The PBAC has previously considered this claim to be poorly supported, as no clinical evidence was presented for use in the secondary prophylaxis setting (netupitant with palonosetron PSD March 2015). No additional clinical evidence for use in secondary prophylaxis was provided in the current submission. The Pre-Sub-Committee Response (PSCR) (p.1) and pre-PBAC Response (p.1) argued that similar evidence was sufficient for aprepitant to receive a PBAC recommendation for use with MEC regimens.
- 6.17 The PBAC considered that the claim of non-inferior effectiveness and safety was reasonable for primary prophylaxis of nausea and vomiting associated with carboplatin/oxaliplatin containing regimens.
- 6.18 The PBAC considered that although the clinical evidence for secondary prophylaxis was lacking, given the clinical evidence available, it was likely that NEPA was also comparatively non-inferior in effectiveness and safety to aprepitant plus a 5-HT₃ receptor antagonist in this population.

Economic analysis

- 6.19 The submission presented a cost-minimisation analysis versus aprepitant in combination with a 5HT₃ antagonist, and an analysis versus aprepitant alone.
- 6.20 The submission proposed that 300mg of oral netupitant with 0.5mg of oral palonosetron could be considered equivalent to 165mg of oral aprepitant with a 5HT₃ antagonist.
- 6.21 Equi-effective doses for 5HT₃ antagonists were based on the eviQ guidelines for the management of chemotherapy induced nausea and vomiting due to MEC.
- 6.22 The submission proposed an approved ex-manufacturer price of \$103.01 for netupitant with palonosetron FDC, which was the same as the current listed price of netupitant with palonosetron FDC for the highly emetogenic and anthracycline plus

cyclophosphamide (breast cancer) indications. The ESC noted that from 1 October 2016, aprepitant has an updated approved ex-manufacturer price of \$97.16.

- 6.23 A 10% Medicare sample was used to determine the distribution of 5HT₃ antagonists used concomitantly with aprepitant. The analysis was limited to intravenous 5HT₃ antagonists. Exclusion of oral 5HT₃ antagonists from the analysis was not reasonable, given that oral 5HT₃ antagonists are likely to be commonly prescribed in clinical practice. The Pre-PBAC Response (p.3) noted that certain oral 5HT₃ antagonists, such as granisetron and ondansetron, are more expensive than the injectable presentations.
- 6.24 The resulting distribution was heavily weighted towards IV palonosetron, which was the most expensive 5HT₃ antagonist. The PSCR (p.5) provided an updated cost-minimised price of \$■■■■■, which included a weighted average cost of \$■■■■■ for the 5HT₃ antagonist component and the updated aprepitant price.
- 6.25 In the absence of evidence to demonstrate that the 5HT₃ component of the FDC is more efficacious or safe than the least expensive PBS listed 5HT₃ antagonist, the use of a weighted average price of 5HT₃ antagonists in the calculation of the proposed price of netupitant with palonosetron FDC is not appropriate.

Drug cost/patient/cycle: \$103.01 (AEMP)

- 6.26 The proposed price was \$103.01 (AEMP) per chemotherapy cycle, compared to \$■■■■■ per cycle for aprepitant + the weighted 5-HT3 antagonist component.

Estimated PBS usage & financial implications

- 6.27 The submission was not considered by DUSC.
- 6.28 The financial analysis was based on a market share approach.
- 6.29 A 10% Medicare sample was used to estimate the historical and future aprepitant secondary prophylaxis utilisation. The submission assumed that the derived secondary prophylaxis utilisation represented ■■■% of the total potential MEC market, and used this relationship to estimate the remaining aprepitant MEC market. The carboplatin/oxaliplatin primary prophylaxis market was determined as ■■■% of this remaining aprepitant MEC market.
- 6.30 Table 7 summarises the estimated utilisation and financial implications associated with PBS listing of netupitant with palonosetron FDC for MEC primary (carboplatin/oxaliplatin) and secondary prophylaxis indications.

Table 7: Estimated netupitant with palonosetron FDC use and net financial implications for the PBS/RPBS

| | Apr-Jun 2017 | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 |
|---|--------------|---------|---------|---------|---------|---------|
| Total aprepitant market MEC (SP and PP carboplatin/oxaliplatin) | ████ | ████ | ████ | ████ | ████ | ████ |
| Netupitant/palonosetron FDC market share ¹ | █% | █% | █% | █% | █% | █% |
| Total netupitant/palonosetron FDC scripts | ████ | ████ | ████ | ████ | ████ | ████ |
| Total cost of netupitant/palonosetron FDC scripts | \$████ | \$████ | \$████ | \$████ | \$████ | \$████ |
| Patient co-payments for netupitant/palonosetron FDC | \$████ | \$████ | \$████ | \$████ | \$████ | \$████ |
| Cost to PBS/RPBS for netupitant/palonosetron FDC (less co-payments) | \$████ | \$████ | \$████ | \$████ | \$████ | \$████ |
| Cost saving from substitution of aprepitant | -\$████ | -\$████ | -\$████ | -\$████ | -\$████ | \$████ |
| Cost saving from substitution of 5HT ₃ antagonists | -\$████ | -\$████ | -\$████ | -\$████ | -\$████ | -\$████ |
| Net cost to PBS/RPBS | -\$████ | -\$████ | -\$████ | -\$████ | -\$████ | -\$████ |

Source: Compiled during the evaluation.

Abbreviations: Apr, April; Jun, June; Jul, July; MEC, moderately emetogenic chemotherapy; SP, secondary prophylaxis; PP, primary prophylaxis; FDC, fixed dose combination.

¹ Predicted market share was the same for primary prophylaxis (carboplatin/oxaliplatin) and secondary prophylaxis indications.

- 6.31 The submission estimated a saving of less than \$10 million in Year 1, increasing to a saving of less than \$10 million in Year 5, resulting in a cumulative saving of less than \$10 million over the first 5 years. The cost savings were predominantly due to a reduction in expenditure on 5HT₃ antagonists.
- 6.32 However, the submission likely over-estimated the cost savings due to:
- exclusion of oral 5HT₃ antagonists from the analysis, resulting in a distribution that was heavily skewed toward intravenous palonosetron, the most expensive of the 5HT₃ antagonists;
 - reliance on 10% Medicare data to derive the 5HT₃ antagonist distribution, which may not capture supply of some inexpensive 5HT₃ antagonists; and
 - application of overly optimistic market share assumptions.
- 6.33 The results of the financial analysis should be interpreted with caution given that:
- the methodology used to predict the future aprepitant secondary prophylaxis and the carboplatin/oxaliplatin primary prophylaxis markets contained multiple assumptions, and involved multiple extrapolations based on historical 10% Medicare sample data;
 - the assumption used to derive the potential MEC market based on the definition of MEC was flawed, and likely to underestimate the total market size;
 - the application of an 'uplift factor' to correct for non-participation of NSW and ACT in the PBS reforms was unnecessary, and would likely lead to over-estimation of market size.
- 6.34 The ESC considered that the cost savings claimed by the submission were highly

uncertain and may be overstated. The ESC considered that listing of netupitant + palonosetron in this setting would more likely be cost-neutral.

Quality Use of Medicines

- 6.35 The submission reiterated the claim that the FDC would improve treatment adherence. The PBAC has previously considered this claim, and did not accept that the availability of a FDC regimen on the PBS would improve adherence and patient compliance (netupitant with palonosetron FDC PSD November 2015). The ESC noted there was no new evidence in the resubmission to support a claim of improved adherence.

Financial Management – Risk Sharing Arrangements

- 6.36 The submission noted that the sponsor currently participates in a Risk Share Arrangement for netupitant with palonosetron FDC for the highly emetogenic and anthracycline plus cyclophosphamide (breast cancer) indications. The submission indicated that the sponsor was willing to negotiate an extension to the current arrangement for the proposed restriction.

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

7 PBAC Outcome

- 7.1 The PBAC recommended listing netupitant with palonosetron (NEPA) fixed dose combination, as an Authority Required (STREAMLINED) benefit on the General Schedule and under the Section 100 (Efficient Funding of Chemotherapy – Related Benefits) program, for the secondary prophylaxis of chemotherapy induced nausea and vomiting associated with moderately emetogenic chemotherapy and for primary prophylaxis of chemotherapy induced nausea and vomiting associated with carboplatin or oxaliplatin chemotherapy regimens.
- 7.2 The recommendation was made on a cost-minimisation basis to aprepitant, where the equi-effective doses, based on the eviQ guidelines, were based on the assumption that each chemotherapy course would be treated with one capsule of netupitant 300 mg with palonosetron 500 micrograms or one capsule of aprepitant 165 mg plus a 5-HT₃ RA. The PBAC noted that NEPA was previously recommended at a price based on aprepitant, with no cost assigned to the 5-HT₃ RA, and considered the same recommendation appropriate in this case. The PBAC further noted that aprepitant had a weighted price across the MEC and non-MEC indications. The PBAC therefore considered that similar pricing weighting assumptions be maintained between the MEC and non-MEC indications for NEPA, i.e. a lower relative price for the MEC indication to maintain cost-effectiveness in this broader population.
- 7.3 The PBAC considered that the requested restriction, based on the current aprepitant listings, was appropriate.
- 7.4 The PBAC noted that the August 2016 update to the eviQ guidelines recommended prophylaxis with an NK1 antagonist for carboplatin regimens.

- 7.5 Although the PBAC accepted that aprepitant plus a 5-HT₃ RA was an appropriate comparator, the PBAC considered that there may be leakage into populations where a 5-HT₃ RA alone would be used.
- 7.6 The PBAC noted that NEPA met the nominated 15% non-inferiority margin for the MEC subgroup in NETU-10-29, the pivotal trial comparing NEPA to aprepitant in combination with oral palonosetron. The PBAC further noted that the majority of patients in the MEC subgroup were on carboplatin/oxaliplatin regimens and that there was limited evidence for the non-carboplatin/oxaliplatin MEC subgroup. However, the Committee considered that pragmatically, it was likely that NEPA was also comparatively non-inferior to aprepitant plus a 5-HT₃ receptor antagonist in this population, noting the risk difference [REDACTED] in overall complete response and the small patient numbers.
- 7.7 The PBAC agreed with the ESC that the cost savings claimed by the submission were likely overstated, and listing of NEPA would most likely be cost-neutral. The market share assumptions (█% in Year 5) were also considered to be very optimistic. The PBAC recommended that the listing of NEPA for use with carboplatin/oxaliplatin regimens from the first chemotherapy cycle, without having a prior episode of CINV, should also be included in the existing aprepitant Risk Sharing Arrangement (RSA), with no increase in those Subsidisation Caps with the same rebate arrangements; and that the current RSA for NEPA be extended to include the secondary prophylaxis in MEC regimens indication to address ongoing concerns about leakage.
- 7.8 The PBAC noted that the submission suggested that the availability of NEPA as a FDC would improve adherence. No new evidence in the resubmission supported a claim of improved adherence. Therefore, as previously, the PBAC decided it was not satisfied as required by subsection 101(4AC) of the National Health Act 1953 (Act) and therefore will not provide advice to the Minister under that section.
- 7.9 The PBAC advised, as previously, that the NEPA FDC should not be treated as interchangeable with any other individual drugs on an individual patient basis, however that therapeutically, NEPA FDC could be considered interchangeable with the free combination of aprepitant with a 5-HT₃ RA.
- 7.10 The PBAC advised that NEPA is suitable for prescribing by nurse practitioners under the general schedule listing.
- 7.11 The PBAC recommended that the Early Supply Rule should not apply.
- 7.12 The PBAC noted that this submission is not eligible for an Independent Review because it received a positive recommendation.

Outcome:

Recommended

8 Recommended listing

8.1 Amend existing listing as follows:

| Name, Restriction, Manner of administration and form | Max. Qty | No. of Rpts | Proprietary Name and Manufacturer | |
|--|-------------|----------------|-----------------------------------|------------------------------------|
| GENERAL SCHEDULE netupitant 300 mg + palonosetron microgram capsule, 1 | 500 | 1 | 5 | Akynzeo® Mundipharma Pty Ltd |

| | | | | |
|--|-----|---|---|--|
| SECTION 100 (CT) netupitant 300 mg + palonosetron microgram capsule, 1 | 500 | 1 | 5 | |
|--|-----|---|---|--|

| | |
|------------------------------------|--|
| Category / Program | GENERAL – General Schedule (GE)* Section 100 – Efficient funding of Chemotherapy (CT) |
| Prescriber type: | <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners* <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives |
| Condition: | Nausea and vomiting |
| PBS Indication: | Nausea and vomiting |
| Restriction Level / Method: | <input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required - Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined |
| Clinical criteria: | 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. |
| Prescriber Instructions | No more than 1 capsule of 300mg netupitant/0.5mg palonosetron fixed dose combination will be authorised per cycle of cytotoxic chemotherapy. |
| Administrative Advice | No increase in the maximum quantity or number of units may be authorised. No Increase in the maximum number of repeats may be authorised. This medicine is not PBS-subsidised for nausea and vomiting associated with radiotherapy being used to treat malignancy. |

| | |
|---------------------------|--|
| Category / Program | GENERAL – General Schedule (GE)* Section 100 – Efficient funding of Chemotherapy (CT) |
|---------------------------|--|

| | |
|------------------------------------|---|
| Prescriber type: | <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners* <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives |
| Condition: | Nausea and vomiting |
| PBS Indication: | Nausea and vomiting |
| Restriction Level / Method: | <input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required - Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined |
| Clinical criteria: | 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. |
| Prescriber Instructions | No more than 1 capsule of 300mg netupitant/0.5mg palonosetron fixed dose combination will be authorised per cycle of cytotoxic chemotherapy. |
| Administrative Advice | No increase in the maximum quantity or number of units may be authorised. No Increase in the maximum number of repeats may be authorised. This medicine is not PBS-subsidised for nausea and vomiting associated with radiotherapy being used to treat malignancy. |

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

10 Sponsor's Comment

The Sponsor welcomes the PBAC's decision and will be working towards ensuring that patients have access to a broader choice of treatments to control chemotherapy induced nausea and vomiting.