CADTH

CADTH COMMON DRUG REVIEW

CADTH Canadian Drug Expert Committee Recommendation

(Final)

Netupitant/Palonosetron (Akynzeo — Purdue Pharma)
Indication: Chemotherapy-induced nausea and vomiting

RECOMMENDATION:
The Canadian Drug Expert Committee (CDEC) recommends that netupitant/palonosetron, in combination with dexamethasone, be reimbursed for once-per-cycle treatment in adult patients for prevention of acute and delayed nausea and vomiting associated with highly emetogenic cancer chemotherapy (HEC), if the following criterion and condition are met:

Criterion:
- Reimburse in a manner similar to aprepitant within drug plans that already reimburse aprepitant for the prevention of nausea and vomiting associated with HEC.

Condition:
- The total cost of treatment with netupitant/palonosetron should not exceed the total drug plan cost of treatment with the least costly neurokinin-1 (NK_1) receptor and 5-hydroxytryptamine-3 ($5\text{-}HT_3$) receptor antagonist drugs combined for the prevention of nausea and vomiting associated with HEC.

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Reasons for the Recommendation

1. In one double-blind, dose-finding, randomized controlled trial (RCT; NETU 7-07; N = 694), the proportion of patients achieving a complete response (CR) in acute-phase chemotherapy-induced nausea and vomiting (CINV) with netupitant/palonosetron was statistically superior to that with palonosetron in patients receiving HEC (absolute difference 8.8%; 95% confidence interval [CI], 3.3% to 14.3%). However, in a phase III double-blind RCT (NETU 8-18; N = 1,455), the difference in CR in the acute phase with netupitant/palonosetron versus palonosetron in patients with breast cancer receiving anthracycline/cyclophosphamide HEC was not statistically significant (absolute difference 3.4%; 95% CI, –0.1% to 6.9%).
2. In both NETU 8-18 (absolute difference 7.4%; 95% CI, 2.9% to 11.9%) and NETU 7-07 (absolute difference 10.2%; 95% CI, 1.9% to 18.6%), the proportion of patients receiving HEC who achieved CR in the delayed phase was statistically significantly higher for netupitant/palonosetron than for palonosetron.
3. In one double-blind, noninferiority, RCT (NETU 12-07; N = 834), netupitant/palonosetron was noninferior to aprepitant/granisetron, as the lower bound of the 95% CI of the between-group difference in the proportion of patients achieving CR in the overall phase (acute plus delayed CINV) was above the –10% noninferiority margin (absolute difference 3.6%; 95% CI, –2.2% to 9.4%) in patients receiving HEC.
4. The comparative clinical benefit of netupitant/palonosetron for the prevention of CINV in patients receiving moderately emetogenic chemotherapy (MEC) is uncertain, given the limited evidence base and the populations studied in the RCTs included. In a subgroup of patients receiving MEC in one double-blind RCT powered to assess safety (NETU 10-29; N = 413) that compared netupitant/palonosetron with aprepitant/palonosetron in patients receiving MEC or HEC, there was no statistically significant difference in the proportion of patients achieving CR in the acute or delayed phases. The trial enrolled patients who received MEC but who were chemotherapy-naive; by contrast, the Health Canada indication for netupitant/palonosetron specifies that patients must have experienced a failure of therapy with a $5\text{-}HT_3$ receptor antagonist and dexamethasone. Moreover, as a result of numerous limitations of a manufacturer-provided indirect comparison, conclusions could not be drawn regarding the comparative efficacy and safety of netupitant/palonosetron for the prevention of CINV in patients receiving MEC.
5. The manufacturer-submitted price of netupitant/palonosetron is $135.00 per fixed-dose capsule. A CADTH Common Drug Review (CDR) reanalysis of the manufacturer-provided cost-utility analysis produced results that were similar to the manufacturer's results for patients receiving HEC (i.e., netupitant/palonosetron/dexamethasone was dominant) based on data from a manufacturer-provided network meta-analysis, suggesting very small gains in quality-adjusted life-years (QALYs) (0.0002) and cost savings (less than $20) compared with aprepitant/ondansetron or granisetron/dexamethasone. CDR undertook another analysis that indicated that, if no incremental benefit is assumed, netupitant/palonosetron/dexamethasone is more costly ($20 to $28), but no more effective, than aprepitant/ondansetron or granisetron/dexamethasone. In patients receiving MEC, the CDR analysis reported incremental cost-utility ratios (ICURs) for netupitant/palonosetron/dexamethasone of

$316,082 and $221,485 per QALY gained compared with ondansetron/dexamethasone and grainsetron/dexamethasone, respectively. Therefore, netupitant/palonosetron was not cost-effective in patients receiving MEC.

Of Note

- CDEC noted several limitations of the comparative evidence for netupitant/palonosetron, especially versus other NK_1 receptor and 5-HT_3 receptor antagonist drug combinations. The RCTs did not consistently compare netupitant/palonosetron with the most clinically appropriate active comparator for CINV. The indirect evidence provided by the manufacturer was associated with numerous limitations, including important limitations in the source data for the network meta-analyses. Therefore, there is insufficient evidence that netupitant/palonosetron is clinically superior to other available NK_1 receptor and 5-HT_3 receptor antagonist drug combinations.

Discussion Points

- CDEC discussed the potential benefits and limitations associated with the administration of netupitant/palonosetron. In the absence of patient input to CADTH, CDEC heard from a clinical expert with expertise in the management of CINV, who stated that patients and clinicians may perceive a single dose, administered orally, per chemotherapy cycle as positive with respect to medication adherence and ease of administration. However, it was noted that the trials for netupitant/palonosetron were not designed to adequately assess its effects on adherence or patient preference.
- The committee also discussed whether the lack of a parenteral formulation would be a limiting factor for the use of the netupitant/palonosetron combination for preventing CINV. CDEC heard from a clinical expert that it is unlikely that having only an oral formulation available for netupitant/palonosetron would have a meaningful impact on administration to patients, because other NK_1 receptor and 5-HT_3 receptor antagonist drug combinations are typically administered orally for adult patients receiving HEC.
- Only one of the studies included (NETU 10-29) was designed to evaluate the effects of netupitant/palonosetron beyond one chemotherapy cycle. However, it was primarily a safety study of netupitant/palonosetron, and the key efficacy analysis was not designed to evaluate netupitant/palonosetron versus aprepitant/palonosetron beyond the first chemotherapy cycle. Study NETU 8-18 also included additional chemotherapy cycles after the first. However, this study was designed to analyze the efficacy of netupitant/palonosetron versus palonosetron at the end of the first cycle, and comparisons conducted in subsequent cycles were considered hypothesis-generating as a result of several limitations of the analyses, including the reduced sample size with each cycle of chemotherapy.

Background

Netupitant/palonosetron (Akynzeo) is a NK_1 receptor/5-HT_3 receptor antagonist combination treatment. It is indicated by Health Canada in combination with dexamethasone as once-per-cycle treatment for prevention of acute and delayed nausea and vomiting associated with HEC or MEC that is uncontrolled by a 5-HT_3 receptor antagonist alone. It is available in capsules containing 300 mg netupitant and 0.5 mg palonosetron.

Summary of CDEC Considerations

The committee considered the following information prepared by CDR: a systematic review of RCTs of netupitant/palonosetron, a manufacturer-provided indirect comparison, and a critique of the manufacturer's pharmacoeconomic evaluation. The committee also considered input from a clinical expert with experience in treating patients with CINV.

No patient groups submitted information about outcomes and issues important to patients.

Clinical Trials

The systematic review included four double-blind RCTs. Patients were chemotherapy-naive in all studies. NETU 8-18 (N = 1,455) was a phase III, double-blind RCT that compared the efficacy and safety of netupitant/palonosetron with that of palonosetron alone in patients receiving anthracycline/cyclophosphamide HEC, 97% of whom had breast cancer. NETU 7-07 (N = 694) was a phase II, double-blind dose-finding RCT that also assessed the efficacy and safety of netupitant/palonosetron compared with palonosetron alone in patients receiving HEC. The most common cancer diagnoses in this trial were lung (27%), head and neck (21%), and

ovarian (16%) cancer. NETU 10-29 (N = 413) was a phase IV, double-blind RCT designed to assess the safety of netupitant/palonosetron compared with aprepitant/palonosetron (an NK_1 receptor antagonist and 5-HT_3 receptor antagonist combination) in patients receiving MEC or HEC. The most common cancer diagnosis was lung cancer (37.4% of patients). Finally, NETU 12-07 (N = 834) was a noninferiority double-blind RCT designed to assess whether netupitant/palonosetron was noninferior to aprepitant/granisetron (an NK_1 receptor antagonist and 5-HT_3 receptor antagonist combination) in patients receiving HEC. The most common cancer diagnosis was lung cancer (58% of patients). Both NETU 8-18 and 10-29 studied the first cycle of chemotherapy and included a multiple-cycle extension phase. NETU 7-07 and 12-07 were conducted for the first cycle of chemotherapy only.

A key limitation was the use of palonosetron alone as a comparator to netupitant/palonosetron in patients receiving HEC (in both NETU 7-07 and NETU 8-18). Contemporary treatment guidelines recommend using a combination drug containing a NK_1 receptor antagonist and a 5-HT_3 receptor antagonist plus dexamethasone in patients receiving HEC. Thus, palonosetron alone is likely not the most relevant comparator to netupitant/palonosetron in patients receiving HEC. As well, the comparative assessment in most of the trials was limited to a single chemotherapy cycle.

Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. Of these, the committee discussed the following:

- CR (defined as no emetic episode and no rescue medication) in the acute phase (0 to 24 hours after chemotherapy), in the delayed phase (24 to 120 hours after chemotherapy), and in the overall phase (0 to 120 hours after)
- Total control (no emesis, no rescue medication, and no nausea [nausea up to a maximum of 5 mm on a visual analogue scale out of 100 mm]) during acute, delayed, and overall phases
- Complete protection (no emesis, no rescue medication, no significant nausea [nausea up to a maximum of 25 mm on a visual analogue scale out of 100 mm]) during acute, delayed, and overall phases
- Patient-reported outcomes (patient satisfaction, function, and quality of life).

The primary outcome in NETU 8-18 was CR in the delayed phase. The primary outcome in NETU 7-07 and 12-07 was CR in the overall phase. The primary outcome in NETU 10-29 was safety and tolerability (assessed via treatment-emergent adverse events).

Efficacy

- Compared with palonosetron alone, netupitant/palonosetron treatment led to a higher proportion of patients achieving CR in the delayed and overall phases. In NETU 7-07, netupitant/palonosetron was statistically superior to palonosetron alone for the proportion of patients achieving CR in the acute phase (absolute difference 8.8%; 95% CI, 3.3% to 14.3%); however, there was no difference in NETU 8-18 (absolute difference 3.4%; 95% CI, –0.1% to 6.9%).
- Compared with other NK_1 receptor and 5-HT_3 receptor antagonist combinations, there was no difference in the proportion of patients achieving CR with netupitant/palonosetron in the delayed, acute, or overall phases.
- In NETU 12-07, netupitant/palonosetron was deemed noninferior to aprepitant/granisetron, as the lower bound of the 95% confidence interval of the between-group difference in the proportion achieving CR in the overall phase was above the –10% noninferiority margin. In the multiple-cycle phase of NETU 10-29, there was no difference in CR for the delayed or acute phases between netupitant/palonosetron and aprepitant/palonosetron in any cycle.
- The proportion of patients with “no impact on daily life” (measured by the score on the Functional Living Index–Emesis [FLIE] questionnaire) was statistically significantly greater in the netupitant/palonosetron arm compared with the palonosetron arm (absolute difference in score 6.3; 95% CI, 1.9 to 10.7) in NETU 8-18; however, there was no significant difference in NETU 12-07 for netupitant/palonosetron compared with aprepitant/granisetron. FLIE is not a well-validated measure of patient function, and the clinical significance of these findings is unclear. In NETU 7-07, there was a small significant difference in global satisfaction between netupitant/palonosetron and palonosetron at 24 hours, as measured by a visual analogue scale out of

100 mm (mean difference 4.26 mm; 95% CI, 0.65 mm to 7.87 mm) and 120 hours (mean difference 4.77 mm; 95% CI, 0.79 mm to 8.75 mm).

- In the multiple-cycle extension phase of NETU 10-29, there was no difference in CR for the delayed or acute phases between netupitant/palonosetron and aprepitant/palonosetron in any cycle. In NETU 8-18, the proportion of patients achieving CR in the acute or delayed phases appeared to continue to be greater for netupitant/palonosetron compared with palonosetron over multiple cycles of chemotherapy. Neither study was specifically designed to evaluate the comparative efficacy of netupitant/palonosetron over multiple cycles.
- Both NETU 7-07 and 8-18 compared netupitant/palonosetron with palonosetron alone in patients receiving HEC. However, contemporary treatment guidelines recommend that patients on HEC receive therapy with NK_1 receptor and 5-HT_3 receptor antagonists (e.g., in Canada, aprepitant plus ondasetron with dexamethasone). Thus, palonosetron alone was likely not a relevant comparator in these trials in the current context. There were limited data available for patients receiving MEC, as only one trial (NETU 10-29) included patients receiving MEC. The validity of how the noninferiority margin in NETU 12-07 was derived is associated with considerable uncertainty. There were also concerns about use of a diary to capture outcome data, as this method may be prone to recall bias and its reliability is unclear.

Harms (Safety and Tolerability)

- The frequency of harms was generally similar between netupitant/palonosetron and its comparators across trials. While adverse events were very common, patients were also receiving chemotherapy, which commonly causes adverse events.
- There were no concerns identified regarding the cardiac safety of netupitant/palonosetron. However, the duration of the studies was likely too short to determine cardiac safety, and the studies were not designed specifically with cardiac safety as a primary outcome.
- The manufacturer-provided indirect comparison did not assess the comparative safety of netupitant/palonosetron versus its comparator treatments.

Indirect Comparison

A manufacturer-provided indirect comparison based on network meta-analyses evaluated the comparative efficacy of a fixed-dose combination of netupitant 300 mg/palonosetron 0.5 mg versus various comparators in the treatment of CINV in adult patients undergoing HEC or MEC. Results from the manufacturer-provided indirect comparisons suggested that, in patients receiving MEC, there was no difference in efficacy between netupitant/palonosetron/dexamethasone and aprepitant/$5HT_3$ receptor antagonist/dexamethasone or $5HT_3$ receptor antagonist/dexamethasone for CR at any time point. In patients receiving HEC, netupitant/palonosetron/dexamethasone provides efficacy similar to that of triple regimens containing aprepitant or fosaprepitant in terms of CR, complete protection, and total control in acute, phase, and overall phases. However, the limitations of the data sources, sparsely populated networks, uncertainty as to outcomes definitions, and inability to test assumptions and/or fully assess sources of heterogeneity in patients receiving MEC or HEC (but especially those receiving MEC) mean that no concrete conclusions could be drawn for the comparative efficacy of netupitant/palonosetron in these populations. Moreover, the absence of analyses of other clinically relevant outcomes, such as quality of life, patient functioning, and adverse events, means the clinical significance of any of the indirect analysis results is unknown.

Cost and Cost-Effectiveness

Netupitant/palonosetron is an oral fixed-dose combination of netupitant and palonosetron, available as a 300 mg/0.5 mg oral capsule, at a manufacturer-submitted price of $135 per capsule, to be taken once per chemotherapy cycle.

The manufacturer submitted a cost-utility analysis from the perspective of the publicly funded health care system in Canada, in which netupitant/palonosetron/dexamethasone was compared with aprepitant/an oral 5-HT_3 receptor antagonist (such as ondansetron or granisetron)/dexamethasone in patients receiving HEC, and an oral 5-HT_3 receptor antagonist (ondansetron or granisetron)/dexamethasone in patients receiving MEC. In the Markov model, all patients were followed for five days (cycle length

and model time horizon) after HEC or MEC administration. No subsequent cycles of treatment were modelled. Response rates for patients receiving netupitant/palonosetron were derived from two pivotal trials (NETU 7-07 for HEC population and NETU 8-18 for MEC population). Treatment outcomes for comparators were derived from a manufacturer-funded network meta-analysis. The manufacturer reported that netupitant/palonosetron /dexamethasone was dominant compared with aprepitant/5-HT_3 receptor antagonist/dexamethasone (i.e., netupitant/palonosetron is associated with additional benefits and less costs) in patients receiving HEC. The manufacturer reported that netupitant/palonosetron/dexamethasone was associated with ICURs of $270,094 per QALY compared with ondansetron/dexamethasone and $163,948 per QALY compared granisetron/dexamethasone in patients receiving MEC.

CDR identified the following key limitations with the manufacturer's submitted economic analysis:

- The patient populations from the pivotal netupitant/palonosetron trials were not representative of population definitions and comparator treatments in current treatment guidelines. These data were used in the network meta-analysis and in the economic evaluation for patients receiving HEC or MEC.
- CDR identified several limitations of the submitted network meta-analysis, which limited the confidence in the comparative effectiveness of netupitant/palonosetron/dexamethasone and 5-HT_3 receptor antagonist/dexamethasone in patients receiving MEC.
- CDR identified several parameter-input assumptions that were associated with uncertainty.
- The manufacturer modelled only the first cycle of chemotherapy. Consideration that patients may develop resistance to antiemetics over prolonged use was not included; thus, the generalizability of the results in the first cycle to those in subsequent cycles is uncertain.

The results of the CDR reanalysis based on the data from the manufacturer-funded network meta-analysis were aligned with the manufacturer's results in patients receiving HEC (i.e., netupitant/palonosetron/dexamethasone was dominant), although the gains in QALYs (0.0002) and cost savings (less than $20) were small. In patients receiving MEC, the CDR re-analyses resulted in ICURs for netupitant/palonosetron/dexamethasone of $316,082 compared with ondansetron/dexamethasone and $221,485 per QALY gained compared with granisetron/dexamethasone.

There is, however, substantial uncertainty with the comparative clinical effectiveness of netupitant/palonosetron/dexamethasone in the relevant patient populations, given changes in clinical practice since the netupitant/palonosetron trials and network meta-analyses were undertaken, which limits the confidence in the economic analyses. In patients receiving HEC, if no incremental benefit were assumed, netupitant/palonosetron/dexamethasone would be more costly but no more effective than aprepitant/5HT_3 receptor antagonist/dexamethasone.

CDEC Members

Dr. James Silvius (Chair), Dr. Silvia Alessi-Severini, Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Dr. Peter Jamieson, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

May 15, 2018 Meeting

Regrets

Two CDEC members

Conflicts of Interest

None