CADTH

CADTH COMMON DRUG REVIEW

# Pharmacoeconomic Review Report

## Netupitant/Palonosetron 300 mg/0.5 mg (Akynzeo)

(Purdue Pharma)

Indication: In combination with dexamethasone, once-per-cycle treatment for the prevention of acute and delayed nausea and vomiting associated with highly emetogenic cancer chemotherapy, or with moderately emetogenic cancer chemotherapy that is uncontrolled by a 5-$HT_3$ receptor antagonist alone.


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**About CADTH:** CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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## Table of Contents

## Tables



## Figure

# Abbreviations

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| **5-HT$_3$** | 5-hydroxytryptamine-3 |
| **AC** | anthracycline/cyclophosphamide |
| **APR** | aprepitant |
| **CDR** | CADTH Common Drug Review |
| **CINV** | chemotherapy-induced nausea and vomiting |
| **CP** | complete protection |
| **CR** | complete response |
| **DEX** | dexamethasone |
| **GRAN** | granisetron |
| **HEC** | highly emetogenic chemotherapy |
| **ICUR** | incremental cost-utility ratio |
| **IR** | incomplete response |
| **IV** | intravenous |
| **MEC** | moderately emetogenic chemotherapy |
| **NEPA** | netupitant/palonosetron |
| **NK$_1$** | neurokinin-1 |
| **NMA** | network meta-analysis |
| **OND** | ondansetron |
| **OR** | odds ratio |
| **QALY** | quality-adjusted life-year |
| **RA** | receptor antagonist |
| **VAS** | visual analogue scale |

## Table 1: Summary of the Manufacturer's Economic Submission

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| **Drug Product** | Netupitant/palonosetron (Akynzeo) |
| **Study Question** | To evaluate the cost-effectiveness of netupitant/palonosetron (NEPA) compared with a 5-hydroxytryptamine-3 ($5\text{-HT}_3$) receptor antagonist (RA) + a neurokinin-1 ($NK_1$) RA for patients receiving highly emetogenic chemotherapy (HEC) and with a $5\text{-HT}_3$RA for patients receiving moderately emetogenic chemotherapy (MEC) from a Canadian health care system perspective |
| **Type of Economic Evaluation** | Cost-utility analysis (CUA) |
| **Target Population** | Patients with cancer receiving prophylactic antiemetics for the prevention of CINV as a result of HEC or MEC treatment |
| **Treatment** | 1 capsule of NEPA administered orally approximately 1 hour prior to the start of each chemotherapy cycle and a dose of dexamethasone (DEX) 12 mg administered orally 30 minutes prior to chemotherapy. Patients also received DEX 8 mg on days 2 to 4. |
| **Outcome** | Quality-adjusted life-year (QALY) |
| **Comparators** | For patients receiving HEC:<br>• Aprepitant + ondansetron + dexamethasone (APR + OND + DEX)<br>• Aprepitant + granisetron + dexamethasone (APR + GRAN + DEX)<br><br>For patients receiving MEC:<br>• Ondansetron + dexamethasone (OND + DEX)<br>• Granisetron + dexamethasone (GRAN + DEX) |
| **Perspective** | Health care system |
| **Time Horizon** | 5 days |
| **Results for Base Case** | In patients receiving HEC, NEPA + DEX compared with either APR + OND + DEX or APR + GRAN + DEX was dominant (i.e., additional QALY gains, lower costs)<br><br>In patients receiving MEC, NEPA + DEX compared with:<br>• OND + DEX = $270,094 per QALY<br>• GRAN + DEX = $163,948 per QALY |
| **Key Limitations** | • The patient populations from the pivotal NEPA trials are not representative of population definitions and comparator treatments in current treatment guidelines. These data were used to inform the NMA, which was used to infer incremental benefits associated with NEPA + DEX in both patient populations.<br>• CDR identified several limitations with the submitted NMA, which limited the confidence in the comparative effectiveness of NEPA + DEX and a $5\text{-HT}_3$RA + DEX in patients receiving MEC.<br>• The assumption of a reduced need for rescue medication with oral palonosetron (component of NEPA) compared with other oral $5\text{-HT}_3$RAs was not supported by comparative clinical evidence.<br>• There was a lack of clarity in the derivation of the utility values and a lack of face validity of the CP utility value.<br>• The manufacturer assumed the risk of CINV in delayed phase was not conditional on whether CINV occurred in the acute phase. Feedback from the clinical expert consulted by CDR suggested this is not an appropriate assumption; patients who experience a CINV in the acute phase have an increased risk of another CINV event in the delayed phase.<br>• The manufacturer modelled only the first cycle of chemotherapy, and the relative treatment effects were assumed to remain over subsequent cycles of chemotherapy. The CDR clinical expert indicated that patients may develop resistance to antiemetics over prolonged use; thus, the generalizability of the results in the first cycle to those in subsequent cycles is uncertain. |

| CDR Estimates | |
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| | • There is substantial uncertainty with the clinical information used to assess the comparative efficacy of NEPA + DEX against relevant comparators in the indicated populations.<br>• The CDR base case incorporated alternative health state utility values and comparative efficacy estimates (based on 5-$HT_3$RA treatments) in both the HEC and MEC populations.<br>• The CDR base case confirmed the manufacturer's results in patients receiving HEC (NEPA + DEX is more effective and less costly than [dominant] APR + 5-$HT_3$RA + DEX), but with very small QALY gains (0.0002 QALY) and cost savings (< $20).<br>• In the MEC population, CDR estimated that NEPA + DEX will result in ICURs of $316,082 and $221,485 per QALY compared with OND + DEX and GRAN + DEX, respectively. A price reduction range of 45% to 65% may be required for NEPA to result in an ICUR of $50,000 per QALY in patients receiving MEC (compared with GRAN and OND, respectively).<br>• CDR undertook a scenario analysis assuming no difference in efficacy between NEPA + DEX and APR + 5-$HT_3$RA + DEX in patients receiving HEC, based on findings from the NMA, which found that NEPA + DEX was as effective but more costly than (i.e., dominated by) APR + 5-$HT_3$RA + DEX. |

5-$HT_3$ = 5-hydroxytryptamine-3; APR = aprepitant; CDR = CADTH Common Drug Review; CINV = chemotherapy-induced nausea and vomiting; CP = complete protection; CUA = cost-utility analysis; DEX = dexamethasone; GRAN = granisetron; HEC = highly emetogenic chemotherapy; ICUR = incremental cost-utility ratio; MEC = moderately emetogenic chemotherapy; NEPA = netupitant/palonosetron; $NK_1$ = neurokinin-1; NMA = network meta-analysis; OND = ondansetron; QALY = quality-adjusted life-year; RA = receptor antagonist.

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| **Drug** | Netupitant/palonosetron (Akynzeo) |
| **Indication** | Netupitant/palonosetron, in combination with dexamethasone, is indicated for once-per-cycle treatment in adult patients for:<br>• Prevention of acute and delayed nausea and vomiting associated with highly emetogenic cancer chemotherapy.<br>• Prevention of acute nausea and vomiting associated with moderately emetogenic cancer therapy that is uncontrolled by a 5-hydroxytryptamine-3 ($5\text{-HT}_3$) receptor antagonist (RA) alone. |
| **Reimbursement Request** | As per indication |
| **Dosage Form** | 300 mg netupitant/ 0.5 mg palonosetron capsules |
| **NOC Date** | 28-09-2017 |
| **Manufacturer** | Purdue Pharma |

# Executive Summary

## Background

Netupitant/palonosetron (Akynzeo) is an oral fixed-dose combination of netupitant, a neurokinin-1 (NK1) receptor antagonist (RA), and palonosetron, a 5-hydroxytryptamine-3 (5-HT3) RA, available as a 300 mg/0.5 mg oral capsule.1 In combination with dexamethasone, netupitant/palonosetron (NEPA) is indicated for once-per-cycle treatment in adult patients for:

- prevention of acute and delayed nausea and vomiting associated with highly emetogenic (HEC) chemotherapy
- prevention of acute nausea and vomiting associated with moderately emetogenic (MEC) therapy that is uncontrolled by a $5\text{-HT}_3$ receptor antagonist alone.

Oral palonosetron was previously reviewed by CADTH Common Drug Review (CDR) in 2013 and received a “do not list” recommendation[2] based on clinical reasons, notably the absence of direct or indirect comparisons of oral palonosetron with other oral $5\text{-HT}_3$RAs for the treatment of chemotherapy-induced nausea and vomiting (CINV), and because “oral palonosetron failed to demonstrate non-inferiority against intravenous palonosetron” in the delayed phase.[2]

The recommended dose for NEPA is one capsule administered orally 1 hour prior to the start of a chemotherapy cycle.[1] The manufacturer is seeking reimbursement in line with the Health Canada indication.[3] The manufacturer submitted a price of $135 per capsule; therefore, the cost of NEPA is $135 per chemotherapy cycle.[3]

The manufacturer submitted a cost-utility analysis based on a Markov model in which all patients were followed for five days (cycle length and model time horizon) after HEC or MEC administration.[4] No subsequent cycles of treatment were modelled. The model consisted of three health states: complete protection (CP) indicates less than 25 mm on visual analogue scale (VAS) (no significant/ mild nausea) without emesis and rescue medication; complete response (CR) at best indicates 25 mm or more on VAS without emesis and rescue medication; and incomplete response (IR) indicates that a patient undergoing emetogenic chemotherapy experienced emesis episodes and/or required rescue medications. Patients

could transition between these health states each day between day 1 and day 5. NEPA + dexamethasone (DEX) was compared with aprepitant (APR; an $NK_1$RA) + an oral 5-$HT_3$ RA (ondansetron [OND] or granisetron [GRAN]) + DEX in patients receiving HEC; and an oral 5-$HT_3$ RA (OND or GRAN) + DEX in patients receiving MEC. Response rates for patients receiving NEPA were derived from two pivotal trials (NETU 7-07 for patients receiving HEC and NETU 8-18 for patients receiving MEC). Treatment outcomes for comparators were derived from a manufacturer-funded network meta-analysis (NMA) that pooled efficacy data from multiple trials and considered a broader range of comparators. Treatment outcomes of comparators to NEPA were estimated based on odds ratios (ORs) derived from the NMA for each patient population (HEC and MEC) and applied to the NEPA response rates for each patient population. The HEC population also included patients who received anthracycline and cyclophosphamide (AC)–based MEC. Utility values were derived from published literature. Treatment costs were obtained from the Ontario Drug Benefit Formulary, while health care resource costs were obtained from the Ontario Health Insurance Plan Schedule of Benefits. The analyses took the perspective of the publicly funded health care system in Canada in relation to costs and quality of life gains accrued by patients in relation to benefits.

In patients receiving HEC, the manufacturer reported that NEPA + DEX was dominant compared with APR + a 5-$HT_3$RA + DEX (i.e., NEPA is associated with additional benefits and less costs than the comparator). In patients receiving MEC, the manufacturer reported probabilistic incremental cost-utility ratios (ICURs) of $270,094 per quality-adjusted life-year (QALY) and $163,948 per QALY for NEPA + DEX compared with OND + DEX and GRAN + DEX, respectively.

## Summary of Identified Limitations and Key Results

CDR identified several limitations with the manufacturer's submitted analysis. However, the key limitation with the submitted economic evaluation was related to the clinical data, specifically the generalizability and representativeness of the studies of NEPA given the changes in the definitions of the patient populations and the guideline-recommended treatments for the relevant patient populations since the studies were undertaken, and the impact of these on assessing the comparative effectiveness of NEPA with the comparator treatments for the relevant patient populations. CDR noted that the manufacturer's safety trial, NETU 10-29, was the only trial that included patients who would be defined as having received MEC based on current treatment guidelines. The CDR clinical review identified several limitations with the submitted NMA; the major limitation was associated with the body of evidence: the data sources used, sparsely populated networks, uncertainty as to outcomes definitions, and inability to test assumptions and/or fully assess sources of heterogeneity. Other assumptions used by the manufacturer were not tested in the NMA. Among these, various doses of 5-$HT_3$RAs were included, which, along with dexamethasone, were not expected to have an impact on efficacy; and both modes of administration (intravenous and oral) were included, leading to uncertainty in the results. Thus, CDR determined that no concrete conclusions could be drawn for the comparative efficacy of NEPA in these populations due to the considerable uncertainty associated with the identified limitations. This limits the confidence that can be placed in the CDR reanalyses. CDR noted important limitations with the submitted model that appeared to overestimate the benefit of NEPA, including the lack of clarity in how the health state utility values were derived and the lack of face validity of the CP utility value, as well as the assumption of differential efficacy among 5-$HT_3$RAs.

The CDR base-case analysis used alternative health states utility values and assumed the efficacy of GRAN was equivalent to that of OND. The results of the CDR base-case analysis in patients receiving HEC was aligned with the manufacturer's results in these patients (i.e., NEPA + DEX was dominant), albeit with very small QALY gains (0.0002) and small cost savings (< $20) compared with APR + OND/GRAN + DEX. In the patients receiving MEC, the CDR base case resulted in ICURs for NEPA + DEX of $316,082 and $221,485 per QALY gained compared with OND + DEX and GRAN + DEX, respectively.

CDR undertook a scenario analysis assuming equivalent efficacy of NEPA + DEX and APR + a 5-$HT_3$RA + DEX in the HEC patient population, which resulted in NEPA + DEX being more costly and as effective as APR + OND/GRAN + DEX (i.e., dominated).

CDR was unable to assess the impact of other potentially significant assumptions, including the assumption that the comparative treatment effects of NEPA and the relevant comparators would not change over subsequent cycles of chemotherapy. Therefore, the manufacturer's and CDR's ICURs for NEPA in patients receiving HEC and MEC should be considered applicable only to the first use of NEPA (i.e., ICUR for cycle 1 of chemotherapy, not per subsequent cycle or per entire chemotherapy regimen).

## Conclusions

There is substantial uncertainty with the comparative clinical effectiveness of NEPA + DEX in the relevant patient populations, given changes in clinical practice since the NEPA trials and the NMA were undertaken, which limits the confidence in the economic analyses.

In patients receiving HEC, if a small incremental benefit is assumed based on the point estimates in the NMA, NEPA + DEX is less costly and more effective than APR + a 5-HT3RA + DEX. However, if no incremental benefit is assumed (i.e., OR = 1), NEPA + DEX is more costly but no more effective than APR + OND/GRAN + DEX. The difference in cost is based on revised health state costs.

In patients receiving MEC, NEPA + DEX is associated with an ICUR of $316,082 per QALY compared with OND + DEX, and $221,485 per QALY compared with GRAN + DEX. A price reduction of 45% to 65% is required for NEPA + DEX to achieve an ICUR of $50,000 per QALY in patients receiving MEC compared with GRAN + DEX and OND + DEX.

# Information on the Pharmacoeconomic Submission

## Summary of the Manufacturer's Pharmacoeconomic Submission

The manufacturer submitted a cost-effectiveness and cost-utility analysis based on a Markov model in which all patients are followed for five days (cycle length and model time horizon) after administration of highly emetogenic chemotherapy (HEC) or moderately emetogenic chemotherapy (MEC).[4] Discounting was not considered, given the five-day time horizon. The model consists of three health states:

- Complete protection (CP) indicates less than 25 mm on visual analogue scale (VAS) (no significant/mild nausea) without emesis and rescue medication.
- Complete response (CR) at best indicates 25 mm or more on VAS without emesis and rescue medication.
- Incomplete response (IR) indicates that a cancer patient undergoing emetogenic chemotherapy experiences emesis episodes and/or requires rescue medications.

All patients enter the economic model on the day 0 and receive antiemetic treatment for their HEC or MEC regimen. The comparator for netupitant/palonosetron (NEPA) for patients receiving HEC was aprepitant (APR) + a 5-hydroxytryptamine-3 ($5\text{-HT}_3$) receptor antagonist (RA) + dexamethasone (DEX), while the comparator for NEPA for patients receiving MEC was a $5\text{-HT}_3$RA + DEX. On day 1 (the first day after receiving treatment; acute phase), patients either responded to treatment (achieved CR or CP), or experienced emesis and/or required rescue medication (IR). On each subsequent day from day 2 to day 5 (delayed phase), patients could transition to a different response health state (CP, CR, or IR).

Efficacy and effectiveness for NEPA were sourced from two pivotal trials (NETU 7-07 and NETU 8-18): response rates for NEPA for patients receiving HEC were derived from NETU 7-07, while data from NETU 8-18 were used for patients receiving MEC. Treatment outcomes for comparators were derived from a network meta-analysis (NMA) that pooled efficacy data from multiple trials and considered a broader range of comparators. Treatment outcomes for the comparators compared with NEPA were estimated based on odds ratios (ORs) derived from the NMA for each patient population (HEC and MEC) and applied to the NEPA response rates for each patient population. At the end of the cycle of antiemetic treatment, the average cumulative costs and effects were calculated for a given treatment arm of the model.

The impact of chemotherapy-induced nausea and vomiting (CINV) treatment-related adverse events was not included in the analysis. The NMA results found that NEPA did not have statistically significant higher odds of CR in the acute, delayed, and overall phases compared with $5\text{-HT}_3$RAs in patients receiving MEC. The NMA also found that NEPA + DEX provided similar efficacy to APR-containing triple regimens (APR + $5\text{-HT}_3$RA + DEX) for patients receiving HEC, MEC, and either HEC or anthracycline-cyclophosphamide in terms of CR, CP, and total control in acute, delayed, and overall phases. This is in contrast to the manufacturer's underlying assumption that NEPA was more effective than the comparators in patients receiving HEC and MEC, despite the results of the NMA.

Utility values were derived from published literature. Treatment costs were obtained from the Ontario Drug Benefit, while health care resource costs were obtained from the Ontario

Health Insurance Plan Schedule of Benefits. The analyses take the perspective of the publicly funded health care system in Canada in relation to costs and consider the survival and quality of life gains accrued by patients in relation to benefits.

## Manufacturer's Base Case

In patients receiving HEC, the manufacturer reported that NEPA + DEX was dominant compared with APR + a 5-$HT_3$RA + DEX (i.e., NEPA is associated with additional benefits at less cost than the comparator). In patients receiving MEC, the manufacturer reported probabilistic incremental cost-utility ratios (ICURs) of $270,094 per quality-adjusted life-year (QALY) and $163,948 per QALY for NEPA + DEX compared with ondansetron (OND) + DEX and granisetron (GRAN) + DEX, respectively (Table 2).

### Table 2: Summary of Results of the Manufacturer's Probabilistic Base Case

| | Regimen | Total Costs ($) | Incremental Cost ($) | Total QALYs | Incremental QALYs | Incremental Cost per QALY |
|---|---|---|---|---|---|---|
| HEC | APR + OND + DEX | $225 | | 0.0114 | | |
| | NEPA + DEX | $220 | –$5 | 0.0117 | 0.0003 | Dominant |
| | APR + GRAN + DEX | $323 | | 0.0109 | | |
| | NEPA + DEX | $220 | –$103 | 0.0117 | 0.0008 | Dominant |
| MEC | OND + DEX | $238 | | 0.0101 | | |
| | NEPA + DEX | $339 | $101 | 0.0105 | 0.0004 | $270,094 |
| | GRAN + DEX | $265 | | 0.0101 | | |
| | NEPA + DEX | $339 | $74 | 0.0105 | 0.0004 | $163,948 |

APR = aprepitant; DEX = dexamethasone; GRAN = granisetron; HEC = highly emetogenic chemotherapy; MEC = moderately emetogenic chemotherapy; NEPA = netupitant/palonosetron; OND = ondansetron; QALY = quality-adjusted life-year.
Source: Adapted from the manufacturer's pharmacoeconomic submission.[4]

## Summary of Manufacturer's Sensitivity Analyses

In the manufacturer's sensitivity analyses in patients receiving HEC, varying the OR of CR for NEPA + DEX compared with APR + OND + DEX and APR + GRAN + DEX in the overall phase resulted in an ICUR ranging from dominant (NEPA + DEX was more effective and less costly) compared with APR + GRAN + DEX, to $91,838 per QALY gained compared with APR + OND + DEX. When the NEPA CR rate in the overall phase varied between 0.85 and 0.95 (mean of 0.90), the ICUR for NEPA + DEX ranged from dominant to $32,863 per QALY gained compared with both APR + OND + DEX and APR + GRAN + DEX. Using the upper values for the OR of CR and the CR rate for NEPA in the overall phase were the only sensitivity analyses that resulted in NEPA no longer dominating APR + OND + DEX or APR + GRAN + DEX (NEPA CR rate only). Other variables tested had only a small impact on the ICUR in patients receiving HEC.

For patients receiving MEC, varying the OR of CR for NEPA + DEX versus OND + DEX in the overall phase resulted in ICUR changes in a range of $72,142 to $683,329 per QALY gained, and ICUR changes in a range of $66,715 to $637,845 per QALY gained compared with GRAN + DEX. When the OR of CP for NEPA + DEX versus OND + DEX in the overall phase was varied, this resulted in an ICUR range of $157,663 to $292,151 per QALY gained for OND + DEX and GRAN + DEX. Changes in the utility value for NEPA + DEX CP resulted in a similar impact on the ICUR. These findings indicate the model was more sensitive to CR

than CP. Other variables tested had only a small impact on the ICUR in patients receiving MEC.

## Limitations of Manufacturer's Submission

- **Uncertainty with NEPA efficacy from pivotal trials:** The manufacturer used efficacy outcomes from two pivotal NEPA trials in the model. Data for NEPA were derived from NETU 7-07 for patients receiving HEC and from NETU 8-18 for those receiving MEC:
  - In NETU 8-18, patients were on anthracycline and cyclophosphamide (AC) treatment, which was classified as MEC. However, current guidelines classify AC combinations within the same classification as HEC, an issue highlighted by the FDA review and Health Canada.[5-7] Based on current guidelines, an $NK_1$RA, a 5-$HT_3$RA, and DEX would be recommended for all patients in NETU 8-18.[5,8-10] Thus, patients in the palonosetron-alone arm in the NETU 8-18 trial could be considered undertreated according to current guidelines.
  - Similarly, in NETU 7-07, all patients were receiving HEC. In this trial, patients in the palonosetron arm were not receiving guideline-recommended antiemetic treatment at the time of the trial. The clinical expert noted that, in patients receiving HEC, palonosetron alone was not a relevant comparator, since an $NK_1$ RA, a 5-$HT_3$ RA, and DEX would be recommended in these patients based on current guidelines and clinical practice.
  - In the NETU 10-29 safety trial, the comparator treatment was a combination of an $NK_1$RA, a 5-$HT_3$RA, and DEX. All patients were chemotherapy-naive, and 75% were receiving MEC, for whom current guidelines recommend antiemetic treatment with a 5-$HT_3$RA and DEX alone (not an $NK_1$RA).[5,8-10] Thus, patients receiving MEC in NETU 10-29 could be considered overtreated based on current guidelines.
- **Limitations of the submitted network meta-analysis:** The CDR clinical review of the manufacturer-submitted NMA identified several limitations, aside from the underlying issue with the quality of the clinical evidence used to inform the NMA. The manufacturer made the following assumptions: the NMA included only papers up until January 2014, indicating that the analysis may be dated; different doses of 5-$HT_3$RAs and DEX were assumed not to affect efficacy; and mode of administration (intravenous [IV] and oral) was assumed not to influence efficacy (for complete details, refer to the CDR clinical review for NEPA). The CDR clinical expert consulted for this review indicated that the assumption of different doses of a 5-$HT_3$RA and DEX is clinically reasonable and acceptable, although the validity of the assumption of the mode of the administration may not be appropriate for all subpopulations (e.g., older patients, those with difficulty swallowing). Furthermore, the definition of CR in the NMA (no nausea, no vomiting, and no rescue) was different from that in the pivotal studies (no vomiting and no rescue). CDR determined that no concrete conclusions could be drawn for the comparative efficacy of NEPA in these populations due to the considerable uncertainty associated with the identified limitations. In order to assess the impact of the available evidence on the efficacy of NEPA versus its comparators in patients receiving HEC and MEC, and based on the significant changes in the results of the manufacturer's scenario analysis when the OR for NEPA against its comparators was varied, CDR conducted a scenario analysis on the CDR base-case analysis that assumed NEPA and its comparators had equal efficacy in patients receiving HEC.

- **Uncertainty in the estimation of the health state utility values:**
  - The manufacturer applied a health state utility of 0.9 for CP, based on the publication by Lordick et al. (2007)[11] that derived this value based on Borjeson et al. (1997) "chemotherapy with no nausea" state (0.993) and Grunberg et al. (1996) "chemotherapy with no nausea/vomiting" state (0.790).[12,13] Although the Lordick publication assigned a utility of 0.9 to the model health state CP, which corresponds to chemotherapy with no appreciable nausea or emesis, it was not clear as to how this utility value was derived.
  - In the "CR at best" model state, a patient has no emesis or rescue medication but may have a small amount of nausea. Lordick et al. (and the manufacturer) assumed the utility for the mild nausea state from Borjeson et al. (0.752), normalized to Lordick's "chemotherapy without nausea and vomiting" anchor value of 0.9, to develop the utility for "CR at best" health state equal to 0.7. The approach in conducting the normalization process is uncertain.
  - The utility value for patients achieving CP used in the model is 0.9, which does not appear to meet face validity, as these patients are undergoing HEC or MEC to treat their base cancer type. Using such a high anchor value likely overestimates the impact of NEPA on patients' quality of life.
- **Assumption of a reduced need for rescue medication with oral palonosetron:** The manufacturer assumed that oral palonosetron was associated with a reduced need for rescue medication compared with oral OND, based on two studies.[4] However, CDR was unable to confirm this assumption; therefore, CDR undertook a literature search that identified another publication that showed palonosetron IV was numerically, but not statistically, better than other IV 5-$HT_3$RAs; oral palonosetron was not included in the publication.[14] Based on the publication findings, it would be implausible to assume that oral palonosetron, as part of the NEPA combination, exhibits superior efficacy compared with other oral 5-$HT_3$RAs. For CDR reanalyses, it was assumed that 5-$HT_3$RAs have similar efficacy and similar needs for rescue medications.
- **Inappropriate assumption of the independence of acute and delayed CINV:** In the manufacturer's model, the risk of CINV in the delayed phase was not conditional on whether the patient experienced CINV in the acute phase. Feedback from the clinical expert consulted by CDR indicated that patients who experience acute emesis with chemotherapy are significantly more likely to experience delayed emesis. Ideally, the model structure would have included two initial health states — patients who experience acute emesis and those who experience acute emesis control. From each of these health states, patients would either experience delayed emesis or delayed emesis control. The impact of this change in the model structure could not be tested in CDR reanalyses.
- **Treatment effect may differ in subsequent cycles:** The manufacturer modelled the first cycle of treatment effects and included an assumption that the treatment effect would not change over subsequent cycles (i.e., at every start of subsequent chemotherapy, an administration of antiemetic regimens will yield efficacy similar to that observed in the first chemotherapy cycle). According to feedback from the CDR clinical expert, there is the potential for treatment efficacy to wane over subsequent cycles of chemotherapy because patients may develop resistance to the antiemetic effects of the compared treatments and possibly of NEPA as well. Because of the model structure and lack of data, CDR could not assess the impact of this in reanalyses.

## CADTH Common Drug Review Reanalyses

CDR identified considerable uncertainty with several parameters in the submitted model, leading CDR to undertake scenario analyses to highlight this uncertainty, when possible. CDR undertook a base-case analysis presented in Table 3, revising the manufacturer's values for health states and assuming similar efficacy of 5-$HT_3$RAs.

1) Using alternative health state utility values: Despite the manufacturer's submission information on the source of the included utility values, the sources do not provide clear information on how these utility values were derived or estimated. To assess the impact of this uncertainty on the model results, a probabilistic reanalysis was conducted by CDR using utility values from a publication by Humphreys et al. (2013) on the cost-effectiveness of an APR regimen for the prevention of CINV.[15]
2) To assess the impact of assuming that OND and GRAN demonstrate similar efficacy in CINV in both patients receiving HEC and MEC, CDR conducted a scenario analysis that assumed the same efficacy for OND and GRAN. Although the manufacturer undertook a scenario analysis that assumed all 5-$HT_3$RAs demonstrate similar efficacy, these data were from an analysis from the NMA that included palonosetron, a 5-$HT_3$RA that had received a "do not list" recommendation for reimbursement in Canada.[2] Therefore, for consistency with interpretation of the base-case analyses, CDR assumed the ORs for OND were applicable to GRAN.

### Table 3: Summary of Results of the CDR Probabilistic Base-Case Analysis

| | Regimen | Total Costs ($) | Incremental Cost ($) | Total QALYs | Incremental QALYs | Incremental Cost per QALY |
|---|---|---|---|---|---|---|
| HEC | APR + OND + DEX | $226 | | 0.0102 | | |
| | NEPA + DEX | $220 | -$6 | 0.0104 | 0.0002 | Dominant |
| | APR + GRAN + DEX | $238 | | 0.0102 | | |
| | NEPA + DEX | $220 | -$18 | 0.0104 | 0.0002 | Dominant |
| MEC | OND + DEX | $239 | | 0.0091 | | |
| | NEPA + DEX | $340 | $101 | 0.0094 | 0.0003 | $316,082 |
| | GRAN + DEX | $264 | | 0.0090 | | |
| | NEPA + DEX | $340 | $76 | 0.0094 | 0.0004 | $221,485 |

APR = aprepitant; DEX = dexamethasone; GRAN = granisetron; HEC = highly emetogenic chemotherapy; MEC = moderately emetogenic chemotherapy; NEPA = netupitant/palonosetron; OND = ondansetron; QALY = quality-adjusted life-year.

The results of the one-way scenario analyses on the manufacturer's base case that assess the individual impact of these parameters are detailed in Table 17 and Table 18.

CDR also undertook a scenario analysis applying similar efficacy to NEPA and comparators in prevention of CINV in patients receiving HEC. Despite the limitations noted with the submitted NMA, CDR clinical reviewers suggested the results indicated that NEPA demonstrated efficacy similar to that of its comparators in preventing CINV in patients receiving HEC. Using the CDR base-case analysis to assess the impact of uncertainty with NEPA efficacy, CDR conducted a scenario analysis that assumed similar efficacy for NEPA

and the comparators (APR + 5-$HT_3$RA + DEX) in patients receiving HEC. The CDR results are aligned with the scenario results provided by the manufacturer that varied the OR for NEPA against the comparators for CR in the overall phase (i.e., the results for NEPA + DEX in HEC patients changed from being dominant to a very high ICUR, Table 19). According to the NMA submitted by the manufacturer, treatment with OND was permitted up to five days for each chemotherapy cycle. This was in contrast to the manufacturer's assumption of a one-day administration of OND (i.e., on day 1). Therefore, the treatment effect for OND applied in the manufacturer's economic submission may be underestimated. The uncertainty associated with OND treatment was assessed in a scenario analysis conducted by CDR, in which the cost of OND was adjusted to reflect a five-day administration. The analysis was conducted on both the manufacturer's and CDR's base-case analyses (Table 20). The scenario results are aligned with the results provided by the manufacturer and the CDR base-case analysis.

A series of price-reduction analyses were undertaken, based on the CDR base-case analysis and manufacturer's base-case analysis for patients receiving MEC. The analyses varied the percentage reduction to illustrate the impact on the ICUR (Table 4). Price-reduction analyses using the CDR base case indicate that a price reduction of 45% to 65% may be required for NEPA + DEX to result in an ICUR of $50,000 per QALY, and using the manufacturer's base case, a price reduction of 40% to 55%, may be required for NEPA + DEX to result in an ICUR of $50,000 per QALY in patients receiving MEC (Table 4).

## Table 4: CDR Reanalysis Price Reduction Scenarios for Patients Receiving Moderately Emetogenic Chemotherapy

| ICURs of NEPA + DEX Versus Comparators | | | | |
|---|---|---|---|---|
| **Price** | **Base-Case Analysis Submitted by Manufacturer** | | **Reanalysis by CDR** | |
| | OND + DEX | GRAN + DEX | OND + DEX | GRAN + DEX |
| **Submitted** | $270,094 | $163,948 | $316,082 | $221,485 |
| **25% reduction** | $187,528 | $89,350 | $183,725 | $122,645 |
| **30% reduction** | $163,236 | $74,997 | $173,203 | $102,724 |
| **40% reduction** | $110,042 | $44,047 | $154,009 | $64,612 |
| **50% reduction** | $72,334 | $14,750 | $90,634 | $25,262 |
| **60% reduction** | $31,470 | Dominant | $64,435 | Dominant |
| **75% reduction** | Dominant | Dominant | Dominant | Dominant |

CDR = CADTH Common Drug Review; DEX = dexamethasone; GRAN = granisetron; NEPA = netupitant/palonosetron; OND = ondansetron.

## Issues for Consideration

- Feedback from the clinical expert consulted by CDR suggested that some patients receiving MEC regimens may receive the three-drug combination (one 5-$HT_3$RA, one steroid regimen [i.e., DEX], and one $NK_1$RA regimen [APR]). The cost-effectiveness of NEPA compared with triple therapy in patients receiving MEC is unknown.
- In clinical practice, 5-$HT_3$RAs are commonly used off-label. Feedback from the CDR clinical expert indicated that, in certain cases, 5-$HT_3$ RAs are taken over a longer period than their recommended dose.
- Although oral palonosetron received a "do not list" recommendation from CDEC, a small number of claims have been filled for it across Canada.

- The clinical expert consulted by CDR suggested that the efficacy of the prophylactic regimen can affect the patient's quality of life, which may, in turn, affect the patient's ability to remain on his or her chemotherapy regimen.

## Patient Input

No patient input was received for this review. A summary from a previous CDR review for palonosetron (Aloxi) noted that there is an expectation that palonosetron may be more effective than some of the current antiemetic drugs, based on clinical trial results. Patient input also noted that side effects for palonosetron will be similar to those with currently available treatments (headaches, constipation, tiredness, and fatigue) and that some patients may not benefit from palonosetron or may not be able to tolerate it. The manufacturer's base-case analysis assumed that the efficacy of palonosetron is superior to that of available 5-$HT_3$RAs.

## Conclusions

There is substantial uncertainty with the comparative clinical effectiveness of NEPA + DEX in the relevant patient populations, given changes in clinical practice since the NEPA trials and NMA were undertaken, which limits the confidence in the economic analyses.

In patients receiving HEC, if a small incremental benefit is assumed based on the point estimates in the NMA, NEPA + DEX is less costly and more effective than APR + a 5-$HT_3$RA + DEX. However, if no incremental benefit is assumed (i.e., OR = 1), NEPA + DEX is more costly but no more effective than APR + OND/GRAN + DEX. The difference in cost is based on revised health state costs.

In patients receiving MEC, NEPA + DEX is associated with an ICUR of $316,082 per QALY compared with OND + DEX, and $221,485 per QALY compared with GRAN + DEX. A price reduction of 45% to 65% is required for NEPA + DEX to achieve an ICUR of $50,000 per QALY in the MEC patient population compared with OND + DEX and GRAN + DEX.

# Appendix 1: Cost Comparison

The comparators presented in Table 5 have been deemed appropriate by clinical experts. Comparators may be recommended (appropriate) practice, rather than actual practice. Comparators are not restricted to drugs but may be devices or procedures. Costs are manufacturer's list prices, unless otherwise specified. Existing Product Listing Agreements are not reflected in the table; as a result, the table may not represent the actual costs to public drug plans.

## Table 5: CDR Cost Comparison Table for the Management of Chemotherapy-Induced Nausea and Vomiting

| Drug/ Comparator | Strength | Dosage Form | Price ($) | Recommended Dose | Average Annual Drug Cost ($) |
|---|---|---|---|---|---|
| **Netupitant/palonosetron (Akynzeo)** | **300 mg / 0.5 mg** | **cap** | **135.0000[a]** | **1 capsule 1 hour before start of each chemotherapy cycle[b]** | **135** |
| **5-HT$_3$ receptor antagonists** | | | | | |
| Granisetron (Generic, Kytril) | 1 mg | tab | 9.0000[c] | 2 mg on the day of chemotherapy (1 mg 1 hour pre-chemotherapy then 1 mg 12 hours post-chemotherapy OR single 2 mg dose 1 hour pre-chemotherapy) | 18 |
| Granisetron (Generic) | 1 mg/mL vial | | 35.0000[c] | 10 mcg/kg 30 minutes before chemotherapy only on the day of chemotherapy[d] | 35[e] |
| Granisetron (Kytril) | | | 70.0000[c] | | 70[e] |
| Ondansetron (generics, branded) | 4 mg | tab<br>ODT<br>ODF | 3.3495<br>3.2720<br>3.2720 | *HEC*: 8 mg to16 mg IV 15 minutes pre-chemotherapy then after first 24 hours 8 mg every 8 hours for up to 5 days<br><br>*MEC*: 8 mg to 16 mg pre-chemotherapy (oral or IV) and 8 mg twice daily for up to 5 days | 82 to 87 |
| | 8 mg | tab<br>ODT<br>ODF | 5.1110<br>4.9930<br>4.9930 | | 56 to 61 |
| | 4 mg/5 mL | O/L | 1.6208 | *HEC*: 8 mg to 16 mg IV 15 minutes pre-chemotherapy then after first 24 hours 8 mg every 8 hours for up to 5 days<br><br>*MEC*: 8 mg to 16 mg pre-chemotherapy (oral or IV) and 8 mg twice daily for up to 5 days | 52 to 55<br><br>36 to 39 |
| Palonosetron (Aloxi) | 0.5 mg<br>0.25 mg / 5 mL | tab<br>vial | 66.0000[c]<br>90.0000[c] | 0.25 mg (IV) 30 minutes before chemotherapy<br>OR<br>0.5 mg capsule one hour before chemotherapy | 66 to 90 |
| **NK$_1$ antagonists** | | | | | |
| Aprepitant (Emend) | 80 mg<br>125 mg<br><br>2 × 80 mg/ | cap<br>cap<br><br>cap | 32.7950[c]<br>32.7920[c]<br><br>98.3763 | 125 mg 1 hour prior to chemotherapy (day 1) and 80 mg once daily in the morning on days 2 and 3 | 98 |

| Drug/ Comparator | Strength | Dosage Form | Price ($) | Recommended Dose | Average Annual Drug Cost ($) |
|---|---|---|---|---|---|
| | 1 × 125 mg | Tri-Pack | | | |
| Fosaprepitant (Emend IV) | 150 mg / 10 mL | vial | 97.2100[c] | 150 mg IV 30 minutes prior to chemotherapy[f] | 97 |
| **Other medications** | | | | | |
| Dexamethasone (generics) | 0.5 mg<br>4 mg | tab | 0.0782<br>0.3046 | 8 mg to 20 mg pre-chemotherapy and 8 mg every 8 hours, up to 5 days[g] | 10 to 11 |

5-$HT_3$ = 5-hydroxytryptamine-3; cap = capsule; HEC = highly emetogenic chemotherapy; IV = intravenous; MEC = moderately emetogenic chemotherapy; ODF = orally disintegrating film; ODT = orally disintegrating tablet; O/L = oral liquid; tab = tablet.
Note: Prices sourced from Ontario Drug Benefit / Comparative Drug Index (effective from January 8, 2018) unless otherwise noted.
Note: Recommended dose sourced from product monographs unless otherwise noted.
[a] Based on manufacturer's submission.[3]
[b] With HEC, in addition to Akynzeo, 12 mg dexamethasone administered orally 30 minutes prior to chemotherapy on day 1, 8 mg dexamethasone orally once daily on days 2 to 4; with MEC, 12 mg dexamethasone administered orally 30 minutes prior to chemotherapy, none on days 2 to 4.[3]
[c] Delta PA database.
[d] Need for additional doses not studied.
[e] Based on a 70 kg weight, wastage included.
[f] Should be administered in conjunction with corticosteroid and a 5-$HT_3$ antagonist.
[g] When used as adjunct in HEC: 12 mg 30 minutes before chemotherapy, 8 mg on days 2 to 4; when used as adjunct in MEC: 12 mg 30 minutes before chemotherapy, 8 mg on days 2 and 3 with palonosetron, ondansetron, or granisetron.

# Appendix 2: Summary of Key Outcomes

## Table 6: When Considering Only Costs, Outcomes, and Quality of Life, How Attractive Is NEPA + DEX Relative to APR + OND + DEX in Patients Receiving Highly Emetogenic Chemotherapy?

| NEPA + DEX Versus APR + OND + DEX | Attractive | Slightly Attractive | Equally Attractive | Slightly Unattractive | Unattractive | N/A |
|---|---|---|---|---|---|---|
| **Costs (total)** | | X | | | | |
| **Drug treatment costs alone** | | X | | | | |
| **Clinical outcomes** | | X | | | | |
| **Quality of life** | | X | | | | |
| **Incremental CE ratio or net benefit calculation** | NEPA + DEX is dominant (i.e., associated with more benefits at lower costs) | | | | | |

APR = aprepitant; CE = cost-effectiveness; DEX = dexamethasone; N/A = not applicable; NEPA = netupitant/palonosetron; OND = ondansetron.
Note: Based on CDR reanalysis.

## Table 7: When Considering Only Costs, Outcomes, and Quality of Life, How Attractive Is NEPA + DEX Relative to APR + GRAN + DEX in Patients Receiving Highly Emetogenic Chemotherapy?

| NEPA + DEX Versus APR + GRAN + DEX | Attractive | Slightly attractive | Equally attractive | Slightly unattractive | Unattractive | N/A |
|---|---|---|---|---|---|---|
| **Costs (total)** | | X | | | | |
| **Drug treatment costs alone** | | X | | | | |
| **Clinical outcomes** | | X | | | | |
| **Quality of life** | | X | | | | |
| **Incremental CE ratio or net benefit calculation** | NEPA + DEX is dominant (i.e., associated with more benefits at lower costs) | | | | | |

APR = aprepitant; CE = cost-effectiveness; DEX = dexamethasone; GRAN = granisetron; N/A = not applicable; NEPA = netupitant/palonosetron.
Note: Based on CDR reanalysis.

## Table 8: When Considering Only Costs, Outcomes, and Quality of Life, How Attractive Is NEPA + DEX Relative to OND + DEX in Patients Receiving Moderately Emetogenic Chemotherapy?

| NEPA + DEX Versus OND + DEX | Attractive | Slightly Attractive | Equally Attractive | Slightly Unattractive | Unattractive | N/A |
|---|---|---|---|---|---|---|
| **Costs (total)** | | | | | X | |
| **Drug treatment costs alone** | | | | | X | |
| **Clinical outcomes** | | X | | | | |
| **Quality of life** | | X | | | | |
| **Incremental CE ratio** | $316,082 per QALY | | | | | |

CE = cost-effectiveness; DEX = dexamethasone; N/A = not applicable; NEPA = netupitant/palonosetron; OND = ondansetron; QALY = quality-adjusted life-year.
Note: Based on CDR reanalysis.

## Table 9: When Considering Only Costs, Outcomes, and Quality of Life, How Attractive Is NEPA + DEX Relative to GRAN + DEX in Patients Receiving Moderately Emetogenic Chemotherapy?

| NEPA + DEX Versus GRAN + DEX | Attractive | Slightly Attractive | Equally Attractive | Slightly Unattractive | Unattractive | N/A |
|---|---|---|---|---|---|---|
| **Costs (total)** | | | | | X | |
| **Drug treatment costs alone** | | | | | X | |
| **Clinical outcomes** | | X | | | | |
| **Quality of life** | | X | | | | |
| **Incremental CE ratio** | $221,485 per QALY | | | | | |

CE = cost-effectiveness; DEX = dexamethasone; GRAN = granisetron; N/A = not applicable; NEPA = netupitant/palonosetron; QALY = quality-adjusted life-year.
Note: Based on CDR reanalysis.

# Appendix 3: Additional Information

## Table 10: Submission Quality

| | Yes/ Good | Somewhat/ Average | No/ Poor |
|---|---|---|---|
| Are the methods and analysis clear and transparent? | X | | |
| Comments | The manufacturer estimated the cost of ondansetron based on the assumption of a single dose administered on the first day of the chemotherapy regimen despite NMA findings indicating that ondansetron may be administered for up to 5 days of chemotherapy regimen. | | |
| Was the material included (content) sufficient? | X | | |
| Comments | None | | |
| Was the submission well organized and was information easy to locate? | X | | |
| Comments | None | | |

NMA = network meta-analysis.

## Table 11: Authors Information

**Authors of the pharmacoeconomic evaluation submitted to CDR**

☐ Adaptation of global model/Canadian model done by the manufacturer

☐ Adaptation of global model/Canadian model done by a private consultant contracted by the manufacturer

☒ Adaptation of global model/Canadian model done by an academic consultant contracted by the manufacturer

☐ Other (please specify)

| | Yes | No | Uncertain |
|---|---|---|---|
| Authors signed a letter indicating agreement with entire document | | | X |
| Authors had independent control over the methods and right to publish analysis | X | | |

# Appendix 4: Summary of Other Health Technology Assessment Reviews of Drug

The cost-effectiveness of netupitant/palonosetron for the treatment of chemotherapy-induced nausea and vomiting (CINV) has been assessed by the Pharmaceutical Benefits Advisory Committee (PBAC) in Australia (four times)[16-19] and the Scottish Medicines Consortium (SMC).[20] Over the four PBAC submissions, the indication evolved and captured both highly emetogenic chemotherapy and moderately emetogenic chemotherapy. The PBAC and SMC reviews are presented in Table 12.

The Haute Autorité de Santé (HAS) in France also assessed netupitant/palonosetron for the treatment of CINV in patients receiving either highly or moderately emetogenic chemotherapy. The Transparency Committee at HAS recommended netupitant/palonosetron for the requested indications, at a reimbursement rate of 65%.[21] Netupitant/palonosetron is also currently under review with Quebec's Institut national d'excellence en santé et en services sociaux (INESSS).

## Table 12: Other Health Technology Assessment Findings

| | PBAC (March 2015, July 2015, November 2015, November 2016)[16-19] | SMC (December 2015)[20] |
|---|---|---|
| **Treatment** | Netupitant/palonosetron (NEPA; 300 mg/0.5 mg) | |
| **Price** | Redacted in 2015 submissions<br>November 2016: A$121.18 (C$120.53) for general schedule, A$103.01 (C$102.45) for Section 100 | Not reported (cost per regimen per cycle with dexamethasone: £83 [C$144.54]) |
| **Similarities to CDR submission** | March, July, November 2015: Same comparators | Same comparators |
| **Differences from CDR submission** | March 2015: CMA submitted, patient population (MEC with previous CINV)<br>July, November 2015: CMA, no MEC indication<br>November 2016: CMA, indications – secondary prophylaxis of CINV associated with MEC, primary prophylaxis of CINV for carboplatin and oxaliplatin chemotherapy regimens, APR with 5-$HT_3$RAs the only comparator considered with MEC | Cost-minimization analysis submitted<br>Efficacy data from NETU 7-07 and not from network meta-analysis |
| **Manufacturer's results** | Results redacted | £18 (C$31.35) more per patient than APR and OND |
| **Issues noted by the review group** | March 2015: No alternative dosage forms of OND considered, unmet clinical need not established, considered the economic analysis a cost-comparison more than a cost-minimization analysis<br>July 2015: No changes from previous submission other than removal of MEC indication, claims that fixed-dose combination would improve patient adherence not accepted<br>November 2015: Net savings only occurs if NEPA replaces 5-$HT_3$ + APR instead of 5-$HT_3$ alone, as this would lead to price increase<br>November 2016: Submission likely overestimated cost savings due to exclusion of oral 5-$HT_3$RAs and overly optimistic market share assumptions, and cost-savings claims were highly uncertain and may be overstated, with NEPA more likely to be cost-neutral with MEC | No statistical comparison between relevant comparators conducted, although comparable efficacy was deemed to be demonstrated. SMC clinical experts noted that OND could be used in different ways, as an IV or oral treatment and on day 1 only, for example, although it remained the cost-effective treatment option. |
| **Results of reanalyses by the review group** | None reported | None reported |
| **Recommendation** | March 2015: NEPA not recommended based on lack of unmet need and uncertainty of place in therapy | NEPA accepted for restricted use within NHS Scotland for |

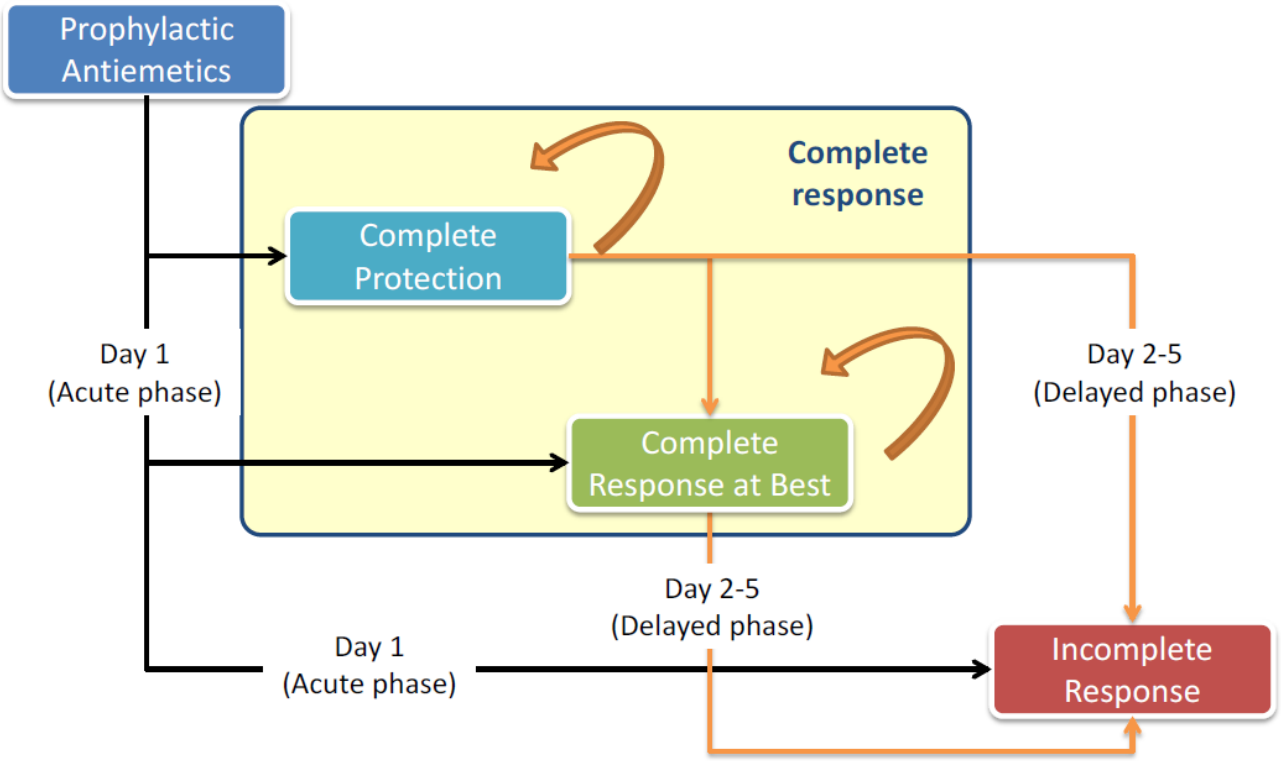
| | PBAC (March 2015, July 2015, November 2015, November 2016)[16-19] | SMC (December 2015)[20] |
|---|---|---|
| | July 2015: NEPA not recommended; concerns from previous submission not addressed<br>November 2015: NEPA not recommended for the prevention of CINV for HEC and anthracycline + cyclophosphamide–based regimens in patients with breast cancer<br>November 2016: NEPA recommended for secondary prophylaxis of CINV with MEC and primary prophylaxis of CINV for carboplatin and oxaliplatin chemotherapy regimens | the prevention of highly emetogenic cisplatin-based cancer chemotherapy |

$5\text{-HT}_3$ = 5-hydroxytryptamine-3; APR = aprepitant; CINV = chemotherapy-induced nausea and vomiting; CMA = cost-minimization analysis; HEC = highly emetogenic chemotherapy; MEC = moderately emetogenic chemotherapy; NEPA = netupitant/palonosetron; OND = ondansetron; PBAC = Pharmaceutical Benefits Advisory Committee; RA = receptor antagonist; SMC = Scottish Medicines Consortium.

# Appendix 5: Reviewer Worksheets

## Manufacturer's Model Structure

### Figure 1: Manufacturer's Markov Cohort Model




Source: Manufacturer pharmacoeconomic submission.[4]

### Table 13: Data Sources

| Data Input | Description of Data Source | Comment |
|---|---|---|
| **Efficacy** | The proportion of patients who responded to treatment was used as a transition probability in the model.<br><br>The response rates (i.e., IR, CR at best, and CP) were obtained at first cycle of chemotherapy from NETU trials for netupitant/palonosetron (i.e., NETU 7-07, NETU 8-18, NETU 10-29).[22-24]<br><br>The response rates of the comparators were calculated based on the ORs of NEPA versus the comparators that were derived from the NMA.[25] | In NETU 8-18, patients were on AC treatment, which was classified as MEC when the trial was run. However, contemporary guidelines classify AC combinations as HEC.[5] Based on current guidelines, all patients in NETU 8-18 patients would be recommended to receive an $NK_1RA$, a 5-$HT_3RA$, and dexamethasone.[5,8-10] Thus, patients in the palonosetron alone (comparator) arm in NETU 8-18 trial could be considered undertreated according to current guidelines. Therefore, it may not be appropriate to consider these patients in the MEC subgroup in the comparative analysis.<br><br>Similarly, in NETU 7-07 all patients were receiving HEC. In this trial, patients in the palonosetron arm were not receiving guideline-recommended antiemetic treatment. The clinical |

| Data Input | Description of Data Source | Comment |
|---|---|---|
| | | expert noted that, in patients receiving HEC, palonosetron alone was not a relevant comparator, since these patients would all be recommended to receive $NK_1$RA, 5-$HT_3$RA, and dexamethasone based on current guidelines and clinical practice.<br><br>The CDR clinical review of the NMA submitted for NEPA noted several limitations related to the assumptions made due to the heterogeneity in the included studies, such as HEC and MEC populations considered similar, various doses of 5-$HT_3$RAs and dexamethasone not having an impact on efficacy, and mode of administration (IV and oral) not having an influence on efficacy (for complete details, refer to the CDR clinical review for NEPA). |
| **Utilities** | Based on values from published literature for CINV<br>• The utility of 0.90 was used for chemotherapy without nausea and vomiting, based on Lordick et al. (2007).[11]<br>• For "incomplete response" health state, the utility value was set at 0.27, based on Grunberg et al. (1996).[13]<br>• For "CR at best," a utility value of 0.7 was used, based on Borjeson et al. (1997).[12] | There is uncertainty with how the utility value used for CR (0.9) in the Lordick et al. publication was derived from a range of 0.79 to 0.993.[4]<br><br>The CDR clinical expert considered a utility value of 0.90 for patients requiring HEC or MEC to be higher than expected, given that these patients are being treated for some form of cancer. |
| **Resource use** | | |
| **Emergency room visit, hospitalization and clinic/office visit** | The probability of emergency room visit, hospitalization, and clinic/office visit among patients with CINV were obtained from a manufacturer-sponsored survey of Canadian oncology nurses.[4] | Acceptable |
| **Costs** | | |
| **Drug** | Drug costs for netupitant/palonosetron were calculated based on the cost of $135 per package, as provided by the manufacturer.[3]<br><br>Treatment costs of the prophylactic antiemetics comparators were calculated based on recommended doses from Canadian sources and unit costs from the Ontario Drug Benefit.[26] | Acceptable.<br>The manufacturer estimated the cost of ondansetron based on the assumption of a single dose administered on the first day of the chemotherapy regimen, despite NMA findings indicating that ondansetron may be administered for up to 5 days of chemotherapy regimen. |
| **Rescue medications (metoclopramide and prochlorperazine)** | The unit cost of both rescue medications were obtained from the Ontario Drug Benefit Formulary.[26] | Acceptable |
| **CINV event** | Unit costs for these resources were derived from the Ontario Schedule of Benefits and Physician Services.[27] | The total cost of a CINV episode, weighted by the proportion of episodes treated on an in-patient or outpatient basis, was estimated at $788.98. |
| **Emergency room visit** | The cost of an emergency room visit was obtained from the a publication by Cummings et al. (2017).[28] | |

| Data Input | Description of Data Source | Comment |
|---|---|---|
| **Hospitalization** | The cost (per day) of in the hospital was obtained from the a publication by Thavorn et al. (2017).[29] | Acceptable |
| **Clinic/office visit** | The cost associated with a clinic/office visit was obtained from the Ontario Schedule of Benefits and Physician Services.[27] | Acceptable |

5-$HT_3$ = 5-hydroxytryptamine-3; AC = anthracycline/cyclophosphamide; CDR = CADTH Common Drug Review; CINV = chemotherapy-induced nausea and vomiting; CP = complete protection; CR = complete response; HEC = highly emetogenic chemotherapy; IR = incomplete response; IV = intravenous; MEC = moderately emetogenic chemotherapy; NMA = network meta-analysis; NK1 = neurokinin-1; OR = odds ratio; RA = receptor antagonist.

## Table 14: Manufacturer's Key Assumptions

| Assumption | Comment |
|---|---|
| The manufacturer assumed that the pivotal studies for NEPA were representative of both assessed patient populations (i.e., HEC and MEC). | Uncertain.<br>Limitations reported with the treatments applied in the pivotal studies raises uncertainty over the manufacturer's assumption. |
| It was assumed that the individual 5-$HT_3$RAs were different with regard to their efficacies. | Uncertain.<br>There is variation in the reported results of available comparative evidence among 5-$HT_3$RAs. |
| An episode of incomplete response is assumed to have a large impact on costs and quality of life, | Appropriate. |
| When a patient achieves complete protection (i.e., no significant nausea without emesis), the model assumes no costs of managing an emetic episode. | Appropriate. |
| The patient is assumed to achieve nearly full health rather than perfect health, as health preference among the patients receiving chemotherapy without such side effects is less than perfect health. | Uncertain.<br>The manufacturer applied a utility of 0.9 for patients with complete protection, despite available literature assuming such patients would have a utility of 0.79. |
| It is assumed that differences in age and gender have no impact on the efficacy and costs, since the target population included in the model consists of patients who received HEC or MEC for cancer treatments. | Uncertain.<br>Age and gender are known risk factors for CINV. The manufacturer noted that applying efficacy weight by the risk factors would be relevant only if the model were to be adapted for a subgroup of patients in a certain age group or a certain type of cancer. |
| The impact of any CINV treatment-related adverse events was not included in the analysis. | Appropriate.<br>No significant differences in CINV treatment-related adverse events were observed between netupitant/palonosetron and the comparators. |
| The manufacturer assumed 100% of patients who experience a CINV event require some form of rescue medication. | Appropriate. |

5-$HT_3$ = 5-hydroxytryptamine-3; CINV = chemotherapy-induced nausea and vomiting; HEC = highly emetogenic chemotherapy; MEC = moderately emetogenic chemotherapy; NEPA = netupitant/palonosetron; RA = receptor antagonist.

## Manufacturer's Results

Results of the manufacturer's base-case probabilistic analyses are presented in Table 15 for patients receiving highly emetogenic chemotherapy (HEC) and in Table 16 for patients receiving moderately emetogenic chemotherapy (MEC). The manufacturer reported differences in clinical events/outcomes, resource use, and costs for both netupitant/palonosetron and the comparators in both patients with HEC and MEC.

The total quality-adjusted life-years (QALYs) associated with the netupitant/palonosetron (NEPA) in patients receiving HEC (0.0117) was marginally higher than the total QALYs associated with aprepitant (APR) + ondansetron (OND) (0.0114) and APR + granisetron (GRAN) (0.0109). The total costs associated with NEPA in patients receiving HEC were $220, while the total costs associated with APR + OND were $225 and with APR + GRAN were $323, resulting in an incremental difference of approximately $5 and $103, respectively. In summary, NEPA dominated APR + either OND or GRAN, as it was associated with increased benefits at a lower cost than the comparators.

In patients receiving MEC, the total QALYs associated with NEPA (0.0105) was marginally higher than the total QALYs associated with APR + OND (0.0101) and APR + GRAN (0.0101). The total costs associated with NEPA were $339, while the total costs associated with APR + OND were $238 and with APR + GRAN were $265, resulting in an incremental difference of approximately $101 and $74, respectively. The incremental cost-utility ratio (ICUR) for NEPA compared with OND was $270,094 per QALY, and for NEPA compared with GRAN was $163,948 per QALY in patients receiving MEC.

### Table 15: Manufacturer's Base-Case Probabilistic Results in Patients Receiving Highly Emetogenic Chemotherapy

| | NEPA + DEX | APR + OND + DEX | APR + GRAN + DEX |
|---|---|---|---|
| **Costs ($)** | | | |
| Treatment drug | 137.88 | 110.01 | 118.09 |
| CINV episode management | 82.02 | 114.84 | 205.28 |
| In-patient care | 23.41 | 32.79 | 58.59 |
| Rescue medication | 2.05 | 2.87 | 5.12 |
| Outpatient care | 48.53 | 67.93 | 121.46 |
| Physician care | 8.04 | 11.26 | 20.11 |
| Cost in acute phase | 11.68 | 22.99 | 21.99 |
| Cost in delayed phase | 70.34 | 91.85 | 183.29 |
| **Total costs** | **219.90** | **224.85** | **323.37** |
| **Health outcomes** | | | |
| Average emesis-free days | 4.703 | 4.569 | 4.233 |
| Average CINV-free days | 4.498 | 4.252 | 4.070 |
| Emesis-free patients (%) | 89.6% | 85.4% | 74.0% |
| Emetic events (estimate) | 0.60 | 0.84 | 1.50 |
| CINV-free patients (%) | 82.9% | 77.4% | 72.5% |
| Quality-adjusted life-days | 4.276 | 4.169 | 3.988 |
| Quality-adjusted life-years | **0.0117** | **0.0114** | **0.0109** |
| **Cost/Outcomes** | | | |
| Cost per emesis-free day (avoided emesis per day) | | Dominant | Dominant |

| | NEPA + DEX | APR + OND + DEX | APR + GRAN + DEX |
|---|---|---|---|
| Cost per avoided emetic event | | Dominant | Dominant |
| Cost per CINV-free day (avoided mild nausea per day) | | Dominant | Dominant |
| **Cost per QALY gained** | | **Dominant** | **Dominant** |

APR = aprepitant; CINV = chemotherapy-induced nausea and vomiting; DEX = dexamethasone; GRAN = granisetron; NEPA = netupitant/palonosetron; OND = ondansetron; QALY = quality-adjusted life-year.
Source: Manufacturer's pharmacoeconomic submission.[4]

## Table 16: Manufacturer's Base-Case Probabilistic Results in Patients Receiving Moderately Emetogenic Therapy

| | NEPA + DEX | OND + DEX | GRAN + DEX |
|---|---|---|---|
| **Costs ($)** | | | |
| Treatment drug | 135.96 | 10.56 | 18.64 |
| CINV episode management | 202.61 | 227.66 | 245.92 |
| In-patient care | 57.82 | 64.95 | 70.18 |
| Rescue medication | 5.05 | 5.68 | 6.13 |
| Outpatient care | 119.90 | 134.75 | 145.53 |
| Physician care | 19.83 | 22.29 | 24.07 |
| Cost in acute phase | 91.32 | 140.21 | 157.41 |
| Cost in delayed phase | 111.29 | 87.45 | 88.51 |
| **Total costs** | **338.57** | **238.22** | **264.56** |
| **Health outcomes** | | | |
| Average emesis-free days | 4.069 | 3.889 | 3.798 |
| Average CINV-free days | 3.652 | 3.361 | 3.413 |
| Emesis-free patients (%) | 74.3% | 71.2% | 68.9% |
| Emetic events (estimate) | 1.48 | 1.66 | 1.80 |
| CINV-free patients (%) | 63.8% | 57.1% | 57.9% |
| Quality-adjusted life-days | 3.834 | 3.698 | 3.669 |
| Quality-adjusted life-years | **0.0105** | **0.0101** | **0.0101** |
| **Cost/Outcomes** | | | |
| Cost per emesis-free day (avoided emesis per day) | | $3,167 | $1,349 |
| Cost per avoided emetic event | | $549 | $234 |
| Cost per CINV-free day (avoided mild nausea per day) | | $1,500 | $1,258 |
| **Cost per QALY gained** | | **$270,094** | **$163,948** |

CINV = chemotherapy-induced nausea and vomiting; DEX = dexamethasone; GRAN = granisetron; NEPA = netupitant/palonosetron; OND = ondansetron; QALY = quality-adjusted life-year.
Source: Manufacturer's pharmacoeconomic submission.[4]

## CADTH Common Drug Review Reanalyses

CADTH Common Drug Review (CDR) undertook the following scenario analyses on the manufacturer's base case:

- Using alternative health state utility values: Despite the manufacturer's submission information on the source of the included utility values, the sources do not provide clear information on how these utility values were derived or estimated. In order to assess the impact of this uncertainty on the model results, a probabilistic reanalysis was conducted by CDR using utility values from a publication by Humphreys et al. (2013) on the cost-

effectiveness of an APR regimen for the prevention of chemotherapy-induced nausea and vomiting (CINV).[15] The results did not change for NEPA in patients receiving HEC (still dominant), but did result in an increase in the ICURs for NEPA in patients receiving MEC, to $309,638 per QALY compared with OND and to $203,234 per QALY compared with GRAN. The results of the CDR reanalysis are summarized in Table 17.

## Table 17: Summary of Results of the CDR Probabilistic Scenario Analysis on Utility

| | | Total Costs | Incremental Cost | Total QALYs | Incremental QALYs | Incremental Cost per QALY |
|---|---|---|---|---|---|---|
| HEC | APR + OND + DEX | $228 | | 0.0102 | | |
| | NEPA + DEX | $220 | –$8 | 0.0105 | 0.0003 | Dominant |
| | APR + GRAN + DEX | $323 | | 0.0098 | | |
| | NEPA + DEX | $220 | –$103 | 0.0105 | 0.0007 | Dominant |
| MEC | OND + DEX | $240 | | 0.0091 | | |
| | NEPA + DEX | $340 | $100 | 0.0095 | 0.0004 | $309,638 |
| | GRAN + DEX | $267 | | 0.0091 | | |
| | NEPA + DEX | $340 | $73 | 0.0095 | 0.0004 | $203,234 |

APR = aprepitant; DEX = dexamethasone; GRAN = granisetron; HEC = highly emetogenic chemotherapy; MEC = moderately emetogenic chemotherapy; NEPA = netupitant/palonosetron; OND = ondansetron; QALY = quality-adjusted life-year.

- CDR also undertook a probabilistic analysis assuming similar efficacy among 5-$HT_3$RAs in patients receiving HEC and MEC, summarized in Table 18. Unlike the manufacturer's analysis, which was based on an analysis of a group of 5-$HT_3$RAs that included palonosetron, the CDR analysis assumed that the odds ratio (OR) for GRAN + DEX was the same as the OR for OND + DEX.

## Table 18: Summary of Results of the CDR Probabilistic Scenario Analysis on Similar Efficacy of 5-$HT_3$ Receptor Antagonists

| | | Total Costs | Incremental Cost | Total QALYs | Incremental QALYs | Incremental Cost per QALY |
|---|---|---|---|---|---|---|
| HEC | APR + OND + DEX | $227 | | 0.0114 | | |
| | NEPA + DEX | $219 | –$9 | 0.0117 | 0.0003 | Dominant |
| | APR + GRAN + DEX | $236 | | 0.0114 | | |
| | NEPA + DEX | $219 | –$17 | 0.0117 | 0.0003 | Dominant |
| MEC | OND + DEX | $241 | | 0.0101 | | |
| | NEPA + DEX | $339 | $97 | 0.0105 | 0.0004 | $246,590 |
| | GRAN + DEX | $262 | | 0.0101 | | |
| | NEPA + DEX | $339 | $76 | 0.0105 | 0.0004 | $178,916 |

APR = aprepitant; DEX = dexamethasone; GRAN = granisetron; HEC = highly emetogenic chemotherapy; MEC = moderately emetogenic chemotherapy; NEPA = netupitant/palonosetron; OND = ondansetron; QALY = quality-adjusted life-year.

CDR undertook the following scenario analyses on the CDR base-case analysis:

- Applying similar efficacy between NEPA and comparators in prevention of CINV: Despite the limitations noted with the submitted network meta-analysis (NMA), the results had indicated that NEPA demonstrated efficacy similar to that of its comparators in preventing CINV in patients receiving HEC. To assess the impact of uncertainty with NEPA efficacy, CDR conducted a scenario analysis that assumed similar efficacy for

NEPA and the comparators (APR combined with 5-$HT_3$RA and dexamethasone) in patients receiving HEC. The CDR results are aligned with the scenario results provided by the manufacturer that varied the OR for NEPA against the comparators for complete response in the overall phase (i.e., the results for NEPA in patients receiving HEC changed from being less costly and more effective to more costly and no more effective). The results of the CDR reanalysis are summarized in Table 19.

### Table 19: Summary of Results of the CDR Probabilistic Scenario Analysis on Efficacy

| | | Total Costs ($) | Incremental Cost ($) | Total QALYs | Incremental QALYs | Incremental Cost per QALY |
|---|---|---|---|---|---|---|
| HEC | APR + OND + DEX | $191 | | 0.0105 | | |
| | NEPA + DEX | $219 | $28 | 0.0105 | 0 | Dominated |
| | APR + GRAN + DEX | $199 | | 0.0105 | | |
| | NEPA + DEX | $219 | $20 | 0.0105 | 0 | Dominated |

APR = aprepitant; DEX = dexamethasone; GRAN = granisetron; HEC = highly emetogenic chemotherapy; NEPA = netupitant/palonosetron; OND = ondansetron; QALY = quality-adjusted life-year.

- Using a five-day costing for OND: According to the NMA submitted by the manufacturer, treatment with OND was permitted up to five days for each chemotherapy cycle. This was in contrast to the manufacturer's assumption of a one-day administration of ondansetron (i.e., on day 1). Based on the findings of the NMA, and assuming five days of treatment of OND, the treatment effect for OND applied in the manufacturer's economic submission may be underestimated. The uncertainty associated with OND treatment was assessed in a scenario analysis conducted by CDR in which the cost of OND was adjusted to reflect a five-day administration. The analysis was conducted on both the manufacturer's and CDR's base-case analyses. The results of the CDR reanalysis are summarized in Table 19.

## Table 20: Summary of Results of the CDR Probabilistic Scenario Analysis on Ondansetron Costing

| | | | Total Costs ($) | Incremental Cost ($) | Total QALYs | Incremental QALYs | Incremental Cost per QALY |
|---|---|---|---|---|---|---|---|
| Manufacturer's base-case analysis | HEC | APR + OND + DEX | 266 | | 0.0114 | | |
| | | NEPA + DEX | 220 | –46 | 0.0117 | 0.0003 | Dominant |
| | | APR + GRAN + DEX | 324 | | 0.0109 | | |
| | | NEPA + DEX | 220 | –104 | 0.0117 | 0.0008 | Dominant |
| | MEC | OND + DEX | 279 | | 0.0101 | | |
| | | NEPA + DEX | 339 | 60 | 0.0105 | 0.0004 | $156,361 |
| | | GRAN + DEX | 265 | | 0.0100 | | |
| | | NEPA + DEX | 339 | 74 | 0.0105 | 0.0005 | $163,632 |
| CDR Base-case analysis | HEC | APR + OND + DEX | 265 | | 0.0102 | | |
| | | NEPA + DEX | 220 | –45 | 0.0105 | 0.0003 | Dominant |
| | | APR + GRAN + DEX | 238 | | 0.0102 | | |
| | | NEPA + DEX | 220 | –18 | 0.0105 | 0.0003 | Dominant |
| | MEC | OND + DEX | 280 | | 0.0091 | | |
| | | NEPA + DEX | 340 | 60 | 0.0094 | 0.0003 | $180,782 |
| | | GRAN + DEX | 263 | | 0.0091 | | |
| | | NEPA + DEX | 340 | 77 | 0.0094 | 0.0003 | $223,041 |

APR = aprepitant; DEX = dexamethasone; GRAN = granisetron; HEC = highly emetogenic chemotherapy; MEC = moderately emetogenic chemotherapy; NEPA = netupitant/palonosetron; OND = ondansetron; QALY = quality-adjusted life-year.

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