APREPITANT
(Emend™ – Merck Frosst Canada Ltd.)

Description:
Aprepitant is a neurokinin-1 receptor antagonist that, when used in combination with a 5-HT\textsubscript{3} antagonist class of antiemetics and dexamethasone, is approved for the prevention of acute and delayed nausea and vomiting due to highly emetogenic cancer chemotherapy and the prevention of nausea and vomiting in women due to treatment with moderately emetogenic cancer chemotherapy consisting of cyclophosphamide and an anthracycline.

Dosage Forms:
80 mg and 125 mg capsules. The recommended dose of aprepitant is 125 mg one hour prior to chemotherapy treatment (day one) and 80 mg once daily in the morning on days two and three.

Recommendation:
The Canadian Expert Drug Advisory Committee (CEDAC) recommends that aprepitant, when used in combination with a 5-HT\textsubscript{3} antagonist and dexamethasone, be listed for the prevention of acute and delayed nausea and vomiting due to highly emetogenic cancer chemotherapy (eg. cisplatin \(>70\) mg/m\(^2\)) in patients who have experienced emesis despite treatment with a combination of a 5-HT\textsubscript{3} antagonist and dexamethasone in a previous cycle of highly emetogenic chemotherapy.

Reasons for the Recommendation:
1. In patients receiving highly emetogenic chemotherapy, aprepitant has been shown to reduce the number of patients experiencing emesis but has not been consistently shown to improve nausea.

2. In patients receiving highly emetogenic chemotherapy, the incremental cost-effectiveness of aprepitant is highly sensitive to whether one or four days of the comparator 5-HT\textsubscript{3} antagonist was used, ranging from $21,000 to $101,000 per quality-adjusted life year (QALY). Given this uncertainty, the Committee felt that aprepitant should be reserved for use in patients who have not responded to a combination of a 5-HT\textsubscript{3} antagonist class of antiemetics and dexamethasone.

3. Aprepitant has not been shown to be cost-effective in patients receiving moderately emetogenic chemotherapy.
Summary of Committee Considerations:

The Committee considered a systematic review of double-blind randomized controlled trials (RCTs) in adult patients receiving highly emetogenic chemotherapy or adult female patients receiving moderately emetogenic chemotherapy consisting of cyclophosphamide and an anthracycline. Four placebo-controlled RCTs met the inclusion criteria for the systematic review, three in patients receiving highly emetogenic chemotherapy (including cisplatin > 70 mg/m²) and one in women receiving moderately emetogenic chemotherapy. In all trials, aprepitant or placebo were added to treatment with ondansetron (a 5-HT3 antagonist) and dexamethasone on day one and aprepitant was continued on days two and three. The control arms of the RCTs consisted of treatment with dexamethasone, with or without ondansetron, with treatments extended to days three or four. Outcomes are reported as acute (within the first 24 hours of chemotherapy), delayed (>24 hours after chemotherapy) or overall (during days one to five).

The following summarizes the results of the three highly emetogenic chemotherapy trials, in which treatment outcomes were only assessed during the first cycle of chemotherapy:

- The primary outcome of all three trials was complete response, a composite endpoint defined as no emesis and no rescue therapy during the five days after initiation of chemotherapy. All three trials reported that aprepitant resulted in statistically significant improvements in complete response during the acute phase, delayed phase and overall.
- All three trials reported statistically significant reductions in favour of aprepitant in the number of patients with emesis during the acute phase, delayed phase and overall.
- Of the two trials that assessed health-related quality of life outcomes, the number of patients reporting that chemotherapy-induced nausea and vomiting had no impact on daily life was statistically significantly higher in the aprepitant group compared with the control group.
- Two of the three trials reported statistically significant differences in favour of aprepitant in the number of patients who required rescue therapy during the acute phase, delayed phase or overall.

In the trial in women receiving moderately emetogenic chemotherapy, patients receiving aprepitant experienced fewer episodes of emesis during the acute phase, delayed phase and overall but there was no statistically significant difference between the groups in the use of rescue therapy for nausea or vomiting during any phase nor in the number of patients who experienced no nausea overall.

There were no significant differences between aprepitant and placebo in serious adverse events, treatment-related adverse events or withdrawals due to adverse events. Aprepitant should be used with caution in patients receiving concomitant medicinal products that are primarily metabolized through CYP3A4 and CYP2C9, including chemotherapy agents, as it causes inhibition of CYP3A4 and induction of CYP2C9.

Aprepitant costs $90.54 for a three day course of therapy. The addition of aprepitant to an anti-emetic regimen for highly emetogenic chemotherapy increases the cost from $115 - $169 (depending on the regimen used) to $201, and addition of aprepitant to an anti-emetic regimen for moderately emetogenic chemotherapy increases the cost from $57 to $110. The manufacturer submitted a cost utility analysis comparing a regimen containing aprepitant to a regimen without, over a 5-day time horizon. The manufacturer reported a cost per QALY of $21,000 for addition of aprepitant in patients receiving highly emetogenic chemotherapy and $126,500 for patients receiving moderately emetogenic chemotherapy. The evaluation assumes the use of ondansetron throughout the delayed phase. If ondansetron is only used on day one, the cost per QALY estimates increase to $101,300 in the treatment of highly emetogenic chemotherapy and $220,000 in moderately emetogenic chemotherapy.

Of Note:

1. Both published and unpublished data were reviewed and taken into consideration in making this recommendation.
**Background:**
CEDAC provides formulary listing recommendations to publicly funded drug plans. Recommendations are based on an evidence-based review of the medication’s effectiveness and safety and an assessment of its cost-effectiveness in comparison to other available treatment options. For example, if a new medication is more expensive than other treatments, the Committee considers whether any advantages of the new medication justify the higher price. If the recommendation is not to list a drug, the Committee has concerns regarding the balance between benefit and harm for the medication, and/or concerns about whether the medication provides good value for public drug plans.