Summary of Canadian Expert Drug Advisory Committee (CEDAC) Discussion
January 23, 2008

Aprepitant (Emend™ — Merck Frosst Canada Ltd.)
Indication — Chemotherapy-induced Nausea and Vomiting

Canadian Expert Drug Advisory Committee (CEDAC) Members Participating

(in person or by teleconference): Dr. Braden Manns (Chair), Dr. Anne Holbrook (Vice-Chair), Dr. Ken Bassett, Dr. Bruce Carleton, Dr. Michael Evans, Dr. Malcolm Man-Son-Hing, Dr. Laurie Mallery, Ms. Nancy McColl, Mr. Brad Neubauer, Dr. Lindsay Nicolle, Dr. Robert Peterson, Dr. Dale Quest, Dr. Kelly Zarnke.

Regrets

None

Conflicts of Interest

Two CEDAC members reported being investigators on research studies funded by Merck Frosst Canada Ltd. As the research was not related to Emend™, this did not preclude their participation.

Description

Aprepitant (Emend) is approved for use, in combination with a serotonin ($5\text{-}HT_3$) antagonist class of antiemetics and dexamethasone, in the prevention of acute and delayed nausea and vomiting due to highly emetogenic cancer chemotherapy (HEC) and in the prevention of nausea and vomiting in women due to treatment with moderately emetogenic cancer chemotherapy (MEC) consisting of cyclophosphamide and an anthracycline. Aprepitant is a neurokinin-1 receptor antagonist that inhibits the binding of substance P and thus prevents emesis related to cytotoxic chemotherapeutic agents.

Discussion of Clinical and Pharmacoeconomic Reviews

CEDAC considered a systematic review of published and unpublished clinical studies prepared by CDR, and a CDR review of a pharmacoeconomic evaluation supplied by the manufacturer. An overview of these reviews and the complete CEDAC Final Recommendation and Reasons for Recommendation (technical and plain language versions) are available in the CDR Drug Database on the CADTH web site (www.cadth.ca).

A presentation by CEDAC members, and the discussion that ensued, addressed the following points:

Therapeutic Rationale and Need
Despite advances in antiemetic therapy with the availability of agents such as the 5-HT_3 receptor antagonists (e.g., ondansetron), up to 50% of patients receiving cancer chemotherapy still frequently experience nausea and vomiting. Consequences include metabolic imbalances, nutritional deficiencies, reduced quality of life, and possible refusal of subsequent cycles of chemotherapy.

Clinical Trials
Four double-blind placebo-controlled randomized controlled trials were evaluated. Three trials investigated the use of aprepitant in combination with ondansetron and dexamethasone, in more than 1,500 patients with solid tumours, who were receiving HEC (including cisplatin) during the first cycle of chemotherapy. The fourth study evaluated aprepitant in combination with ondansetron and dexamethasone, in 489 breast cancer patients receiving MEC with doxorubicin and cyclophosphamide, over four cycles of chemotherapy. For all four studies, the dose of aprepitant was 125 mg on day one, followed by 80 mg daily on days two and three; ondansetron and dexamethasone dosing varied. A modified intention-to-treat analysis was conducted.

Comparators or Other Available Treatment Options
Standard antiemetic therapy was used in all four trials, including ondansetron and dexamethasone. The dose of dexamethasone in the treatment arm was reduced to mitigate a documented pharmacokinetic interaction with aprepitant that leads to the elevation of dexamethasone serum concentrations. This interaction confounds the interpretation of the efficacy results.

Outcomes
The primary efficacy outcome for all four studies was complete response, defined as no emesis and no rescue antiemetic therapy. Other outcomes studied included total control (no nausea, emesis, or rescue therapy) and complete protection (no significant nausea, no emesis, no rescue therapy). Also, nausea, emesis, and use of rescue therapy were each considered separately as an outcome. Quality of life was assessed by the Functional Living Index Emesis (FLIE) questionnaire, a validated patient report measure, specific to nausea and emesis. Some reported outcomes were from post-hoc analyses and were not pre-planned endpoints for analysis.

Effectiveness
In all four studies, complete response was improved, but there was a wide range in numbers needed to treat (NNT), with wide confidence intervals. Quality of life was improved in the two HEC studies that evaluated FLIE, as well as in the MEC study. In patients treated with HEC, aprepitant improved delayed and overall nausea, but not acute nausea, in one study; showed no difference in another; and was not evaluated in the last study. For MEC, aprepitant did not improve nausea. Vomiting was reduced in all four trials. Rescue therapy was reduced in two of the three HEC trials, but not in the MEC trial.

Safety and Tolerability (harms)
There were no significant differences reported in adverse events, serious adverse events, or deaths.

Cost and Pharmacoeconomic Evaluation

The cost of aprepitant is an added cost to that of present antiemetic regimens. The pharmacoeconomic analysis submitted by the manufacturer assumed the continued use of ondansetron after day one, which is associated with a favourable incremental cost per quality-adjusted life year (QALY). If ondansetron is used on the first day only, the incremental cost per QALY for aprepitant is significantly higher. Because the incremental cost-effectiveness of aprepitant is highly sensitive to the dose regime of a 5-HT_3 antagonist, the cost-effectiveness was uncertain for the first-line use of aprepitant. The impact of use for subsequent cycles of chemotherapy (i.e. beyond cycle one of HEC) was not evaluated, nor was the use with multiple-day chemotherapy. Cost-effectiveness was not demonstrated with the use of aprepitant with MEC.

Other Discussion Points

- Aprepitant is an inhibitor of CYP3A4 and an inducer of the CYP2C9 isoenzyme. The potential for interactions with drugs metabolized by these pathways was noted.
- The potential conflicts of interest with respect to the analysis of study data for two of the HEC trials and the relationship of study authors with Merck Laboratories for the MEC trial were raised. These conflicts were disclosed in the published studies.
- The effect of aprepitant after cycle one of chemotherapy is unknown, but it was recognized that a trial of aprepitant may be a reasonable option for patients who develop emesis despite standard antiemetics therapy during the first cycle of HEC.
- There is a high potential for off-label use of aprepitant.
- Aprepitant appears effective in achieving the primary outcome (complete response, meaning no emesis and need for rescue therapy) and reducing emesis; however, interpretation of the results is limited by the varying doses of ondansetron used in the studies.
- Aprepitant appears cost-effective only under limited circumstances.

CEDAC Recommendation

CEDAC recommends that aprepitant, when used in combination with a 5-HT_3 antagonist and dexamethasone, be listed for the prevention of acute and delayed nausea and vomiting due to highly emetogenic cancer chemotherapy (e.g., cisplatin >70 mg/m^2) for patients who have experienced emesis despite treatment with a combination of a 5-HT_3 antagonist and dexamethasone in a previous cycle of highly emetogenic chemotherapy.

Reasons for the Recommendation

- 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.
- 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_3 antagonist was used, ranging from $21,000 to $101,000 per QALY. Given this uncertainty, CEDAC felt that aprepitant should be reserved for use in patients who have not responded to a combination of a 5-HT_3 antagonist class of antiemetics and dexamethasone.
- Aprepitant has not been shown to be cost-effective as first-line therapy in patients receiving moderately emetogenic chemotherapy.

The Summary of CEDAC Discussion

This document contains a summary of the relevant discussion by CEDAC members in making the formulary listing recommendation for participating public drug plans regarding this drug. This summary is not a complete record of the proceedings of the CEDAC meeting at which the drug was considered.

The information in this summary should not be used as a substitute for clinical judgment in the care of a particular patient, nor is it intended to replace professional advice. CADTH is not liable for any damages arising from the use or misuse of any information contained in or implied by the contents of this document.

The statements, conclusions, and views expressed herein do not necessarily represent the view of Health Canada, the federal government, any provincial or territorial government, or any pharmaceutical manufacturer.

The manufacturer has reviewed this document and has not requested the deletion of any confidential information.