CDEC FINAL RECOMMENDATION

PLERIXAFOR
(Mozobil – Genzyme Canada Inc.)
Indication: Hematopoietic Stem Cell Mobilizer in Non-Hodgkin Lymphoma and Multiple Myeloma

Recommendation:
The Canadian Drug Expert Committee (CDEC) recommends that plerixafor not be listed.

Reason for the Recommendation:
No randomized controlled trials (RCTs) included in the systematic review adequately identified a patient population that might be expected to benefit from plerixafor (i.e., those predicted or proven to be poor mobilizers when treated with granulocyte colony stimulating factor [G-CSF] alone); thus, the clinical and cost-effectiveness of plerixafor in the relevant patient population is uncertain.

Of Note:
The Committee considered that patients who have an insufficient collection of stem cells with G-CSF alone, or G-CSF plus chemotherapy, may benefit from an alternative therapy. However, this subpopulation of patients was excluded from the reviewed RCTs. The Committee noted that while there is lower quality (observational) evidence of the benefit of plerixafor in this subpopulation, the lack of a control group precludes an adequate estimate of the effect size and thus cost-effectiveness. Thus, further study is required in patients who have failed collection attempts with G-CSF alone or G-CSF plus chemotherapy. The Committee noted that jurisdictions may wish to consider funding plerixafor for such patients who have no other options, on a case by case basis.

Background:
Plerixafor has a Health Canada indication for use in combination with G-CSF to mobilize hematopoietic stem cells to the peripheral blood for collection and subsequent autologous transplantation in patients with non-Hodgkin lymphoma (NHL) and multiple myeloma (MM).

Plerixafor is a CXCR4 chemokine receptor antagonist. It is available as a 20 mg/mL solution for injection. Health Canada recommends that plerixafor treatment begin, at a dose of 0.24 mg/kg by subcutaneous injection 10 to 11 hours before initiation of each apheresis, after patients have

received G-CSF once daily for four days. Dosage adjustment of plerixafor is recommended for patients with renal impairment.

Summary of CDEC Considerations:
The Committee considered the following information prepared by the Common Drug Review (CDR): a systematic review of RCTs of plerixafor, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group-submitted information about outcomes and issues important to patients.

Clinical Trials
The systematic review included two double-blind, randomized, placebo-controlled trials of patients with NHL (study 3101, N = 298) and MM (study 3102, N = 302). In both trials, all patients received concomitant G-CSF and were randomized to plerixafor 0.24 mg/kg or placebo for up to four days; randomized treatments began on day four of G-CSF.

Patients who were successful in collecting sufficient numbers of CD34+ cells underwent autologous stem cell transplant, and were followed for up to one year. Patients who were unsuccessful in collecting sufficient numbers of CD34+ cells had the option of undergoing a rescue protocol with another course of G-CSF and open-label plerixafor at the same doses and schedule, followed by stem cell collection and possible autologous stem cell transplant. In study 3101, patients who failed to collect ≥ 0.8 x 10^6 CD34+ cells/kg after two apheresis days or ≥ 2 x10^6 CD34+ cells/kg within four apheresis days were eligible for the rescue protocol. In study 3102, patients who failed to collect ≥ 0.8 x 10^6 CD34+ cells/kg after two apheresis days or ≥ 2 x10^6 CD34+ cells/kg within four apheresis days, or were planned for tandem transplant and collected < 4 x10^6 CD34+ cells/kg within four apheresis days were eligible for the rescue protocol.

In both studies, approximately two-thirds of patients were male, and the median age was 58 years. The percentage of patients who were in their first complete or partial remission was 47% in study 3101 and 94% in study 3102.

In study 3101, the percentage of patients completing the study was lower in the placebo group compared with the plerixafor group (46% versus 75%), largely due to a higher percentage of placebo-treated patients who were unsuccessful in collecting sufficient numbers of CD34+ cells and subsequently entered the rescue protocol; 35% versus 7% for placebo and plerixafor respectively. In study 3102, 87% and 79% of patients in the plerixafor and placebo groups respectively completed the study.

The reviewed trials suffered from a number of limitations, including the exclusion of patients who had failed prior stem cell collection attempts and the fact that neither trial specifically attempted to enrol patients who might be predicted to mobilize poorly. There are no universally agreed upon criteria for what factors predict whether a patient will be a poor mobilizer. The manufacturer-supplied post-hoc subgroup analysis, based on circulating CD34+ cell counts, was considered by the Committee to be hypothesis generating.

Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. Of these, the Committee discussed the following: percentage of patients achieving CD34+ cell collection targets and adverse events. The primary outcome in study 3101 was the percentage of patients achieving a collection target of ≥ 5 x 10^6 CD34+ cells/kg within four apheresis days. The primary outcome in study 3102 was the percentage of patients achieving a collection target of ≥ 6 x 10^6 CD34+ cells/kg within two apheresis days.

Quality of life was not assessed in either study. Patient input indicated that achieving the minimum number of CD34+ to allow them to proceed to transplantation was an important outcome, since transplantation may prolong life or potentially cure the disease.

Results

Efficacy or Effectiveness

- The percentage of patients achieving the primary outcome was statistically significantly greater for plerixafor groups compared with placebo in both studies 3101 and 3102; 59% versus 20%, and 72% versus 34%, respectively.
- In a post hoc subgroup analysis of patients with peripheral blood CD34+ counts below 20 cells/mcL on day four of mobilization, results for the primary outcome were statistically significant in favour of plerixafor compared with placebo in both study 3101 (52% versus 15%) and study 3102 (63% versus 37%).
- The percentage of patients achieving at least 2 x 10^6 cells/kg (considered to be the minimum number of cells for transplantation), within four apheresis days, was statistically significantly higher for plerixafor groups compared with placebo, in both studies 3101 and 3102; 87% versus 47% and 95% versus 88% respectively.
- Compared with placebo, the time to reach the mobilization target (as defined by the primary outcome) was statistically significantly shorter for plerixafor groups in both trials; median of three days versus median not reached in study 3101, and one day versus four days in study 3102.

Harms (Safety and Tolerability)

- In study 3101, the percentage of patients experiencing any serious adverse event or serious febrile neutropenia was statistically significantly greater for plerixafor compared with placebo; 37% versus 26%, and 9% versus 3% respectively. In study 3102, the percentages of patients experiencing any serious adverse event or serious febrile neutropenia were numerically, but not statistically significantly, greater in the plerixafor group.
- There were no statistically significant differences in the overall incidence of adverse events between plerixafor and placebo groups in either of the included studies.
- Few patients withdrew due to an adverse event in either study, and there were no statistically significant differences in the rates of withdrawals due to adverse events between groups.

Cost and Cost-Effectiveness

The manufacturer submitted a cost-utility analysis to compare plerixafor plus G-CSF with G-CSF alone, in adults with MM or NHL who are “poor mobilizers” (defined as patients with 0 to 10 CD34+ cells/mcL before apheresis) over a five-year time horizon. Efficacy in the model is driven by the proportion of patients that mobilize an adequate number of hematopoietic stem

cells to proceed to autologous stem cell transplant. The probability of achieving the specified number of cells in the initial mobilization to proceed with autologous stem cell transplant is obtained from RCT participants, considering only the subset of patients with the pre-specified CD34+ cell count before apheresis, as well as observational data to estimate the probability of success in rescue mobilization. In the base case, the manufacturer reported that plerixafor plus G-CSF compared with G-CSF alone was associated with a cost per quality-adjusted life-year (QALY) of $19,191 for NHL and $60,835 per QALY for MM.

CDR noted the following limitations: there is currently no standard definition of poor mobilizers and the relative efficacy, and subsequent cost-effectiveness, of using alternate definitions is unknown; it is not established that the benefits with plerixafor, using trial specified outcomes (mobilization of cells over time) will result in differences in the proportion of patients proceeding to autologous stem cell transplant.

The cost for plerixafor, per day of apheresis, is $7,555 (1 vial). The cost for a four-day course (1 vial per day) is $30,220.

Patient Input Information:
The following is a summary of information received from one patient group that responded to the CDR Call for Patient Input.

- Failure to produce enough cells for a successful transplant is devastating news to the patient and caregiver, as patients believe they have no other option and will die. They see plerixafor as an option that will allow them to continue to live.
- Patients consider subcutaneous plerixafor to be faster and easier to administer than an intravenously infused medication.
- A reduction in the number of apheresis sessions required to produce sufficient cells for transplant is an important outcome for patients.

Other Discussion Points:

- The Committee recognized that there is no universally agreed upon definition of poor mobilizer or criteria for predicting who will be a poor mobilizer.
- The Committee noted that cyclophosphamide, in combination with G-CSF, is used in some centres in Canada to increase stem cell mobilization.
- The Committee noted that, due to the use of rescue protocols, the reviewed trials were unable to establish the comparative benefit of plerixafor in terms of performance of stem cell transplant, graft durability, or survival.

CDEC Members:
Dr. Robert Peterson (Chair), Dr. Lindsay Nicolle (Vice-Chair), Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Ms. Cate Dobhran, Mr. Frank Gavin, Dr. John Hawboldt, Dr. Peter Jamieson, Dr. Julia Lowe, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. James Silvius, and Dr. Adil Virani.

June 20, 2012 Meeting

Regrets:
None

Conflicts of Interest:
None

September 19, 2012 Meeting

Regrets:
Two CDEC members did not attend.

Conflicts of Interest:
None

About this Document:
CDEC provides formulary listing recommendations to publicly funded drug plans. Both a technical recommendation and plain language version of the recommendation are posted on the CADTH website when available.

CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CDEC made its recommendation. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CDEC deliberations.

The manufacturer has reviewed this document and has not requested the removal of confidential information in conformity with the *CDR Confidentiality Guidelines*.

The Final CDEC Recommendation neither takes the place of a medical professional providing care to a particular patient nor is it intended to replace professional advice.

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