CADTH CANADIAN DRUG EXPERT COMMITTEE FINAL RECOMMENDATION

FILGRASTIM
(Grastofil — Apotex Inc.)
Indications: Prevention or Treatment of Neutropenia

Recommendation:
The CADTH Canadian Drug Expert Committee (CDEC) recommends that Grastofil (filgrastim subsequent entry biologic [SEB]) be listed in accordance with the Health Canada–approved indications, if the following conditions are met:

Conditions:
- List in a manner similar to Neupogen
- The cost of treatment with Grastofil should provide significant cost savings for jurisdictions compared with the cost of treatment with Neupogen.

Reasons for Recommendation:
1. Similarity between Grastofil and the reference product (Neupogen) was established in four phase1, comparative pharmacokinetic and pharmacodynamic studies conducted in healthy volunteers and one phase 3, uncontrolled, open-label study conducted in breast cancer patients receiving myelosuppressive chemotherapy.
2. At the submitted price ($144.31 per 300 mcg/0.5 mL pre-filled syringe), Grastofil is less costly than Neupogen ($192.42 per 300 mcg/mL vial) for all Health Canada–approved indications.

Of Note
- CDEC noted that a patient being treated with Neupogen should be considered for switching to Grastofil, following a discussion between the patient and his or her physician.
- [redacted].

Background:
Grastofil is an SEB of filgrastim based on the reference product Neupogen. Both Grastofil and Neupogen have been approved by Health Canada for the following indications:
- Cancer patients receiving myelosuppressive chemotherapy
- Patients with acute myeloid leukemia

- Cancer patients receiving myeloablative chemotherapy followed by bone marrow transplantation
- Cancer patients undergoing peripheral blood progenitor cell collection and therapy
- Patients with severe chronic neutropenia
- Patients with human immunodeficiency virus (HIV) infection.

Grastofil is available as a 300 mcg/0.5 mL pre-filled syringe.

Summary of CDEC Considerations

CDEC considered the following information prepared by the CADTH Common Drug Review (CDR): a review of manufacturer-provided information on the clinical efficacy, safety, and biosimilarity of and the extrapolation of data for Grastofil, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group–submitted information about outcomes and issues important to patients.

Patient Input Information

One patient group responded to the CDR call for patient input (the Consumer Advocare Network). Information was obtained from a survey that was developed through interviews with four key patient informants and two clinicians who had conducted clinical trials using Grastofil. All of the patients who responded had one of the six indications; a smaller number of caregivers also responded. The following is a summary of key information provided by the patient group:

- The symptoms of neutropenia negatively affect the quality of life of patients who are affected by this condition.
- Patients reported experience with a variety of treatments, including antibiotics, immunosuppressive medications, and filgrastim. Patients who had received filgrastim indicated that the drug was effective and the side effects were mild.
- Patients indicated that Grastofil should be made available as a treatment option through hospital or public drug plans.
- The patient group noted that patients would prefer that the SEB and Neupogen not be substituted for one another without the consent of the patient's physician.

Clinical Trials

The manufacturer provided pharmacodynamics (PD), pharmacokinetics (PK), efficacy, and safety data from five pivotal clinical trials:

- Four randomized, double-blind phase 1 clinical trials evaluated the PD, PK, and safety of single-dose or multi-dose Grastofil compared with Neupogen in healthy volunteers: KWI-300-101 (N = 36, single-dose, crossover design), KWI-300-102 (N = 73, single-dose, crossover design), KWI-300-103 (N = 78, multi-dose, parallel design), and GCSF-SUIN-05SB01-3FA-(5) (N = 48, single-dose, crossover design; the only study to compare Grastofil obtained from the manufacturing process intended for the Canadian market with European Union–sourced and United States–sourced Neupogen). The study drugs were administered at a fixed dose (ranging from 75 mcg to 300 mcg) or at a weight-based dose (5 mcg/kg/day). The main PD end point was absolute neutrophil count (ANC), and the main PK end points were Area Under the Curve (AUC) and maximum concentration (C_{max}) for filgrastim.
- One single-arm study (N = 120) was a phase 3 study designed to assess the effect of Grastofil on duration of severe neutropenia and safety of Grastofil in breast cancer patients receiving chemotherapy.

Outcomes

CDEC discussed the following outcomes:

- PD end point — ANC. Equivalence between Grastofil and Neupogen was demonstrated if the 90% confidence intervals (CIs) of the PD parameters were within the equivalence margin of 80% to 125%.
- PK end point — AUC and C_{max} for filgrastim. Equivalence between Grastofil and Neupogen was demonstrated if the 90% CIs of the PK parameters were within the equivalence margin of 80% to 125%.
- Duration of severe neutropenia in cycle one chemotherapy: severe neutropenia is defined as occurrence of ANC below 0.5×10^9/L. This outcome was reported in a non-comparative study; therefore, the results were assessed along with those for Neupogen published in the literature to determine their comparability.
- Safety: serious adverse events, total adverse events, and withdrawals due to adverse events.

Bioequivalence and Efficacy

- In four randomized trials in healthy volunteers, Grastofil met the predefined equivalence criteria for all the PK and PD parameters: the 90% CIs of the ratios (Grastofil/Neupogen) of the geometric means were all contained within the 80% to 125% margin.
- In the one non-comparative study conducted in breast cancer patients receiving myelosuppressive chemotherapy, the mean duration of severe neutropenia was 1.4 days (standard deviation 1.07). This is comparable to the values reported for Neupogen in similar patient populations.

Harms (Safety and Tolerability)

- In the integrated dataset for all four randomized controlled trials enrolling healthy subjects, the risk of experiencing at least one adverse event was [redacted] for Grastofil and [redacted] for Neupogen. No serious adverse events were reported.
- In breast cancer patients receiving chemotherapy, the most common adverse events during the treatment of Grastofil were nausea (53.3%) and bone pain (66.7%).
- [redacted]

Extrapolation

Health Canada granted the extrapolation of data from the manufacturer's studies in healthy subjects and breast cancer patients to the indications of cancer patients receiving myelosuppressive antineoplastic drugs, patients with acute myeloid leukemia, patients undergoing myeloablative therapy followed by bone marrow transplantation, cancer patients undergoing peripheral blood progenitor cell collection and therapy, patients with severe chronic neutropenia, and patients with HIV infection. Health Canada stated that the indications for the indicated patient populations were granted on the basis of similarity and the absence of meaningful differences between Grastofil and Neupogen with respect to quality, mechanism of action, disease pathophysiology, safety, dosage regimen, and clinical experience with the reference product (i.e., Neupogen).

Cost and Cost-Effectiveness

The manufacturer submitted a cost comparison of Grastofil with the reference product filgrastim (Neupogen) for the six indications under review: cancer patients receiving myelosuppressive chemotherapy, patients with acute myeloid leukemia, cancer patients receiving myeloablative chemotherapy followed by bone marrow transplantation, cancer patients undergoing peripheral blood progenitor cell collection and therapy, patients with severe chronic neutropenia, and patients with HIV infection. The manufacturer-submitted cost of Grastofil ($144.31 per 300 mcg/0.5 mL pre-filled syringe) is 25% less than that of Neupogen when using the Ontario Drug Benefit formulary price of Neupogen ($192.42 for 300 mcg/1 mL vial).

CDR identified the following issues for consideration:

- The use of Grastofil pre-filled syringes in place of Neupogen vials (pre-filled syringes of Neupogen are not currently marketed in Canada) may lead to savings in nursing time and related costs, as patients can self-inject with less need for supervision or instruction.
- Expected cost savings with the use of Grastofil may vary between the participating drug plans due to differences in the list price for Neupogen.
- Some of the indications for filgrastim, such as severe chronic neutropenia and HIV infection, are chronic in nature and may require daily treatment. The relative costs of Grastofil and Neupogen are not expected to vary for these conditions, although absolute savings per patient associated with use of Grastofil are likely to be larger compared with indications requiring episodic or short-term use.

Other Discussion Points:

CDEC noted the following:

- The lack of comparative data in patients for whom Grastofil will be indicated is a limitation; however, extrapolation of efficacy results from healthy subjects has been accepted by regulators for SEBs of filgrastim.

Research Gaps:

CDEC noted that there is insufficient evidence regarding the following:

- There are no controlled clinical trials evaluating the safety and efficacy of Grastofil in the indicated patient populations.
- The total safety population of healthy subjects exposed to both Grastofil and Neupogen was relatively small. Rarer adverse events associated with one or both of Grastofil and Neupogen would not necessarily have been observed in the reviewed trials.

CDEC Members:

Dr. Lindsay Nicolle (Chair), Dr. James Silvius (Vice-Chair), Dr. Silvia Alessi-Severini, Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Mr. Frank Gavin, Dr. Peter Jamieson, Dr. Anatoly Langer, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. Adil Virani, and Dr. Harindra Wijeysundera.

February 17, 2016 Meeting
Regrets:
Three CDEC members were unable to attend the meeting.

Conflicts of Interest:
None

About This Document:
CDEC provides formulary listing recommendations or advice to CDR-participating drug plans. CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CDEC deliberated on a review and made a recommendation or issued a record of advice. 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 requested the removal of confidential information. CADTH has redacted the requested confidential information in accordance with the *CDR Confidentiality Guidelines*.

The CDEC recommendation or record of advice 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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