Common Drug Review
Patient Group Input Submissions

filgrastim (Grastofil) for prevention or treatment of neutropenia in various indications:

1. Cancer Patients Receiving Myelosuppressive Chemotherapy
2. Patients with Acute Myeloid Leukemia
3. Cancer Patients Receiving Myeloablative Chemotherapy Followed by Bone Marrow Transplantation
4. Cancer Patients Undergoing Peripheral Blood Progenitor Cell (PBPC) Collection and Therapy
5. Patients with Severe Chronic Neutropenia (SCN) 6. Patients with HIV Infection
6. Patients with HIV Infection

Patient group input submissions were received from the following patient groups. Those with permission to post are included in this document.
Consumer Advocare Network — permission granted to post.

CADTH received patient group input for this review on or before October 1, 2015

CADTH posts all patient input submissions to the Common Drug Review received on or after February 1, 2014 for which permission has been given by the submitter. This includes patient input received from individual patients and caregivers as part of that pilot project.

The views expressed in each submission are those of the submitting organization or individual; not necessarily the views of CADTH or of other organizations. While CADTH formats the patient input submissions for posting, it does not edit the content of the submissions.

CADTH does use reasonable care to prevent disclosure of personal information in posted material; however, it is ultimately the submitter's responsibility to ensure no personal information is included in the submission. The name of the submitting patient group and all conflict of interest information are included in the posted patient group submission; however, the name of the author, including the name of an individual patient or caregiver submitting the patient input, are not posted.

Consumer Advocare Network

1. General Information

Name of the drug	Grastofil (SEB filgrastim)
Indication of interest	Neutropenia (due to six conditions)
Name of the patient group	Consumer Advocare Network
Name of the primary contact for this submission:	[redacted]
Position or title with patient group	[redacted]
Email	[redacted]
Telephone number(s)	[redacted]
Name of author (if different)	
Patient group's contact information:	
Address	151 Bloor Street West, Suite 600, Toronto, Ontario M5S 1S4
Website	www.consumeradvocare.org
Permission is granted for CADTH to post this submission	Yes

1.1 Submitting Organization

The Consumer Advocare Network is a registered not-for-profit organization set up in 1999 to provide education and support to patient groups to promote engagement in healthcare policy and decision-making. Advocare regularly provides training and produces educational materials for use by patient groups and also provides input to health policy makers and healthcare providers. In 2012, Advocare created the Canadian Expert Patients in Health Technology, a network of individuals committed to promoting informed patient engagement at all levels of health policy and decision-making.

1.2 Conflict of Interest Declarations

a) We have the following declaration(s) of conflict of interest in respect of corporate members and joint working, sponsorship, or funding arrangements:

With reference to this submission, the Consumer Advocare Network has received unrestricted educational grants over the past 12 years to develop materials and workshops on health technology assessment, including patient engagement with the Common Drug Review, from Canada's Research-Based Pharmaceutical Companies (Rx&D), Merck Canada, Pfizer Canada, Sanofi, Janssen-Ortho, Amgen Canada, Lilly Canada, Hoffman-LaRoche, Novartis Canada, and Wyatt Health Management as well as in-kind support from the University of Alberta to develop and conduct trainings.

b) We have the following declaration(s) of conflict of interest in respect of those playing a significant role in compiling this submission:

[redacted] is a volunteer with the Consumer Advocare Network; she is paid by the Canadian Organization for Rare Disorders and the Institute for Optimizing Health Outcomes, both of which also

receive unrestricted funding from these entities for other programmes. She has no conflict of interest to declare in the preparation of this submission.

Section 2 — Condition and Current Therapy Information

2.1 Information Gathering

To gain an understanding of the impact of neutropenia and the treatments experienced in order to develop our survey, we conducted interviews with four key "patient informants", specifically, two cancer patients who had undergone chemotherapy, one patient with chronic neutropenia, and one caregiver of a patient with Aplastic Anemia. We also interviewed two clinicians who had conducted clinical trials using Grastofil, one here in Canada and the other in Italy.

Potential respondents were recruited in two ways: (1) by direct email request to patients and patient groups that have consented to receive information about activities conducted by Advocare and/or the Canadian Organization for Rare Disorders, and (2) notification of the survey posted by the primary author through the social media, namely Twitter and Facebook. The email requests were sent twice and the Facebook/Twitter postings were made several times. In both the email requests and the Twitter/Facebook postings, the participants requested were identified as patients "who had experienced or were at risk of experiencing neutropenia (low white blood cells) as a result of one of six conditions: receiving [myelosuppressive] chemotherapy for cancer, acute myeloid leukemia, undergoing bone marrow transplant and receiving high-dose chemotherapy, undergoing peripheral blood progenitor cell (PBPC) collection, congenital, cyclic, or idiopathic neutropenia, and HIV infection. In addition to email and social media postings, we used snowballing technique, asking recipients to forward the survey to other patients and caregivers who fit the criteria.

There were 60 respondents who completed the survey between September 14 and September 28, 2015. The largest group, slightly more than one-quarter, identified themselves as "cancer patients receiving myelosuppressive chemotherapy"; the second largest grouping, about one-fifth, were those with congenital, cyclic, or idiopathic neutropenia; and self-identifications of the remainder were somewhat evenly dispersed among the other categories (about one-eighth had acute myeloid leukemia, one-eighth received a bone marrow transplant, one-twentieth were undergoing PBPC collection, and one or two "others" had lymphoma, bone marrow failure, aplastic anemia, amyloidosis, MDS, or vasculitis.

More than half of the patients (represented) were over 60 years of age, with about one-fourth under 30 years old, and the remainder between 30 and 60 years of age. Less than one-tenth of the respondents were caregivers and the remainder identified as the "person with the condition."

2.2 Impact of Condition on Patients

There are three key caveats that must be noted with respect to the data provided here regarding the patients' report of their symptoms. First, while patients were asked about the symptoms experienced as a result of neutropenia, we recognize that most of the respondents are also dealing with other conditions, and some of their symptoms would be similar to those associated with neutropenia. However, we know, based on our interviews, that they could identify specific symptoms associated with the period of time in which they were either diagnosed with neutropenia, were undergoing treatment in which neutropenia was an adverse effect, or experienced an increase in these symptoms and subsequently were informed about the decline in white blood cell counts.

A second caveat is that many of these patients were reporting about an experience with neutropenia that was in the past and episodic, so they relying on recall. In only a few cases were these patients who

reported chronic neutropenia or other chronic conditions (e.g., aplastic anemia) where neutropenia may occur repeatedly. However, we did not find that the answers of those with chronic neutropenia differed in any noticeable way from those with episodic neutropenia. We are confident, based on the feedback from the patients interviewed, they were able to recall and report quite accurately on their experience of the impact of neutropenia. However, we acknowledge that the feedback is subject to recall bias.

Third, we specified in our recruitment that we wanted to hear from patients who had experienced neutropenia, or low white blood counts, as a result of the indicated conditions, so we do not know to what degree all patients with these conditions experienced neutropenia or the degree to which these responses are reflective of the total patient population (of the conditions represented).

Notwithstanding these caveats, our data show that patients experience multiple symptoms with neutropenia and these were severe and frequent. The most frequently experienced symptoms were fatigue and high fever, with about one-third of respondents indicating fatigue was the most difficult symptom and one-third responding the worst symptom was high fever. Nearly one-fourth said they were most troubled by infections in the mouth or on the skin in the form of ulcers or rashes. Nearly one-tenth experienced the most severe problems were laryngeal, including sore throats, coughing, sinus infections or shortness of breath. Other severe or frequent symptoms included diarrhea, pain urinating, nausea, vomiting, and one case of sepsis from gall bladder infection.

Cancer and other patients were, for the most part, aware of the risk of acquiring neutropenia as a result of their treatment, so many were not surprised and "recognized" the symptoms when they occurred. About "one in eight" said they had no symptoms of neutropenia; about half of this group (one in 16) said they had received filgrastim prophylactically. Among those with symptoms, all respondents reported that neutropenia had a tremendous impact on their quality of life and daily living. In addition to the fatigue, they were constantly on the alert for potential infections, which, in some cases, were experienced as "life-threatening." One respondent considered it "ironic" that she felt she had "beaten cancer" with chemotherapy but then nearly died from the "side effects" of the cure, namely the infections due to a suppressed immune system.

One respondent described her husband's symptoms experienced from a drop in white blood counts during chemotherapy as, *"my husband had one life threatening infection after another that put him in hospital for a week or more each time. He had terrible nausea and couldn't sleep despite terrible fatigue. Then he was put on low dose antibiotics prophylactically as well, but he contracted clostridium difficile and suffered for months unable to eat and with diarrhea so bad he was sick. Finally his heart was affected, he went into congestive heart failure, and his kidneys failed. In this emergency a temporary catheter into his heart was placed to dialyze him. Although his heart has been permanently damaged he is still alive today, and dialyzes at home. He is starting another round of chemo…"*

Another patient described the impact of neutropenia on her ability to participate in regular activities, *"I was at increased risk of infections for a year after my treatment … as my WBC and Neutrophil counts were less than 1. I took a prophylactic oral antibiotic for an entire year to prevent life threatening infections during my immune-suppressed state. I avoided crowds, family with infections, and ate an immune-suppression diet.*

2.3 Patients' Experiences With Current Therapy

Types of Treatments: Participants were asked to indicate what types of treatment they had received for neutropenia and the effectiveness of these in managing, reducing, or eliminating the symptoms. About three-fourths said they had received antibiotics to treat symptoms of neutropenia; about two-fifths said they had received immunosuppressive medications (such as cyclosporine, monoclonal antibodies,

and/or corticosteroids), and about the same number said they had received filgrastim or some other form of granulocyte-colony stimulating factor (G-CSF). Finally, about one-fourth said the physician had changed their medication to reduce the risk of neutropenia. Some had received more than one treatment.

Effectiveness of Treatments: According to respondents, antibiotics worked. In terms of effectiveness, among those receiving antibiotics, about one-fourth said they were "not at all" or "somewhat" effective, while three-fourths said they were "much or very much" effective. Participants were slightly less clear about the effectiveness of taking immunosuppressive drugs, with about four-fifths saying they were effective or very effective. However almost one-fourth said they did not know how well the medications worked to reduce neutropenia. Similarly, those who had had their medications changed were evenly split between those who felt the change worked "well" or "very well" to reduce neutropenia, and the remainder said they "didn't know." In contrast, all those who received filgrastim said the drug worked "well" or "very well."

Overall, those taking antibiotics or filgrastim were clear as to the effectiveness in resolving their symptoms of neutropenia ("got my energy back"; "cleared up the infections and got rid of the rash", "just wanted to hug my doctor, or someone, and now I can.") However, with immunosuppressive therapy or with a change in medication, the benefits were less clear, maybe because the strategy was to reduce "more, new" symptoms from happening and not so much to clear up the neutropenia.

Adverse Effects on Treatments: When asked about the degree to which they experienced adverse effects related to their neutropenia treatments, nearly two-thirds who received antibiotics said they had experienced none or mild side effects, while one-fourth reported the adverse effects as moderate. Only "one in eight" said they had severe side effects. In contrast, about two-thirds who received some form of immunosuppression said they had experienced "much" or "severe" adverse effects and the remainder reported the side effects as "some" or "moderate." Those who had received a "change in medication" responded that they had only mild reactions to the switch or they were unaware of any negative effects. Similarly, those receiving filgrastim said side effects to the drug itself were mild or nonexistent. In other words, patients had lots of adverse effects and some had severe unwanted reactions to the immunosuppressive drugs but most had little or no problems with the other treatments, including antibiotics and filgrastim.

"We were told that the [GSF] could cause some pain or discomfort, but she never had any reactions, thank God." "I thought I may have spiked a fever with the injection but it came down pretty quickly so I'm not sure whether it was related to the drug, or not."

We did not ask about ability to access treatments due to cost. No one brought this up spontaneously as an issue in the interviews or in the surveys. Based on the comments, most patients relied on their physician to decide on the course of treatment with neutropenia. We had no feedback that choice of therapy for neutropenia was based on cost-considerations, including insurance coverage or drug listing limitations.

2.4 Impact on Caregivers

We did not ask questions specifically about the impact on caregivers; however, there were a number of comments provided through the open-ended comment sections on the survey. Caregivers (especially spouses and parents) expressed greater distress with the impact of neutropenia on the patient than on themselves. *"It is so unfair that [he] has to deal with this [infections due to lower immune functioning] when he is already so weakened by his cancer and also the chemotherapy. Up to now, I have been encouraging him to hang in there but this last thing may have been the last straw."*

"When you have a child with chronic neutropenia, you have to always be on guard as to what he is doing or what risks he is exposed to. With [filgrastim], we're like a normal family doing normal things with normal worries.

Most expressed fears and concerns about the potential risks when neutropenia was deliberately "caused" by chemotherapy to prepare a patient for bone marrow transplant or other procedure. Unlike other conditions, because neutropenia was a "secondary effect" of the main condition and often an episodic occurrence, attention was .

"When we learned that the best and maybe only option was a bone marrow transplant, we were more frightened about the chemotherapy and wiping out [x's] immune system than about the BMT. But thanks to all of the preventive treatment, we were able to get through it with no serious problems other than extreme fatigue."

Section 5 — Information About the SEB Being Reviewed

5.1 What Are Patients' Expectations for the SEB?

Although most respondents seemed to rely on their physician to decide treatment for neutropenia (including prophylaxis or not), the majority, when asked about their awareness of filgrastim, responded that they were familiar with the drug, at least by "brand name." About one-third was familiar with the term "filgrastim" while two-thirds said they were "not at all" aware of this drug (prior to the survey or interview). However, about two-thirds were aware of Neupogen and about one-third said they had "much" or "very much" knowledge. Almost none of the respondents had heard of Grastofil (by name) although a few were "unsure."

In the interviews, none of the participants had heard of the term "SEB" or "biosimilar" (which was a bit surprising based on feedback from other patient populations) but we believe that SEBs or biosimilars do not factor into therapies for these patient populations at this time, so they have not paid attention to this category of products. Moreover, while we know that the patient leaders of many of these groups are familiar with SEBs and/or biosimilars, they have not done much to pass on education to the patients. We chose not to pursue the knowledge about SEBs or biosimilars in the survey.

In the introduction to the survey, we provided a brief "high-level" introduction to SEBs and biosimilars. We asked respondents, based on that explanation, to provide their opinion as to how they felt the "SEB Grastofil" would work compared to Neupogen (the original filgrastim) in managing five symptoms associated with neutropenia (stimulating white blood cells, reducing or preventing infection, reducing or preventing fever, increasing tolerance of primary therapy, and reducing fatigue). Not surprisingly, about 4 out of 5 respondents indicated they had no knowledge or opinion as to whether the SEB Grastofil would be "better", "no different" or "worse" than the original Neupogen in terms of each of these symptoms. The remaining one-fifth said they felt SEB would work the same. In terms of cost or affordability, 9 out of 10 said they had no opinion or knowledge, while the remaining one-tenth said they felt it would be the same in cost.

When asked how they felt the SEB would perform in terms of seven different adverse effects (bone pain, nausea, headache, itching, rash, high blood pressure, or injection site reactions), the responses were similar. About four-fifths said they had "no knowledge or opinion" as to whether there would be "fewer/less severe", "same" or "more severe" side effects, while the remaining one-fifth said they expected side effects would be the same.

Overall, no one felt the SEB Grastofil would be less effective than the original Neupogen nor did they feel it would have more or worse side effects.

Section 6 — Key Messages

- Patients undergoing chemotherapy or other treatments affecting bone marrow production experience moderate to severe symptoms of neutropenia.
- Patients with neutropenia due to chemotherapy or other treatments as well as chronic or cyclic neutropenia experience filgrastim as effective in managing, reducing, or preventing symptoms with relatively mild side effects.
- Patients with neutropenia rely mostly on the physician to decide what treatment to use to prevent or treat neutropenia.
- Patients in Canada with neutropenia (secondary or primary) tend to be unaware of SEB filgrastim.
- Patients with neutropenia (due to treatment for another condition) or with chronic neutropenia accept use of SEB filgrastim with physician approval.

Section 7 — Additional Information

Respondents were asked how they felt the SEBs should be made available to Canadian patients through an open-ended question and a series of close-ended options. About half of the respondents said the SEB should be available as an option through the hospital or public drug plans; the remainder were not sure or had no opinion. Physician approval was the key to SEB use among these respondents. About half said it could be used instead of the original, with physician approval, even if the patient had received Neupogen previously. The remainder were not sure. None of the respondents said they would support Grastofil use without physician approval, regardless of their previous experience with Neupogen. Moreover, almost half said the SEB should not be exchanged (back and forth) without physician consent.

Section 8 — Comments on Potential Ways SEBs Can be Used

CDR reviewers and CDEC members will not review or use information in Section 8; however, drug plans may consider this information in their decision-making.

Duplicate from Section 7: Respondents were asked how they felt the SEBs should be made available to Canadian patients through an open-ended question and a series of close-ended options. About half of the respondents said the SEB should be available as an option through the hospital or public drug plans; the remainder were not sure or had no opinion. Physician approval was the key to SEB use among these respondents. About half said it could be used instead of the original, with physician approval, even if the patient had received Neupogen previously. The remainder were not sure. None of the respondents said they would support Grastofil use without physician approval, regardless of their previous experience with Neupogen. Moreover, almost half said the SEB should not be exchanged (back and forth) without physician consent.