

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761134Orig1s000

**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	BLA
Application Number	761134
PDUFA Goal Date	March 30, 2022
OSE RCM #	2021-667; 2021-669
Reviewer Name(s)	Till Olickal, Ph.D., Pharm.D.
Team Leader	Naomi Boston, Pharm.D.
Associate Director for REMS	Laura Zendel, Pharm.D.
Design and Evaluation	
Review Completion Date	March 28, 2022
Subject	Evaluation of Need for a REMS
Established Name	efbemalenograstim alfa-vuxw
Trade Name	Ryzneuta
Name of Applicant	Evive Biotechnology Singapore PTE LTD
Therapeutic Class	Leukocyte growth factor
Formulation(s)	20 mg/mL solution in a single-dose prefilled syringe
Dosing Regimen	The recommended dosage is a single subcutaneous injection of 20 mg administered once per chemotherapy cycle.

Table of Contents

EXECUTIVE SUMMARY	3
1 Introduction.....	3
2 Background	4
2.1 Product Information	4
2.2 Regulatory History.....	4
3 Therapeutic Context and Treatment Options	4
3.1 Description of the Medical Condition	4
3.2 Description of Current Treatment Options	5
4 Benefit Assessment.....	6
5 Risk Assessment & Safe-Use Conditions	7
6 Expected Postmarket Use.....	8
7 Risk Management Activities Proposed by the Applicant.....	8
8 Discussion of Need for a REMS	8
9 Conclusion & Recommendations	9
10 References	9

EXECUTIVE SUMMARY

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Ryzneuta (efbemalenograstim alfa-vuxw) is necessary to ensure the benefits outweigh its risks. Evive Biotechnology Singapore PTE LTD submitted Biologic Licensing Application (BLA) 761134 for efbemalenograstim alfa-vuxw with the proposed indication to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia. The serious risks associated with the use of efbemalenograstim alfa-vuxw are splenic rupture, acute respiratory distress syndrome (ARDS), serious allergic reactions, use in patients with sickle cell disorders, glomerulonephritis, leukocytosis, thrombocytopenia, capillary leak syndrome, potential for tumor growth stimulatory effects on malignant cells, aortitis and interference with nuclear imaging. The Applicant did not submit a REMS with this application, but included a non-REMS risk management plan consisting of labeling and routine pharmacovigilance activities.

The Division of Risk Management (DRM) and the Division of Nonmalignant Hematology (DNH) have determined that if approved, a REMS is not necessary to ensure the benefits of efbemalenograstim alfa-vuxw outweigh its risks. Chemotherapy-induced neutropenia (CIN) and/or febrile neutropenia (FN) often result in high costs, severe infections, aggressive hospital management, life-threatening morbidity, and even mortality. Granulocyte colony stimulating factors (G-CSFs) shorten the time taken for the white blood cells to return to normal levels, and are known to decrease the duration of febrile neutropenia as well as the duration of antibiotics use, and in addition, they enable the delivery of full chemotherapy dose intensity. There is a clear need for therapeutic strategies with new alternative modalities that encompass multiple modes of action with a longer half-life. Efbemalenograstim alfa-vuxw appeared efficacious in its primary outcome of mean duration of severe (Grade 4) neutropenia, and its risks can be communicated and managed through labeling. Based on the efficacy and safety information currently available, the clinical reviewer stated that efbemalenograstim alfa-vuxw shows clinically meaningful benefit, and recommends approval of efbemalenograstim alfa-vuxw to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia. The safety profile is similar to other G-CSFs approved for similar indications which do not require a REMS. The likely prescribers are expected to be familiar with risks, therefore additional risk mitigation is not necessary. If approved, labeling, including information in Warnings and Precautions, Patient Counseling Information, and a Patient Package Insert will be used to communicate the safety issues and management of toxicities associated with efbemalenograstim alfa-vuxw.

1 Introduction

This review evaluates whether a REMS for the new molecular entity (NME) Ryzneuta (efbemalenograstim alfa-vuxw) is necessary to ensure the benefits outweigh its risks. Evive Biotechnology Singapore PTE LTD submitted a Biologic Licensing Application (BLA) 761134 for efbemalenograstim alfa-vuxw with the proposed indication¹ to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia. The Applicant did not submit a REMS with this application but included a non-REMS risk management plan consisting of labeling and routine pharmacovigilance activities.

2 Background

2.1 PRODUCT INFORMATION

Efbemalenograstim alfa-vuxw is an NME BLA type 351(a) pathway application.^a It is a recombinant human granulocyte colony stimulating factor (G-CSF) receptor agonist with a Fc fusion protein.² Efbemalenograstim alfa-vuxw is a colony-stimulating factor that acts on hematopoietic cells by binding to specific cell surface receptors, thereby stimulating proliferation, differentiation, commitment, and end cell functional activation. Efbemalenograstim alfa-vuxw will be supplied 20 mg/mL solution in a single-dose prefilled syringe. The recommended dosage is a single subcutaneous injection of 20 mg administered once per chemotherapy cycle. Efbemalenograstim alfa-vuxw must not be administered between 14 days before and 24 hours after administration of cytotoxic chemotherapy.^{b,1} Efbemalenograstim alfa-vuxw is not currently approved in any jurisdiction.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for efbemalenograstim alfa-vuxw (BLA 761134) relevant to this review:

- 04/02/2012 Investigation New Drug IND 112198 submission for F-627 received.
- 05/01/2020: A Pre-BLA meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that the Agency agrees that if the observed safety profile of F-627 is similar to that of pegfilgrastim, a formal REMS may not be necessary for F-627. However, the final determination will be made during the review of the BLA.
- 03/30/2021: BLA 761134 submission for efbemalenograstim alfa-vuxw with the proposed indication to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia, received.
- 09/13/2021: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that no safety issues have been identified for efbemalenograstim alfa-vuxw that would require a REMS.

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

Chemotherapy-induced neutropenia (CIN) is a common complication in cancer treatment.³ CIN is a major cause of hematological and dose-limiting toxicities of chemotherapy. It may have short- or long-term impacts on treatment plans, which may result in unfavorable disease control and survival. CIN is generally characterized as a decreased absolute neutrophil count (ANC) < 2,000 cells/mm³ in peripheral blood.⁴ Further classification of the severity of CIN is evaluated by the National Cancer Institute

^a Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

^b Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

Common Terminology Criteria for Adverse Events, version 5.0.⁵ According to this grading system, neutropenia is classified according to the following 4 grades: (i) Grade 1 with an ANC of 1,500–2,000 cells/mm³, (ii) Grade 2 with an ANC of 1,000–1,500 cells/mm³, (iii) Grade 3 with an ANC of 500–1,000 cells/mm³, and (iv) Grade 4 with an ANC < 500 cells/mm³. The most important clinical implication of CIN is febrile neutropenia (FN). The clinical definition of febrile neutropenia is $\geq 38.3^{\circ}\text{C}$ measured orally for a duration of over 1 hour.² The degree and duration of neutropenia is directly related to development of FN and determines the risk of infection.⁶ Neutropenia blunts the inflammatory response to nascent infections, allowing bacterial multiplication and invasion. Because neutropenia reduces the signs and symptoms of infection, patients with neutropenia often may present with fever as the only sign of infection.⁶ Febrile neutropenia can also lead to dose reduction of chemotherapeutic regimens which can then reduce the anti-cancer effect of the therapy.

As per 2012 National Inpatient Sample and Kids' Inpatient Database, in the United States in 2012, 91,560 adults and 16,859 children with cancer were treated at a hospital because of neutropenia.^c On average, adult cancer patients who were treated at a hospital because of neutropenia stayed about three days longer and paid about \$5,700 more than adult cancer patients who went to the hospital for other reasons. The total cost for adults being hospitalized for cancer-related neutropenia was \$2.3 billion, and \$439 million for children.⁷

CIN and/or FN often result in high costs, severe infections, aggressive hospital management, life-threatening morbidity, and even mortality.^{4,d}

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

Patients with fever and neutropenia, or FN, must be treated aggressively, typically with intravenous antibiotics and hospitalization, because of the risk of death from rapidly spreading infection.⁶ Currently, the standard treatment for CIN is the use of a G-CSF to attenuate white blood cell counts and ANCs. G-CSFs have been used frequently to reduce the incidence and duration of chemotherapy-induced neutropenia and febrile neutropenia.³ G-CSF stimulates the proliferation and differentiation of neutrophil precursors, and increased survival and activity of mature neutrophils in the body after chemotherapy.⁸ G-CSFs shorten the time taken for the white blood cells to return to normal levels, and are known to decrease the duration of febrile neutropenia as well as the duration of antibiotic use.⁹ In addition, they enable the delivery of full chemotherapy dose intensity.¹⁰ The American Society for Clinical Oncology (ASCO) recommendations for the Use of White Blood Cell Growth Factors Guidelines recommend G-CSFs be used when the risk of febrile neutropenia is in the range of 20% or higher.¹¹

The first approved product in this drug class was filgrastim (Neupogen), approved in 1991.¹² Eleven years later in 2002, pegfilgrastim (Neulasta) was approved.¹³ Afterwards in 2012, tbo-filgrastim (Granix) was approved.¹⁴ Between 2015 and 2020, six biosimilars were approved. None of these products have a boxed warning in their labels, nor was a REMS required for approval. Filgrastim and tbo-filgrastim

^c Section 505-1 (a) of the FD&C Act: FDAAA factor (A): *The estimated size of the population likely to use the drug involved.*

^d Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

require daily injections per cycle. Pegfilgrastim lasts longer in the body and is only needed once per chemotherapy cycle.¹⁵

The availability of hematopoietic growth factors and improvements in antibiotic therapy have changed how clinicians approach the management of neutropenia, yet this complication remains a central concern in the delivery of cancer chemotherapy.⁶ There is a clear need for therapeutic strategies with new alternative modalities that encompass multiple modes of action with a longer half-life.

4 Benefit Assessment

The efficacy of efbemalenograstim alfa-vuxw was evaluated in two randomized, controlled studies (GC627-04; NCT02872103 and GC627-05; NCT03252431).

Study 1 (GC627-04) was a randomized, double-blind, placebo-controlled study that employed doxorubicin 60 mg/m² and docetaxel 75 mg/m² administered every 21 days for up to 4 cycles for the treatment of metastatic or non-metastatic breast cancer. A total of 122 patients were randomized to receive a single subcutaneous injection of efbemalenograstim alfa-vuxw (20 mg) or placebo on day 2 of chemotherapy cycle 1. All patients received efbemalenograstim alfa-vuxw (20 mg) on day 2 of chemotherapy cycles 2 – 4. In Study 1, the patients were 30 to 69 years of age and all female. The ethnicity was 99% Caucasian, 2% Hispanic, and <1% Asian, Black, or other. Study 2 (GC627-05) was a randomized, active-controlled study that compared efbemalenograstim alfa-vuxw to pegfilgrastim. Study 2 employed docetaxel 75 mg/m² and cyclophosphamide 600 mg/m² administered every 21 days for up to 4 cycles for the treatment of non-metastatic breast cancer. A total of 393 patients were randomized to receive a single subcutaneous injection of efbemalenograstim alfa-vuxw (20 mg) or pegfilgrastim (6 mg) on day 2 of each chemotherapy cycle.^{1,2} In Study 2, the patients were 26 to 83 years of age and all females. The ethnicity was 100% Caucasian.¹

The primary endpoint was the duration of Grade 4 neutropenia in cycle 1 for both studies. Study 1 met the primary endpoint with lower mean duration of Grade 4 neutropenia for efbemalenograstim alfa-vuxw-treated patients as compared to placebo-treated patients (1.4 days versus 4.3 days, respectively, $p < 0.001$; 2.9 day difference). A key secondary endpoint of the incidence of febrile neutropenia (defined as temperature $\geq 38.3^{\circ}\text{C}$, or $> 38.0^{\circ}\text{C}$ sustained for at least 1 hour, and $\text{ANC} < 0.5 \times 10^9/\text{L}$) was also lower for efbemalenograstim alfa-vuxw-treated patients compared to placebo-treated patients in cycle 1 (4.8% versus 25.6%) in Study 1. Study 2 also met the primary endpoint by demonstrating that the mean days of Grade 4 neutropenia of efbemalenograstim alfa-vuxw -treated patients did not exceed that of pegfilgrastim-treated patients by a clinically significant margin in cycle 1 of chemotherapy. The mean days of cycle 1 severe neutropenia in Study 2 were 0.2 days in both the efbemalenograstim alfa-vuxw and pegfilgrastim arms [difference in means 0.0 days (95% CI -0.1, 0.1)].^{1,2,e}

The clinical reviewer concluded that efbemalenograstim alfa-vuxw shows clinically meaningful benefit, and recommends approval of efbemalenograstim alfa-vuxw to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.^{1,2,16}

^e Section 505-1 (a) of the FD&C Act: *FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition*

5 Risk Assessment & Safe-Use Conditions

The safety of efbemalenograstim alfa-vuxw was evaluated in two randomized, controlled studies (GC627-04 and GC627-05; see Section 4: Benefit Assessment).

The most common adverse reaction ($\geq 5\%$ difference in incidence compared to placebo) was nausea (36% vs 30%).¹ The most common treatment emergent adverse events (TEAEs) for efbemalenograstim alfa-vuxw vs placebo over all cycles were alopecia (73.5% vs 66.7%), neutropenia (68.7% vs 64.1%), and nausea (61.4% vs 59.0%) in Study 1. The most commonly reported TEAEs by subject incidence (efbemalenograstim alfa-vuxw vs. pegfilgrastim) were alopecia (52.3% vs. 51.0%), nausea (36.0% vs. 29.6%), asthenia (29.4% vs. 23.5%), neutropenia (20.3% vs. 25.5%), anemia (23.9% vs. 19.4%), leukopenia (19.8% vs. 22.4%), and bone pain (20.8% vs. 17.3%) in Study 2.¹⁶

Deaths

There were no deaths in Study 1. In Study 2, there were 3 deaths; 1 patient randomized to the 20 mg efbemalenograstim alfa-vuxw and 2 patients were randomized to pegfilgrastim. The patient that died in the efbemalenograstim alfa-vuxw arm was from a result of a fatal pulmonary embolism on Cycle 3, Day 12 of the treatment period; this was assessed as unrelated to study treatment. One of the patients that died in the pegfilgrastim arm was during post-treatment follow-up on Study Day 117 from fatal purulent peritonitis. This was assessed as unrelated to study treatment. An additional pegfilgrastim patient died on Study Day 235 (170 days after completing the last study drug treatment) due to disease/treatment-related complications.^{16,17}

Serious Adverse Events (SAE)

In Study 1, there were 17 SAEs reported in 15 (12.3%) subjects overall, including 4 SAEs in 4 (4.8%) subjects randomized to efbemalenograstim alfa-vuxw and 13 SAEs in 11 (28.2%) subjects randomized to Placebo. In Study 2, there were 17 SAEs reported in 15 (3.8%) subjects overall, including 12 SAEs in 12 (6.1%) subjects randomized to efbemalenograstim alfa-vuxw and 5 SAEs in 3 (1.5%) subjects randomized to pegfilgrastim.¹⁶ The most common SAE in patients who received F-627 was febrile neutropenia. The clinical reviewer stated that febrile neutropenia due to the chemotherapy is an expected event in this population. Most of the SAEs reviewed were considered unrelated to the study drug. Most SAEs were in the system organ class (SOC) of blood and lymphatic system disorders and investigations, and these SAEs are expected because patients are also receiving chemotherapeutic agents which affect all hematopoietic cells and other cells in the body especially those cells with rapid turnover.² Overall, the adverse events (AEs) leading to discontinuation were less than 2%. Most events were related to neutropenia or febrile neutropenia. These were the only two AEs that were reported in two or more patients. In the comparator arms, there were 8 (3.1%) patients on pegfilgrastim and no patients on placebo with TEAEs leading to discontinuation. In Study GC-627-05, other events leading to discontinuation in the efbemalenograstim alfa-vuxw arms included events of angioedema, dermatitis allergic, pulmonary embolism, breast cancer recurrent, urticaria, and alanine aminotransferase increased. The clinical reviewer stated that angioedema and urticaria do appear to be allergic reactions after the injection of efbemalenograstim alfa-vuxw. However, it is less likely that the recurrence of breast cancer, a solid tumor, would be because of a G-CSF product.²

Similar to other G-CSFs, such as pegfilgrastim (Neulasta)¹³, if approved, labeling will include the risks of splenic rupture, acute respiratory distress syndrome (ARDS), serious allergic reactions, use in patients with sickle cell disorders, glomerulonephritis, leukocytosis, thrombocytopenia, capillary leak syndrome, potential for tumor growth stimulatory effects on malignant cells, aortitis and interference with nuclear imaging in the Warnings and Precautions section.¹ None of these AEs rose to a level of a boxed warning. Adverse events of special interest (AESI) attributed to the G-CSF drug class G-CSFs are rare. The most well known events include leukocytosis, musculoskeletal pain and allergic reaction. Overall, AESIs were not commonly seen with efbemalenograstim alfa-vuxw.² Similar to other G-CSFs, such as pegfilgrastim, labeling will also include a limitation of use statement as efbemalenograstim alfa-vuxw is not indicated for the mobilization of peripheral blood progenitor cells for hematopoietic stem cell transplantation.¹

6 Expected Postmarket Use

According to the currently proposed indication, if approved, efbemalenograstim alfa-vuxw will be used in both inpatient and outpatient settings and the likely prescribers will be hematologists and oncologists, who are involved in the management and treatment of malignancies. The AEs associated with efbemalenograstim alfa-vuxw are similar to currently approved G-CSFs, therefore it is expected that the prescribing community are likely aware of the management of the AEs associated with the use of these drugs.

7 Risk Management Activities Proposed by the Applicant

The applicant did not propose any risk management activities for efbemalenograstim alfa-vuxw beyond routine pharmacovigilance and labeling.

8 Discussion of Need for a REMS

When evaluating factors of whether a REMS is necessary to ensure that the benefits outweigh the risks for efbemalenograstim alfa-vuxw, this reviewer considered the patient population, seriousness of the disease, expected benefit of the drug, seriousness of known or potential adverse events, and the likely prescribing population.

Efbemalenograstim alfa-vuxw is a leukocyte growth factor, with the proposed indication to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia. CIN is a major cause of hematological and dose-limiting toxicities of chemotherapy. Based on the efficacy and safety information currently available, the clinical reviewer stated that efbemalenograstim alfa-vuxw shows clinically meaningful benefit, and recommends approval of efbemalenograstim alfa-vuxw to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.^{1,2,16}

DRM and DNH have determined that if approved, a REMS is not necessary to ensure the benefits of efbemalenograstim alfa-vuxw outweigh its risks. Efbemalenograstim alfa-vuxw appeared efficacious in its primary outcome of mean duration of severe (Grade 4) neutropenia, and its risks can be communicated and managed through labeling.^{1,2} The most concerning adverse reactions observed with the use of efbemalenograstim alfa-vuxw are risks for splenic rupture, ARDS, serious allergic reactions,

use in patients with sickle cell disorders, glomerulonephritis, leukocytosis, thrombocytopenia, capillary leak syndrome, potential for tumor growth stimulatory effects on malignant cells, aortitis and interference with nuclear imaging, which are the same as in the currently approved G-CSFs such as pegfilgrastim¹³. None of the G-CSF products have a boxed warning in their labels, nor was a REMS required for approval. At the time this review was completed, none of these risks will receive a boxed warning in the label, however labeling negotiations were still ongoing with the Applicant. If efbemalenograstim alfa-vuxw is approved, similar to other G-CSFs such as pegfilgrastim, Warnings and Precautions in the labeling will be used to communicate the safety issues and management of toxicities associated with efbemalenograstim alfa-vuxw, as well as information to be included in Patient Counseling Information, and a PPI.

The likely prescribers will be hematologists and oncologists. The risks identified are risks that these providers have likely encountered in their practice experience in the treatment of hematologic malignancies, as well as with the use of G-CSF drug therapy.

9 Conclusion & Recommendations

If approved, DRM has determined that a REMS is not necessary to ensure the benefits outweigh the risks of efbemalenograstim alfa-vuxw. The management of the risks associated with efbemalenograstim alfa-vuxw treatment will be communicated through labeling. Please notify DRM if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10 References

- ¹ Draft Prescribing Information for efbemalenograstim alfa-vuxw as currently edited by the FDA, last updated March 1, 2022.
- ² Division of Nonmalignant Hematology (DNH) Interdisciplinary Assessment (draft) for efbemalenograstim alfa-vuxw, BLA 761134, dated March 23, 2022.
- ³ Hashiguchi Y, Kasai M, Fukuda T, Ichimura T, Yasui T, Sumi T. Chemotherapy-induced neutropenia and febrile neutropenia in patients with gynecologic malignancy. *Anticancer Drugs*. 2015;26(10):1054-1060.
- ⁴ Ba Y, Shi Y, Jiang W, et al. Current management of chemotherapy-induced neutropenia in adults: key points and new challenges: Committee of Neoplastic Supportive-Care (CONS), China Anti-Cancer Association Committee of Clinical Chemotherapy, China Anti-Cancer Association. *Cancer Biol Med*. 2020;17(4):896-909.
- ⁵ National Institutes of Health (NIH). National Cancer Institute (NCI). Division of Cancer Treatment & Diagnosis (DCTD). Cancer Therapy Evaluation Program (CTEP). Common Terminology Criteria for Adverse Events (CTCAE) v5.0. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm#ctc_50. Accessed February 23, 2022.
- ⁶ Crawford J, Dale DC, Lyman GH. Chemotherapy-induced neutropenia: risks, consequences, and new directions for its management. *Cancer*. 2004;100(2):228-237.
- ⁷ Centers for Disease Control and Prevention (CDC). Cancer. Cost of Cancer-Related Neutropenia or Fever Hospitalizations. <https://www.cdc.gov/cancer/dpcp/research/articles/neutropenia.htm>. Accessed February 23, 2022.

⁸ Welte K, Gabrilove J, Bronchud MH, Platzer E, Morstyn G. Filgrastim (r-metHuG-CSF): the first 10 years. *Blood*. 1996;88(6):1907-1929.

⁹ Mhaskar R, Clark OA, Lyman G, Engel Ayer Botrel T, Morganti Paladini L, Djulbegovic B. Colony-stimulating factors for chemotherapy-induced febrile neutropenia. *Cochrane Database Syst Rev*. 2014;2014(10):Cd003039.

¹⁰ Lyman GH. A comparison of international guidelines for the prevention of chemotherapy-induced neutropenia. *Curr Opin Hematol*. 2011;18(1):1-10.

¹¹ Lyman GH. A comparison of international guidelines for the prevention of chemotherapy-induced neutropenia. *Curr Opin Hematol*. 2011;18(1):1-10.

¹² Neupogen. Prescribing Information (last updated 02/2021).

¹³ Neulasta. Prescribing Information (last updated 03/2021).

¹⁴ Granix. Prescribing Information (last updated 04/2020).

¹⁵ Evive Biotechnology Singapore PTE LTD. Clinical Overview, dated March 30, 2021.

¹⁶ Whyte-Stewart D. Clinical Safety Review Presentation. Mid-Cycle Meeting, dated September 1, 2021.

¹⁷ Evive Biotechnology Singapore PTE LTD. Summary of Clinical Safety, dated March 30, 2021.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

TILL OLICKAL
03/28/2022 09:42:46 PM

NAOMI S BOSTON
03/29/2022 09:51:33 AM

LAURA A ZENDEL
03/29/2022 10:05:11 AM