

## Drug Class Update: Colony Stimulating Factors

**Date of Review:** January 2019

**Date of Last Review:** January 2015

**Dates of Literature Search:** September 2018

### **Current Status of PDL Class:**

See **Appendix 1**.

### **Purpose for Class Update:**

The colony stimulating factor (CSF) class update was prompted by four new approvals since the last review, peg-filgrastim-jmdb, filgrastim-sndz, filgrastim-aafi and pegfilgrastim-cbqv. New comparative evidence published since the last review for the CSF class will be reviewed and moderate to high quality evidence will be evaluated and presented.

### **Research Questions:**

1. Is there any new comparative evidence for CSF treatments for important outcomes such as mortality, infection or hospitalizations?
2. Is there any new comparative evidence based on the harm outcomes (i.e., bone pain, nausea, therapy-related myeloid neoplasms) of CSF treatments?
3. Are there subpopulations of patients for which specific CSF therapies may be more effective or associated with less harm?
4. What is the efficacy and harms evidence for the three new CSF treatments, peg-filgrastim-jmdb, filgrastim-sndz, filgrastim-aafi and pegfilgrastim-cbqv?

### **Conclusions:**

- There is limited new evidence of moderate to high quality available for evaluation of this class. No systematic reviews met inclusion criteria for the review, based on our methods. Two guidelines are included in the review. Both were limited by panel members having conflicts of interest with industry. Overall evidence supports previous recommendations with no compelling evidence of efficacy or harms differences between granulocyte colony-stimulating factors (G-CSFs).<sup>1,2</sup>
- *Prophylaxis* - There is moderate quality evidence for the use of G-CSFs (filgrastim, tbo-filgrastim, filgrastim-sndz or pegfilgrastim) as prophylactic therapy for the prevention of febrile neutropenia (FN) in patients receiving myelosuppressive chemotherapy that has a 20% or greater risk of FN and who are being treated for solid tumors or non-myeloid malignancies (filgrastim-aafi and pegfilgrastim-jmdb were not available at the time recommendations were published).<sup>1,2</sup>
- *Treatment* - There is moderate quality of evidence for the use of CSFs in patients with FN who are at high risk for infection-related complications.<sup>1,2</sup>
- *Transplant* - There is moderate quality evidence for the use of CSFs after autologous stem-cell transplantation to reduce the duration of severe FN; however, there is low quality evidence for patients undergoing allogenic stem-cell transplantation.<sup>1,2</sup>

- There is low quality evidence that the biosimilar pegfilgrastim-jmdb (Fulphila™) is bioequivalent to pegfilgrastim for the outcome of days of severe neutropenia based on two trials in women with breast cancer receiving myelosuppressive chemotherapy.<sup>3,4</sup> The mean treatment difference between pegfilgrastim-jmdb and pegfilgrastim was 0.04 (95% CI, -0.15 to -0.24) to 0.16 (95% CI, -0.40 to -0.08) days, demonstrating noninferiority.
- The biosimilar filgrastim-sndz (Zarxio®) demonstrated biosimilar equivalency to filgrastim for the outcome of severe neutropenia and febrile neutropenia based on two trials in women with breast cancer (low quality evidence). Mean treatment differences were 0.04 days (lower limit of 97.5% CI of -0.26 days) and a mean treatment difference of 3.4% (95% CI, -9.65% to 4.96%) in a second trial, both trials demonstrating noninferiority.<sup>5,6</sup>
- Filgrastim-aafi (Nivestym™) is a biosimilar to filgrastim which recently became FDA approved. Data from two pharmacokinetic/pharmacodynamic studies in patients with advanced metastatic colorectal cancer demonstrated bioequivalence.<sup>7</sup> No additional evidence was available for evaluation.
- Pegfilgrastim-cbqv (Udenyca™) was approved in November 2018 as a biosimilar to pegfilgrastim for patients at high risk of febrile neutropenia due to myelosuppressive chemotherapy administration for non-myeloid malignancies. No clinical trial data has been published.
- Common adverse events (e.g., bone pain, rash) were similar upon comparison of biosimilar therapies to their reference products.
- There was insufficient evidence to determine a difference in efficacy or harms in subpopulations of patients prescribed CSFs.

#### Recommendations:

- No changes to the PDL are recommended.
- Evaluate comparative drug costs in executive session. After executive session, filgrastim-sndz (Zarxio) was designated as non-preferred.

#### Summary of Prior Reviews and Current Policy

- This class was last reviewed in 2015. Evidence supports a benefit of primary CSF treatment in reducing hospitalizations, need for antibiotics and incidence of neutropenic fever.<sup>2</sup> Treatment with CSFs has not definitively shown a positive impact on survival. There is insufficient evidence on differences in efficacy or harms between CSF treatments.
- All therapies in this class that have been previously reviewed are preferred.

#### Background:

Colony stimulating factors are used to regulate the proliferation, differentiation, survival and activation of myeloid cells. There are two categories of CSFs: recombinant human granulocyte colony stimulating factor (G-CSF) and granulocyte-macrophage stimulating factor (GM-CSF) (**Table 1**).<sup>1,2</sup> G-CSFs increase the level of neutrophil proliferation while GM-CSF stimulate the production of neutrophils, monocytes, red blood cells and platelet precursors. There is insufficient evidence to suggest superiority of one CSF therapy (G-CSF, GM-CSF or biosimilars) over another; however, administration frequency and route may influence treatment choice.<sup>8</sup>

**Table 1. Colony Stimulating Factors**

Drugs	Administration	Dosing*	FDA Approved Indications
<i>G-CSF</i>			
Filgrastim (Neupogen®) <sup>9</sup>	Subcutaneous or intravenous infusion	Once or twice daily	<ul style="list-style-type: none"> <li>• Febrile neutropenia prophylaxis following myelosuppressive chemotherapy for non-myeloid malignancies</li> <li>• Induction or consolidation treatment in patients with AML</li> </ul>

			<ul style="list-style-type: none"> <li>• Decrease the incidence of febrile neutropenia in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by BMT</li> <li>• Harvesting of peripheral blood stem cells</li> <li>• Chronic neutropenic disorder (severe, symptomatic)</li> <li>• Increase survival in patients acutely exposed to myelosuppressive doses of radiation</li> </ul>
Tbo-filgrastim (Granix®) <sup>10</sup>	Subcutaneous	Daily SQ administration	<ul style="list-style-type: none"> <li>• Febrile neutropenia prophylaxis following myelosuppressive chemotherapy for non-meyloid malignancies</li> </ul>
Filgrastim-sndz (Zarxio®) <sup>11</sup>	Subcutaneous or intravenous infusion	Once or twice-daily or by continuous infusion	<ul style="list-style-type: none"> <li>• Febrile neutropenia prophylaxis following myelosuppressive chemotherapy for non-myeloid malignancies</li> <li>• Induction or consolidation treatment in patients with AML</li> <li>• Severe neutropenia</li> </ul>
Filgrastim-aafi (Nivestym™) <sup>12</sup>	Subcutaneous or intravenous infusion	Once or twice daily	<ul style="list-style-type: none"> <li>• Decrease the incidence of febrile neutropenia</li> <li>• Harvesting of peripheral blood stem cells</li> <li>• Reduce the incidence and sequelae of severe neutropenia of severe neutropenia in patients who are symptomatic and have chronic neutropenia</li> <li>• Reduce the incidence and sequelae of severe neutropenia in patients with non-myeloid malignancies undergoing myeloablative chemotherapy followed by BMT</li> <li>• Induction or consolidation treatment in patients with AML</li> </ul>
Pegfilgrastim (Neulasta®) <sup>13</sup>	Subcutaneous	One dose per chemotherapy cycle	<ul style="list-style-type: none"> <li>• Decrease the incidence of febrile neutropenia in patients with non-myeloid malignancies</li> <li>• Increase survival in patients acutely exposed to myelosuppressive doses of radiation</li> </ul>
Pegfilgrastim-jmdb (Fulphila™) <sup>14</sup>	Subcutaneous	One dose per chemotherapy cycle	<ul style="list-style-type: none"> <li>• Decrease infection associated with febrile neutropenia in patients with non-myeloid cancers receiving myelosuppressive chemotherapy associated with clinically significant rates of febrile neutropenia</li> </ul>
Pegfilgrastim-cbqv (Udenyca™)	Subcutaneous	One dose per chemotherapy cycle	<ul style="list-style-type: none"> <li>• 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</li> </ul>
<i>GM-CSF</i>			
Sargramostim (Leukine®) <sup>15</sup>	Subcutaneous or intravenous	Daily or by continuous infusion	<ul style="list-style-type: none"> <li>• In adult patients, 55 years and older, with AML undergoing induction therapy to shorten time to neutrophil recovery and to reduce the incidence of severe and life-threatening infections</li> <li>• Mobilization of hematopoietic progenitor cells and autologous transplant</li> <li>• Acceleration of myeloid reconstitution in autologous BMT</li> </ul>

			<ul style="list-style-type: none"> <li>• Acceleration of myeloid reconstitution in allogenic BMT</li> <li>• For treatment of delayed neutrophil recovery or graft failure in BMT</li> <li>• Increase survival in patients acutely exposed to myelosuppressive doses of radiation</li> </ul>
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Key: \* Consult prescribing information for exact doses and timing of dosing in relation to chemotherapy.

Abbreviations: AML – acute myeloid leukemia; BMT – bone marrow transplant

CSFs are indicated for several conditions as described in **Table 2**.<sup>8</sup> When CSFs are used for prophylaxis of FN in patients receiving cytotoxic chemotherapy regimens, the recommendations are for use when there is a 20% or higher incidence of neutropenic fever; however, consideration of the patient’s risk factors is advised especially in scenarios where the risk of FN is intermediate (10-20%). Patients who are 65 years or older and receive full dose intensity chemotherapy have the highest risk of severe neutropenia.<sup>2</sup> CSFs are not recommended in secondary prevention of neutropenia in patients receiving palliative chemotherapy or patients receiving concomitant chemoradiotherapy for head and neck cancer or lung cancer.<sup>8</sup> There is no evidence to suggest a benefit of using CSFs as initial therapy in patients with severe neutropenia after chemotherapy or as an adjunct to antibiotics; however, if patients remain febrile and neutropenic while taking antibiotics then there may be a benefit of CSFs.

**Table 2. Indications for Colony Stimulating Factors<sup>8</sup>**

Type of CSF	Indication
G-CSF	Reduction in the duration and severity of neutropenia in patients undergoing cytotoxic chemotherapy*
G-CSF	Post hematopoietic cell transplant to mobilize progenitor cells or as supportive care after transplantation†
G-CSF	Severe chronic neutropenia
GM-CSF	Induction therapy for AML and hematopoietic cell transplantation
* Neutropenia is the result of decreased neutrophil count, less than 500 micro/L, which is associated with an increased risk of infection	
† Most evidence is with filgrastim. GM-CSFs can be used but G-CSFs are favored.	

Off-label uses of CSFs are for neutropenia associated with hepatitis-C treatment, acquired immune deficiency syndrome (AIDs), aplastic anemia and Crohn’s disease.

Important outcomes related to CSF treatments include mortality, hospitalizations, need for antibiotics and neutropenia. CSF prophylaxis has been shown to reduce the need for antibiotics and hospitalizations but evidence to support a mortality benefit is limited. The use of CSF prophylactically is not recommended due to risk of secondary myelodysplastic syndrome, acute myeloid leukemia and splenic rupture. Common adverse events related to CSFs are transient leukopenia, bone pain, flu-like symptoms and rash.<sup>8</sup>

Oregon Health Plan (OHP) fee-for-service (FFS) point-of-sale (POS) pharmacy utilization is low with 13 claims in the first quarter of 2018 for the preferred products filgrastim (Neupogen<sup>®</sup>), pegfilgrastim (Neulasta<sup>®</sup>) and filgrastim-sndz (Zarxio<sup>®</sup>). Physician administered drug (PAD) utilization in quarter 1 of 2018 was for the same preferred products as claims for POS, with utilization divided equally between the three treatments.

## Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

## New Systematic Reviews:

No new systematic reviews met inclusion criteria.

After review, 10 systematic reviews were excluded due to poor quality, wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).<sup>16–22,23–25</sup>

## New Guidelines:

### ***National Comprehensive Cancer Network – Myeloid Growth Factors***

NCCN released a clinical practice guideline on the myeloid growth factors in August of 2018.<sup>2</sup> Guidelines are based on a literature search on relevant evidence with a methods clearly described. Evidence is graded and presented in **Table 3**. The guidelines are not funded by industry; however, almost half of the 36 panel members have conflicts of interest with industry. While this produces inherent bias, there are limited high-quality guidelines and evidence available, and therefore, guidelines will be included with noted limitations. CSFs included in the guidelines include filgrastim, pegfilgrastim, filgrastim-sndz, and tbo-filgrastim. At the time of guideline publication there was insufficient data on filgrastim-aafi and pegfilgrastim-jmdb so they were not included in the recommendations.

**Table 3. NCCN Categories of Evidence and Consensus<sup>2</sup>**

Category	Description
1	Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate
2A	Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate
2B	Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate
3	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate
All recommendations are 2A unless otherwise indicated	

### *Febrile Neutropenia Prophylaxis*

The NCCN guidelines recommend the use of CSFs for prophylaxis in adults patients with a 20% or greater risk of FN who are treated for solid tumors and non-myeloid malignancies.<sup>2</sup> G-CSFs (filgrastim, tbo-filgrastim or filgrastim-sndz) are recommended for prophylaxis based on category 1 evidence for the reduction of febrile neutropenia, hospitalization, and intravenous antibiotics. The prophylactic use of G-CSF has also been shown to reduce infection-related mortality during

the course of treatment based on category 2A evidence. Pegfilgrastim, one dose of 6 mg per cycle of treatment, is also recommended based on category 1 evidence. Patients with intermediate risk of FN (10-20%) should be considered for G-CSFs based on patient risk factors (e.g., prior chemotherapy or radiation, persistent neutropenia, bone marrow involvement by tumor, recent surgery and/or open wounds, liver dysfunction, renal dysfunction, or age greater than 65 receiving full chemotherapy dose intensity).<sup>2</sup> Patients should be evaluated for FN or a dose-limiting neutropenic event prior to second and subsequent chemotherapy cycles. Patients with FN or an event may be candidates for dose reduction of chemotherapy, change in chemotherapy regimen, or eligible for G-CSF if not previously used.<sup>2</sup>

*Febrile Neutropenia Treatment*

Patients who develop FN and were given G-CSF during chemotherapy cycle should continue to get daily prophylactic G-CSF; patients receiving long-lasting pegfilgrastim should not be treated with additional G-CSF (category 2A evidence).<sup>2</sup> If patients did not receive prophylactic G-CSF and have no risk factors for infection-associated complications, they should not receive therapeutic G-CSF or GM-CSF. Consider use of G-CSF or GM-CSF if infection-associated complication risk factors are present.

*Mobilization of Hematopoietic Progenitor Cells in Autologous Setting*

NCCN recommends the use of filgrastim, filgrastim-sndz or tbo-filgrastim beginning during apheresis on day 4 or 5 and continuing till leukapheresis (2A recommendation).<sup>2</sup> An alternative CSF option is the addition of sargramostim to concurrent filgrastim/filgrastim-sndz (Category 2B). Filgrastim/filgrastim-sndz/tbo-filgrastim with plerixafor is approved for use in patients with non-Hodgkin lymphoma and multiple myeloma for mobilizing autologous hematopoietic stem cells (Category 2A).

*Mobilization and Post Hematopoietic Cell Transplant*

The use of filgrastim is preferred in allogeneic donors. Filgrastim-sndz or tbo-filgrastim are recommended as category 2B alternatives.<sup>2</sup> In patients receiving a granulocyte transfusion filgrastim (Category 2A), filgrastim-sndz or tbo-filgrastim (both Category 2B) are recommended. Filgrastim, filgrastim-sndz or tbo-filgrastim are recommended as options for supportive care in patients undergoing post-autologous hematopoietic cell, haploidentical transplant or cord blood transplant. Pegfilgrastim is an option for patients with post-autologous hematopoietic cell transplant.

**American Society of Clinical Oncology – Use of WBC Growth Factors Guideline**

The ASCO updated their 2006 recommendations on the use of CSFs in adults or children with solid tumor or lymphoma treated with chemotherapy.<sup>1</sup> Patients with acute myeloid leukemia (AML) or myelodysplastic syndromes were excluded. Guideline methods were described, evidence quality was graded and overall strength of the recommendations were provided (weak, moderate and high). Evidence was identified via a systematic review of databases with dates ranging from October 2005 through September 2014. Limitations to the guideline include 10 of the 14 authors with conflicts of interest and funding for guideline development was not disclosed. Recommendations are presented in **Table 4**.

**Table 4. ASCO Guideline Recommendations for CSF Use in Patients with Cancer<sup>1</sup>**

Recommendation	Evidence Quality	Recommendation Strength
<ul style="list-style-type: none"> <li>Primary prophylaxis for patients with a 20% or higher risk of FN and those receiving dose dense chemotherapy if appropriate</li> </ul>	High	Strong
<ul style="list-style-type: none"> <li>Secondary prophylaxis with CSFs are recommended for patients who experienced a neutropenic complication from a prior cycle of chemotherapy (previously untreated</li> </ul>	High	Strong

with CSFs) in which a reduced dose or treatment delay may compromise disease-free survival, overall survival or outcome		
<ul style="list-style-type: none"> <li>CSFs are not recommended for patients who are neutropenic and afebrile</li> </ul>	High	Strong
<ul style="list-style-type: none"> <li>CSFs should not be routinely used as adjunctive therapy with antibiotic treatment for patients with fever and neutropenia</li> <li>CSF should be considered in patients with fever and neutropenia who are at high risk for infection-associated complications or have prognostic factors which predict a poor clinical outcome</li> </ul>	High	Strong
<ul style="list-style-type: none"> <li>Dose-dense regimens with CSF support should only be used if supported by convincing efficacy data or in a clinical trial</li> </ul>	High/intermediate*	Strong/moderate*
<ul style="list-style-type: none"> <li>CSFs, with or without plerixafor, may be used to after chemotherapy to mobilize peripheral-blood progenitor cells</li> </ul>	High	Strong
<ul style="list-style-type: none"> <li>CSFs should be used in patients after autologous stem-cell transplantation to reduce the duration of severe neutropenia</li> </ul>	High	Strong
<ul style="list-style-type: none"> <li>The use of CSFs in allogenic stem-cell transplantation may be employed to reduce the duration of neutropenia</li> </ul>	Low	Weak
<ul style="list-style-type: none"> <li>Prophylactic use of CSF in patients with diffuse aggressive lymphoma, age 65 years or older, treated with curative chemotherapy should be considered, especially if comorbidities are present</li> </ul>	Intermediate	Moderate
<ul style="list-style-type: none"> <li>Use of CSFs in pediatric patients should be guided by clinical protocols. Recommendations are similar to those for adults</li> </ul>	High	Strong
<ul style="list-style-type: none"> <li>CSFs are recommended in pediatric patients with indications in which dose-intense chemotherapy is known to have a survival benefit</li> </ul>	High	Strong
<ul style="list-style-type: none"> <li>CSFs should not be used in pediatric patients with nonrelapsed ALL or nonrelapsed AML who do not have an infection</li> </ul>	Intermediate	Moderate
<ul style="list-style-type: none"> <li>Pegfilgrastim, filgrastim, tbo-filgrastim and filgrastim-sndz (and other biosimilars as they become available) can be used for the prevention of treatment-related febrile neutropenia</li> <li>Choice of CSF should be based on convenience, cost and clinical situation</li> </ul>	High	Strong
<ul style="list-style-type: none"> <li>Patients exposed to total-body radiotherapy, but not doses high enough to result in certain death, include the prompt administration of CSFs or pegylated granulocyte CSFs.</li> </ul>	Intermediate	Moderate
<b>Key: * Dependent upon cancer type</b> <b>Abbreviations: ALL – acute lymphoblastic leukemia; AML – acute myeloid leukemia; CSF – colony stimulating factor; FN – febrile neutropenia</b>		

Excluded Guidelines:

After review, one guideline was excluded due to poor quality.<sup>26</sup>

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## New Formulations or Indications:

### New Biosimilar Products

#### FULPHILA

Pegfilgrastim-jmdb is a biosimilar product to pegfilgrastim (Neulasta®) which was approved in 2018.<sup>14</sup> Pegfilgrastim-jmdb is a leukocyte growth factor indicated to decrease the incidence of infection, manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive chemotherapy associated with a high incidence of febrile neutropenia. Studies which support equivalency of pegfilgrastim to the reference product are outlined in **Table 5** and abstracts may be found in Appendix 1. Bone pain and pain in extremity are the most common adverse events with a 5% or higher incidence compared to placebo. Pegfilgrastim-jmdb has warnings for serious but rare adverse events including: splenic rupture, ARDS, serious allergic reactions, fatal sickle cell crisis, and glomerulonephritis.

**Table 5. Pegfilgrastim-jmdb Equivalency Trials**

Study	Comparison	Population	Primary Outcome	Results
Harbeck, et al <sup>3</sup>	Pegfilgrastim (P) vs. Pegfilgrastim-jmdb (P-jmdb)	Women with breast cancer receiving myelosuppressive chemotherapy (n=316)	Mean duration of severe neutropenia during cycle 1*	P: 0.75 days P-jmdb: 0.79 days MTD 0.04 days (95% CI, -0.15 to -0.24) <i>Considered equivalent (noninferiority margin of -1 day)</i>
Blackwell, et al <sup>4</sup>	Pegfilgrastim (P) vs. Pegfilgrastim-jmdb (P-jmdb)	Women with breast cancer receiving myelosuppressive chemotherapy (n=275)	Mean duration of severe neutropenia during cycle 1*	P: 1.19 days P-jmdb: 1.34 days MTD 0.16 days (95% CI, -0.40 to -0.08) <i>Considered equivalent (noninferiority margin of -1 day)</i>

Key: \* Severe neutropenia defined as ANC <0.5 X 10<sup>9</sup>/1 (grade 4 neutropenia)  
Abbreviations: ANC – absolute neutrophil count; CI – confidence interval; MTD – mean treatment difference

#### ZARXIO

Filgrastim-sndz (Zarxio®) is a new biosimilar for the reference drug filgrastim (Neupogen).<sup>11</sup> Filgrastim-sndz is a white blood cell growth factor which increases the production of neutrophils from bone marrow. Table 1 describes the indications for filgrastim-sndz. Studies supporting clinical equivalent efficacy of filgrastim-sndz to the reference product are shown in **Table 6** and abstracts may be found in Appendix 1.

**Table 6. Filgrastim-sndz Equivalency Trials**

Study	Comparison	Population	Primary Outcome	Results
Blackwell, et al <sup>5</sup>	Filgrastim (F) vs. Filgrastim-sndz (F-sndz)	Women receiving adjuvant chemotherapy for breast cancer (n=214)	Mean duration of severe neutropenia during cycle 1*	F: 1.20 days F-sndz: 1.17 days MTD 0.04 days; with lower limit of 97.5% CI of -0.26 days <i>Considered equivalent (noninferiority margin of -1 day)</i>

Blackwell, et al <sup>6</sup>	Filgrastim (F) vs. Filgrastim-sndz (F-sndz)	Women receiving adjuvant chemotherapy for breast cancer (n=161)	Febrile neutropenia rates between pooled switched groups compared to unswitched reference groups during cycles 2-6 <sup>†</sup>	F: 0 (0%) F-sndz: 3 (3.4%) MTD 3.4% (95% CI, -9.65% to 4.96%) <i>Considered equivalent (noninferiority margin set at -15%)</i>
Key: † four arms of trial in which 2 arms received only one product (unswitched) and 2 arms received alternating treatments every other cycle between biosimilar and reference treatment (switched)				
Abbreviations: CI – confidence interval; MTD – mean treatment difference				

Adverse reactions are similar for filgrastim-sndz as with other CSFs. The most common adverse events are pyrexia, rash and bone pain.<sup>11</sup> Severe adverse reactions include fatal splenic rupture, acute respiratory distress syndrome, serious allergic reaction and fatal sickle cell crisis.<sup>11</sup>

### NIVESTYM

Filgrastim-aafi (Nivestym™) is a biosimilar to filgrastim (Neupogen®) and was approved in July 2018.<sup>12</sup> Filgrastim-aafi indications are listed in table 1 and are similar to filgrastim. Filgrastim-aafi is given subcutaneously at a dose of 5-10 mcg/kg/day depending on the indication.<sup>12</sup>

Two pharmacokinetic/pharmacodynamic studies were completed to support biosimilarity filgrastim.<sup>27</sup> Both studies were conducted in healthy volunteers and were of a randomized, open-label design. The first study was a 5 mcg/kg/day, single-dose, cross-over study and the second study was a 5 mcg/kg/day, 5 consecutive daily dose, cross-over study. An additional immunogenicity study was done to assess risk and safety. All studies confirmed bioequivalence of filgrastim-aafi to filgrastim.

Adverse reactions with filgrastim-aafi are similar to other CSFs with rash, pain, pyrexia, headache and epistaxis being the most common.<sup>12</sup> Rare but serious side effects include fatal splenic rupture, ARDS, anaphylaxis, fatal sickle cell crisis, and glomerulonephritis.

### UDENYCA

A biosimilar to pegfilgrastim (Neulasta) called pegfilgrastim-cbqv (Udenyca™) was approved by the FDA in November of this year. Pegfilgrastim-cbqv is dosed once per chemotherapy cycle as a 6 mg dose. The indication for pegfilgrastim-cbqv is provided in Table 1. Clinical trial information is not published. Most common adverse reactions are bone pain and pain in the extremity.

### New FDA Safety Alerts:

**Table 7. Description of new FDA Safety Alerts<sup>10</sup>**

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Tbo-filgrastim	Granix®	February 2017	Warnings and precautions	Glomerulonephritis risk has been reported. Consider dose-reduction or interruption if causality is likely.

## Expanded Indications:

In March of 2018 the Food and Drug Administration (FDA) granted sargramostim (Leukine®) an expanded indication for survival in adult and pediatric patients acutely exposed to myelosuppressive doses of radiation (Table 1).<sup>15</sup>

## Randomized Controlled Trials:

A total of 49 citations were manually reviewed from the initial literature search. After further review, 48 citations were excluded because of wrong population (entirely non-US population), study design (e.g., observational or post-hoc analyses), comparator (e.g., no control), or outcome studied (e.g., non-clinical). The remaining trial is summarized in the table below. The full abstract is included in **Appendix 2**.

**Table 8. Description of Randomized Comparative Clinical Trials**

Study	Comparison	Population	Primary Outcome	Results
Pinter, et al <sup>7</sup>	Pegfilgrastim (PF) vs. Placebo (P)	Patients with advanced metastatic colorectal cancer (n=845)	Incidence of grade 3/4 neutropenia in the first 4 cycles (FOLOFOX or FOLFIRI)	PF: 2.4% P: 5.7% OR 0.41 (95% CI, 0.19 to 0.86) P=0.014
Abbreviations: FOLFIRI – leucovorin, 5-fluorouracil, irinotecan; FOLOFOX – leucovorin, 5-fluorouracil, oxaliplatin; OR – odds ratio; RCT – randomized controlled trial				

## References:

1. Smith TJ, Bohlke K, Lyman GH, et al. Recommendations for the Use of WBC Growth Factors: American Society of Clinical Oncology Clinical Practice Guideline Update. [Review]. *Journal of Clinical Oncology*. 2015;33(28):3199-3212. doi:10.1200/JCO.2015.62.3488
2. National Comprehensive Cancer Network. Myeloid Growth Factors. Version 2.2018-August 03,2018. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). Available at: NCCN.org. Accessed September 15, 2018.
3. Harbeck N, Lipatov O, Frolova M, et al. Randomized, double-blind study comparing proposed biosimilar LA-EP2006 with reference pegfilgrastim in breast cancer. *Future Oncology*. 2016;12(11):1359-1367. doi:10.2217/fon-2016-0016
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**Appendix 1: Current Preferred Drug List**

<u>Generic</u>	<u>Brand</u>	<u>Route</u>	<u>FormDesc</u>	<u>PDL</u>
filgrastim	NEUPOGEN	IJ	SYRINGE	Y
filgrastim	NEUPOGEN	IJ	VIAL	Y
filgrastim-sndz	ZARXIO	IJ	SYRINGE	Y
pegfilgrastim	NEULASTA	SQ	SYR W/ INJ	Y
pegfilgrastim	NEULASTA	SQ	SYRINGE	Y
sargramostim	LEUKINE	IJ	VIAL	Y
tbo-filgrastim	GRANIX	SQ	SYRINGE	Y
pegfilgrastim-jmdb	FULPHILA	SQ	SYRINGE	N
filgrastim-aafi	NIVESTYM	SQ	SYRINGE	N
pegfilgrastim-cbqv	UDENYCA	SQ	SYRINGE	N

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## Appendix 2: Abstracts of New Comparative Clinical Trials and Trials of Newly Approved Treatments

### **Safety and efficacy of alternating treatment with EP2006, a filgrastim biosimilar, and reference filgrastim: a phase III, randomised, double-blind clinical study in the prevention of severe neutropenia in patients with breast cancer receiving myelosuppressive chemotherapy.**

Blackwell K, Gascon P, Krendyukov A, Gattu S, Li Y, Harbeck N

#### *BACKGROUND:*

In 2015, the biosimilar filgrastim EP2006 became the first biosimilar approved by the US Food and Drug Administration for commercial use in the United States, marketed as Zarxio® (Sandoz). This phase III randomised, double-blind registration study in patients with breast cancer receiving (neo)adjuvant myelosuppressive chemotherapy (TAC; docetaxel + doxorubicin + cyclophosphamide) compares reference filgrastim, Neupogen® (Amgen), with two groups receiving alternating treatment with reference and biosimilar every other cycle.

#### *PATIENTS AND METHODS:*

A total of 218 patients receiving 5 µg/kg/day filgrastim over six chemotherapy cycles were randomised 1: 1: 1: 1 into four arms. Two arms received only one product, biosimilar or reference (unswitched), and two arms (switched) received alternating treatments every other cycle (biosimilar then reference or vice versa over six cycles). Since the switch occurred from cycle 2 onwards, this analysis compared pooled switched groups to the unswitched reference group for efficacy during cycles 2-6. Safety was also assessed. Non-inferiority in febrile neutropenia (FN) rates between groups for cycles 2-6 was shown if 95% were within a pre-defined margin of - 15%.

#### *RESULTS:*

A total of 109 patients switched treatment, and 52 patients received reference in all cycles. Baseline characteristics were similar between groups. The incidence of FN was 0% (reference) versus 3.4% (n = 3, switched) across cycles 2-6, with a difference of - 3.4% (95% confidence interval: -9.65% to 4.96%), showing non-inferiority. Infections occurred in 9.3% (switched) versus 9.9% (reference). Hospitalisation due to FN was low (one patient in cycle 6; switched). Adverse events related to filgrastim were reported in 42.1% (switched) versus 39.2% (reference) (all cycles). Musculoskeletal/connective tissue disorders related to filgrastim occurred in 35.5% (switched) versus 39.2% (reference) (all cycles), including bone pain (30.8% versus 33.3%). No neutralising antibodies were detected.

#### *CONCLUSIONS:*

There were no clinically meaningful results regarding efficacy, safety or immunogenicity when switching from reference to biosimilar filgrastim/EP2006, or vice versa.

### **Comparison of EP2006, a filgrastim biosimilar, to the reference: a phase III, randomized, double-blind clinical study in the prevention of severe neutropenia in patients with breast cancer receiving myelosuppressive chemotherapy.**

Blackwell K, Semiglazov V, Krasnozhan D, Davidenko I, Nelyubina L, Nakov R, Stiegler G, Singh P, Schwebig A, Kramer S, Harbeck N

#### *BACKGROUND:*

Biosimilars of filgrastim are in widespread clinical use in Europe. This phase III study compares biosimilar filgrastim(EP2006), with the US-licensed reference product, Neupogen®, in breast cancer patients receiving (neo)adjuvant myelosuppressive chemotherapy (TAC).

#### *PATIENTS AND METHODS:*

A total of 218 patients receiving 5 µg/kg/day filgrastim over six chemotherapy cycles were randomized 1:1:1:1 into four arms. Two arms received only one product (nonalternating), biosimilar or reference, and two arms (alternating) received alternating treatments during each cycle (biosimilar then reference or vice versa). The primary end point was duration of severe neutropenia (DSN) during cycle 1.

#### *RESULTS:*

The baseline characteristics were balanced between the four treatment arms. Noninferiority of biosimilar versus the reference was demonstrated: DSN (days) in cycle 1 was  $1.17 \pm 1.11$  (biosimilar, N = 101) and  $1.20 \pm 1.02$  (reference, N = 103), 97.5% confidence interval lower boundary for the difference was -0.26 days (above the predefined limit of -1 day). No clinically meaningful differences were observed regarding any other efficacy parameter: incidence of febrile neutropenia (FN); hospitalization due to FN; incidence of infections; depth and time of absolute neutrophil count (ANC) nadir and time to ANC recovery during cycle 1 and across all cycles. The pattern and frequency of adverse events were similar across all treatments.

#### *CONCLUSION:*

This study demonstrates that biosimilar and the reference filgrastim are similar with no clinically meaningful differences regarding efficacy and safety in prevention of severe neutropenia. Biosimilar filgrastim could represent an important alternative to the reference product, potentially benefiting public health by increasing access to filgrastim treatment.

### **A Comparison of Proposed Biosimilar LA-EP2006 and Reference Pegfilgrastim for the Prevention of Neutropenia in Patients With Early-Stage Breast Cancer Receiving Myelosuppressive Adjuvant or Neoadjuvant Chemotherapy: Pegfilgrastim Randomized Oncology (Supportive Care) Trial to Evaluate Comparative Treatment (PROTECT-2), a Phase III, Randomized, Double-Blind Trial.**

Blackwell K, Donskih R, Jones CM, Nixon A, Vidal MJ, Nakov R, Singh P, Schaffar G, Gascón P, Harbeck N.

#### *BACKGROUND:*

Pegfilgrastim is widely used for the prevention of chemotherapy-induced neutropenia. In highly regulated markets, there are currently no approved biosimilars of pegfilgrastim. Pegfilgrastim Randomized Oncology (Supportive Care) Trial to Evaluate Comparative Treatment (PROTECT-2) was a confirmatory efficacy and safety study designed to compare proposed biosimilar LA-EP2006 with reference pegfilgrastim (Neulasta, Amgen) in early-stage breast cancer patients receiving adjuvant or neoadjuvant myelosuppressive chemotherapy.

#### *METHODS:*

A total of 308 patients were randomized to LA-EP2006 or reference pegfilgrastim. Each patient received TAC (intravenous docetaxel 75 mg/m<sup>2</sup>, doxorubicin 50 mg/m<sup>2</sup>, and cyclophosphamide 500 mg/m<sup>2</sup>) on day 1 of each cycle, for six or more cycles. Pegfilgrastim (LA-EP2006 or reference) was given subcutaneously (6 mg in 0.6 mL) on day 2 of each cycle. The primary endpoint was duration of severe neutropenia (DSN) during cycle 1 (number of consecutive days with an absolute neutrophil count  $<0.5 \times 10^9/L$ ), with equivalence confirmed if 90% and 95% confidence intervals (CIs) were within a 1-day margin.

#### *RESULTS:*

Baseline characteristics were well balanced. DSN was equivalent between groups at mean  $\pm$  SD  $1.36 \pm 1.13$  (LA-EP2006, n = 155) and  $1.19 \pm 0.98$  (reference, n = 153) in cycle 1. With a treatment difference (reference minus LA-EP2006) of -0.16 days (90% CI -0.36 to 0.04; 95% CI -0.40 to 0.08), LA-EP2006 was equivalent to reference pegfilgrastim. Secondary efficacy parameters were similar between groups during cycle 1 and across cycles. Safety profiles were also similar between groups. No neutralizing antibodies against pegfilgrastim, filgrastim, or polyethylene glycol were detected.

#### *CONCLUSION:*

LA-EP2006 and reference pegfilgrastim were therapeutically equivalent and comparable regarding efficacy and safety in the prevention of neutropenia in patients with early-stage breast cancer receiving TAC.

#### *IMPLICATIONS FOR PRACTICE:*

The granulocyte colony-stimulating factor pegfilgrastim is widely used for the prevention of chemotherapy-induced neutropenia. Biosimilars are biologics with similar quality, safety, and efficacy to a reference product that may increase the affordability of treatment compared with their reference compounds. There are currently no approved biosimilars of pegfilgrastim in highly regulated markets. No previous phase III studies have been performed with LA-EP2006. PROTECT-2 was conducted to confirm the similarity of the proposed biosimilar LA-EP2006 to pegfilgrastim. Biosimilar pegfilgrastim (LA-EP2006) may benefit oncology patients by offering increased access to biological treatments that may improve clinical outcomes. This means that patients could potentially be treated prophylactically with biologics rather than only after complications have occurred.

#### **Randomized, double-blind study comparing proposed biosimilar LA-EP2006 with reference pegfilgrastim in breast cancer.**

Harbeck N, Lipatov O, Frolova M, Udovitsa D, Topuzov E, Ganea-Motan DE, Nakov R, Singh P, Rudy A, Blackwell K

#### *AIM:*

This randomized, double-blind trial compared proposed biosimilar LA-EP2006 with reference pegfilgrastim in women receiving chemotherapy for breast cancer (PROTECT-1).

#### *PATIENTS & METHODS:*

Women ( $\geq 18$  years) were randomized to receive LA-EP2006 ( $n = 159$ ) or reference ( $n = 157$ ) pegfilgrastim (Neulasta<sup>®</sup>, Amgen) for  $\leq 6$  cycles of (neo)-adjuvant TAC chemotherapy. Primary end point was duration of severe neutropenia (DSN) during cycle 1 (number of consecutive days with absolute neutrophil count  $< 0.5 \times 10^9/l$ ) with equivalence confirmed if 90% and 95% CIs were within a  $\pm 1$  day margin.

#### *RESULTS:*

For DSN, LA-EP2006 was equivalent to reference (difference: 0.07 days; 90% CI: -0.09-0.23; 95% CI: -0.12-0.26).

#### *CONCLUSION:*

LA-EP2006 and reference pegfilgrastim showed no clinically meaningful differences regarding efficacy and safety in breast cancer patients receiving chemotherapy.

#### **A Phase III, Randomized, Double-Blind, Placebo-Controlled Trial of Pegfilgrastim in Patients Receiving First-Line FOLFOX/Bevacizumab or FOLFIRI/Bevacizumab for Locally Advanced or Metastatic Colorectal Cancer: Final Results of the Pegfilgrastim and Anti-VEGF Evaluation Study (PAVES).**

Pinter T, Klippel Z, Cesas A, Croitoru A, Decaestecker J, Gibbs P, Hotko Y, Jassem J, Kurteva G, Novotny J, O'Reilly S, Salek T, Reiner M, Morrow PK, Choi MR, Whittaker S, Blanke C

#### *BACKGROUND:*

Pegfilgrastim's role in reducing the risk of febrile neutropenia (FN) in patients with colorectal cancer (CRC) receiving chemotherapy plus bevacizumab was not previously evaluated in a prospective study. The present phase III, double-blind trial evaluated the efficacy of pegfilgrastim versus placebo in reducing the incidence of grade 3/4 FN in patients with advanced CRC receiving bevacizumab combined with first-line chemotherapy (FOLFOX [leucovorin, 5-fluorouracil, oxaliplatin] or FOLFIRI [leucovorin, 5-fluorouracil, irinotecan]).

#### *PATIENTS AND METHODS:*

Patients aged  $\geq 18$  years with locally advanced or metastatic CRC were randomized 1:1 to placebo or 6 mg of pegfilgrastim  $\sim 24$  hours after receiving chemotherapy plus bevacizumab every 14 days. The study treatment period included 4 cycles, but patients could continue treatment for  $\leq 60$  months. The primary endpoint was incidence of grade 3/4 FN in the first 4 cycles. The secondary endpoints included the objective response rate (ORR), overall survival, and progression-free survival, analyzed at the end of the long-term follow-up period.

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**RESULTS:**

A total of 845 patients were randomized from November 2009 to January 2012 (422, pegfilgrastim; 423, placebo). Pegfilgrastim significantly reduced the incidence of grade 3/4 FN in the first 4 treatment cycles (pegfilgrastim, 2.4%; 95% confidence interval [CI], 1.1%-4.3%; placebo, 5.7%; 95% CI, 3.7%-8.3%; odds ratio [OR], 0.41; P = .014). No significant differences were observed between the 2 arms in ORR (OR, 1.15; P = .330), overall survival (hazard ratio, 0.94; P = .440), and progression-free survival (hazard ratio, 0.93; P = .300).

**CONCLUSION:**

Pegfilgrastim reduced the FN incidence in patients with advanced CRC receiving chemotherapy and bevacizumab. Administration of pegfilgrastim was tolerable and did not negatively affect the tumor response or survival in this patient population.

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### Appendix 3: Medline Search Strategy

Database(s): Ovid MEDLINE(R) 1946 to September Week 2 2018

Search Strategy:

#	Searches	Results
1	filgrastim.mp. or FILGRASTIM/	2406
2	filgrastim-sndz.mp. or Filgrastim/	1868
3	pegfilgrastim.mp.	641
4	sargramostim.mp.	179
5	tbo-filgrastim.mp.	14
6	1 or 2 or 3 or 4 or 5	2613
7	limit 6 to (english language and humans and yr="2014 -Current")	412
8	limit 7 to (clinical trial, phase iii or guideline or meta analysis or practice guideline or systematic reviews)	49

## Appendix 4. Prescribing Information Highlights

### HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use FULPHILA safely and effectively. See full prescribing information for FULPHILA.

**FULPHILA**<sup>™</sup> (pegfilgrastim-jmdb) injection, for subcutaneous use  
Initial U.S. Approval: 2018

**FULPHILA**<sup>™</sup> (pegfilgrastim-jmdb) is biosimilar\* to NEULASTA<sup>®</sup> (pegfilgrastim). (1)

### INDICATIONS AND USAGE

Fulphila is a leukocyte growth factor indicated 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. (1.1)

### Limitations of Use

Fulphila is not indicated for the mobilization of peripheral blood progenitor cells for hematopoietic stem cell transplantation.

### DOSAGE AND ADMINISTRATION

- Patients with cancer receiving myelosuppressive chemotherapy
  - 6 mg administered subcutaneously once per chemotherapy cycle. (2.1)
  - Do not administer between 14 days before and 24 hours after administration of cytotoxic chemotherapy. (2.1)
  - Use weight based dosing for pediatric patients weighing less than 45 kg; refer to Table 1. (2.2)

### DOSAGE FORMS AND STRENGTHS

- Injection: 6 mg/0.6 mL solution in a single-dose prefilled syringe for manual use only. (3)

### CONTRAINDICATIONS

Patients with a history of serious allergic reactions to human granulocyte colony-stimulating factors such as pegfilgrastim or filgrastim products. (4)

### WARNINGS AND PRECAUTIONS

- Fatal splenic rupture: Evaluate patients who report left upper abdominal or shoulder pain for an enlarged spleen or splenic rupture. (5.1)
- Acute respiratory distress syndrome (ARDS): Evaluate patients who develop fever, lung infiltrates, or respiratory distress. Discontinue Fulphila in patients with ARDS. (5.2)
- Serious allergic reactions, including anaphylaxis: Permanently discontinue Fulphila in patients with serious allergic reactions. (5.3)
- Fatal sickle cell crises: Have occurred. (5.4)
- Glomerulonephritis: Evaluate and consider dose-reduction or interruption of Fulphila if causality is likely. (5.5)

### ADVERSE REACTIONS

Most common adverse reactions ( $\geq 5\%$  difference in incidence compared to placebo) are bone pain and pain in extremity. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Mylan at 1-877-446-3679 (1-877-4-INFO-RX) or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

\*Biosimilar means that the biological product is approved based on data demonstrating that it is highly similar to an FDA-approved biological product, known as a reference product, and that there are no clinically meaningful differences between the biosimilar product and the reference product. Biosimilarity of Fulphila has been demonstrated for the condition(s) of use (e.g. indication(s), dosing regimen(s)), strength(s), dosage form(s), and route(s) of administration described in its Full Prescribing Information.

Revised: 6/2018

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ZARXIO safely and effectively. See full prescribing information for ZARXIO.

ZARXIO®(filgrastim-sndz) injection, for subcutaneous or intravenous use  
Initial U.S. Approval: 2015

### RECENT MAJOR CHANGES

Warnings and Precautions: Glomerulonephritis (5.5) 03/2016

### INDICATIONS AND USAGE

ZARXIO is a leukocyte growth factor indicated to:

- Decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a significant incidence of severe neutropenia with fever (1.1)
- Reduce the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of patients with acute myeloid leukemia (AML) (1.2)
- Reduce the duration of neutropenia and neutropenia-related clinical sequelae, e.g., febrile neutropenia, in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplantation (BMT) (1.3)
- Mobilize autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis (1.4)
- Reduce the incidence and duration of sequelae of severe neutropenia (e.g., fever, infections, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia (1.5)

### DOSAGE AND ADMINISTRATION

- Patients with cancer receiving myelosuppressive chemotherapy or induction and/or consolidation chemotherapy for AML
  - Recommended starting dose is 5 mcg/kg/day subcutaneous injection, short intravenous infusion (15 to 30 minutes), or continuous intravenous infusion. See Full Prescribing Information for recommended dosage adjustments and timing of administration (2.1)
- Patients with cancer undergoing bone marrow transplantation
  - 10 mcg/kg/day given as an intravenous infusion no longer than 24 hours. See Full Prescribing Information for recommended dosage adjustments and timing of administration. (2.2)
- Patients undergoing autologous peripheral blood progenitor cell collection and therapy
  - 10 mcg/kg/day subcutaneous injection (2.3)
  - Administer for at least 4 days before first leukapheresis procedure and continue until last leukapheresis (2.3)
- Patients with congenital neutropenia
  - Recommended starting dose is 6 mcg/kg subcutaneous injection twice daily (2.4)
- Patients with cyclic or idiopathic neutropenia

- Recommended starting dose is 5 mcg/kg subcutaneous injection daily (2.4)
- Direct administration of less than 0.3 mL is not recommended due to potential for dosing errors (2.5)

### DOSAGE FORMS AND STRENGTHS

- Injection: 300 mcg/0.5 mL in a single-dose prefilled syringe with BD UltraSafe Passive® Needle Guard (3)
- Injection: 480 mcg/0.8 mL in a single-dose prefilled syringe with BD UltraSafe Passive® Needle Guard (3)

### CONTRAINDICATIONS

Patients with a history of serious allergic reactions to human granulocyte colony-stimulating factors such as filgrastim or pegfilgrastim products. (4)

### WARNINGS AND PRECAUTIONS

- **Fatal splenic rupture:** Evaluate patients who report left upper abdominal or shoulder pain for an enlarged spleen or splenic rupture. (5.1)
- **Acute respiratory distress syndrome (ARDS):** Evaluate patients who develop fever and lung infiltrates or respiratory distress for ARDS. Discontinue ZARXIO in patients with ARDS. (5.2)
- **Serious allergic reactions, including anaphylaxis:** Permanently discontinue ZARXIO in patients with serious allergic reactions. (5.3)
- **Fatal sickle cell crises:** Have occurred. (5.4)
- **Glomerulonephritis:** Evaluate and consider dose-reduction or interruption of ZARXIO if causality is likely. (5.5)

### ADVERSE REACTIONS

Most common adverse reactions in patients:

- With nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs ( $\geq 5\%$  difference in incidence compared to placebo) are pyrexia, pain, rash, cough, and dyspnea. (6.1)
- With AML ( $\geq 2\%$  difference in incidence) are pain, epistaxis and rash. (6.1)
- With nonmyeloid malignancies undergoing myeloablative chemotherapy followed by BMT ( $\geq 5\%$  difference in incidence) is rash. (6.1)
- Undergoing peripheral blood progenitor cell mobilization and collection ( $\geq 5\%$  incidence) are bone pain, pyrexia and headache. (6.1)
- With severe chronic neutropenia (SCN) ( $\geq 5\%$  difference in incidence) are pain, anemia, epistaxis, diarrhea, hypoesthesia and alopecia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Sandoz Inc. at 1-800-525-8747 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

### USE IN SPECIFIC POPULATIONS

- ZARXIO should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. (8.1)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 02/2017

January 2019

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use NIVESTYM safely and effectively. See full prescribing information for NIVESTYM.

NIVESTYM™ (filgrastim-aafi) injection, for subcutaneous or intravenous use

Initial U.S. Approval: 2018

NIVESTYM (filgrastim-aafi) is biosimilar\* to NEUPOGEN (filgrastim).

## INDICATIONS AND USAGE

NIVESTYM is a leukocyte growth factor indicated to

- Decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a significant incidence of severe neutropenia with fever. (1.1)
- Reduce the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of patients with acute myeloid leukemia (AML). (1.2)
- Reduce the duration of neutropenia and neutropenia-related clinical sequelae, e.g., febrile neutropenia, in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplantation (BMT). (1.3)
- Mobilize autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis. (1.4)
- Reduce the incidence and duration of sequelae of severe neutropenia (e.g., fever, infections, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia. (1.5)

## DOSAGE AND ADMINISTRATION

- Patients with cancer receiving myelosuppressive chemotherapy or induction and/or consolidation chemotherapy for AML.
  - Recommended starting dose is 5 mcg/kg/day subcutaneous injection, short intravenous infusion (15 to 30 minutes), or continuous intravenous infusion. See Full Prescribing Information for recommended dosage adjustments and timing of administration. (2.1)
- Patients with cancer undergoing bone marrow transplantation.
  - 10 mcg/kg/day given as an intravenous infusion no longer than 24 hours. See Full Prescribing Information for recommended dosage adjustments and timing of administration. (2.2)
- Patients undergoing autologous peripheral blood progenitor cell collection and therapy.
  - 10 mcg/kg/day subcutaneous injection. (2.3)
  - Administer for at least 4 days before first leukapheresis procedure and continue until last leukapheresis. (2.3)
- Patients with congenital neutropenia.
  - Recommended starting dose is 6 mcg/kg subcutaneous injection twice daily. (2.4)
- Patients with cyclic or idiopathic neutropenia.
  - Recommended starting dose is 5 mcg/kg subcutaneous injection daily. (2.4)
- Direct administration of less than 0.3 mL (180 mcg) using NIVESTYM prefilled syringe is not recommended due to potential for dosing errors. (2.5)

## DOSAGE FORMS AND STRENGTHS

### Vial

- Injection: 300 mcg/mL in a single-dose vial (3)
- Injection: 480 mcg/1.6 mL in a single-dose vial (3)

### Prefilled Syringe

- Injection: 300 mcg/0.5 mL in a single-dose prefilled syringe (3)
- Injection: 480 mcg/0.8 mL in a single-dose prefilled syringe (3)

## CONTRAINDICATIONS

Patients with a history of serious allergic reactions to human granulocyte colony-stimulating factors such as filgrastim products or pegfilgrastim products. (4)

## WARNINGS AND PRECAUTIONS

- Fatal splenic rupture: Evaluate patients who report left upper abdominal or shoulder pain for an enlarged spleen or splenic rupture. (5.1)
- Acute respiratory distress syndrome (ARDS): Evaluate patients who develop fever and lung infiltrates or respiratory distress for ARDS.
- Discontinue NIVESTYM in patients with ARDS. (5.2)
- Serious allergic reactions, including anaphylaxis: Permanently discontinue NIVESTYM in patients with serious allergic reactions. (5.3)
- Fatal sickle cell crises: Have occurred. (5.4)
- Glomerulonephritis: Evaluate and consider dose-reduction or interruption of NIVESTYM if causality is likely. (5.5)

## ADVERSE REACTIONS

Most common adverse reactions in patients:

- With nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs ( $\geq 5\%$  difference in incidence compared to placebo) are pyrexia, pain, rash, cough, and dyspnea. (6.1)
- With AML ( $\geq 2\%$  difference in incidence) are pain, epistaxis and rash. (6.1)
- With nonmyeloid malignancies undergoing myeloablative chemotherapy followed by BMT ( $\geq 5\%$  difference in incidence) is rash. (6.1)
- Undergoing peripheral blood progenitor cell mobilization and collection ( $\geq 5\%$  incidence) are bone pain, pyrexia and headache. (6.1)
- With severe chronic neutropenia (SCN) ( $\geq 5\%$  difference in incidence) are pain, anemia, epistaxis, diarrhea, hypoesthesia and alopecia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Pfizer Inc at 1-800-438-1985 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

\*Biosimilar means that the biological product is approved based on data demonstrating that it is highly similar to an FDA-approved biological product, known as a reference product, and that there are no clinically meaningful differences between the biosimilar product and the reference product. Biosimilarity of NIVESTYM has been demonstrated for the condition(s) of use (e.g. indication(s), dosing regimen(s), strength(s), dosage form(s), and route(s) of administration described in its Full Prescribing Information.

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use UDENYCA safely and effectively. See full prescribing information for UDENYCA.

UDENYCA™ (pegfilgrastim-cbqv) injection, for subcutaneous use

INITIAL U.S. APPROVAL: 2018

UDENYCA (pegfilgrastim-cbqv) is biosimilar\* to Neulasta (pegfilgrastim) for the indications listed. (1)

### INDICATIONS AND USAGE

UDENYCA is a leukocyte growth factor indicated 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)

#### Limitations of Use

UDENYCA is not indicated for the mobilization of peripheral blood progenitor cells for hematopoietic stem cell transplantation.

### DOSAGE AND ADMINISTRATION

Patients with cancer receiving myelosuppressive chemotherapy

- 6 mg administered subcutaneously once per chemotherapy cycle. (2.1)
- Do not administer between 14 days before and 24 hours after administration of cytotoxic chemotherapy. (2.1)
- Use weight based dosing for pediatric patients weighing less than 45 kg; refer to Table 1. (2.2)

### DOSAGE FORMS AND STRENGTHS

Injection: 6 mg/0.6 mL in a single-dose prefilled syringe for manual use only. (3)

### CONTRAINDICATIONS

Patients with a history of serious allergic reaction to human granulocyte colony-stimulating factors such as pegfilgrastim or filgrastim products. (4)

## WARNINGS AND PRECAUTIONS

- Fatal splenic rupture: Evaluate patients who report left upper abdominal or shoulder pain for an enlarged spleen or splenic rupture. (5.1)
- Acute respiratory distress syndrome (ARDS): Evaluate patients who develop fever, lung infiltrates, or respiratory distress. Discontinue UDENYCA in patients with ARDS. (5.2)
- Serious allergic reactions, including anaphylaxis: Permanently discontinue UDENYCA in patients with serious allergic reactions. (5.3)
- Fatal sickle cell crises: Have occurred. (5.4)
- Glomerulonephritis: Evaluate and consider dose-reduction or interruption of UDENYCA if causality is likely. (5.5)

## ADVERSE REACTIONS

Most common adverse reactions ( $\geq 5\%$  difference in incidence compared to placebo) are bone pain and pain in extremity. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Coherus Biosciences 1-800-4UDENYCA (1-800-483-3692) or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

\* Biosimilar means that the biological product is approved based on data demonstrating that it is highly similar to an FDA-approved biological product, known as a reference product, and that there are no clinically meaningful differences between the biosimilar product and the reference product. Biosimilarity of UDENYCA has been demonstrated for the condition(s) of use (e.g. indication(s), dosing regimen(s), strength(s), dosage form(s), and route(s) of administration) described in its Full Prescribing Information.

Revised: 11/2018

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**Appendix 5: Key Inclusion Criteria**

<b>Population</b>	United States population
<b>Intervention</b>	CSF listed in <b>Appendix 1</b>
<b>Comparator</b>	Active comparisons of drugs listed in <b>Appendix 1</b>
<b>Outcomes</b>	Symptom Improvement Morbidity Mortality Serious Adverse Events Discontinuation from Serious Adverse Events
<b>Timing</b>	Any study duration; literature search from 1/1/2015 to
<b>Setting</b>	Outpatient