Tbo-filgrastim (Teva Pharmaceuticals)

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Tbo-filgrastim (Teva Pharmaceuticals)

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Tbo-filgrastim (Teva Pharmaceuticals)

Executive Summary

Introduction: Tbo-filgrastim subcutaneous injection (XM02) is a biopharmaceutical product approved by FDA through an original Biologic License Application (BLA). Tbo-filgrastim is labeled to shorten the duration of chemotherapy-induced, severe neutropenia in adults with nonmyeloid cancers. Other agents labeled for use in this setting include filgrastim (Neupogen®) and pegfilgrastim (Neulasta®). The National Comprehensive Cancer Network (NCCN) recommends prophylactic therapy with the granulocyte colony-stimulating factors (G-CSF) filgrastim or pegfilgrastim in patients with ≥20% risk of developing febrile neutropenia. Tbo-filgrastim was not available when the NCCN guidelines were published; the current guidelines do not address its place in therapy or the role of biosimilar G-CSF agents.

Tbo-filgrastim was approved through the traditional BLA pathway in the US and is not considered a biosimilar product. The term biosimilar is used to describe a biopharmaceutical similar in composition to a reference biologic product. This is different from small-molecule drugs where the generic is identical to the reference product. A biosimilar meets very high standards for similarity compared with the reference biologic product, but is never completely identical because of the complex structure of biologics and intricate synthesis process.

Pharmacology / Pharmacokinetics: Similar to endogenous G-CSF, tbo-filgrastim is a G-CSF receptor agonist that stimulates neutrophil proliferation, increases neutrophil activity, and increases neutrophil counts. The maximum serum concentration of tbo-filgrastim is achieved a median of 4-6 hours following a subcutaneous dose, and it has a median elimination half-life of 3.2-3.8 hours. The pharmacokinetic parameters of tbo-filgrastim and European-manufactured filgrastim were similar in 2 pharmacokinetic studies conducted in healthy volunteers.

Clinical Efficacy: Tbo-filgrastim has not been directly compared with US-manufactured filgrastim (Neupogen®). Three multicenter, randomized, controlled, clinical trials compared tbo-filgrastim with European filgrastim (manufactured by Amgen) for reducing the duration of severe neutropenia in patients receiving myelotoxic chemotherapy for breast cancer, lung cancer, or non-Hodgkin lymphoma. The breast cancer trial also included a placebo group. The mean duration of severe neutropenia following the first chemotherapy cycle was 0.5-1.1 days in patients who received tbo-filgrastim, 0.3-1.1 days in patients who received European filgrastim (p=not significant [NS] vs. tbo-filgrastim), and 3.8 days in patients who received placebo (p<0.001 vs. tbo-filgrastim). In a meta-analysis of all 3 studies, febrile neutropenia occurred in a similar proportion patients taking tbo-filgrastim (13.2%) and European filgrastim (12.2%, adjusted Odds Ratio 1.08, 95% CI 0.66-1.77, p=NS).

Adverse Drug Reactions / Drug Interactions: In clinical trials evaluating tbo-filgrastim, bone pain was the most common drug-related adverse reaction and occurred in 3.4% of patients taking tbo-filgrastim, 7.5% of patients taking filgrastim, and 1.4% of patients taking placebo following the first chemotherapy cycle (no statistical comparison). Other possible adverse drug reactions reported with G-CSF agents include anaphylaxis or serious allergic reactions, leukocytosis,
ruptured spleen, sickle cell crisis, and acute respiratory distress syndrome. No pharmacokinetic drug interactions are expected with tbo-filgrastim.

**Dosage and Administration:** Administer tbo-filgrastim 5 mcg/kg once daily by subcutaneous injection. Initiate therapy at least 24 hours after completing chemotherapy and continue until the neutrophil count is within the normal range and the expected neutrophil nadir has passed. Monitor complete blood counts before initiating chemotherapy and 2 times per week during treatment with tbo-filgrastim.

**Summary:** Tbo-filgrastim is a G-CSF agent labeled to shorten the duration of severe neutropenia following treatment with myelotoxic chemotherapy in adults with nonmyeloid cancers. Similar to filgrastim (Neupogen®), tbo-filgrastim is a nonglycosalated methionyl form of human G-CSF manufactured using recombinant DNA technology.
Introduction

Tbo-filgrastim subcutaneous injection (XM02) is a biologic product approved by FDA in August 2012 through an original Biologic License Application (BLA).\(^1,2\) Tbo-filgrastim is a recombinant, granulocyte colony-stimulating factor (G-CSF) labeled to shorten the duration of chemotherapy-induced, severe neutropenia in patients with nonmyeloid cancers.\(^2,3\) Other G-CSF agents labeled for use in this setting include filgrastim (Neupogen\(^\circledR\)) and pegfilgrastim (Neulasta\(^\circledR\)).\(^4,5\) Filgrastim (Neupogen\(^\circledR\)) and tbo-filgrastim are also known as r-metHuG-CSF (recombinant methionyl human granulocyte colony-stimulating growth factor).\(^3,5\) In Europe, tbo-filgrastim is marketed under the brand name Tevagratist\(^\circledR\) and is approved as a biosimilar to the European version of Neupogen\(^\circledR\).\(^1,2\) Since tbo-filgrastim was approved through the traditional BLA pathway in the US, it is not considered a biosimilar product. Neupogen\(^\circledR\) and tbo-filgrastim are not automatically interchangeable.\(^1,2\) Table 1 provides a comparison of the FDA-approved G-CSF agents. As of July 2013, tbo-filgrastim does not have a brand name.\(^6,7\) It is expected to be available on the US market in the 4\(^{th}\) Quarter of 2013 or the 1\(^{st}\) Quarter of 2014.\(^6,7\)
### Table 1. Comparison of FDA-Approved G-CSF Agents

<table>
<thead>
<tr>
<th>Labeled Indications</th>
<th>Tbo-filgrastim</th>
<th>Filgrastim (Neupogen®)</th>
<th>Pegfilgrastim (Neulasta®)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Shorten duration of chemotherapy-induced severe neutropenia in nonmyeloid cancers</td>
<td>• Reduce infection associated with chemotherapy-induced febrile neutropenia in nonmyeloid cancers</td>
<td>• Reduce infection associated with chemotherapy-induced febrile neutropenia in nonmyeloid cancers</td>
<td></td>
</tr>
<tr>
<td>• Reduce infection associated with chemotherapy-induced febrile neutropenia in nonmyeloid cancers</td>
<td>• Shorten duration of fever and time until neutrophil recovery following consolidation or induction chemotherapy in AML</td>
<td>• Increase number of hematopoietic progenitor cells collected by leukapheresis</td>
<td></td>
</tr>
<tr>
<td>• Shorten duration of neutropenia and febrile neutropenia following myeloablative chemotherapy and BMT in nonmyeloid cancers</td>
<td>• Shorten duration of neutrophil recovery following consolidation or induction chemotherapy in AML</td>
<td>• Reduce the consequences of neutropenia in patients with severe, chronic neutropenia</td>
<td></td>
</tr>
<tr>
<td>• Increase number of hematopoietic progenitor cells collected by leukapheresis</td>
<td>• Increase number of hematopoietic progenitor cells collected by leukapheresis</td>
<td>• Increase number of hematopoietic progenitor cells collected by leukapheresis</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Routes</th>
<th>Subcutaneous</th>
<th>Subcutaneous</th>
<th>Subcutaneous</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Once daily beginning ≥ 24 hours after chemotherapy and continuing until neutrophil count is within the normal range</td>
<td>• Once daily beginning ≥ 24 hours after chemotherapy is complete and continuing for 14 days or until ANC = 10,000 cells/mL</td>
<td>• Once per chemotherapy cycle ≥ 24 hours after chemotherapy is complete</td>
<td></td>
</tr>
<tr>
<td>• Do not administer ≤ 14 days before the subsequent chemotherapy cycle</td>
<td></td>
<td>• Do not administer ≤ 14 days before the subsequent chemotherapy cycle</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>How Supplied</th>
<th>Single-use, prefilled syringe</th>
<th>Single-use, prefilled syringe</th>
<th>Single-use, prefilled syringe</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Single-use vials</td>
<td>• Single-use vials</td>
<td>• Single-use, prefilled syringe</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Structure and Synthesis</th>
<th>Nonglycosylated human G-CSF with 1 more methionine residue than endogenous G-CSF</th>
<th>Nonglycosylated human G-CSF with 1 more methionine residue than endogenous G-CSF</th>
<th>Conjugate of monomethoxypolyethylene glycol and filgrastim</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Manufactured with recombinant DNA technology using E. Coli strain K802</td>
<td>• Manufactured with recombinant DNA technology using E. Coli</td>
<td>• The N-terminal methionyl residue of filgrastim is covalently bound to monomethoxypolyethylene glycol</td>
<td>• Filgrastim is manufactured with recombinant DNA technology using E. Coli</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Inactive Ingredients</th>
<th>Glacial acetic acid</th>
<th>Acetate</th>
<th>Acetate</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Polysorbate 80</td>
<td>Polyisorbate 80</td>
<td>Polyisorbate 20</td>
<td></td>
</tr>
<tr>
<td>• Sodium Hydroxide</td>
<td>Sodium</td>
<td>Sodium</td>
<td></td>
</tr>
<tr>
<td>• Sorbitol</td>
<td>Sorbitol</td>
<td>Sorbitol</td>
<td></td>
</tr>
<tr>
<td>• Water for injection</td>
<td>Water for injection</td>
<td>Water for injection</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** AML = acute myelogenous leukemia; ANC = absolute neutrophil count; BMT = bone marrow transplant; G-CSF = granulocyte colony-stimulating factor; IV = intravenously; SubQ = subcutaneously
Biologics and Biosimilars

Biologics, also called biologicals, are structurally the most complex drug therapies to produce. By the US Pharmacopeia (USP) definition, a biologic is produced in a living system and is any allergenic product, antitoxin, blood, blood component or derivative, therapeutic serum, toxin, virus, or analogous product used for the prevention, treatment, or cure of disease in humans. The USP defines an analogous product as any biotechnology-derived product. A biologic drug is 100 to 1,000 times larger than small molecule chemically synthesized drugs and has a fragile, 3-dimensional structure. The manufacturing process is dynamic and any alteration to the host cell line, production, purification, handling, or storage procedures can impact the physical characterization of a biologic and have safety and efficacy consequences.

Table 2 compares manufacturing processes of chemically synthesized small molecule drugs with biologics.

Table 2. Manufacturing Considerations of Chemically Synthesized Small Molecule Drugs and Biologics

<table>
<thead>
<tr>
<th>Item</th>
<th>Small Molecule Drug</th>
<th>Biologic</th>
</tr>
</thead>
</table>
| Synthesis  | • Chemically manufactured  
             • Easy to replicate in different laboratories  
             • Reference product manufacturing information readily available | • Produced in a living system (eg, prokaryotes, eukaryotes)  
             • Living system requires nutrient supplementation during production  
             • Difficult to replicate  
             • Potential variation between lots of reference product  
             • Reference product manufacturing information not readily available |
| Purification| • Active ingredient stable throughout production  
             • No release of toxins throughout production | • Potential for active ingredient to become denatured during process  
             • Living system can release toxins throughout production |
| Handling   | • Does not require additional handling precautions | • Generally injectable products  
             • Mishandling of product can denature chemical structure |
| Storage    | • Generally can be stored at room temperature | • Generally requires controlled temperature ranges (eg, refrigeration, freezer) |

The number of approved biologic products has expanded considerably over the last decade. Approximately 30% of the pharmaceutical industry is composed of biologic drug therapies and 33% of these are monoclonal antibodies. By 2016, it is estimated 10 of the top-selling 20 drugs will be biologics. However, patents for many of these top grossing biologics will be expiring by 2020, prompting the development of biologic products similar to these reference products. Table 3 lists estimated patent expiry dates by 2020 for some of the top-selling biologics.

The term biosimilar is used to describe a biopharmaceutical similar in composition to a reference biologic product. This is different from small-molecule drugs where the generic is identical to the reference product. A biosimilar meets very high standards for similarity compared with the reference biologic product, but is never completely identical because of the complex structure of biologics and intricate synthesis process. The terms, generic biologic and
biogeneric are misleading to describe biosimilars because it implies the same concepts for interchangeability of small molecule drugs can be applied.8, 17 Biosimilars are unique molecular entities, not generic versions of the reference biologic product.10, 13

Table 3. Biologic Patent Expiry Dates by 2020 of Top-Selling Biologics19, 20

<table>
<thead>
<tr>
<th>Biologic</th>
<th>Estimated Patent Expiration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epogen® (epoetin alfa)</td>
<td>August 2013</td>
</tr>
<tr>
<td>Neupogen® (filgrastim)</td>
<td>December 2013</td>
</tr>
<tr>
<td>Synagis® (pavilizumab)</td>
<td>October 2015</td>
</tr>
<tr>
<td>Neulasta® (pegfilgrastim)</td>
<td>October 2015</td>
</tr>
<tr>
<td>Rituxan® (rituximab)</td>
<td>September 2016</td>
</tr>
<tr>
<td>Humira® (adalimumab)</td>
<td>December 2016</td>
</tr>
<tr>
<td>Avastin® (bevacizumab)</td>
<td>April 2017</td>
</tr>
<tr>
<td>Erbitux® (cetuximab)</td>
<td>February 2018</td>
</tr>
<tr>
<td>Remicade® (infliximab)</td>
<td>September 2018</td>
</tr>
<tr>
<td>Herceptin® (trastuzumab)</td>
<td>June 2019</td>
</tr>
</tbody>
</table>

Biosimilar Development – Regulatory Pathway

In 2004, The European Medicines Agency (EMA) was the first to adopt the term biosimilar and publish general guidelines recognizing different regulatory processes were needed for biotechnology-derived products.10, 15 In 2006, the first EMA approved biosimilars entered the international market.14, 15 There are currently 13 approved biosimilars on the European market, including epoetin alfa, filgrastim, and somatropin products.21, 22 The EMA has detailed product class requirements for approval of these medications as biosimilars. Biosimilarity to the reference product is evaluated on a case-by-case basis. Biosimilar manufacturers are also required to identify a single reference product and conduct tests to demonstrate structural similarity.10, 13

In the United States, biologics are approved under the Public Health Services (PHS) Act through submission of a new Biologics License Application (BLA). This is different from new small molecule drugs, which are approved under the Food Drug and Cosmetic Act (FDCA) through submission of a New Drug Application (NDA). The Hatch-Waxman Act under the FDCA created an abbreviated licensure pathway for approval of generic, small molecule drugs through submission of an Abbreviated New Drug Application (ANDA).8, 11 In 2010, the Biologics Price Competition and Innovation (BCPI) Act amended the PHS Act, creating an abbreviated licensure for the approval of biosimilar drugs.23 There was no legislation prior to this act for development of biosimilars. FDA proposed steps toward biosimilarity, which details a complex, lengthy, and expensive approval process.14 Table 4 outlines FDA’s proposed steps for biosimilar approval using a totality of evidence approach and specifies new studies different from the reference biologic product must be completed. Additionally, 3 draft guidance documents were issued addressing the complexity of biologic products, consequences of changing the manufacturing process, and issues regarding the quality of the products and its safety and efficacy.24-28 There are currently no biosimilars available in the United States.
Table 4. FDA’s Proposed Steps for Biosimilar Approval Using a Totality of Evidence Approach^14, 23-28

<table>
<thead>
<tr>
<th>Steps</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 1: Structural and Functional Characterization</td>
<td>• Focus on analytical studies relevant to assessing analytical, physiochemical, and biologic characterization</td>
</tr>
<tr>
<td></td>
<td>• Goal is to facilitate “fingerprint-like” analysis</td>
</tr>
<tr>
<td></td>
<td>• Additional FDA guidance will be provided to manufacturer after functional analyses are performed</td>
</tr>
<tr>
<td></td>
<td>• FDA has limited experience comparing similar biotechnology products produced through different manufacturing process</td>
</tr>
<tr>
<td></td>
<td>• Laboratory assays may not be sensitive enough to determine the exact composition of a reference biologic</td>
</tr>
<tr>
<td>Step 2: Human pharmacokinetics (PK) and pharmacodynamics (PD)</td>
<td>• A new, single phase I study is required</td>
</tr>
<tr>
<td></td>
<td>• Any alteration in the chemical structure from the reference biologic can alter pharmacokinetic and pharmacodynamic properties</td>
</tr>
<tr>
<td>Step 3: Clinical studies</td>
<td>• At least 1 new, Phase III clinical study must be conducted</td>
</tr>
<tr>
<td></td>
<td>• Need to compare biosimilar to a biologic available on the United States Market</td>
</tr>
<tr>
<td></td>
<td>• Labor intensity and expense of clinical trials is a potential deterrent for using this pathway</td>
</tr>
<tr>
<td>Step 4: Clinical immunogenicity studies</td>
<td>• A new, single immunogenicity study is required</td>
</tr>
<tr>
<td></td>
<td>• New immunogenicity studies will be required</td>
</tr>
<tr>
<td></td>
<td>• It is not known which biologics will have immediate or delayed antibody responses</td>
</tr>
<tr>
<td>Step 5: Animal studies</td>
<td>• Additional animal studies may be requested</td>
</tr>
<tr>
<td></td>
<td>• Extrapolation of results from animal studies can be difficult</td>
</tr>
<tr>
<td>Step 6: Post-marketing studies</td>
<td>• Post-marketing studies will be required</td>
</tr>
<tr>
<td></td>
<td>• Long term safety data for reference biologics has yet to be determined</td>
</tr>
</tbody>
</table>

Despite this proposed pathway, there are still many unanswered questions regarding the use of biosimilars in the United States including: biosimilar naming, therapeutic substitution, cost-savings, and reimbursement. Traditional concepts to naming cannot be applied. The World Health Organization’s (WHO) International Nonproprietary Naming (INN) system aims at identifying every drug product. Small molecule drugs are named with the same name as the reference product since they are identical copies. The INN system was originally developed to be applied to well defined, chemical substances. The addition of prefixes or suffixes may help identify differences in structural features between biologic and biosimilar products. Additionally, unlike the majority of small molecule generics, therapeutic equivalence and automatic substitution cannot be applied. The principle behind substitution of small molecule drugs is that the original drug and generic are identical and have the same therapeutic effect. This is not the case with biologics and biosimilars. There is no Orange Book to determine therapeutic equivalence and appropriate substitution. This also creates potential problems for government agencies and insurance companies paying for treatment. It is not known how reimbursement could be impacted by the availability of biosimilar products.

Disease Overview

Antineoplastic agents can cause neutropenia or febrile neutropenia necessitating treatment delays, dose reductions, hospitalization, and antibiotic therapy. Granulocyte colony-stimulating factors are used to reduce the risk of neutropenia and its clinical consequences. The National Comprehensive Cancer Network (NCCN, 2013) guidelines provide recommendations for the prophylactic use of G-CSF agents based on the risk of neutropenia associated with the chemotherapy regimen and patient-specific risk factors. The NCCN guidelines recommend prophylactic therapy with filgrastim or pegfilgrastim in patients with ≥20% risk of developing
febrile neutropenia. Tbo-filgrastim was not available when the NCCN guidelines were published and its place in therapy is not addressed. The current guidelines do not address the use of biosimilar G-CSF agents for the management of chemotherapy-induced neutropenia.\(^{30}\)

**Pharmacology**

Endothelial cells, monocytes, and fibroblasts produce endogenous G-CSF.\(^{31}\) Granulocyte colony-stimulating factor binds to G-CSF receptors on hematopoietic cells and regulates neutrophil production within the bone marrow.\(^{31}\) Tbo-filgrastim is a synthetic form of endogenous human G-CSF and is manufactured from the *E. coli* bacteria strain K802 using recombinant DNA technology.\(^3\) Human G-CSF is glycosylated, and tbo-filgrastim is nonglycosylated with an additional methionine amino acid residue. Similar to endogenous G-CSF, tbo-filgrastim is a G-CSF receptor agonist that stimulates neutrophil proliferation, increases neutrophil activity, and increases neutrophil counts.\(^3\)

**Pharmacokinetics**

Tbo-filgrastim is 33% bioavailable following a 5 mcg/kg subcutaneous injection in healthy subjects.\(^3\) Exposure to tbo-filgrastim is increased and more variable in cancer patients compared with healthy subjects. The maximum serum concentration of tbo-filgrastim is achieved a median of 4-6 hours following a subcutaneous dose. Tbo-filgrastim has a median elimination half-life of 3.2-3.8 hours. Tbo-filgrastim does not accumulate after multiple doses.\(^3\)

Two studies compared the pharmacokinetics of tbo-filgrastim with a European formulation of filgrastim in healthy volunteers.\(^{32,33}\) The pharmacokinetic parameters of tbo-filgrastim and European filgrastim were similar and the 90% confidence intervals fell within the accepted bioequivalence limits of 80-125%.\(^{32,33}\) The results of the pharmacokinetic studies are displayed in Table 5.

**Table 5. Pharmacokinetic Parameters of Tbo-Filgrastim and European Filgrastim in Healthy Volunteers Following a Single 5 mcg/kg Subcutaneous Injection\(^{32,33}\)**

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameter</th>
<th>Tbo-filgrastim (XM02)</th>
<th>Filgrastim</th>
<th>Ratio for XM02:Filgrastim</th>
<th>90% CI for Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lubenau and Sveikata 2009(^{33})</strong> (filgrastim manufactured by Roche, Switzerland)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(C_{\text{max}})</td>
<td>24.1±5.8 ng/mL</td>
<td>21.7±3.1 ng/mL</td>
<td>110.8%</td>
<td>102.2%-120.1%</td>
</tr>
<tr>
<td>(T_{\text{max}})</td>
<td>4±1.1 hours</td>
<td>4±0.6 hours</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>AUC</td>
<td>175.2 ng*hr/mL</td>
<td>159.6 ng*hr/mL</td>
<td>109.9%</td>
<td>101.9%-118.6%</td>
</tr>
<tr>
<td><strong>Elimination (t_{1/2})</strong></td>
<td>2.1±0.46 hours</td>
<td>2.2±0.7 hours</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td><strong>Lubenau and Bias 2009(^{32})</strong> (filgrastim manufactured by Amgen, Germany)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(C_{\text{max}})</td>
<td>17,976 pg/mL</td>
<td>18,416 pg/mL</td>
<td>97.55%</td>
<td>87.22%-109.10%</td>
</tr>
<tr>
<td>AUC</td>
<td>158,975 pg*hr/mL</td>
<td>160,783 pg*hr/mL</td>
<td>98.66%</td>
<td>92.15%-105.64%</td>
</tr>
<tr>
<td><strong>Terminal (t_{1/2})</strong></td>
<td>7.81±1.59 hours</td>
<td>8.94±1.25 hours</td>
<td>87.84%</td>
<td>77.15%-100.01%</td>
</tr>
</tbody>
</table>

Abbreviations: AUC = area under the curve extrapolated to infinity; \(C_{\text{max}}\) = peak serum concentration; \(t_{1/2}\) = half-life; \(T_{\text{max}}\) = time to achieve peak concentration;
Special Populations

The pharmacokinetics of tbo-filgrastim are similar in men and women.\textsuperscript{3} It is not known if the pharmacokinetics of tbo-filgrastim are affected by age, hepatic dysfunction, or moderate-to-severe renal dysfunction. Pharmacokinetic parameters of tbo-filgrastim were not altered in patients with mild renal dysfunction (creatinine clearance 60-89 mL/min).\textsuperscript{3}

Clinical Efficacy

Tbo-filgrastim has not been directly compared with any US-manufactured filgrastim product.\textsuperscript{34} Three multicenter, randomized, controlled, clinical trials evaluated the efficacy of tbo-filgrastim for reducing the duration of severe neutropenia in patients receiving myelotoxic chemotherapy.\textsuperscript{35-38} Two trials\textsuperscript{36, 37} compared tbo-filgrastim with a European filgrastim (manufactured by Amgen) in the first chemotherapy cycle. All patients received tbo-filgrastim in subsequent cycles. A third trial\textsuperscript{35} compared tbo-filgrastim with a European filgrastim (manufactured by Amgen) and with placebo in the first chemotherapy cycle. Patients in the placebo group were switched to tbo-filgrastim in subsequent cycles.\textsuperscript{35} In all 3 trials, study medication was administered as a subcutaneous injection once daily by unblinded study personnel starting the day after chemotherapy was completed.\textsuperscript{35-38} Blinding was not possible because tbo-filgrastim and European filgrastim were provided in different volumes. The patients and the study investigators who assessed the patients were blinded. Study medication was continued for a minimum of 5 days following each chemotherapy cycle, and was discontinued on day 14 or when the absolute neutrophil count (ANC) had recovered (ANC $\geq$ 10 x 10\textsuperscript{9} cells/L and ANC nadir had passed), whichever occurred first. The dose of study medication was weight-based and was calculated using the patients’ actual body weight. The same outcomes were evaluated in all 3 trials and are defined in Table 6.\textsuperscript{35-38} The mean duration of severe neutropenia following the first chemotherapy cycle was 0.5-1.1 days in patients who received tbo-filgrastim (3 studies\textsuperscript{35-37}), 0.3-1.1 days in patients who received European filgrastim (3 studies\textsuperscript{35-37}, and 3.8 days in patients who received placebo (1 study\textsuperscript{35}). The details of the trials are summarized in Table 7. A meta-analysis of the 3 clinical trials is also published and evaluated the incidence of febrile neutropenia following the first chemotherapy cycle in the 608 patients who received either tbo-filgrastim or European filgrastim.\textsuperscript{38} Across all 3 studies, febrile neutropenia occurred in a similar proportion of patients taking tbo-filgrastim (13.2\%) and European filgrastim (12.2\%, adjusted Odds Ratio 1.08, 95\% CI 0.66-1.77, p = not significant [NS]).\textsuperscript{38}

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of severe neutropenia</td>
<td>Number of days with ANC $&lt; 0.5 \times 10^9$ cells/L</td>
</tr>
<tr>
<td>Observed febrile neutropenia</td>
<td>Both of the following occurring on the same day:</td>
</tr>
<tr>
<td></td>
<td>• ANC $&lt; 0.5 \times 10^9$ cells/L</td>
</tr>
<tr>
<td></td>
<td>• Body temperature $&gt;38.5^\circ$ C for $\geq 1$ hour</td>
</tr>
<tr>
<td>Protocol-defined febrile neutropenia</td>
<td>Use of systemic antibiotics</td>
</tr>
<tr>
<td>Incidence of febrile neutropenia</td>
<td>Proportion of patients with observed febrile neutropenia or protocol-defined febrile neutropenia</td>
</tr>
</tbody>
</table>

Abbreviations: ANC = absolute neutrophil count
Del Gilglio and colleagues compared tbo-filgrastim, European filgrastim, and placebo in breast cancer patients treated with docetaxel (75 mg/m²) and doxorubicin (60 mg/m²). This trial was the only efficacy study submitted to FDA for approval of tbo-filgrastim and is also summarized in the FDA statistical review. Patients were randomized to tbo-filgrastim 5 mcg/kg/day (n=140), European filgrastim 5 mcg/kg/day (n=136) or placebo (n=72) administered in the first cycle of chemotherapy. Baseline demographics and disease characteristics were similar in all 3 groups. An analysis of covariance (ANCOVA) was used to compare the duration of severe neutropenia in patients receiving tbo-filgrastim and placebo following chemotherapy cycle 1. If the duration of severe neutropenia was statistically significantly shorter (2-sided p-value < 0.05) in patients receiving tbo-filgrastim, European filgrastim and tbo-filgrastim were compared. If the 2-sided 95% CI for the difference in the duration of severe neutropenia was within 1 day for tbo-filgrastim vs. European filgrastim, the 2 treatments were considered equivalent. The full analysis set (n=348) of all randomized patients was used to compare tbo-filgrastim vs. placebo. The per-protocol set (n=320) was used to compare tbo-filgrastim vs. European filgrastim. The study had 90% power to detect a difference between tbo-filgrastim and placebo and to demonstrate equivalence of tbo-filgrastim and European filgrastim. The mean duration of severe neutropenia in the full analysis set was 3.9 days in the placebo group and 1.1 days in the tbo-filgrastim group (least-squares mean difference 2.7 days, 95% CI 2.2–3.2 days, p<0.001). The mean duration of severe neutropenia in the per-protocol set was 1.1087 days in the European filgrastim group and 1.119 days in the tbo-filgrastim group (least-squares mean difference -0.03 days, 95% CI -0.33 to +0.26 days, p=0.83). The results were similar in the FDA Statistical Review when more conservative methods were used to account for dropouts and protocol violations. Other outcomes assessed following chemotherapy cycle 1 are summarized in Table 7. Patients initially randomized to placebo were switched to tbo-filgrastim for chemotherapy cycles 2-4. The mean duration of severe neutropenia, mean ANC nadir, median time to ANC recovery, and the incidence of febrile neutropenia were similar in all 3 treatment groups in cycles 2-4.

Gatzemeier and colleagues compared tbo-filgrastim 5 mcg/kg/day (n=160) and European filgrastim 5 mcg/kg/day (n=80) in lung cancer patients following the first cycle of platinum-based chemotherapy. Baseline demographics and disease characteristics were similar in both treatment groups. Most patients had non-small cell lung cancer (83.5%) and 14% had received chemotherapy prior to study entry. Chemotherapy regimens included cisplatin + etoposide (48.8%), cisplatin + gemcitabine (15.3%), carboplatin + vinorelbine (8.3%), carboplatin + etoposide (7.4%), carboplatin + gemcitabine (6.2%), carboplatin + paclitaxel (6.2%), and cisplatin + vinorelbine (5.4%). The primary objective of the study was to assess the safety of tbo-filgrastim. Alpha adjustments were not performed for efficacy analyses, and efficacy endpoints were considered exploratory. In the full analysis set of all randomized patients (n=240) following chemotherapy cycle 1, the mean duration of severe neutropenia was 0.5 days in the tbo-filgrastim group and 0.3 days in the European filgrastim group (estimated treatment difference 0.157 days, 95% CI -0.114 to +0.428 days). Patients initially randomized to European filgrastim were switched to tbo-filgrastim for chemotherapy cycles 2-6. Other outcomes assessed following chemotherapy cycle 1 and cycle 4 are summarized in Table 7. Across all chemotherapy cycles, the incidence of febrile neutropenia was 33.1% in the tbo-filgrastim group.
and 23.8% in the European filgrastim/tbo-filgrastim group. Adverse events were similar in patients randomized to tbo-filgrastim and European filgrastim during chemotherapy cycle 1.37

Engert and colleagues36 compared tbo-filgrastim 5 mcg/kg/day (n=63) and European filgrastim 5 mg/kg/day (n=29) in adults with aggressive non-Hodgkin lymphoma (ie, anaplastic large cell lymphoma, diffuse large B-cell lymphoma, Grade 3 follicular lymphoma, mediastinal large B-cell lymphoma) following the first cycle of chemotherapy. Baseline demographics and disease characteristics were similar in both groups. Most patients (74%) had diffuse large B-cell lymphoma. All patients received cyclophosphamide + hydroxydaunomycin (doxorubicin) + Oncovin® (vincristine) + prednisolone (ie, CHOP) for treatment of non-Hodgkin lymphoma. Rituximab use was allowed and was added to the CHOP regimen (ie, R-CHOP) in 15% of patients. The primary objective of the study was to assess the safety of tbo-filgrastim. Alpha adjustments were not performed for efficacy analyses, and efficacy endpoints were considered exploratory. All patients completed chemotherapy cycle 1, 91% completed chemotherapy cycle 4, and 83% completed all 6 cycles. In the full analysis set of all randomized patients, the mean duration of severe neutropenia was 0.5 days in the tbo-filgrastim group and 0.9 days in the European filgrastim group (estimated treatment difference -0.379 days, 95% CI -0.837 to +0.081, p=0.1055) following chemotherapy cycle 1. Patients initially randomized to European filgrastim were switched to tbo-filgrastim for chemotherapy cycles 2-6. Other outcomes assessed following chemotherapy cycle 1 and cycle 4 are summarized in Table 7. Across all chemotherapy cycles, the incidence of febrile neutropenia was similar in patients randomized to tbo-filgrastim (31.7%) and tbo-filgrastim/European filgrastim (41.4%, p=0.2094). Adverse events were similar in patients randomized to tbo-filgrastim and European filgrastim during chemotherapy cycle 1.36
Table 7. Clinical Trials of Tbo-Filgrastim for Reducing the Duration of Severe Neutropenia in Patients Receiving Myelotoxic Chemotherapy34-37

<table>
<thead>
<tr>
<th>Reference/Study Design</th>
<th>N</th>
<th>Patient Selection</th>
<th>Treatment Interventions</th>
<th>Significant Outcomes</th>
<th>Response Rate</th>
<th>Discontinuation Rate and Adverse Events</th>
<th>Grade*</th>
</tr>
</thead>
<tbody>
<tr>
<td>del Giglio et al, 2008</td>
<td>348</td>
<td>Adults with high risk Stage II, Stage III, or Stage IV breast cancer treated with doxorubicin and docetaxel</td>
<td>Cycle 1:</td>
<td>Tbo-filgrastim &gt; placebo</td>
<td>Primary Outcome</td>
<td>Discontinuations</td>
<td>Total</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(n=140)</td>
<td>Cycle 2-4:</td>
<td>Tbo-filgrastim = filgrastim</td>
<td>Efficacy following chemotherapy cycle 1, differences between groups assessed by ANCOVA</td>
<td>Mean duration of severe neutropenia (full analysis set)</td>
<td>Total</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Placebo (n=72)</td>
<td></td>
<td></td>
<td>Tbo-filgrastim: 1.1 days</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cycle 1: Tbo-filgrastim 5 mcg/kg/day (n=136)</td>
<td>Cycle 2-4:</td>
<td></td>
<td>Filgrastim: 1.1 days</td>
<td>Tbo-filgrastim: 3.6%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo (n=72)</td>
<td>Placebo patients</td>
<td></td>
<td>Placebo: 3.8 days</td>
<td>Filgrastim: 4.6%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>switched to tbo-filgrastim</td>
<td>switched to tbo-filgrastim</td>
<td></td>
<td>Placebo: 5.6%</td>
<td>Due to Adverse Event: (different #’s in FDA and pub)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dose calculated using actual body weight</td>
<td></td>
<td></td>
<td></td>
<td>Tbo-filgrastim: 1.4%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Unblinded study personnel administered study medication as a subcutaneous injection</td>
<td></td>
<td></td>
<td>Filgrastim: 2.2%</td>
<td>Tbo-filgrastim: 1.4%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Study medication initiated 24 hours after completion of chemotherapy and continued for 5-14 days after each cycle</td>
<td></td>
<td></td>
<td>Placebo: 5.6%</td>
<td>Drug-Related Adverse Events Across All Cycles</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Median total study drug exposure: 38 days (range 16-56)</td>
<td></td>
<td></td>
<td></td>
<td>Tbo-filgrastim: 25.7%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Filgrastim: 39.7%, p=0.015</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ANC = absolute neutrophil count; ANCOVA = analysis of covariance; BMI = body mass index; ECOG = Eastern Cooperative Oncology Group; IPI = International Prognostic Index; LS = least-squares; N or n = number of patients enrolled in trial or specific treatment group; NS = not statistically significant and p > 0.1.

* Grade of Scientific Evidence. Refer to Appendix A for definitions.
**Table 7. Clinical Trials of Tbo-Filgrastim for Reducing the Duration of Severe Neutropenia in Patients Receiving Myelotoxic Chemotherapy, continued**

<table>
<thead>
<tr>
<th>Reference/Study Design</th>
<th>N</th>
<th>Patient Selection/Characteristics</th>
<th>Treatment Interventions</th>
<th>Significant Outcomes</th>
<th>Response Rate</th>
<th>Discontinuation Rate and Adverse Events</th>
<th>Grade*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gatzemeier et al, 2009</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Experimental parallel: Randomized, controlled, single-blind, multicenter | 240 | Adults with nonsmall cell or small cell lung cancer receiving platinum-based chemotherapy | Cycle 1:  
  - Tbo-filgrastim 5 mcg/kg/day (n=160)  
  - Filgrastim 5 mcg/kg/day (n=80)  
  Cycles 2-6: All patients received tbo-filgrastim | Tbo-filgrastim = filgrastim | Efficacy following chemotherapy cycle 1, full analysis set, no adjustment for alpha error | Discontinuations  
  - During Cycle 1: 8.7%  
  - Overall: 47.9%  
  - Due to disease progression: 17.1%  
  - Due to adverse events: 8.3%  
  - Due to death: 5% | 1 |
| Inclusion criteria:  
  - ECOG ≤2  
  - ANC≥ 1.5 x 10^9 cells/L  
  - Platelet count ≥100 x 10^9 cells/L  
  - Prior treatment with ≤1 chemotherapy regimen | Baseline Characteristics  
  - Female: 20.4%  
  - Mean age: 58.6 years  
  - Race: 93.8% Caucasian  
  - Mean BMI: 24 kg/m² (range 16-40) | Dose calculated using actual body weight Unblinded study personnel administered study medication as a subcutaneous injection Study medication initiated 24 hours after completion of chemotherapy and continued for 5-14 days | Mean duration of severe neutropenia (ANCOVA)  
  - Tbo-filgrastim: 0.5 days  
  - Filgrastim: 0.3 days  
  - Estimated treatment difference: 0.157 days, 95% CI -0.114 to +0.428, no p-value provided | Mean ANC nadir (ANCOVA)  
  - Tbo-filgrastim: 2.1 x 10^9 cells/L  
  - Filgrastim: 2.9 x 10^9 cells/L, no p-value provided | Mean time to ANC recovery (ANCOVA)  
  - Tbo-filgrastim: 6.3 days  
  - Filgrastim: 4.5 days, no p-value provided | Mean incidence of febrile neutropenia (Cochran-Mantel-Haenszel)  
  - Tbo-filgrastim: 15%  
  - Filgrastim: 8.8%, p=0.2347 |

Abbreviations: ANC = absolute neutrophil count; ANCOVA = analysis of covariance; BMI = body mass index; ECOG = Eastern Cooperative Oncology Group; IPI = International Prognostic Index; LS = least-squares; N or n = number of patients enrolled in trial or specific treatment group; NS = not statistically significant and p > 0.1.  

*a Grade of Scientific Evidence. Refer to Appendix A for definitions.*
### Table 7. Clinical Trials of Tbo-Filgrastim for Reducing the Duration of Severe Neutropenia in Patients Receiving Myelotoxic Chemotherapy, continued

| Reference/Study Design | N  | Patient Selection                                                                 | Treatment Interventions                                                                 | Significant Outcomes                                                                                     | Response Rate                                                                                           | Discontinuation Rate and Adverse Events                                                                 |
|------------------------|----|------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------|
| Engert et al, 2009<sup>b</sup> | 92 | Adults with aggressive Non-Hodgkin lymphoma undergoing CHOP chemotherapy ± rituximab | Cycle 1  
- Tbo-filgrastim 5 mcg/kg/day (n=63)  
- Filgrastim 5 mcg/kg/day (n=29)  
Cycles 2-6: All patients received tbo-filgrastim  
Dose calculated using actual body weight  
Unblinded study personnel administered study medication as a subcutaneous injection  
Study medication initiated 24 hours after completion of chemotherapy and continued for 5-14 days  
Median total study drug exposure: 59.5 days (range 16-83) | Tbo-filgrastim = filgrastim  
Efficacy following chemotherapy cycle 1, full analysis set, no adjustment for alpha error  
Mean duration of severe neutropenia (ANCOVA)  
- Tbo-filgrastim: 0.5 days  
- Filgrastim: 0.9 days  
- Estimated treatment difference: -0.378 days, 95% CI -0.837 to +0.081, p=NS  
Mean ANC nadir (ANCOVA)  
- Tbo-filgrastim: 1.7 x 10^9 cells/L  
- Filgrastim: 1.1 x 10^9 cells/L, p=NS  
Mean time to ANC recovery (ANCOVA)  
- Tbo-filgrastim: 6 days  
- Filgrastim: 6.7 days, p=NS  
Incidence of febrile neutropenia (Cochran-Mantel-Haenszel)  
- Tbo-filgrastim: 11.1%  
- Filgrastim: 20.7%, p=NS  
Efficacy following chemotherapy cycle 4, full analysis set, p-values not provided  
Mean duration of severe neutropenia (ANCOVA)  
- Tbo-filgrastim: 0.2 days  
- Filgrastim/tbo-filgrastim: 0.7 days  
Mean ANC nadir (ANCOVA)  
- Tbo-filgrastim: 2.1 x 10^9 cells/L  
- Filgrastim/tbo-filgrastim: 1.8 x 10^9 cells/L  
Mean time to ANC recovery (ANCOVA)  
- Tbo-filgrastim: 4.9 days  
- Filgrastim/tbo-filgrastim: 6.1 days | Discontinuations  
Total:  
- Tbo-filgrastim: 8/63 (13%)  
- Filgrastim: 8/29 (28%)  
Due to adverse event: 5/92 (5.4%)  
Drug-Related Adverse Events in Cycle 1  
Anemia  
- Tbo-filgrastim: 0  
- Filgrastim: 1/29 (3.4%)  
Arthralgia  
- Tbo-filgrastim: 2/63 (3.2%)  
- Filgrastim: 1/29 (3.2%)  
Back Pain  
- Tbo-filgrastim: 0  
- Filgrastim: 1/29 (3.4%)  
Bone Pain  
- Tbo-filgrastim: 4/63 (6.3%)  
- Filgrastim: 0%  
Diarrhea  
- Tbo-filgrastim: 2/63 (3.2%)  
- Filgrastim: 0  
Fatigue  
- Tbo-filgrastim: 0  
- Filgrastim: 1/29 (3.4%)  
Flu-like symptoms  
- Tbo-filgrastim: 0  
- Filgrastim: 1/29 (3.4%)  
Musculoskeletal pain  
- Tbo-filgrastim: 0  
- Filgrastim: 1/29 (3.4%)  
Pyrexia  
- Tbo-filgrastim: 2/63 (3.2%)  
- Filgrastim: 0  | Grade<sup>a</sup> 1 |

**Abbreviations:** ANC = absolute neutrophil count; ANCOVA = analysis of covariance; BMI = body mass index; ECOG = Eastern Cooperative Oncology Group; IPI = International Prognostic Index; LS = least-squares; N or n = number of patients enrolled in trial or specific treatment group; NS = not statistically significant and p > 0.1.

<sup>a</sup> Grade of Scientific Evidence. Refer to Appendix A for definitions.
Engert and colleagues\textsuperscript{38} conducted a meta-analysis of the 3 published clinical trials\textsuperscript{35-37} discussed above. The primary outcome of the meta-analysis was the incidence of febrile neutropenia following chemotherapy cycle 1 in patients randomized to tbo-filgrastim or European filgrastim. Patients randomized to placebo in the breast cancer study\textsuperscript{35} (n=72) were not included in the meta-analysis. The incidence of febrile neutropenia by study, across all studies, and by myelotoxicity of the chemotherapy regimen was assessed. The incidence of febrile neutropenia was similar across all studies and all categories of myelotoxicity. Across all studies, the incidence of febrile neutropenia was similar in patients taking tbo-filgrastim (13.2\%) and filgrastim (12.2\%). The estimated risk difference in the proportion of patients who developed febrile neutropenia was 1.7\% (odds ratio 1.08, 95\% CI 0.66 – 1.77) when adjusted by study. The myelotoxicity category of each chemotherapy regimen was determined based on the pooled mean number of days of severe neutropenia that occurred with each chemotherapy regimen. Table 8 summarizes the myelotoxicity categories and the incidence of febrile neutropenia within each category. The overall estimated risk difference between tbo-filgrastim and filgrastim in the incidence of febrile neutropenia was 0.6\% (odds ratio 1.08. 95\% CI 0.66-1.78) when adjusted by myelotoxicity of the chemotherapy regimen.\textsuperscript{38}

### Table 8. Myelotoxicity Categories Used to Evaluate the Incidence of Febrile Neutropenia Following Chemotherapy Cycle 1 in Patients Treated with tbo-Filgrastim and European Filgrastim\textsuperscript{38}

<table>
<thead>
<tr>
<th>Category</th>
<th>Pooled Mean DSN</th>
<th>Chemotherapy Regimens</th>
<th>Incidence of Febrile Neutropenia</th>
</tr>
</thead>
</table>
| Category 1 | 1.1 days | • Doxorubicin + Docetaxel | • Tbo-filgrastim (n=140): 12.1\% (95\% CI 7.7-18.6)  
• Filgrastim (n=136): 12.5\% (95\% CI 8-19.1)  
• Treatment difference: -0.4\% (95\% CI -8.3 to +7.5) |
| Category 2 | 0.6 days | • Cisplatin + vinorelbine  
• Carboplatin + vinorelbine  
• Cisplatin + etoposide  
• Carboplatin + etoposide  
• CHOP  
• R-CHOP | • Tbo-filgrastim (n=178): 13.5\% (95\% CI 9.2-19.3)  
• Filgrastim (n=84): 11.9\% (95\% CI 6.6-20.5)  
• Treatment Difference: 1.6 (-8.1 to +9.4) |
| Category 3 | 0.1 days | • Cisplatin + gemcitabine  
• Carboplatin + gemcitabine  
• Carboplatin + paclitaxel | • Tbo-filgrastim (n=45): 15.6\% (95\% CI 7.7-28.8)  
• Filgrastim (n=25): 12\% (95\% CI 4.2-30)  
• Treatment Difference: 3.6\% (95\% CI -16 to +18.9) |

Abbreviations: CHOP = cyclophosphamide + hydroxydaunomycin (doxorubicin) + Oncovin® (vincristine) + prednisolone; DSN = duration of severe neutropenia; R-CHOP = rituximab + CHOP

### Off-Label Use – Peripheral Blood Stem Cell Mobilization

Two published case series have evaluated tbo-filgrastim for mobilization of peripheral blood stem cells prior to bone marrow transplant.\textsuperscript{39, 40} Andreola and colleagues\textsuperscript{39} administered tbo-filgrastim 10 mg/kg/day for 4 days to patients with multiple myeloma (n=8), non-Hodgkin lymphoma (n=4), and Hodgkin disease (n=2) prior to peripheral blood stem cell collection for autologous transplantation. Plerixafor was administered on day 4 in 13 of the 14 patients whose CD34+ counts were <20 cells/mcL. Adequate quantities of CD34+ cells (≥ 2 x 10\(^6\) cells/kg) were collected using leukopheresis in all patients on day 5.\textsuperscript{39} Schmitt and colleagues\textsuperscript{40} compared tbo-
filgrastim and an unspecified reference filgrastim product for peripheral blood stem cell mobilization and allogenic stem cell transplantation in 22 healthy donors. Study medication was administered at a dose of 10 mcg/kg twice daily for 9 doses. Leukophoresis was performed 2 hours after the last dose of study medication. A second round of leukaphoresis was performed if <5 x 10^6 CD34+ cells per kg (based on body weight of the recipient) were collected. Donors requiring a second leukaphoresis procedure received 2 additional doses of study medication. Tbo-filgrastim and the reference filgrastim product were similarly effective for producing adequate quantities of CD34+ cells after mobilization.40

Special Populations
  Tbo-filgrastim was similarly effective in younger (<65 years) vs. older (> 65 years) adult cancer patients.3, 34 Approximately 16% of patients enrolled in the clinical trials evaluating tbo-filgrastim were ≥65 years of age. No studies have evaluated the efficacy of tbo-filgrastim in children.3, 34

Adverse Drug Reactions

In clinical trials evaluating tbo-filgrastim, bone pain was the most common drug-related adverse reaction and occurred in 3.4% of patients taking tbo-filgrastim, 7.5% of patients taking filgrastim, and 1.4% of patients taking placebo following the first chemotherapy cycle.3 Less than 1% of patients taking tbo-filgrastim experienced leukocytosis and none of the patients experienced any clinic complications. Anaphylaxis and serious allergic reactions can occur during therapy with G-CSF medications, including with the initial dose. Treat allergic reactions with antihistamines, bronchodilators, epinephrine, or steroids if needed, and permanently discontinue tbo-filgrastim. Do not use tbo-filgrastim in patients who previously experienced a severe allergic reaction with filgrastim or pegfilgrastim. Patients receiving tbo-filgrastim may develop antibodies against the drug. The exact incidence of antibody development in patients taking tbo-filgrastim is not known.3

Acute respiratory distress syndrome (ARDS), ruptured spleen, and sickle cell crises have rarely occurred in patients taking G-CSF agents.3 Discontinue tbo-filgrastim in patients with ARDS, symptoms of splenic rupture (eg, upper abdominal pain, shoulder pain) or sickle cell crisis. Tbo-filgrastim may bind to tumor cell G-CSF receptors and act as a growth factor for the tumor.3

Contraindications and Black Box Warnings

There are no contraindications or black box warnings included in the product labeling for tbo-filgrastim.3 Do not use tbo-filgrastim in patients with a history of hypersensitivity to filgrastim, pegfilgrastim, tbo-filgrastim or any of its ingredients.
Drug Interactions

No studies have evaluated potential drug interactions with tbo-filgrastim. No pharmacokinetic drug interactions are expected. Lithium and tbo-filgrastim both increase neutrophil release. Use caution in patients taking tbo-filgrastim and lithium concomitantly. Patients taking lithium were excluded from the clinical trials evaluating tbo-filgrastim.

Dosage and Administration

Administer tbo-filgrastim 5 mcg/kg once daily by subcutaneous injection. Recommended injection sites include the middle thighs, back of upper arms, upper buttocks, and abdomen. Rotate injection sites and do not inject into red, tender, bruised, or scarred skin. The product label states that tbo-filgrastim is approved only for administration by a health care professional. Initiate therapy with tbo-filgrastim at least 24 hours after completing chemotherapy and continue until the neutrophil count is within the normal range and the expected neutrophil nadir has passed. Patients with creatinine clearance 60-89 mL/min (mild renal insufficiency) do not require a dose reduction. Tbo-filgrastim has not been evaluated in patients with hepatic impairment or moderate-to-severe renal impairment and no dosing recommendations are available for these patient populations.

Tbo-filgrastim is available in preservative-free, single-use, 300 mcg/0.5 mL or 480 mcg/0.8 mL prefilled syringes. The glass syringes are available with or without a safety needle guard. Inactive ingredients include water for injection, sorbitol, glacial acetic acid, polysorbate 80, and sodium hydroxide to adjust to a pH of 4.2. Tbo-filgrastim solution is clear and colorless. Do not use if the solution contains particulates or is discolored. Refrigerate tbo-filgrastim prefilled syringes at 36° to 46° F (2° to 8° C) and protect from light. The stability of tbo-filgrastim is not affected by a single 24-hour exposure to temperatures of -13° to +5° F (-25° to -15° C), a single 72-hour exposure to temperatures of 23° to 30°F (-5° to -1° C), or a single 5-day exposure to room temperature (73° to 81°F or 23° to 27°C). If tbo-filgrastim is not used within 5 days of room temperature exposure, return to the refrigerator and use before the expiration date. Tbo-filgrastim syringes are for single-use only. Discard any unused solution immediately. Table 9 summarizes the dosing and administration issues of the G-CSF agents. Appendix B summarizes implications for pharmacy operations.
Table 9. Dosing and Administration Issues of G-CSF Agents According to Product Labels3-5

<table>
<thead>
<tr>
<th></th>
<th>Tbo-filgrastim</th>
<th>Filgrastim (Neupogen®)</th>
<th>Pegfilgrastim (Neulasta®)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recommended</strong></td>
<td><strong>Dosing</strong></td>
<td><strong>Dosing</strong></td>
<td><strong>Dosing</strong></td>
</tr>
<tr>
<td></td>
<td>• Inject 5 mcg/kg SubQ once daily</td>
<td>• Inject 5 mcg/kg SubQ or IV once daily</td>
<td>• Inject 6 mg one time per chemotherapy cycle</td>
</tr>
<tr>
<td></td>
<td>• Initiate treatment ≥ 24 hours after chemotherapy is complete</td>
<td>• Initiate treatment ≥ 24 hours after chemotherapy is complete</td>
<td>• Initiate treatment ≥ 24 hours after chemotherapy is complete</td>
</tr>
<tr>
<td></td>
<td>• Continue until ANC is within the normal range and the expected neutrophil nadir has passed</td>
<td>• May administer by bolus SubQ injection, continuous SubQ injection, short IV infusion, or continuous IV infusion</td>
<td>• Do not administer within 14 days of subsequent chemotherapy cycle</td>
</tr>
<tr>
<td></td>
<td>• Labeled for administration by a healthcare professional</td>
<td>• Continue for 14 days or until ANC = 10,000 cells/mL</td>
<td>• Labeled for patient self-administration</td>
</tr>
<tr>
<td></td>
<td>• Increase the dose in 5 mcg/kg increments with subsequent chemotherapy cycles if clinically indicated based on extent of ANC nadir</td>
<td>• Increase the dose in 5 mcg/kg increments with subsequent chemotherapy cycles if clinically indicated based on extent of ANC nadir</td>
<td></td>
</tr>
<tr>
<td><strong>Recommended</strong></td>
<td><strong>Storage</strong></td>
<td><strong>Storage</strong></td>
<td><strong>Storage</strong></td>
</tr>
<tr>
<td></td>
<td>• Refrigerate at 36° to 46° F (2° to 8° C)</td>
<td>• Refrigerate at 36° to 46° F (2° to 8° C)</td>
<td>• Refrigerate at 36° to 46° F (2° to 8° C)</td>
</tr>
<tr>
<td></td>
<td>• May be stored at room temperature for ≤ 5 days</td>
<td>• May be stored at room temperature for ≤ 24 hours</td>
<td>• May be stored at room temperature for ≤ 48 hours</td>
</tr>
<tr>
<td></td>
<td>• Stability is not affected by a single 24-hour exposure to -13° to 5° F or a single 72-hour exposure to 23° to 30°F</td>
<td>• Discard any unused portion</td>
<td>• If frozen, allow to thaw in refrigerator</td>
</tr>
<tr>
<td></td>
<td>• Discard any unused portion</td>
<td>• Do not enter a vial more than once</td>
<td>• Do not use if frozen more than once</td>
</tr>
<tr>
<td></td>
<td>• Protect from light</td>
<td>• Protect from light</td>
<td>• Discard any unused portion</td>
</tr>
<tr>
<td></td>
<td>• Do not shake</td>
<td>• Do not shake</td>
<td>• Protect from light</td>
</tr>
<tr>
<td><strong>Presentations</strong></td>
<td><strong>Available</strong></td>
<td><strong>Available</strong></td>
<td><strong>Available</strong></td>
</tr>
<tr>
<td></td>
<td>• Prefilled syringes: 300 mcg/0.5 mL, 480 mcg/0.8 mL</td>
<td>• Single-use vials: 300 mcg/mL, 480 mcg/1.6 mL</td>
<td>• Prefilled syringes: 6 mg/0.6 mL</td>
</tr>
<tr>
<td></td>
<td>• Available with or without needle guard</td>
<td>• Prefilled syringes: 300 mcg/0.5 mL, 480 mcg/0.8 mL</td>
<td>• Available only with needle guard</td>
</tr>
<tr>
<td><strong>Inactive</strong></td>
<td><strong>Ingredients</strong></td>
<td><strong>Ingredients</strong></td>
<td><strong>Ingredients</strong></td>
</tr>
<tr>
<td></td>
<td>• Glacial acetic acid</td>
<td>• Acetate</td>
<td>• Acetate</td>
</tr>
<tr>
<td></td>
<td>• Polysorbate 80</td>
<td>• Polysorbate 80</td>
<td>• Polysorbate 20</td>
</tr>
<tr>
<td></td>
<td>• Sodium Hydroxide</td>
<td>• Sodium</td>
<td>• Sodium</td>
</tr>
<tr>
<td></td>
<td>• Sorbitol</td>
<td>• Sorbitol</td>
<td>• Sorbitol</td>
</tr>
<tr>
<td></td>
<td>• Water for injection</td>
<td>• Water for injection</td>
<td>• Water for injection</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Needle cover of prefilled syringes contains latex</td>
<td>• Needle cover contains latex</td>
</tr>
</tbody>
</table>

Abbreviations: ANC = absolute neutrophil count; IV = intravenously; SubQ = subcutaneously
Monitoring

Monitor complete blood counts before initiating chemotherapy and 2 times per week during treatment with tbo-filgrastim. Discontinue tbo-filgrastim when the neutrophil count is within the normal range. Monitor patients for signs and symptoms of splenic rupture (eg, left shoulder pain, left, upper abdominal pain), ARDS (eg, fever with lung infiltrates, shortness of breath), and serious allergic reactions (eg, rash, shortness of breath, swelling). Discontinue tbo-filgrastim if any of these conditions occur. Tbo-filgrastim increases bone marrow hematopoiesis and may cause temporary changes on bone imaging tests.

Critical Issues

- Tbo-filgrastim and filgrastim (Neupogen®) are both recombinant methionyl human granulocyte colony-stimulating growth factor (r-metHuG-CSF). However, tbo-filgrastim was FDA-approved via an original BLA and is not a biosimilar product. Tbo-filgrastim and US-manufactured Neupogen® have not been compared in clinical trials and are not automatically interchangeable.
- Tbo-filgrastim was similar to European filgrastim manufactured by Amgen for shortening the duration of severe neutropenia associated with myelotoxic chemotherapy in patients with breast cancer, lung cancer, and non-Hodgkin lymphoma.
- In clinical trials, adverse drug reactions were similar in patients receiving tbo-filgrastim and European filgrastim.

Summary

Tbo-filgrastim is a recombinant G-CSF agent labeled to shorten the duration of severe neutropenia following treatment with myelotoxic chemotherapy in adults with nonmyeloid cancers. Similar to filgrastim (Neupogen®), tbo-filgrastim is a nonglycosalated methionyl form of human G-CSF manufactured using recombinant DNA technology. No clinical trials have compared tbo-filgrastim with US-manufactured filgrastim. The mean duration of severe neutropenia following the first chemotherapy cycle was 0.5-1.1 days with tbo-filgrastim, 0.3-1.1 days with European filgrastim (p=NS vs. tbo-filgrastim), and 3.8 days with placebo (p<0.001 vs. tbo-filgrastim). In patients with breast cancer, lung cancer, or non-Hodgkin lymphoma, the incidence of febrile neutropenia was similar in patients taking tbo-filgrastim (13.2%) and European filgrastim (12.2%, adjusted Odds Ratio 1.08, 95% CI 0.66-1.77, p=NS). In clinical trials, bone pain was the most common drug-related adverse reaction and occurred in 3.4% of patients taking tbo-filgrastim. Tbo-filgrastim is available in prefilled syringes for subcutaneous injection. The recommended dosing is similar for tbo-filgrastim and filgrastim (Neupogen®), but the 2 products are not considered biosimilar and are not automatically interchangeable.
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**Document Information**

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Edited by: Erin R. Fox, PharmD, Director, Drug Information Service

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**Appendix A: Grades of Scientific Evidence**

Grade 1. Evidence from randomized, blinded, placebo-controlled, clinical trials in peer reviewed journals

Grade 2. Non-randomized controlled trials

Grade 3. Non-randomized historical cohort studies. Other studies with non-experimental designs (eg, population based studies, case-control studies)

Grade 4. Case reports, case series, abstracts of trials

Grade 5. Consensus of experts where data are incomplete or inconsistent
### Appendix B: Summary of Safety Issues and Implications for Pharmacy Operations

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug generic name (brand name)</td>
<td>Tbo-filgrastim</td>
</tr>
<tr>
<td>Drug manufacturer</td>
<td>Teva Pharmaceuticals</td>
</tr>
<tr>
<td>Does the product package insert currently have any black box warnings?</td>
<td>No</td>
</tr>
<tr>
<td>Contraindications against medication use</td>
<td>Hypersensitivity to pegfilgrastim, filgrastim, or tbo-filgrastim or any of its ingredients</td>
</tr>
<tr>
<td>Is there a Risk Evaluation and Management Strategy (REMS) program for the medication? If so, how may healthcare providers find information about the program?</td>
<td>No</td>
</tr>
<tr>
<td>Does the manufacturer require patients to meet specific criteria for treatment with this medication (eg, patient or prescriber must enroll with manufacturer to access drug; pharmacogenomic test required prior to starting therapy; negative pregnancy test required before starting therapy)? If so, where may healthcare providers find these criteria?</td>
<td>No</td>
</tr>
<tr>
<td>Are healthcare providers required to give patients a Medication Guide when dispensing this medication?</td>
<td>No</td>
</tr>
<tr>
<td>Does the manufacturer have a restricted or special distribution program? If so, how may healthcare providers contact the program?</td>
<td>No</td>
</tr>
<tr>
<td>Is the medication (brand name, generic name, product packaging) similar to any other medication on the Institute for Safe Medication Practices (ISMP) Sound-Alike-Look-Alike (SALA) list? If not, is the medication expected to be added to the list?</td>
<td>Tbo-filgrastim could be confused with filgrastim or pegfilgrastim.</td>
</tr>
<tr>
<td>Recommended storage conditions for medication, and how to manage excursions outside these conditions.</td>
<td>Refrigerate at 36° to 46° F (2° to 8° C). The stability of tbo-filgrastim is not affected by a single 24-hour exposure to 5° to -13° F, a single 72-hour exposure to 23° to 30°F, or a single 5-day exposure to room temperature (73° to 81° F).</td>
</tr>
<tr>
<td>Are Safe Handling precautions required?</td>
<td>No</td>
</tr>
<tr>
<td>Does the medication require disposal in a Resource Conservation and Recovery Act (RCRA) black box?</td>
<td>No</td>
</tr>
<tr>
<td>Can medication doses be sent to patient care units via a pneumatic tube system?</td>
<td>No</td>
</tr>
<tr>
<td>Is filtration required during preparation or administration of the IV medication?</td>
<td>No</td>
</tr>
<tr>
<td>Is the IV medication a vesicant or irritant?</td>
<td>No</td>
</tr>
<tr>
<td>Is special monitoring recommended when starting therapy with this medication (eg, telemetry)?</td>
<td>No</td>
</tr>
<tr>
<td>Does this medication contain egg or soy products (eg, lecithin, soybean oil), as active or inactive ingredients?</td>
<td>No</td>
</tr>
<tr>
<td>Could this medication interact with point-of-care glucose test strips (ie, does medication contain or is it metabolized to non-glucose sugars such as galactose, maltose, or D-xylose)?</td>
<td>No</td>
</tr>
<tr>
<td>Date on current package insert.</td>
<td>August 2012</td>
</tr>
<tr>
<td>Date Appendix prepared.</td>
<td>July 11, 2013</td>
</tr>
</tbody>
</table>