Zarxio (Filgrastim-sndz): First Biosimilar Approved in the United States

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Colony-stimulating factors (CSFs) are endogenous glycoproteins that regulate the production and the functioning of infection-protective granulocytes and macrophages.[1] Overall, 2 types of recombinant CSF drugs—granulocyte CSF (filgrastim, pegfilgrastim) and granulocyte-macrophage CSF (sargramostim)—have been prescribed for more than 20 years to stimulate neutrophils and macrophages, primarily in patients with cancer who are undergoing treatment with cytotoxic chemotherapy.[1] CSFs also have clinical value in the transplantation of hematopoietic cells to replace aplastic bone marrow.[1]

Biosimilars

Biologic drugs, including granulocyte CSFs and granulocyte-macrophage CSFs, are large-molecule compounds that are produced in living organisms.[2] Additional examples of frequently used biologics include vaccines, monoclonal antibodies, human insulins, interferons, interleukins, blood coagulation modulators, enzymes, gonadotropins, human growth hormones, tissue plasminogen activators, and erythropoietins.[2]

Biologics represent a significant and growing proportion of drug expenditures.[3] It is estimated that 6 of the top 10 drugs in 2018, in the United States and globally, will be biologics, and will account for 49% of the top-selling 100 drugs.[3]

Signed into law in March 2010, the Biologics Price Competition and Innovation Act (BPCIA) of 2009 was passed in conjunction with the Affordable Care Act of 2010.[4] The goal of the BPCIA was to give drug manufacturers a pathway to an abbreviated approval process for biologics that are shown to be biosimilar to or interchangeable with a reference drug, which is a biologic drug that is licensed by the US Food and Drug Administration (FDA).[4] Modeled after the legislation that allows the development and the approval of generic alternatives to small-molecule drugs, BPCIA was designed to encourage competition and innovation.[4]

Specifically, BPCIA created a pathway for developers of biosimilars to rely on existing scientific data about the safety and effectiveness of the reference drug.[4] Approval of a biosimilar does not require a full complement of drug-specific preclinical and clinical data. For the FDA to approve a biosimilar, the following criteria must be met[4]:

- The biosimilar must have the same mechanisms of action, routes of administration, dosage forms, and dosage strengths as the reference drug
- Only the indications and conditions of use that have been approved for the reference drug can be approved for the biosimilar
- Facilities in which biosimilars are manufactured must meet FDA standards.

To meet a higher standard known as "interchangeability," a drug developer must also demonstrate that the biosimilar drug can be expected to produce the same clinical result as the reference drug in any given patient.[4] For a biologic drug that is administered more than once, the risk for alternating between the use of the biosimilar drug and the reference drug must be no greater than the risk for the patient continuing to use the reference drug.[4] An interchangeable biosimilar can be substituted for the reference drug by pharmacists without the intervention of prescribing healthcare providers.[4]

The main objective of introducing biosimilars to the US market is the expected lower costs of biosimilars compared with their reference drugs. Although the cost is not expected to be as low as for small-molecule generics, it is expected to be less than the original biologic, which will result in increased patient access.[4,5]

For now, biosimilars are expected to be priced at a 15% cost reduction compared with the cost of the originator drug.[6] Industry experts and Congress expect that biosimilars will eventually cost consumers only approximately 40% of the cost of the originator drug, but that remains to be seen.[7]

FDA Approved Zarxio for Multiple Indications

On March 6, 2015, the FDA approved filgrastim-sndz (Zarxio; Sandoz/Novartis), the first biosimilar ever to receive approval in the United States.[5] Filgrastim-sndz is biosimilar to filgrastim (Neupogen; Amgen), a granulocyte CSF agent, which was originally approved by the FDA in 1991.[5] The formulation of filgrastim-sndz differs from that of filgrastim by 1 inactive component.[8]

Filgrastim-sndz is approved for the same 5 indications as its reference drug filgrastim[9,10]:

1. To reduce the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid

malignancies receiving myelosuppressive anticancer drugs associated with a significant incidence of severe neutropenia with fever
2. To reduce the time to neutrophil recovery and the duration of fever after induction or consolidation chemotherapy treatment of patients with acute myeloid leukemia (AML)
3. To reduce the duration of neutropenia and neutropenia-related clinical sequelae, such as febrile neutropenia, in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplantation
4. To mobilize autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis
5. To reduce the incidence and the duration of sequelae of neutropenia (eg, fever, infections, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia.

The FDA's approval of filgrastim-sndz was based on a review of evidence that included structural and functional characterization, animal study data, human pharmacokinetic and pharmacodynamics data, clinical immunogenicity data, and other clinical safety and effectiveness data that demonstrate that filgrastim-sndz is biosimilar to filgrastim.[5,8] Filgrastim-sndz has been approved as a biosimilar drug, but not as an "interchangeable" drug; therefore, it cannot be substituted for filgrastim without authorization from the prescriber.[5]

According to FDA Commissioner Margaret A. Hamburg, MD, "Biosimilars will provide access to important therapies for patients who need them. Patients and the health care community can be confident that biosimilar products approved by the FDA meet the agency's rigorous safety, efficacy and quality standards."[5]

At the time of launch of filgrastim-sndz in the United States in September 2015, filgrastim-sndz was priced at a 15% lower cost than its reference drug filgrastim.[6]

According to the manufacturer of the biosimilar, the US wholesale price of filgrastim-sndz for 300-mcg dosing is $275.66, and $438.98 for the 480-mcg formulation.[11] By comparison, the cost of filgrastim (Neupogen), the originator biologic, is $324.30 for the 300-mcg formulation and $516.45 for the 480-mcg dosing, according to the manufacturer.[11]

Mechanism of Action

Filgrastim-sndz is a granulocyte CSF, like its reference drug. CSFs affect hematopoietic cells, including neutrophil progenitors, by binding to specific cell-surface receptors and stimulating growth, differentiation commitment, and some end-cell functional activation.[9]

Monocytes, fibroblasts, and endothelial cells produce endogenous granulocyte CSF to regulate neutrophil production in the bone marrow and affect the activity of neutrophil progenitors.[9]

Granulocyte CSF only minimally affects the production of hematopoietic cell types other than neutrophils.[9]

Dosing and Administration

Filgrastim-sndz is available in single-use prefilled syringes with an UltraSafe Passive Needle Guard. Overall, filgrastim-sndz is available in 2 dosage strengths—300 mcg/0.5 mL and 480 mcg/0.8 mL. Direct administration of <0.3 mL of filgrastim-sndz is not recommended because of potential dosing errors.[9] The starting dose of filgrastim-sndz varies for specific patient populations, as described below.

Patients receiving myelosuppressive chemotherapy or induction and/or consolidation chemotherapy for AML. The recommended starting dose is 5 mcg/kg daily via subcutaneous injection, short intravenous (IV) infusion (15-30 minutes), or continuous IV infusion.[9]

Patients with cancer undergoing bone marrow transplantation. The recommended starting dose is 10 mcg/kg daily administered as an IV infusion for no longer than 24 hours.[9]

Patients undergoing autologous peripheral blood progenitor cell (PBPC) collection and therapy. The recommended starting dose is 10 mcg/kg daily via subcutaneous injection.[9] The drug should be administered for at least 4 days before the first leukapheresis procedure and continued until the last procedure.[9]

Patients with congenital neutropenia. The recommended starting dose is 6 mcg/kg twice daily via subcutaneous injection.[9]

Patients with cyclic or idiopathic neutropenia. The recommended starting dose is 5 mcg/kg daily via subcutaneous injection.[9]

Clinical Trials with Filgrastim

Overall, 11 clinical trials were performed in the 1980s and 1990s to demonstrate the efficacy and safety of filgrastim (the reference drug) for its 5 FDA-approved indications.[9,10] The results of these clinical trials are summarized in the prescribing information for filgrastim-sndz.[10] The BPCIA legislation states that biosimilar drugs are not required to replicate the same clinical trials of the reference drug.[4]

The PIONEER Trial with Filgrastim-sndz

Comprehensive studies were performed to fully characterize and evaluate filgrastim-sndz to meet the FDA's requirements for its approval as a biosimilar (**Table**).[6,9,10,12]

In addition, a randomized, double-blind, 4-group, multicenter, phase 3 noninferiority clinical trial known as PIONEER enrolled patients with breast cancer who

received myelosuppressive chemotherapy. The study was designed to compare the efficacy and safety of filgrastim-sndz with filgrastim in terms of reducing the duration of severe neutropenia.[13]

Patients enrolled in PIONEER received the biosimilar or the reference drug at a daily dose of 5 µg/kg body weight via subcutaneous injection starting on day 2 of each chemotherapy cycle until the absolute neutrophil count recovered to 10×10^9/L after nadir or for a maximum of 14 days. The study lasted 25 weeks—3 weeks of screening, 18 weeks of treatment (a total of 6 cycles, 3 weeks each), and 1 follow-up visit 4 weeks after the last dose of the study drug.[13]

The primary objective of PIONEER was to assess the efficacy of filgrastim-sndz in reducing the duration of severe neutropenia after the first chemotherapy cycle. The per-protocol patient group included 204 of the 218 randomized patients. The safety data set included 214 patients who received at least 1 dose of the study drug. On average, each patient received treatment with filgrastim-sndz or with filgrastim for 8 to 9 days per chemotherapy cycle.[13]

The mean duration of severe neutropenia in cycle 1 was 1.17 ± 1.11 days for filgrastim-sndz and 1.20 ± 1.02 days for filgrastim. The mean difference in the duration of severe neutropenia was 0.04 days (97.5% confidence interval, lower limit of –0.26 days). The predefined noninferiority criteria were met, and filgrastim-sndz was deemed noninferior to filgrastim.[13]

No differences in the rates of treatment-emergent adverse events were observed among the treatment arms in the PIONEER clinical trial. Overall, 12 patients experienced serious adverse events, including 1 death because of pulmonary embolism, but none of these events was deemed related to the study drug. None of the pa-

Table FDA's Biosimilar Requirements and Filgrastim-sndz

Statutory requirement		Fulfillment of requirement
Demonstrates high similarity	Analytical data	Studies demonstrate that filgrastim-sndz has the same amino acid sequence as filgrastim
		Functional properties (biological activity, receptor binding) and physicochemical properties (higher-order structure, product-related substances, impurities) of filgrastim-sndz are highly similar to that of filgrastim
		Filgrastim-sndz has a similar stability profile as filgrastim
	Animal studies	Five animal studies confirmed that the pharmacologic and toxicologic profiles of filgrastim-sndz and filgrastim are similar
	Clinical studies	Four pharmacokinetic and pharmacodynamics studies evaluated SC doses of 1-10 mcg/kg of filgrastim-sndz and filgrastim in healthy individuals; these studies included absolute neutrophil count and CD34+ cell counts as markers of neutropenia and mobilization of hematopoietic stem cells. All comparisons of filgrastim-sndz and filgrastim met prespecified criteria for analytical similarity
		Safety data were evaluated in 204 healthy individuals and in 214 patients with breast cancer; the safety profile of filgrastim-sndz was similar to that of filgrastim
		One study (PIONEER) compared the efficacy and safety of filgrastim-sndz with filgrastim in 218 patients with breast cancer who received myelosuppressive chemotherapy
Same as reference drug	Mechanism of action	The mechanism of action of filgrastim is mediated by selective binding to the G-CSF receptor and is similar across all labeled indications
	Route of administration, dosage form, and strength	Filgrastim-sndz has the same routes of administration, dosage forms, and strengths as filgrastim

G-CSF indicates granulocyte colony-stimulating factor; SC, subcutaneous.

Sources: Sandoz. www.zarxio.com/info/hcp/pioneer.jsp; US Food and Drug Administration. www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm436953.htm; Zarxio (filgrastim-sndz) injection prescribing information; August 2015; Stanton D; for BioPharma-Reporter. www.biopharma-reporter.com/Markets-Regulations/Biosimilars-land-in-the-US-as-Sandoz-launches-Zarxio.

tients enrolled in the PIONEER study developed anti-drug antibodies.[13]

Adverse Events

The most common adverse reactions observed in clinical studies that supported the approval of the reference drug, filgrastim, include[9]:

- ***Patients with nonmyeloid malignancies receiving myelosuppressive anticancer drugs.*** Pyrexia, pain, rash, cough, and dyspnea (≥5% difference in incidence compared with placebo)
- ***Patients with AML.*** Pain, epistaxis, and rash (≥2% difference in incidence)
- ***Patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplantation.*** Rash (≥5% difference in incidence)
- ***Patients undergoing PBPC mobilization and collection.*** Bone pain, pyrexia, and headache (≥5% difference in incidence)
- ***Patients with severe chronic neutropenia.*** Pain, anemia, epistaxis, diarrhea, hypoesthesia, and alopecia (≥5% difference in incidence).

Contraindications

Filgrastim-sndz is contraindicated in patients with a history of serious allergic reactions to human granulocyte CSFs, such as filgrastim or pegfilgrastim drugs.[9]

Warnings and Precautions

Splenic rupture. Splenic rupture, including fatal cases, can occur after the administration of filgrastim drugs. Patients who report left upper abdominal or shoulder pain should be evaluated for an enlarged spleen or splenic rupture.[9]

Acute respiratory distress syndrome (ARDS). ARDS has been reported in patients receiving filgrastim therapy. Filgrastim-sndz should be discontinued in patients with ARDS.[9]

Serious allergic reactions. Serious allergic reactions, including anaphylaxis, have been reported in patients receiving filgrastim therapy, with the majority occurring after the initial exposure. Allergic reactions, including anaphylaxis, can recur in patients receiving filgrastim therapy within days after the discontinuation of the initial antiallergic treatment. Filgrastim-sndz should be permanently discontinued in patients with serious allergic reactions.[9]

Sickle-cell disorders. Patients with sickle-cell trait or disease can experience sickle-cell crisis after receiving filgrastim.[9]

Alveolar hemorrhage and hemoptysis. Alveolar hemorrhage has been reported in healthy donors undergoing PBPC mobilization and collection who received filgrastim drugs. Filgrastim-sndz is not approved for use in these patients.[9]

Capillary leak syndrome (CLS). CLS has been reported after the use of a granulocyte CSF, including filgrastim drugs; these episodes can be life-threatening.[9] Patients with symptoms of CLS should be closely monitored and should receive standard symptomatic treatment, which may include a need for intensive care.[9]

Severe chronic neutropenia. Myelodysplastic syndrome and AML can occur in the natural history of congenital neutropenia without cytokine therapy.[9] Transformation to myelodysplastic syndrome or AML and cytogenetic abnormalities have been observed in patients with severe chronic neutropenia who received filgrastim. The risk for myelodysplastic syndrome and AML appears to be confined to patients with congenital neutropenia. If a patient with severe chronic neutropenia develops abnormal cytogenetics or myelodysplastic syndrome, the risks and benefits of filgrastim-sndz should be evaluated carefully.[9]

Thrombocytopenia. Thrombocytopenia has been reported in patients receiving filgrastim therapy.[9]

Leukocytosis: patients with cancer receiving myelosuppressive chemotherapy. White blood cell counts of ≥100,000/mm^3 have occurred in patients receiving filgrastim at dosages of >5 mcg/kg daily. Complete blood counts should be checked at least twice weekly during filgrastim-sndz therapy. Treatment should be discontinued if the absolute neutrophil count exceeds 10,000/mm^3 after the chemotherapy-induced absolute neutrophil count nadir has occurred.[9]

Leukocytosis. Filgrastim-sndz should be discontinued if the leukocyte count increases to >100,000/mm^3 during the administration of filgrastim-sndz for PBPC mobilization.[9]

Cutaneous vasculitis. Patients who receive filgrastim can experience cutaneous vasculitis. Filgrastim-sndz therapy should be held in patients who develop cutaneous vasculitis; it can be restarted at a reduced dose when the symptoms resolve.[9]

Potential effect on malignant cells. The potential for filgrastim-sndz to act as a growth factor in any patient with cancer cannot be excluded.[9]

Simultaneous use with chemotherapy and radiation therapy not recommended. The safety and efficacy of filgrastim-sndz with cytotoxic chemotherapy have not been established. Because of the potential sensitivity of rapidly dividing myeloid cells to cytotoxic chemotherapy, filgrastim-sndz should not be used 24 hours before through 24 hours after cytotoxic chemotherapy. Filgrastim-sndz should not be used together with chemotherapy or radiation therapy.[9]

Nuclear imaging. Transient positive bone-imaging changes can occur in response to growth factor therapy

and should be considered when interpreting bone-imaging results.[9]

Use in Specific Populations

Pregnancy. The use of filgrastim-sndz in pregnant women has not been adequately studied. Filgrastim-sndz should only be used during pregnancy if its potential benefits justify the potential risk to the fetus.[9]

Nursing mothers. It is not known whether filgrastim drugs are excreted in human milk.[9]

Filgrastim-sndz is the first biosimilar drug approved by the FDA for use in the United States. According to the manufacturer, filgrastim-sndz is priced 15% lower than the price of its originator drug.

Pediatric use. Because the filgrastim-sndz prefilled syringe may not accurately measure volumes <0.3 mL, the direct administration of volumes <0.3 mL is not recommended. The safety and effectiveness of filgrastim have been established in pediatric patients with severe chronic neutropenia. Limited data do not suggest alterations in sexual maturation or endocrine function. Cytogenetic abnormalities and transformation to myelodysplastic syndrome and AML have been reported in pediatric patients with congenital neutropenia who received filgrastim treatment. The relationship between these events and filgrastim administration is not known.[9]

Geriatric use. No overall differences in the safety or effectiveness of filgrastim were observed between older and younger patients who received myelosuppressive chemotherapy.[9]

Conclusion

Filgrastim-sndz is the first biosimilar drug approved by the FDA for use in the United States. A series of studies, including a large clinical trial, demonstrated that the efficacy and safety of filgrastim-sndz is comparable to the reference drug, filgrastim, in preventing neutropenia in patients with cancer. According to the manufacturer, filgrastim-sndz is priced 15% lower than the price of its originator drug. Healthcare stakeholders hope that biosimilars will eventually be priced up to 40% less than their reference drugs, which may occur when more biosimilars are approved for the same originator drug; this may help to bring costs down through market forces. ■

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