Zarxio (Filgrastim-sndz): The First Biosimilar Approved by the FDA
Mina Awad, PharmD Candidate; Pavit Singh, PharmD Candidate; and Olga Hilas, PharmD, MPH

INTRODUCTION
Leukocytes are the body's main defense against infection. The most abundant leukocytes are neutrophils, also called granulocytes, which are important in fighting various microorganisms. Therefore, a decline in neutrophils—a condition called neutropenia—may predispose an individual to a host of illnesses.1

Absolute neutrophil count (ANC) is generally used to grade the severity of neutropenia, although there is no standard classification system.2 Neutropenia is defined as an ANC of less than 1.5 x 10^9/L, and its presentation may be mild (1–1.5 x 10^9/L), moderate (0.5–0.99 x 10^9/L), or severe (less than 0.5 x 10^9/L).3 In addition, neutropenia can be acute (occurring over hours to a few days) or chronic (lasting months to years).3

The most common causes of neutropenia in adults are infections, followed by drug-induced neutropenia.2 Acquired bone marrow diseases (e.g., leukemia, lymphoma, aplastic anemia) are relatively common causes of neutropenia in adults, as are certain nutritional deficiencies.3

Approximately half of cancer patients receiving chemotherapy experience some type of neutropenia and are at increased risk for infection.3 Other risk factors for neutropenia include bone marrow transplantation (BMT) and autologous peripheral blood progenitor cell (PBPC) collection and therapy. The latter is usually performed in patients undergoing chemotherapy.2

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MECHANISM OF ACTION
Endogenous G-CSF is a lineage-specific colony-stimulating factor produced by monocytes, fibroblasts, and endothelial cells. It regulates the production of neutrophils within the bone marrow and affects neutrophil progenitor proliferation, differentiation, and selected end-cell functions (including enhanced phagocytic ability, priming of the cellular metabolism associated with respiratory burst, antibody-dependent killing, and the increased expression of some cell surface antigens). G-CSF is not species-specific and has been shown to have minimal direct in vivo or in vitro effects on the production or activity of hematopoietic cell types other than the neutrophil lineage.10

INDICATIONS
Zarxio is approved for several indications, the first of which is to decrease the incidence of infection in patients with nonmyeloid malignancies receiving myelosuppressive chemotherapy associated with a significant incidence of febrile neutropenia. It is approved to reduce the time to neutrophil recovery and the duration of fever following induction or consolidation chemotherapy treatment of patients with acute myeloid leukemia (AML); and to reduce the duration of neutropenia and neutropenia-related clinical sequelae (e.g., febrile neutropenia) in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by BMT. In addition, Zarxio is indicated to mobilize autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis; and for chronic administration to reduce the incidence and duration of sequelae of neutropenia (e.g., fever, infections, oropharyngeal ulcers) in symptomatic patients with congenital, cyclic, or idiopathic neutropenia.10

DOSAGE AND ADMINISTRATION
Zarxio may be administered as a subcutaneous injection, a short intravenous (IV) infusion over 15–30 minutes, or a continuous IV infusion, dependent on the indication.10
For patients with cancer receiving myelosuppressive chemotherapy and/or consolidation chemotherapy for AML, the recommended dose is 5 mcg/kg per day by any of the three approved routes of administration. A complete blood count (CBC) and platelet count should be performed before the patient begins treatment. During treatment, monitor the patient twice weekly for changes in ANC and platelet count. Zarxio is not recommended in patients with an ANC greater than 10,000/mm³.10

Zarxio should not be administered within the 24-hour period before chemotherapy and should be administered at least 24 hours after cytotoxic chemotherapy. ANC levels will increase transiently one to two days after the first treatment. To ensure a sustained response, administer Zarxio daily for up to two weeks or until the ANC has reached 10,000/mm³ following the expected chemotherapy-induced neutrophil nadir.10

For patients with cancer who have undergone BMT, the recommended dosage is 10 mcg/kg daily, which should be administered as an IV infusion for no longer than 24 hours. Administer the first dose of Zarxio at least 24 hours after cytotoxic chemotherapy and at least 24 hours after bone marrow infusion.10

For patients with cancer undergoing autologous PBPC collection and therapy, the recommended dosage is 10 mcg/kg per day given by subcutaneous injection. Administer Zarxio for at least four days before the first leukapheresis procedure and continue until the last leukapheresis procedure. Although the optimal duration of Zarxio administration and leukapheresis schedule have not been established, administration of filgrastim for six to seven days with leukapheresis on days 5, 6, and 7 was found to be safe and effective.10

For patients with suspected SCN, confirm the diagnosis by evaluating serial CBCs with differential and platelet counts, and by evaluating bone marrow morphology and karyotype. If Zarxio is used before confirming the correct diagnosis, diagnostic efforts may be impaired, thus impairing or delaying the evaluation and treatment of an underlying condition (other than SCN) causing the neutropenia.10

The starting dose for patients with congenital neutropenia is 6 mcg/kg as a twice-daily subcutaneous injection. The recommended starting dosage in patients with idiopathic or cyclic neutropenia is 5 mcg/kg as a single daily subcutaneous injection.10

PIVOTAL PHASE 3 STUDY

A rigorous program of clinical trials that demonstrates no clinically meaningful differences between the biosimilar product and the reference product must be completed for a biosimilar to receive FDA approval.11 The totality of evidence presented to the FDA for Zarxio compared with Neupogen showed no clinically meaningful differences between them.11

The phase 3 PIONEER trial, a randomized, double-blind, parallel-group, multicenter study, was conducted to demonstrate the noninferiority of Zarxio to Neupogen in the prevention of neutropenic complications in 218 breast cancer patients treated with myelosuppressive chemotherapy.12 The study also provided safety and efficacy outcomes for Zarxio compared with Neupogen. Key inclusion criteria encompassed patients with histologically proven breast cancer approved for neoadjuvant or adjuvant chemotherapy; women 18 years of age and older; estimated life expectancy of more than six months; an Eastern Cooperative Oncology Group performance score of 2 or less; adequate bone marrow function prior to chemotherapy administration; and an ANC of 1.5 x 10⁹/L or greater, a platelet count of 100 x 10⁹/L or greater, and a hemoglobin level of 10 g/dL or greater.12

Patients were initially randomized to either Zarxio or Neupogen. Half of the patients remained on the therapy started in the first treatment cycle for the duration of the trial, while the other half of the patients received alternating treatment with either Zarxio or Neupogen starting with the second cycle of chemotherapy. This design was used to assess whether switching the therapies during the treatment period had any impact on safety, efficacy, and immunogenicity.11

Patients in the study received 5 mcg/kg of Zarxio or Neupogen daily starting on day 2 of each chemotherapy cycle and continued until ANC levels recovered to 10 x 10⁹/L or for a maximum of 14 days of treatment, whichever occurred first. The primary endpoint was duration of chemotherapy-induced severe neutropenia, which was defined as the number of consecutive days with grade 4 neutropenia (ANC less than 0.5 x 10⁹/L). Secondary efficacy endpoints included incidence of febrile neutropenia by cycle and across all cycles; the number of days of fever for each cycle; depth of ANC nadir; time to ANC recovery; frequency of infections by cycle and across all cycles; and incidence and duration of hospitalization due to febrile neutropenia. Safety endpoints included incidence, occurrence, and severity of serious adverse events, local tolerability at the injection site, and systemic tolerability.12

The mean duration of grade 4 neutropenia in cycle 1 was approximately 1.2 days (range, zero to four days) in both groups. The mean difference in duration of neutropenia was 0.04 days. The incidence of febrile neutropenia was low in both groups, with no clinically relevant differences for cycle 1. The mean time to ANC recovery in cycle 1 was also similar for Zarxio compared with Neupogen. In all, there were no substantial differences between the treatment arms.12

The data assessed from cycle 2, which represented switching the therapies about halfway through the trial, also showed similar results for all treatment arms. The incidence of febrile neutropenia in the group that received the same treatment throughout the study was 2.3%, while the incidence in the group that switched therapies was 6.7%, which did not exceed the noninferiority margin of –15%.12

The safety analysis included a total of 214 patients, approximately 96.3% of whom experienced one adverse event. Most adverse events were related to chemotherapy, and the safety profiles of Zarxio and Neupogen were similar. No statistically significant difference in safety was reported.12

The most frequent treatment-emergent adverse events for the two therapies were alopecia, nausea, asthenia, fatigue, and bone pain. The most notable adverse drug reactions were bone pain (Zarxio, 23%, versus Neupogen, 33%) and musculoskeletal pain (Zarxio, 7%, versus Neupogen, 2%).12

ADVERSE DRUG REACTIONS

Adverse drug reactions vary according to the indication for which Zarxio is used. The most common adverse reactions in patients with nonmyeloid malignancies receiving myelosuppressive anticancer drugs are pyrexia, pain, rash, cough, and...
dyspnea (5% or greater difference in incidence compared to placebo). In patients with AML, adverse reactions include pain, epistaxis, and rash (2% or greater difference in incidence compared to placebo). Patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by BMT most often experience rash (5% or greater difference in incidence compared to placebo). In patients undergoing PBPC mobilization and collection, the most common adverse effects are bone pain, pyrexia, and headache (5% or greater difference in incidence compared to placebo). Pain, anemia, epistaxis, diarrhea, hypoesthesia, and alopecia may occur (5% or greater difference in incidence compared to placebo) in patients with SCN.10

**WARNINGS AND PRECAUTIONS**

Splenic ruptures and sickle cell crises, including fatal cases, have been reported after treatment with filgrastim products. In addition, treatment may cause acute respiratory distress syndrome; serious allergic reactions, including anaphylaxis; glomerulonephritis; alveolar hemorrhage and hemoptysis; thrombocytopenia; leukocytosis; and cutaneous vasculitis. Symptomatic patients should be monitored for capillary leak syndrome.10

Cytogenetic abnormalities and transformation to myelodysplastic syndromes (MDS) and AML have been reported in patients with SCN treated with filgrastim products.10

Because the G-CSF receptor through which Zarxio acts has also been found on tumor cell lines, the possibility that the treatment acts as a growth factor for any tumor type cannot be excluded.10

Simultaneous use of Zarxio with chemotherapy or radiation therapy has not been evaluated and is not recommended.10

Growth factor therapy has been associated with transient positive bone imaging changes, which should be taken into account when interpreting nuclear imaging results.10

**DRUG INTERACTIONS**

Zarxio administration is not recommended within 24 hours of cytotoxic chemotherapy because of the increased risk of sensitivity of rapidly dividing myeloid progenitor cells in response to chemotherapy.10

**CONTRAINDICATIONS**

Zarxio is contraindicated in patients with a history of serious allergic reactions to human G-CSF, such as filgrastim or pegfilgrastim.10

**SPECIAL POPULATIONS**

**Pregnancy and Lactation**

There are no adequate and well-controlled studies of filgrastim products in pregnant women; studies in rats and rabbits revealed no fetal malformations, although rabbits administered two to 10 times the human dose experienced maternal toxicity, reduced embryo-fetal survival, and increased abortions. Because the risk to humans is unknown, filgrastim products should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.10

It is unknown if filgrastim products are excreted in human milk; therefore, caution should be exercised if they are administered to women who are breastfeeding.10

**Pediatric Use**

Because the Zarxio prefilled syringe may not accurately measure volumes less than 0.3 mL, the direct administration of a volume less than 0.3 mL is not recommended due to the potential for dosing errors.10

Several studies have established the pharmacokinetics, safety, and effectiveness of filgrastim in pediatric patients. Additional information is available from a post-marketing surveillance study, which includes long-term follow-up of patients in the clinical studies and information from additional patients who entered directly into the post-marketing study. Of the 731 patients in the surveillance study, 429 were pediatric patients less than 18 years of age (range, 0.9–17 years). Long-term follow-up data suggest that height and weight are not adversely affected in patients who received up to five years of filgrastim treatment. Limited data from patients who were followed for 1.5 years did not suggest alterations in sexual maturation or endocrine function.10

Pediatric patients with congenital types of neutropenia (Kostmann’s syndrome, congenital agranulocytosis, or Schwachman–Diamond syndrome) have developed cytogenetic abnormalities and have undergone transformation to MDS and AML while receiving chronic filgrastim treatment. The relationship of these events to filgrastim administration is unknown.10

**Geriatric Use**

In three randomized, placebo-controlled trials of a total of 855 filgrastim-treated patients receiving myelosuppressive chemotherapy, 232 patients were age 65 years or older and 22 were age 75 years or older. No overall differences in safety or effectiveness were observed between these patients and the younger population. Clinical studies of filgrastim in other approved indications (i.e., BMT recipients, PBPC mobilization, and SCN) did not include sufficient numbers of patients 65 years of age and older to determine whether elderly people respond differently than those who are younger.10

**COST**

Zarxio is provided in prefilled syringes in dosage strengths of 300 mcg/0.5 mL and 480 mcg/0.8 mL. The average wholesale prices (AWPs) of Zarxio are $331 and $527 for 300 mcg/0.5 mL and 480 mcg/0.8 mL, respectively.13 In contrast, the AWPs of Neupogen in the same dosages, also provided in prefilled syringes, are $389 and $620, respectively.13

**P&T COMMITTEE CONSIDERATIONS**

A biosimilar product is identical in function to its reference biologic drug, but offers a lower-cost alternative. Zarxio, the first biosimilar approved by the FDA, offers lower costs, potentially greater accessibility to treatment, and increased flexibility in prescribing, which makes it a landmark agent for future biosimilars. P&T committees can consider adding Zarxio to their formularies alongside or in place of Neupogen to treat neutropenia.

**CONCLUSION**

Neutropenia is a condition that, if left untreated, can result in significant health consequences. With its FDA approval, Zarxio is the first biosimilar to provide an alternative to Neupogen that is similar in safety and efficacy. This allows providers and the market more than one option in treating the various forms of neutropenia at a lower cost.

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REFERENCES


