FREQUENTLY ASKED QUESTIONS

INDICATIONS:

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   ZARXIO is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a significant incidence of severe neutropenia with fever.

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   ZARXIO is indicated 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).

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IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS
- ZARXIO is contraindicated in patients with a history of serious allergic reactions to human granulocyte colony-stimulating factors such as filgrastim or pegfilgrastim products.

Please see Important Safety Information throughout and accompanying full Prescribing Information.
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SECTION 1: BIOSIMILARS

Q: WHAT ARE BIOSIMILARS?1

A: Biosimilars are biologic medicines that are highly similar to their reference biologic, and have demonstrated no clinically meaningful differences in safety, purity, and potency compared to that of the reference biologic. ZARXIO is a biosimilar of NEUPOGEN® (filgrastim).

Q: HOW DO BIOSIMILARS DIFFER FROM INTERCHANGEABLE BIOSIMILARS?2,3

A: While biosimilars are biological products that have been demonstrated to be highly similar to their “reference” biologic, another category for biosimilars includes biological products that are interchangeable with their reference biologic. According to the Biologic Price Competition and Innovation Act of 2009 (BPCIA), an interchangeable biological product, in addition to meeting the biosimilarity standard, is expected to produce the same clinical result as the reference product in any given patient. For a product that is given to a patient more than once, the risk in terms of safety and effectiveness of alternating or switching between the interchangeable and the reference product is not greater than the risk of using the reference product without alternating or switching. Only approved interchangeable biosimilars are substitutable (similar to generics). The BPCIA guidelines also mention that “the [interchangeable] biological product may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product.”
SECTION 2: GRANULOCYTE-COLONY STIMULATING FACTORS (G-CSFs)

Q: WHAT ARE G-CSFs?4

A: G-CSFs are glycoproteins which act on hematopoietic cells by binding to specific cell surface receptors and stimulating proliferation, differentiation commitment, and some end-cell functional activation.

Q: WHAT IS ZARXIO?4

A: ZARXIO is a 175–amino acid human G-CSF manufactured by recombinant DNA technology. ZARXIO is produced by Escherichia coli (E coli) bacteria into which has been inserted the human G-CSF gene. ZARXIO has a molecular weight of 18,800 daltons. The protein has an amino acid sequence that is identical to the natural sequence predicted from human DNA sequence analysis, except for the addition of an N-terminal methionine necessary for expression in E coli. Because ZARXIO is produced in E coli, the product is non-glycosylated and thus differs from G-CSF isolated from a human cell.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

• Splenic rupture, including fatal cases, has been reported following the administration of filgrastim products. Patients who report left upper abdominal or shoulder pain should be evaluated.

• Acute respiratory distress syndrome (ARDS) has been reported in patients receiving filgrastim products. Patients who develop fever and lung infiltrates or respiratory distress should be evaluated. Discontinue ZARXIO in patients with ARDS.

• Serious allergic reactions, including anaphylaxis, have been reported in patients receiving filgrastim products. The majority of reported events occurred upon initial exposure. Provide symptomatic treatment for allergic reactions. Allergic reactions, including anaphylaxis, in patients receiving filgrastim products can recur within days after the discontinuation of initial anti-allergic treatment. Permanently discontinue ZARXIO in patients with serious allergic reactions.
Q: WHAT ARE THE FDA-APPROVED SHORT-ACTING G-CSF THERAPIES?4-6
A: FDA-approved short-acting G-CSF therapies include: ZARXIO, NEUPOGEN® (filgrastim), and GRANIX® (tbo-filgrastim).

Q: DOES ZARXIO HAVE THE SAME DOSAGES AS OTHER SHORT-ACTING G-CSF THERAPIES?4-6
A: Yes, the ZARXIO prefilled syringe shares the same dosages as the NEUPOGEN® prefilled syringe and Granix® prefilled syringe.

<table>
<thead>
<tr>
<th>BRAND</th>
<th>DOSAGES</th>
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</thead>
<tbody>
<tr>
<td>ZARXIO prefilled syringe</td>
<td>300 mcg/0.5 mL and 480 mcg/0.8 mL*</td>
</tr>
<tr>
<td>NEUPOGEN® prefilled syringe</td>
<td>300 mcg/0.5 mL and 480 mcg/0.8 mL</td>
</tr>
<tr>
<td>NEUPOGEN® vial</td>
<td>300 mcg/mL and 480 mcg/1.6 mL</td>
</tr>
<tr>
<td>GRANIX® prefilled syringe</td>
<td>300 mcg/0.5 mL and 480 mcg/0.8 mL</td>
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*The direct administration of doses less than 0.3 mL of ZARXIO is not recommended due to the potential for dosing errors.

IMPORTANT SAFETY INFORMATION
WARNINGS AND PRECAUTIONS (cont’d)

- Sickle cell crisis, in some cases fatal, has been reported with the use of filgrastim products in patients with sickle cell trait or sickle cell disease.

- Glomerulonephritis has occurred in patients receiving filgrastim products. The diagnoses were based upon azotemia, hematuria (microscopic and macroscopic), proteinuria, and renal biopsy. Generally, events of glomerulonephritis resolved after dose reduction or discontinuation of filgrastim products. If glomerulonephritis is suspected, evaluate for cause. If causality is likely, consider dose-reduction or interruption of ZARXIO.
SECTION 3: ZARXIO

Q: WHAT ARE THE FDA-APPROVED INDICATIONS FOR ZARXIO?

A: 1. Patients with Cancer Receiving Myelosuppressive Chemotherapy
   ZARXIO is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a significant incidence of severe neutropenia with fever.

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Q: WHAT IS THE MECHANISM OF ACTION OF ZARXIO?

A: Colony-stimulating factors are glycoproteins which act on hematopoietic cells by binding to specific cell surface receptors and stimulating proliferation, differentiation commitment, and some end-cell functional activation. Endogenous G-CSF is a lineage-specific colony-stimulating factor that is produced by monocytes, fibroblasts, and endothelial cells. G-CSF 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.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (cont’d)

- Alveolar hemorrhage manifesting as pulmonary infiltrates and hemoptysis requiring hospitalization have been reported in healthy donors treated with filgrastim products undergoing peripheral blood progenitor cell (PBPC) collection mobilization. Hemoptysis resolved with discontinuation of filgrastim. The use of ZARXIO for PBPC mobilization in healthy donors is not an approved indication.

Please see Important Safety Information throughout and accompanying full Prescribing Information.
**Q: WHAT IS THE RECOMMENDED DOSAGE OF ZARXIO?**

**A:** The recommended dosage of ZARXIO varies according to indication.

- **Patients with cancer receiving myelosuppressive chemotherapy or induction and/or consolidation chemotherapy for AML**
  - Recommended starting dosage is 5 mcg/kg/day subcutaneous injection, short intravenous infusion (15 to 30 minutes), or continuous intravenous infusion. See full Prescribing Information for recommended dosage adjustments and timing of administration

- **Patients with cancer undergoing bone marrow transplantation**
  - 10 mcg/kg/day given as an intravenous infusion no longer than 24 hours. See full Prescribing Information for recommended dosage adjustments and timing of administration

- **Patients undergoing autologous peripheral blood progenitor cell collection and therapy**
  - 10 mcg/kg/day subcutaneous injection
  - Administer for at least 4 days before first leukapheresis procedure and continue until last leukapheresis

- **Patients with congenital neutropenia**
  - Recommended starting dosage is 6 mcg/kg subcutaneous injection twice daily

- **Patients with cyclic or idiopathic neutropenia**
  - Recommended starting dosage is 5 mcg/kg subcutaneous injection daily

- Direct administration of less than 0.3 mL is not recommended due to potential for dosing errors

### IMPORTANT SAFETY INFORMATION

**WARNINGS AND PRECAUTIONS (cont’d)**

- Capillary leak syndrome (CLS) has been reported after G-CSF administration, including filgrastim products, and is characterized by hypotension, hypoalbuminemia, edema and hemoconcentration. Episodes vary in frequency, severity and may be life-threatening if treatment is delayed. Patients who develop symptoms of capillary leak syndrome should be closely monitored and receive appropriate treatment.

- Confirm the diagnosis of severe chronic neutropenia (SCN) before initiating ZARXIO therapy. Myelodysplastic syndrome (MDS) and acute myelogenous leukemia (AML) have been reported to occur in the natural history of congenital neutropenia without cytokine therapy. Cytogenetic abnormalities, transformation to MDS, and AML have also been observed in patients treated with filgrastim products for SCN. Abnormal cytogenetics and MDS have been associated with the eventual development of myeloid leukemia. The effect of filgrastim products on the development of abnormal cytogenetics and the effect of continued filgrastim administration in patients with abnormal cytogenetics or MDS are unknown. If a patient with SCN develops abnormal cytogenetics or myelodysplasia, the risks and benefits of continuing ZARXIO should be carefully considered.

Please see Important Safety Information throughout and accompanying full Prescribing Information and Instructions for Use.
Q: WHAT WERE THE RESULTS OF THE SAFETY AND EFFICACY STUDY (PIONEER)?
A: Information about the PIONEER study and its results can be found in the ZARXIO Product Monograph.

Q: WHAT ARE THE POSSIBLE SIDE EFFECTS OF ZARXIO?
A: Most common adverse reactions in patients:
- With nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs (≥ 5% difference in incidence compared to placebo) are thrombocytopenia, nausea, pyrexia, chest pain, pain, fatigue, back pain, arthralgia, bone pain, pain in extremity, dizziness, cough, dyspnea, rash, blood lactate dehydrogenase increased and blood alkaline phosphatase increased
- With AML (≥ 2% difference in incidence) are epistaxis, back pain, pain in extremity, erythema, and rash maculo-papular
- With nonmyeloid malignancies undergoing myeloablative chemotherapy followed by BMT (≥ 5% difference in incidence) is rash and hypersensitivity
- Undergoing peripheral blood progenitor cell mobilization and collection (≥ 5% incidence) are bone pain, pyrexia, blood alkaline phosphatase increased and headache
- With severe chronic neutropenia (SCN) (> 5% difference in incidence) are arthralgia, bone pain, back pain, muscle spasms, musculoskeletal pain, pain in extremity, splenomegaly, anemia, upper respiratory tract infection, urinary tract infection, epistaxis, chest pain, diarrhea, hypoesthesia, and alopecia

IMPORTANT SAFETY INFORMATION
WARNINGS AND PRECAUTIONS (cont’d)
- Thrombocytopenia has been reported in patients receiving filgrastim products. Monitor platelet counts.
- Leukocytosis:
  - Patients with Cancer Receiving Myelosuppressive Chemotherapy: White blood cell counts of 100,000/mm³ or greater were observed in approximately 2% of patients receiving filgrastim at dosages above 5 mcg/kg/day. In patients with cancer receiving ZARXIO as an adjunct to myelosuppressive chemotherapy, to avoid the potential risks of excessive leukocytosis, it is recommended that ZARXIO therapy be discontinued if the ANC surpasses 10,000/mm³ after the chemotherapy-induced ANC nadir has occurred. Monitor CBCs at least twice weekly during therapy.

Please see Important Safety Information throughout and accompanying full Prescribing Information.
Q: HOW IS ZARXIO SUPPLIED AND STORED?4

A: Injection: Single-dose, preservative-free, prefilled syringes with an UltraSafe Passive® Needle Guard, containing 300 mcg/0.5 mL of filgrastim-sndz:
• Pack of 1 prefilled syringe (NDC 61314-304-01)
• Pack of 10 prefilled syringes (NDC 61314-304-10)

Injection: Single-dose, preservative-free, prefilled syringes with an UltraSafe Passive® Needle Guard, containing 480 mcg/0.8 mL of filgrastim-sndz:
• Pack of 1 prefilled syringe (NDC 61314-312-01)
• Pack of 10 prefilled syringes (NDC 61314-312-10)

Latex-sensitive individuals: The removable needle cap of ZARXIO prefilled syringe contains natural rubber latex which may cause allergic reaction. The safe use of ZARXIO in latex-sensitive individuals has not been studied.

Storage: Store in the refrigerator at 2°C to 8°C (36°F to 46°F) in the original pack to protect from light. Avoid shaking. Protect from freezing. Prior to injection, ZARXIO may be allowed to reach room temperature for a maximum of 24 hours. Any prefilled syringe left above 25°C (77°F) for >24 hours should be discarded.

Avoid freezing; if frozen, thaw in the refrigerator before administration. Discard ZARXIO if frozen more than once.

IMPORTANT SAFETY INFORMATION
WARNINGS AND PRECAUTIONS (cont’d)

• Leukocytosis (cont’d):
  • Peripheral Blood Progenitor Cell (PBPC) Collection and Therapy: During the period of administration of ZARXIO for PBPC mobilization in patients with cancer, discontinue ZARXIO if the leukocyte count rises to >100,000/mm³.

• Cutaneous vasculitis has been reported in patients treated with filgrastim products. In most cases, the severity of cutaneous vasculitis was moderate or severe. Most of the reports involved patients with SCN receiving long-term filgrastim therapy. Hold ZARXIO therapy in patients with cutaneous vasculitis. ZARXIO may be started at a reduced dose when the symptoms resolve and the ANC has decreased.

• The possibility that ZARXIO acts as a growth factor for any tumor type cannot be excluded. The safety of filgrastim products in chronic myeloid leukemia (CML) and myelodysplasia has not been established. When ZARXIO is used to mobilize PBPC, tumor cells may be released from the marrow and subsequently collected in the leukapheresis product. Available data is limited and inconclusive.
Q: WHAT SUPPORT SERVICES ARE AVAILABLE FROM SANDOZ FOR PATIENTS PRESCRIBED ZARXIO?

A: Sandoz One Source™ is a comprehensive program designed to simplify and support patient access. Sandoz One Source offers a variety of customized services for patients, including:

- General payer policy information
- Comprehensive insurance verifications
- Claims tracking
- Alternate coverage options
- Commercial Co-Pay Program
- Billing and coding
- Prior authorization information
- Denials/Appeals
- External resources information
- Patient Assistance Program (PAP) requests

Sandoz One Source contact information:

Phone: 1-844-SANDOZ1 (1-844-726-3691)
M-F 9 AM to 8PM ET
Fax: 1-844-726-3695
Address: PO Box 220188
Charlotte, NC 28222-0188
Online: www.sandozonesource.com

Program Eligibility Requirements:

Maximum benefit of $10,000 annually. Prescription must be for an approved indication. This program is not health insurance. This program is for insured patients only; cash-paying or uninsured patients are not eligible. Patients are not eligible if prescriptions are paid, in whole or in part, by any state or federally funded programs, including but not limited to Medicare (including Part D, even in the coverage gap) or Medicaid, Medigap, VA, DOD, or TriCare, or private indemnity, or HMO insurance plans that reimburse the patient for the entire cost of their prescription drugs, or where prohibited by law. Co-Pay Program may apply to out-of-pocket expenses that occurred within 120 days prior to the date of the enrollment. Patients can participate for a maximum of 12 months. Co-Pay Program may not be combined with any other rebate, coupon, or offer. Sandoz reserves the right to rescind, revoke, or amend this offer without further notice.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (cont’d)

- The safety and efficacy of ZARXIO given simultaneously with cytotoxic chemotherapy have not been established. Do not use ZARXIO in the period 24 hours before through 24 hours after the administration of cytotoxic chemotherapy. The safety and efficacy of ZARXIO have not been evaluated in patients receiving concurrent radiation therapy. Avoid the simultaneous use of ZARXIO with chemotherapy and radiation therapy.

- Increased hematopoietic activity of the bone marrow in response to growth factor therapy has been associated with transient positive bone-imaging changes on nuclear imaging.

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Sandoz One Source is a trademark of Novartis AG.
FREQUENTLY ASKED QUESTIONS

INDICATIONS:

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To report SUSPECTED ADVERSE REACTIONS, contact Sandoz Inc. at 1-800-525-8747 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.
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REFERENCES

2. US Food and Drug Administration. Christl L. Overview of the regulatory pathway and FDA’s guidance for the development and approval of biosimilar products in the US (approved in European Union under the trade name Zarzio).

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