ZARXIO®
(filgrastim-sndz)
Subcutaneous or Intravenous Injection
300 mcg/0.5 mL | 480 mcg/0.8 mL

PRODUCT INFORMATION FORM

INDICATIONS:

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.

2. **Patients with Acute Myeloid Leukemia Receiving Induction or Consolidation Chemotherapy**
   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).

3. **Patients with Cancer Undergoing Bone Marrow Transplantation**
   ZARXIO is indicated 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 bone marrow transplantation.

4. **Patients Undergoing Autologous Peripheral Blood Progenitor Cell Collection and Therapy**
   ZARXIO is indicated for the mobilization of autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis.

5. **Patients with Severe Chronic Neutropenia**
   ZARXIO is indicated for chronic administration to reduce the incidence and duration of sequelae of neutropenia (e.g., fever, infections, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia.

Please see Important Safety Information on pages 14-16 and accompanying full Prescribing Information.

SANDOZ A Novartis Division

1. AMERICAN HOSPITAL FORMULARY SERVICE (AHFS®) DRUG INFORMATION CLASSIFICATION NUMBER[1]

20:16 – Hematopoietic Agents

2. GENERIC NAME[2]

filgrastim-sndz

3. THERAPEUTIC NAME[2]

ZARXIO® (filgrastim-sndz)

4. THERAPEUTIC CLASS[2]

ZARXIO is a human granulocyte colony-stimulating factor (G-CSF) manufactured by recombinant DNA technology.

5. SOURCE OF SUPPLY[2]

A product of Austria.

6. BIOLOGICS LICENSE APPLICATION (BLA) NUMBER AND DATE OF FDA APPROVAL[3,4]

FDA Application No. (BLA) 125553
FDA approval: March 6, 2015

7. PHYSICAL PROPERTIES:

ZARXIO injection is a sterile, clear, colorless to slightly yellowish, preservative-free liquid containing filgrastim-sndz at a specific activity of 1.0 x 10^8 U/mg (as measured by a cell mitogenesis assay). The product is available in single-dose prefilled syringes. The single-dose prefilled syringes contain either 300 mcg/0.5 mL or 480 mcg/0.8 mL of filgrastim-sndz. See the table below for product composition of each single-dose prefilled syringe.

	300 mcg/0.5 mL Syringe	480 mcg/0.8 mL Syringe
Filgrastim-sndz	300 mcg	480 mcg
Glutamic acid	0.736 mg	1.178 mg
Polysorbate 80	0.02 mg	0.032 mg
Sorbitol	25 mg	40 mg
Sodium hydroxide	q.s.	q.s.
Water for injection USP q.s. ad*	ad 0.5 mL	ad 0.8 mL

*q.s. ad (*quantum sufficiat ad*) = quantity sufficient to make.

8. CHEMICAL PROPERTIES:

ZARXIO is produced by *Escherichia coli (E coli)* bacteria into which has been inserted the human granulocyte colony-stimulating factor 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.

9. PHARMACOLOGIC CLASSIFICATION

Mechanism of Action

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.

Pharmacodynamics

In phase 1 studies involving 96 patients with various nonmyeloid malignancies, administration of filgrastim resulted in a dose-dependent increase in circulating neutrophil counts over the dose range of 1 to 70 mcg/kg/day. This increase in neutrophil counts was observed whether filgrastim was administered intravenous (1 to 70 mcg/kg twice daily), subcutaneous (1 to 3 mcg/kg once daily), or by continuous subcutaneous infusion (3 to 11 mcg/kg/day). With discontinuation of filgrastim therapy, neutrophil counts returned to baseline in most cases within 4 days. Isolated neutrophils displayed normal phagocytic (measured by zymosan-stimulated chemoluminescence) and chemotactic (measured by migration under agarose using N-formyl-methionyl-leucyl phenylalanine [fMLP] as the chemotaxin) activity *in vitro*.

The absolute monocyte count was reported to increase in a dose-dependent manner in most patients receiving filgrastim; however, the percentage of monocytes in the differential count remained within the normal range. Absolute counts of both eosinophils and basophils did not change and were within the normal range following administration of filgrastim. Increases in lymphocyte counts following filgrastim administration have been reported in some normal subjects and patients with cancer.

White blood cell (WBC) differentials obtained during clinical trials have demonstrated a shift towards earlier granulocyte progenitor cells (left shift), including the appearance of promyelocytes and myeloblasts, usually during neutrophil recovery following the chemotherapy-induced nadir. In addition, Döhle bodies, increased granulocyte granulation, and hypersegmented neutrophils have been observed. Such changes were transient and were not associated with clinical sequelae, nor were they necessarily associated with infection.

9. PHARMACOLOGIC CLASSIFICATION (cont'd)

Pharmacokinetics

Filgrastim exhibits nonlinear pharmacokinetics. Clearance is dependent on filgrastim concentration and neutrophil count: G-CSF receptor-mediated clearance is saturated by high concentration of filgrastim and is diminished by neutropenia. In addition, filgrastim is cleared by the kidney.

Subcutaneous administration of 3.45 mcg/kg and 11.5 mcg/kg of filgrastim resulted in maximum serum concentrations of 4 and 49 ng/mL, respectively, within 2 to 8 hours. After intravenous administration, the volume of distribution averaged 150 mL/kg and the elimination half-life was approximately 3.5 hours in both normal subjects and subjects with cancer. Clearance rates of filgrastim were approximately 0.5 to 0.7 mL/minute/kg. Single parenteral doses or daily intravenous doses, over a 14-day period, resulted in comparable half-lives. The half-lives were similar for intravenous administration (231 minutes, following doses of 34.5 mcg/kg) and for subcutaneous administration (210 minutes, following filgrastim dosages of 3.45 mcg/kg). Continuous 24-hour intravenous infusions of 20 mcg/kg over an 11 to 20-day period produced steady-state serum concentrations of filgrastim with no evidence of drug accumulation over the time period investigated. The absolute bioavailability of filgrastim after subcutaneous administration is 60% to 70%.

Specific Populations

Pediatric Patients: The pharmacokinetics of filgrastim in pediatric patients after chemotherapy are similar to those in adult patients receiving the same weight-normalized doses, suggesting no age-related differences in the pharmacokinetics of filgrastim products.

Renal Impairment: In a study with healthy volunteers, subjects with moderate renal impairment, and subjects with end stage renal disease (n=4 per group), higher serum concentrations were observed in subjects with end-stage renal disease. However, dose adjustment in patients with renal impairment is not necessary.

Hepatic Impairment: Pharmacokinetics and pharmacodynamics of filgrastim are similar between subjects with hepatic impairment and healthy subjects (n=12/group). The study included 10 subjects with mild hepatic impairment (Child-Pugh Class A) and 2 subjects with moderate hepatic impairment (Child-Pugh Class B). Therefore, dose adjustment for ZARXIO in patients with hepatic impairment is not necessary.

10. DOSAGE AND ADMINISTRATION

Dosage in Patients with Cancer Receiving Myelosuppressive Chemotherapy or Induction and/or Consolidation Chemotherapy for AML

The recommended starting dosage of ZARXIO is 5 mcg/kg/day, administered as a single daily injection by subcutaneous injection, by short intravenous infusion (15 to 30 minutes), or by continuous intravenous infusion. Obtain a complete blood count (CBC) and platelet count before instituting ZARXIO therapy and monitor twice weekly during therapy. Consider dose escalation in increments of 5 mcg/kg for each chemotherapy cycle, according to the duration and severity of the absolute neutrophil count (ANC) nadir. Recommend stopping ZARXIO if the ANC increases beyond 10,000/mm^3.

Administer ZARXIO at least 24 hours after cytotoxic chemotherapy. Do not administer ZARXIO within the 24-hour period prior to chemotherapy. A transient increase in neutrophil count is typically seen 1 to 2 days after initiation of ZARXIO therapy. Therefore, to ensure a sustained therapeutic response, administer ZARXIO daily for up to 2 weeks or until the ANC has reached 10,000/mm^3 following the expected chemotherapy-induced neutrophil nadir. The duration of ZARXIO therapy needed to attenuate chemotherapy-induced neutropenia may be dependent on the myelosuppressive potential of the chemotherapy regimen employed.

Dosage in Patients with Cancer Undergoing Bone Marrow Transplantation

The recommended dosage of ZARXIO following bone marrow transplantation (BMT) is 10 mcg/kg/day given as an intravenous infusion 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. Monitor CBCs and platelet counts frequently following marrow transplantation.

During the period of neutrophil recovery, titrate the daily dosage of ZARXIO against the neutrophil response (see the table below).

RECOMMENDED DOSAGE ADJUSTMENTS DURING NEUTROPHIL RECOVERY IN PATIENTS WITH CANCER FOLLOWING BMT

Absolute Neutrophil Count	ZARXIO Dosage Adjustment
When ANC greater than 1000/mm^3 for 3 consecutive days	Reduce to 5 mcg/kg/day*
Then, if ANC remains greater than 1000/mm^3 for 3 more consecutive days	Discontinue ZARXIO
Then, if ANC decreases to less than 1000/mm^3	Resume at 5 mcg/kg/day

*If ANC decreases to less than 1000/mm^3 at any time during the 5 mcg/kg/day administration, increase ZARXIO to 10 mcg/kg/day, and then follow the above steps.

Dosage in Patients Undergoing Autologous Peripheral Blood Progenitor Cell Collection and Therapy

The recommended dosage of ZARXIO for the mobilization of autologous peripheral blood progenitor cells (PBPC) is 10 mcg/kg/day given by subcutaneous injection. Administer ZARXIO for at least 4 days before the first leukapheresis procedure and continue until the last leukapheresis. Although the optimal duration of ZARXIO administration and leukapheresis schedule have not been established, administration of filgrastim for 6 to 7 days with leukaphereses on days 5, 6, and 7 was found to be safe and effective. Monitor neutrophil counts after 4 days of ZARXIO, and discontinue ZARXIO if the white blood cell (WBC) count rises to greater than 100,000/mm^3.

Please see Important Safety Information on pages 14-16 and accompanying full Prescribing Information.

ZARXIO® (filgrastim-sndz)

10. DOSAGE AND ADMINISTRATION (cont'd)

Dosage in Patients with Severe Chronic Neutropenia

Prior to starting ZARXIO in patients with suspected chronic neutropenia, confirm the diagnosis of severe chronic neutropenia (SCN) by evaluating serial CBCs with differential and platelet counts, and evaluating bone marrow morphology and karyotype. The use of ZARXIO prior to confirmation of a correct diagnosis of SCN may impair diagnostic efforts and may thus impair or delay evaluation and treatment of an underlying condition, other than SCN, causing the neutropenia.

The recommended starting dosage in patients with Congenital Neutropenia is 6 mcg/kg as a twice daily subcutaneous injection, and the recommended starting dosage in patients with idiopathic or Cyclic Neutropenia is 5 mcg/kg as a single daily subcutaneous injection.

Dosage Adjustments in Patients with Severe Chronic Neutropenia

Chronic daily administration is required to maintain clinical benefit. Individualize the dosage based on the patient's clinical course as well as ANC. In the SCN postmarketing surveillance study, the reported median daily doses of filgrastim were: 6 mcg/kg (congenital neutropenia), 2.1 mcg/kg (cyclic neutropenia), and 1.2 mcg/kg (idiopathic neutropenia). In rare instances, patients with congenital neutropenia have required doses of filgrastim greater than or equal to 100 mcg/kg/day.

Monitor CBCs for Dosage Adjustments

During the initial 4 weeks of ZARXIO therapy and during the 2 weeks following any dosage adjustment, monitor CBCs with differential and platelet counts. Once a patient is clinically stable, monitor CBCs with differential and platelet counts monthly during the first year of treatment. Thereafter, if the patient is clinically stable, less frequent routine monitoring is recommended.

Important Administration Instructions

Patient self-administration and administration by a caregiver may benefit from training by a healthcare professional. Training should aim to demonstrate to those patients and caregivers how to measure the dose using the prefilled syringe, and the focus should be on ensuring that a patient or caregiver can successfully perform all of the steps in the Instructions for use of ZARXIO prefilled syringe with BD UltraSafe Passive® Needle Guard. If a patient or caregiver is not able to demonstrate that they can measure the dose and administer the product successfully, you should consider whether the patient is an appropriate candidate for self-administration of ZARXIO.

ZARXIO prefilled syringe with BD UltraSafe Passive® Needle Guard is not designed to allow for direct administration of doses of less than 0.3 mL (180 mcg). The spring mechanism of the needle guard apparatus affixed to the prefilled syringe interferes with the visibility of the graduation markings on the syringe barrel corresponding to 0.1 mL and 0.2 mL. The visibility of these markings is necessary to accurately measure doses of ZARXIO less than 0.3 mL (180 mcg) for direct administration to patients. Thus, the direct administration to patients requiring doses of less than 0.3 mL (180 mcg) is not recommended due to the potential for dosing errors.

ZARXIO is supplied in single-dose prefilled syringes (for subcutaneous use). Prior to use, remove the prefilled syringe from the refrigerator and allow ZARXIO to reach room temperature for a minimum of 30 minutes and a maximum of 24 hours. Discard any prefilled syringe left at room temperature for greater than 24 hours. Visually inspect ZARXIO for particulate matter and discoloration prior to administration (the solution is clear and colorless to slightly yellowish). Do not administer ZARXIO if particulates or discoloration are observed.

Discard unused portion of ZARXIO in prefilled syringes. Do not save unused drug for later administration.

If you miss a dose of ZARXIO, talk to your doctor about when you should give your next dose.

Please see Important Safety Information on pages 14-16 and accompanying full Prescribing Information.

ZARXIO® (filgrastim-sndz)

10. DOSAGE AND ADMINISTRATION (cont'd)

Subcutaneous Injection

Inject ZARXIO subcutaneously in the outer area of upper arms, abdomen, thighs, or upper outer areas of the buttock. If patients or caregivers are to administer ZARXIO, instruct them in appropriate injection technique and ask them to follow the subcutaneous injection procedures in the Patient Information included in the full Prescribing Information.

Training by the healthcare provider should aim to demonstrate to those patients and caregivers how to measure the dose of ZARXIO, and the focus should be on ensuring that a patient or caregiver can successfully perform all of the steps in the Instructions for Use for the prefilled syringe. If a patient or caregiver is not able to demonstrate that they can measure the dose and administer the product successfully, you should consider whether the patient is an appropriate candidate for self-administration of ZARXIO.

If the patient or caregiver misses a dose of ZARXIO, instruct them to contact their healthcare provider.

Administration Instructions for the Prefilled Syringe

Persons with latex allergies should not administer the ZARXIO prefilled syringe, because the needle cap contains natural rubber latex (derived from latex).

Dilution

If required for intravenous administration, ZARXIO may be diluted in 5% Dextrose Injection, USP to concentrations between 5 mcg/mL and 15 mcg/mL. ZARXIO diluted to concentrations from 5 mcg/mL to 15 mcg/mL should be protected from adsorption to plastic materials by the addition of Albumin (Human) to a final concentration of 2 mg/mL. When diluted in 5% Dextrose Injection, USP, or 5% Dextrose plus Albumin (Human), ZARXIO is compatible with glass, polyvinylchloride, polyolefin, and polypropylene.

Do not dilute with saline at any time, because the product may precipitate.

Diluted ZARXIO solution can be stored at room temperature for up to 24 hours. This 24-hour time period includes the time during room temperature storage of the infusion solution and the duration of the infusion.

How Supplied/Storage and Handling

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 greater than 24 hours should be discarded.

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

Please see Important Safety Information on pages 14-16 and accompanying full Prescribing Information.

ZARXIO® (filgrastim-sndz)

11. ADVERSE REACTIONS

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) are 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

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Adverse Reactions in Patients with Cancer Receiving Myelosuppressive Chemotherapy

The following adverse reaction data are from three randomized, placebo-controlled studies in patients with:

- small cell lung cancer receiving standard dose chemotherapy with cyclophosphamide, doxorubicin, and etoposide (Study 1)
- small cell lung cancer receiving ifosfamide, doxorubicin, and etoposide (Study 2), and
- non-Hodgkin's lymphoma (NHL) receiving doxorubicin, cyclophosphamide, vindesine, bleomycin, methylprednisolone, and methotrexate ("ACVBP") or mitoxantrone, ifosfamide, mitoguazone, teniposide, methotrexate, folinic acid, and methylprednisolone ("VIM3") (Study 3)

A total of 451 patients were randomized to receive subcutaneous filgrastim 230 mcg/m^2 (Study 1), 240 mcg/m^2 (Study 2) or 4 or 5 mcg/kg/day (Study 3) (n = 294) or placebo (n = 157). The patients in these studies were median age 61 (range 29 to 78) years and 64% were male. The ethnicity was 95% Caucasian, 4% African American, and 1% Asian.

Please see Important Safety Information on pages 14-16 and accompanying full Prescribing Information.

ZARXIO® (filgrastim-sndz)

11. ADVERSE REACTIONS (cont'd)

Adverse Reactions in Patients with Cancer Receiving Myelosuppressive Chemotherapy (With ≥ 5% Higher Incidence in Filgrastim Compared to Placebo)[2]

System Organ Class Preferred Term	Filgrastim (N = 294)	Placebo (N = 157)
Blood and lymphatic system disorders		
Thrombocytopenia	38%	29%
Gastrointestinal disorders		
Nausea	43%	32%
General disorders and administration site conditions		
Pyrexia	48%	29%
Chest pain	13%	6%
Pain	12%	6%
Fatigue	20%	10%
Musculoskeletal and connective tissue disorders		
Back pain	15%	8%
Arthralgia	9%	2%
Bone pain	11%	6%
Pain in extremity*	7%	3%
Nervous system disorders		
Dizziness	14%	3%
Respiratory, thoracic and mediastinal disorders		
Cough	14%	8%
Dyspnea	13%	8%
Skin and subcutaneous tissue disorders		
Rash	14%	5%
Investigations		
Blood lactate dehydrogenase increased	6%	1%
Blood alkaline phosphatase increased	6%	1%

*Percent difference (Filgrastim – Placebo) was 4%.

12. 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.

13. WARNINGS AND PRECAUTIONS

- **Splenic Rupture**

Splenic rupture, including fatal cases, has been reported following the administration of filgrastim products. Evaluate patients who report left upper abdominal or shoulder pain for an enlarged spleen or splenic rupture.

- **Acute Respiratory Distress Syndrome**

Acute respiratory distress syndrome (ARDS) has been reported in patients receiving filgrastim products. Evaluate patients who develop fever and lung infiltrates or respiratory distress for ARDS. Discontinue ZARXIO in patients with ARDS.

- **Serious Allergic Reactions**

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

- **Sickle Cell Disorders**

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**

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.

- **Alveolar Hemorrhage and Hemoptysis**

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.

- **Capillary Leak Syndrome**

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 standard symptomatic treatment, which may include a need for intensive care.

- **Patients with Severe Chronic Neutropenia**

Confirm the diagnosis of 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. Based on available data including a postmarketing surveillance study, the risk of developing MDS and AML appears to be confined to the subset of patients with congenital neutropenia. Abnormal cytogenetics and MDS have

13. WARNINGS AND PRECAUTIONS (cont'd)

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.

• Thrombocytopenia

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/mm^3 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/mm^3 after the chemotherapy-induced ANC nadir has occurred. Monitor CBCs at least twice weekly during therapy. Dosages of ZARXIO that increase the ANC beyond 10,000/mm^3 may not result in any additional clinical benefit. In patients with cancer receiving myelosuppressive chemotherapy, discontinuation of filgrastim therapy usually resulted in a 50% decrease in circulating neutrophils within 1 to 2 days, with a return to pretreatment levels in 1 to 7 days.

Peripheral Blood Progenitor Cell 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/mm^3.

• Cutaneous Vasculitis

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.

• Potential Effect on Malignant Cells

ZARXIO is a growth factor that primarily stimulates neutrophils. The granulocyte-colony stimulating factor (G-CSF) receptor through which ZARXIO acts has also been found on tumor cell lines. 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. The effect of reinfusion of tumor cells has not been well studied, and the limited data available are inconclusive.

• Simultaneous Use with Chemotherapy and Radiation Therapy Not Recommended

The safety and efficacy of ZARXIO given simultaneously with cytotoxic chemotherapy have not been established. Because of the potential sensitivity of rapidly dividing myeloid cells to cytotoxic chemotherapy, 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.

Please see Important Safety Information on pages 14-16 and accompanying full Prescribing Information.

13. WARNINGS AND PRECAUTIONS (cont'd)

• Nuclear Imaging

Increased hematopoietic activity of the bone marrow in response to growth factor therapy has been associated with transient positive bone-imaging changes. This should be considered when interpreting bone-imaging results.

14. DRUG INTERACTIONS

None.

15. USE IN SPECIFIC POPULATIONS

Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women. The potential risk to the fetus is unknown. Reports in the scientific literature have described transplacental passage of filgrastim products in pregnant women when administered ≤ 30 hours prior to preterm delivery (≤ 30 weeks gestation). ZARXIO should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Effects of filgrastim on prenatal development have been studied in rats and rabbits. No malformations were observed in either species. Filgrastim has been shown to have adverse effects in pregnant rabbits at doses 2 to 10 times higher than the human doses. In pregnant rabbits showing signs of maternal toxicity, reduced embryofetal survival (at 20 and 80 mcg/kg/day) and increased abortions (at 80 mcg/kg/day) were observed. In pregnant rats, no maternal or fetal effects were observed at doses up to 575 mcg/kg/day.

Offspring of rats administered filgrastim during the peri-natal and lactation periods exhibited a delay in external differentiation and growth retardation (≥ 20 mcg/kg/day) and slightly reduced survival rate (100 mcg/kg/day).

Nursing Mothers

It is not known whether filgrastim products are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised if ZARXIO is administered to women who are breastfeeding.

Pediatric Use

ZARXIO prefilled syringe with BD UltraSafe Passive® Needle Guard may not accurately measure volumes less than 0.3 mL due to the needle spring mechanism design. Therefore, the direct administration of a volume less than 0.3 mL is not recommended due to the potential for dosing errors.

In patients with cancer receiving myelosuppressive chemotherapy, 15 pediatric patients median age 2.6 (range 1.2-9.4) years with neuroblastoma were treated with myelosuppressive chemotherapy (cyclophosphamide, cisplatin, doxorubicin, and etoposide) followed by subcutaneous filgrastim at doses of 5, 10, or 15 mcg/kg/day for 10 days (n = 5/dose) (Study 8). The pharmacokinetics of filgrastim in pediatric patients after chemotherapy are similar to those in adults receiving the same weight-normalized doses, suggesting no age-related differences in the pharmacokinetics of filgrastim. In this population, filgrastim was well tolerated. There was one report of palpable splenomegaly and one report of hepatosplenomegaly associated with filgrastim therapy; however, the only consistently reported adverse event was musculoskeletal pain, which is no different from the experience in the adult population.

Please see Important Safety Information on pages 14-16 and accompanying full Prescribing Information.

15. USE IN SPECIFIC POPULATIONS (cont'd)

The safety and effectiveness of filgrastim have been established in pediatric patients with SCN. In a phase 3 study (Study 7) to assess the safety and efficacy of filgrastim in the treatment of SCN, 123 patients with a median age of 12 years (range 7 months to 76 years) were studied. Of the 123 patients, 12 were infants (7 months to 2 years of age), 49 were children (2 to 12 years of age), and 9 were adolescents (12 to 16 years of age). Additional information is available from a SCN postmarketing surveillance study, which includes long-term follow-up of patients in the clinical studies and information from additional patients who entered directly into the postmarketing surveillance study. Of the 731 patients in the surveillance study, 429 were pediatric patients < 18 years of age (range 0.9-17).

Long-term follow-up data from the postmarketing surveillance study suggest that height and weight are not adversely affected in patients who received up to 5 years of filgrastim treatment. Limited data from patients who were followed in the phase 3 study for 1.5 years did not suggest alterations in sexual maturation or endocrine function.

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.

Geriatric Use

Among 855 subjects enrolled in 3 randomized, placebo-controlled trials of filgrastim-treated patients receiving myelosuppressive chemotherapy, there were 232 subjects age 65 or older, and 22 subjects age 75 or older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects. Clinical studies of filgrastim in other approved indications (ie, BMT recipients, PBPC mobilization, and SCN) did not include sufficient numbers of subjects aged 65 and older to determine whether elderly subjects respond differently from younger subjects.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

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

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.
- 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.
- 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.
- 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.
- 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/mm^3 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/mm^3 after the chemotherapy-induced ANC nadir has occurred. Monitor CBCs at least twice weekly during therapy.
  - 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/mm^3.
- 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 filgrastim 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.
- 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.

Please see Important Safety Information continued on next page and accompanying full Prescribing Information.

ZARXIO® (filgrastim-sndz)

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ADVERSE REACTIONS

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) are 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

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.

References: 1. AHFS® Drug Information website. http://ahfs.ashp.org/drug-assignments-2015.aspx. Accessed March 29, 2017. **2.** ZARXIO Prescribing Information. Sandoz Inc. February 2017. **3.** US Food and Drug Administration. FDA ODAC Brief. http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/oncologicdrugsadvisorycommittee/ucm428780.pdf. Accessed March 29, 2017. **4.** US Food and Drug Administration. https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/UCM071436.pdf. Accessed March 29, 2017.

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