CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125553Orig1s000

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ZARXIO safely and effectively. See full prescribing information for ZARXIO.

ZARXIO™ (filgrastim-sndz) injection, for subcutaneous or intravenous use
Initial U.S. Approval: 2015

----------INDICATIONS AND USAGE----------
ZARXIO is a leukocyte growth factor 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 (1.1)
- Reduce the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of patients with acute myeloid leukemia (AML) (1.2)
- 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 (BMT) (1.3)
- Mobilize autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis (1.4)
- Reduce the incidence and duration of sequelae of severe neutropenia (e.g.,fever, infections, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia (1.5)

----------DOSAGE AND ADMINISTRATION----------
- Patients with cancer receiving myelosuppressive chemotherapy or induction and/or consolidation chemotherapy for AML
  - Recommended starting dose 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 (2.1)
- 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. (2.2)
- Patients undergoing autologous peripheral blood progenitor cell collection and therapy
  - 10 mcg/kg/day subcutaneous injection (2.3).
  - Administer for at least 4 days before first leukapheresis procedure and continue until last leukapheresis (2.3)
- Patients with congenital neutropenia
  - Recommended starting dose is 6 mcg/kg subcutaneous injection twice daily (2.4)
- Patients with cyclic or idiopathic neutropenia
  - Recommended starting dose is 5 mcg/kg subcutaneous injection daily (2.4)
- Direct administration of less than 0.3 mL is not recommended due to potential for dosing errors (2.5)

----------DOSAGE FORMS AND STRENGTHS----------
- Injection: 300 mcg/0 5 mL in a single-use prefilled syringe with BD UltraSafe Passive™ Needle Guard (3)
- Injection: 480 mcg/0.8 mL in a single-use prefilled syringe with BD UltraSafe Passive™ Needle Guard (3)

----------CONTRAINDICATIONS----------
Patients with a history of serious allergic reactions to human granulocyte colony-stimulating factors such as filgrastim or pegfilgrastim products. (4)

----------WARNINGS AND PRECAUTIONS----------
- Fatal splenic rupture: Evaluate patients who report left upper abdominal or shoulder pain for an enlarged spleen or splenic rupture. (5.1)
- Acute respiratory distress syndrome (ARDS): Evaluate patients who develop fever and lung infiltrates or respiratory distress for ARDS. Discontinue ZARXIO in patients with ARDS. (5.2)
- Serious allergic reactions, including anaphylaxis: Permanently discontinue ZARXIO in patients with serious allergic reactions. (5.3)
- Fatal sickle cell crises: Have occurred. (5.4)

----------ADVERSE REACTIONS----------
Most common adverse reactions in patients: (6.1)

- With nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs (≥ 5% difference in incidence compared to placebo) are pyrexia, pain, rash, cough, and dyspnea
- With AML (≥ 2% difference in incidence) are pain, epistaxis and rash
- With nonmyeloid malignancies undergoing myeloablative chemotherapy followed by BMT (≥ 5% difference in incidence) is rash
- Undergoing peripheral blood progenitor cell mobilization and collection (≥ 5% incidence) are bone pain, pyrexia and headache. (6.1)
- (Symptomatic) with severe chronic neutropenia (SCN) (≥ 5% difference in incidence) are pain, anemia, epistaxis, 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*.

----------USE IN SPECIFIC POPULATIONS----------
- ZARXIO should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. (8.1)
- It is not known whether filgrastim products are excreted in human milk. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: [3/2015]

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 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 *[see Clinical Studies (14.1)]*.

1.2 Patients with Acute Myeloid Leukemia Receiving Induction or Consolidation Chemotherapy

ZARXIO is indicated for reducing the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of patients with acute myeloid leukemia (AML) *[see Clinical Studies (14.2)]*.

1.3 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 *[see Clinical Studies (14.3)]*.

1.4 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 *[see Clinical Studies (14.4)]*.

1.5 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 *[see Clinical Studies (14.5)]*.

2 DOSAGE AND ADMINISTRATION

2.1 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 *[see Warnings and Precautions (5.9)]*.

Administer ZARXIO at least 24 hours after cytotoxic chemotherapy. Do not administer ZARXIO within the 24-hour period prior to chemotherapy *[see Warnings and Precautions (5.11)]*. 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.

2.2 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 Table 1).

Table 1: 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[a]
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

[a] 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.

2.3 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 10mcg/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 *[see Clinical Studies (14.4)]*. 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.

2.4 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.

2.5 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 *[see Instructions for Use]*.

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 0.1mL 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) *[see Dosage Forms and Strengths (3)]*. 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

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*.

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 intraveneous 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.

3 DOSAGE FORMS AND STRENGTHS

- Injection: 300 mcg/0.5 mL in a single-use prefilled syringe with BD UltraSafe Passive™ Needle Guard
- Injection: 480 mcg/0.8 mL in a single-use prefilled syringe with BD UltraSafe Passive™ Needle Guard

4 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 *[see Warnings and Precautions (5.3)]*.

5 WARNINGS AND PRECAUTIONS
5.1 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.

5.2 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.

5.3 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.

5.4 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.

5.5 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.

5.6 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.

5.7 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 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.

5.8 Thrombocytopenia
Thrombocytopenia has been reported in patients receiving filgrastim products. Monitor platelet counts.

5.9 Leukocytosis
<u>Patients with Cancer Receiving Myelosuppressive Chemotherapy</u>
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 *[see Warnings and Precautions (5.13)]*. 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.

<u>Peripheral Blood Progenitor Cell Collection and Therapy</u>
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.

5.10 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.

5.11 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.

5.12 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 *[see Dosage and Administration (2.2)]*.

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.

5.13 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.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the labeling:

- Splenic Rupture [see Warnings and Precautions (5.1)]
- Acute Respiratory Distress Syndrome [see Warnings and Precautions (5.2)]
- Serious Allergic Reactions [see Warnings and Precautions (5.3)]
- Sickle Cell Disorders [see Warnings and Precautions (5.4)]
- Alveolar Hemorrhage and Hemoptysis [see Warnings and Precautions (5.5)]
- Capillary Leak Syndrome [see Warnings and Precautions (5.6)]
- Thrombocytopenia [see Warnings and Precautions (5.8)]
- Leukocytosis [see Warnings and Precautions (5.9)]
- Cutaneous Vasculitis [see Warnings and Precautions (5.10)]

6.1 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.

<u>Adverse Reactions in Patients with Cancer Receiving Myelosuppressive Chemotherapy</u>

The following adverse reaction data in Table 2 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, methylprednisolone, and methotrexate ("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, and1% Asian.

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

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%.

Adverse events with ≥ 5% higher incidence in filgrastim patients compared to placebo and associated with the sequelae of the underlying malignancy or cytotoxic chemotherapy delivered included anemia, constipation, diarrhea, oral pain, vomiting, asthenia, malaise, edema peripheral, hemoglobin decreased, decreased appetite, oropharyngeal pain, and alopecia.

Adverse Reactions in Patients with Acute Myeloid Leukemia

Adverse reaction data below are from a randomized, double-blind, placebo-controlled study in patients with AML (Study 4) who received an induction chemotherapy regimen of intravenous daunorubicin days 1, 2, and 3; cytosine arabinoside days 1 to 7; and etoposide days 1 to 5 and up to 3 additional courses of therapy (induction 2, and consolidation 1, 2) of intravenous daunorubicin, cytosine arabinoside, and etoposide. The safety population included 518 patients randomized to receive either 5 mcg/kg/day filgrastim (n = 257) or placebo (n = 261). The median age was 54 (range 16 to 89) years and 54% were male.

Adverse reactions with ≥ 2% higher incidence in filgrastim patients compared to placebo included epistaxis, back pain, pain in extremity, erythema, and rash maculo-papular.

Adverse events with ≥ 2% higher incidence in filgrastim patients compared to placebo and associated with the sequelae of the underlying malignancy or cytotoxic chemotherapy included diarrhea, constipation, and transfusion reaction.

Adverse Reactions in Patients with Cancer Undergoing Bone Marrow Transplantation

The following adverse reaction data are from one randomized, no treatment-controlled study in patients with acute lymphoblastic leukemia or lymphoblastic lymphoma receiving high-dose chemotherapy (cyclophosphamide or cytarabine, and melphalan) and total body irradiation (Study 5) and one randomized, no treatment controlled study in patients with Hodgkin's disease (HD) and NHL undergoing high-dose chemotherapy and autologous bone marrow transplantation (Study 6). Patients receiving autologous bone marrow transplantation only were included in the analysis. A total of 100 patients received either 30 mcg/kg/day as a 4 hour infusion (Study 5) or 10 mcg/kg/day or 30 mcg/kg/day as a 24 hour infusion (Study 6) filgrastim (n = 72), no treatment control or placebo (n = 28). The median age was 30 (range 15 to 57) years, 57% were male.

Adverse reactions with ≥ 5% higher incidence in filgrastim patients compared to patients receiving no filgrastim included rash and hypersensitivity.

Adverse reactions in patients receiving intensive chemotherapy followed by autologous BMT with ≥ 5% higher incidence in filgrastim patients compared to patients receiving no filgrastim included thrombocytopenia, anemia, hypertension, sepsis, bronchitis, and insomnia.

Adverse Reactions in Patients with Cancer Undergoing Autologous Peripheral Blood Progenitor Cell Collection The adverse reaction data in Table 3 are from a series of 7 trials in patients with cancer undergoing mobilization of autologous peripheral blood progenitor cells for collection by leukapheresis. Patients (n = 166) in all these trials underwent a similar mobilization/collection regimen: filgrastim was administered for 6 to 8 days, in most cases the apheresis procedure occurred on days 5, 6, and 7. The dosage of filgrastim ranged between 5 to 30 mcg/kg/day and was administered subcutaneously by injection or continuous infusion. The median age was 39 (range 15 to 67) years, and 48% were male.

Table 3. Adverse Reactions in Patients with Cancer Undergoing Autologous PBPC in the Mobilization Phase (≥ 5% Incidence in Filgrastim Patients)

System Organ Class	Mobilization Phase (N = 166)
Musculoskeletal and connective tissue disorders	
Bone pain	30%
General disorders and administration site conditions	
Pyrexia	16%
Investigations	
Blood alkaline phosphatase increased	11%
Nervous system disorders	
Headache	10%

Adverse Reactions in Patients with Severe Chronic Neutropenia

The following adverse reaction data were identified in a randomized, controlled study in patients with SCN receiving filgrastim (Study 7). 123 patients were randomized to a 4 month observation period followed by subcutaneous filgrastim treatment or immediate subcutaneous filgrastim treatment. The median age was 12 years (range 7 months to 76 years) and 46% were male. The dosage of filgrastim was determined by the category of neutropenia.

Initial dosage of filgrastim:

- Idiopathic neutropenia: 3.6 mcg/kg/day
- Cyclic neutropenia: 6 mcg/kg/day
- Congenital neutropenia: 6 mcg/kg/day divided 2 times per day

The dosage was increased incrementally to 12 mcg/kg/day divided 2 times per day if there was no response. Adverse

reactions with ≥ 5% higher incidence in filgrastim patients compared to patients receiving no filgrastim included arthralgia, bone pain, back pain, muscle spasms, musculoskeletal pain, pain in extremity, splenomegaly, anemia, upper respiratory tract infection, and urinary tract infection (upper respiratory tract infection and urinary tract infection were higher in the filgrastim arm, total infection related events were lower in filgrastim treated patients), epistaxis, chest pain, diarrhea, hypoesthesia, and alopecia.

6.2 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The incidence of antibody development in patients receiving filgrastim has not been adequately determined. While available data suggest that a small proportion of patients developed binding antibodies to filgrastim, the nature and specificity of these antibodies has not been adequately studied. In clinical studies using filgrastim, the incidence of antibodies binding to filgrastim was 3% (11/333). In these 11 patients, no evidence of a neutralizing response was observed using a cell-based bioassay. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay, and the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, timing of sampling, sample handling, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to filgrastim reported in this section with the incidence of antibodies in other studies or to other filgrastim products may be misleading.

Cytopenias resulting from an antibody response to exogenous growth factors have been reported on rare occasions in patients treated with other recombinant growth factors.

6.3 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of filgrastim products. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- splenic rupture and splenomegaly (enlarged spleen) *[see Warnings and Precautions (5.1)]*
- acute respiratory distress syndrome *[see Warnings and Precautions (5.2)]*
- anaphylaxis *[see Warnings and Precautions (5.3)]*
- sickle cell disorders *[see Warnings and Precautions (5.4)]*
- alveolar hemorrhage and hemoptysis *[see Warnings and Precautions (5.5)]*
- capillary leak syndrome *[see Warnings and Precautions (5.6)]*
- leukocytosis *[see Warnings and Precautions (5.9)]*
- cutaneous vasculitis *[see Warnings and Precautions (5.10)]*
- Sweet's syndrome (acute febrile neutrophilic dermatosis)
- decreased bone density and osteoporosis in pediatric patients receiving chronic treatment with filgrastim products.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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 embryo-fetal 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).

8.3 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.

8.4 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.

The safety and effectiveness of filgrastim have been established in pediatric patients with SCN *[see Clinical Studies (14.5)]*. 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) *[see Indications and Usage (1.5), Dosage and Administration (2.5), and Clinical Studies (14.5)]*.

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 *[see Warnings and Precautions (5.7), Adverse Reactions (6)]*.

8.5 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 (i.e., 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.

10 OVERDOSAGE

The maximum tolerated dose of filgrastim products has not been determined. In filgrastim clinical trials of patients with cancer receiving myelosuppressive chemotherapy, WBC counts > 100,000/mm^3 have been reported in less than 5% of patients, but were not associated with any reported adverse clinical effects. Patients in the BMT studies received up to 138 mcg/kg/day without toxic effects, although there was a flattening of the dose response curve above daily doses of greater than 10 mcg/kg/day.

11 DESCRIPTION

ZARXIO (filgrastim-sndz) is a 175 amino acid human granulocyte colony-stimulating factor (G-CSF) manufactured by recombinant DNA technology.

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.

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-use prefilled syringes. The single-use prefilled syringes contain either 300 mcg/0.5 mL or 480 mcg/0.8 mL of filgrastim-sndz. See table below for product composition of each single-use 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

12 CLINICAL PHARMACOLOGY

12.1 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.

12.2 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 to70 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, Dohle 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.

12.3 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 *[see Use in Specific Populations (8.6)]*.

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

The pharmacokinetics of filgrastim were studied in pediatric patients with advanced neuroblastoma *[see Use in Specific Populations (8.4)]*, in subjects with renal impairment, and in subjects with hepatic impairment.

Pediatric Patients: 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 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.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenic potential of filgrastim has not been studied. Filgrastim failed to induce bacterial gene mutations in either the presence or absence of a drug metabolizing enzyme system. Filgrastim had no observed effect on the fertility of male or female rats at doses up to 500 mcg/kg.

13.2 Animal Toxicology and/or Pharmacology

Filgrastim was administered to monkeys, dogs, hamsters, rats, and mice as part of a nonclinical toxicology program, which included studies up to 1 year duration.

In the repeated-dose studies, changes observed were attributable to the expected pharmacological actions of filgrastim (i.e., dose-dependent increases in white blood cell counts, increased circulating segmented neutrophils, and increased myeloid:erythroid ratio in bone marrow). Histopathologic examination of the liver and spleen revealed evidence of ongoing extramedullary granulopoiesis, and dose-related increases in spleen weight were seen in all species. These changes all reversed after discontinuation of treatment.

14 CLINICAL STUDIES

14.1 Patients with Cancer Receiving Myelosuppressive Chemotherapy

The safety and efficacy of filgrastim to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs were established in a randomized, double-blind, placebo-controlled trial conducted in patients with small cell lung cancer (Study 1).

In Study 1, patients received up to 6 cycles of intravenous chemotherapy including intravenous cyclophosphamide and doxorubicin on day 1; and etoposide on days 1, 2, and 3 of 21 day cycles. Patients were randomized to receive filgrastim (n=99) at a dose of 230 mcg/m^2 (4 to 8 mcg/kg/day) or placebo (n=111). Study drug was administered subcutaneously daily beginning on day 4, for a maximum of 14 days. A total of 210 patients were evaluable for efficacy and 207 were evaluable for safety. The demographic and disease characteristics were balanced between arms with a median age of 62 (range 31 to 80) years; 64% males; 89% Caucasian; 72% extensive disease and 28% limited disease.

The main efficacy endpoint was the incidence of febrile neutropenia. Febrile neutropenia was defined as an ANC < 1000/mm^3 and temperature > 38.2°C. Treatment with filgrastim resulted in a clinically and statistically significant reduction in the incidence of infection, as manifested by febrile neutropenia, 40% for filgrastim-treated patients and 76% for placebo-treated patients ($p < 0.001$). There were also statistically significant reductions in the incidence and overall duration of infection manifested by febrile neutropenia; the incidence, severity and duration of severe neutropenia (ANC < 500/mm^3); the incidence and overall duration of hospital admissions; and the number of reported days of antibiotic use.

14.2 Patients with Acute Myeloid Leukemia Receiving Induction or Consolidation Chemotherapy

The safety and efficacy of filgrastim 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) was established in a randomized, double-blind, placebo-controlled, multi-center trial in patients with newly diagnosed, *de novo* AML (Study 4).

In Study 4 the initial induction therapy consisted of intravenous daunorubicin days 1, 2, and 3; cytosine arabinoside days 1 to 7; and etoposide days 1 to 5. Patients were randomized to receive subcutaneous filgrastim (n=259) at a dose of 5 mcg/kg/day or placebo (n=262) from 24 hours after the last dose of chemotherapy until neutrophil recovery (ANC ≥1000/mm^3 for 3 consecutive days or ≥ 10,000/mm^3 for 1 day) or for a maximum of 35 days. The demographic and disease characteristics were balanced between arms with a median age of 54 (range 16 to 89) years; 54% males; initial white count (65% - <25,000 /mm^3 and 27% > 100,000/mm^3); 29% unfavorable cytogenetics.

The main efficacy endpoint was median duration of severe neutropenia defined as neutrophil count < 500/mm^3. Treatment with filgrastim resulted in a clinically and statistically significant reduction in median number of days of severe neutropenia, filgrastim-treated patients 14 days, placebo-treated patients 19 days ($p = 0.0001$: difference of 5 days (95% CI: -6.0, -4.0)). There was a reduction in the median duration of intravenous antibiotic use, filgrastim-treated patients: 15 days versus placebo-treated patients: 18.5 days; a reduction in the median duration of hospitalization, filgrastim-treated patients: 20 days versus placebo-treated patients: 25 days. There were no statistically significant differences between the filgrastim and the placebo groups in complete remission rate (69% - filgrastim, 68% - placebo), median time to progression of all randomized patients (165 days - filgrastim, 186 days - placebo), or median overall survival (380 days - filgrastim, 425 days - placebo).

14. 3 Patients with Cancer Undergoing Bone Marrow Transplantation

The safety and efficacy of filgrastim to reduce the duration of neutropenia in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by autologous bone marrow transplantation was evaluated in 2 randomized controlled trials of patients with lymphoma (Study 6 and Study 9). The safety and efficacy of filgrastim to reduce the duration of neutropenia in patients undergoing myeloablative chemotherapy followed by allogeneic bone marrow transplantation was evaluated in a randomized placebo controlled trial (Study10).

In Study 6 patients with Hodgkin's disease received a preparative regimen of intravenous cyclophosphamide, etoposide, and BCNU ("CVP"), and patients with non-Hodgkin's lymphoma received intravenous BCNU, etoposide, cytosine arabinoside and melphalan ("BEAM"). There were 54 patients randomized 1:1:1 to control, filgrastim 10 mcg/kg/day, and filgrastim 30 mcg/kg/day as a 24 hour continuous infusion starting 24 hours after bone marrow infusion for a maximum of 28 days. The median age was 33 (range 17 to 57) years; 56% males; 69% Hodgkin's

disease and 31% non-Hodgkin's lymphoma.

The main efficacy endpoint was duration of severe neutropenia ANC < 500/mm^3. A statistically significant reduction in the median number of days of severe neutropenia (ANC < 500/mm^3) occurred in the filgrastim- treated groups versus the control group (23 days in the control group, 11 days in the 10 mcg/kg/day group, and 14 days in the 30 mcg/kg/day group [11 days in the combined treatment groups, p = 0.004]).

In Study 9, patients with Hodgkin's disease and non-Hodgkin's lymphoma received a preparative regimen intravenous cyclophosphamide, etoposide, and BCNU ("CVP"). There were 43 evaluable patients randomized to continuous subcutaneous infusion filgrastim 10 mcg/kg/day (n=19), filgrastim 30 mcg/kg/day (n=10) and no treatment (n=14) starting the day after marrow infusion for maximum of 28 days. The median age was 33 (range 17 to 56) years; 67% males; 28% Hodgkin's disease and 72% non-Hodgkin's lymphoma.

The main efficacy endpoint was duration of severe neutropenia. There was statistically significant reduction in the median number of days of severe neutropenia (ANC < 500/mm^3) in the filgrastim-treated groups versus the control group (21.5 days in the control group versus 10 days in the filgrastim-treated groups, p < 0.001). The number of days of febrile neutropenia was also reduced significantly in this study (13.5 days in the control group versus 5 days in the filgrastim-treated groups, p < 0.0001).

In Study 10, 70 patients scheduled to undergo bone marrow transplantation for multiple underlying conditions using multiple preparative regimens were randomized to receive filgrastim 300 mcg/m^2/day (n=33) or placebo (n=37) days 5 through 28 after marrow infusion. The median age was 18 (range 1 to 45) years, 56% males. The underlying disease was: 67% hematologic malignancy, 24% aplastic anemia, 9% other. A statistically significant reduction in the median number of days of severe neutropenia occurred in the treated group versus the control group (19 days in the control group and 15 days in the treatment group, p < 0.001) and time to recovery of ANC to ≥ 500/mm^3 (21 days in the control group and 16 days in the treatment group, p < 0.001).

14.4 Patients Undergoing Autologous Peripheral Blood Progenitor Cell Collection and Therapy

The safety and efficacy of filgrastim to mobilize autologous peripheral blood progenitor cells for collection by leukapheresis was supported by the experience in uncontrolled trials, and a randomized trial comparing hematopoietic stem cell rescue using filgrastim mobilized autologous peripheral blood progenitor cells to autologous bone marrow (Study 11). Patients in all these trials underwent a similar mobilization/collection regimen: filgrastim was administered for 6 to 7 days, in most cases the apheresis procedure occurred on days 5, 6, and 7. The dose of filgrastim ranged between 10 to 24 mcg/kg/day and was administered subcutaneously by injection or continuous intravenous infusion.

Engraftment was evaluated in 64 patients who underwent transplantation using filgrastim mobilized autologous hematopoietic progenitor cells in uncontrolled trials. Two of the 64 patients (3%) did not achieve the criteria for engraftment as defined by a platelet count ≥ 20,000/mm^3 by day 28. In clinical trials of filgrastim for the mobilization of hematopoietic progenitor cells, filgrastim was administered to patients at doses between 5 to 24 mcg/kg/day after reinfusion of the collected cells until a sustainable ANC (≥ 500/mm^3) was reached. The rate of engraftment of these cells in the absence of filgrastim post transplantation has not been studied.

Study 11 was a randomized, unblinded study of patients with Hodgkin's disease or non-Hodgkin's lymphoma undergoing myeloablative chemotherapy, 27 patients received filgrastim-mobilized autologous hematopoietic progenitor cells and 31 patients received autologous bone marrow. The preparative regimen was intravenous BCNU, etoposide, cytosine arabinoside and melphalan ("BEAM"). Patient received daily filgrastim 24 hours after stem cell infusion at a dose of 5 mcg/kg/day. The median age was 33 (range 1 to 59) years; 64% males; 57% Hodgkin's disease and 43% non-Hodgkin's lymphoma. The main efficacy endpoint was number of days of platelet transfusions. Patients randomized to filgrastim-mobilized autologous peripheral blood progenitor cells compared to autologous bone marrow had significantly fewer days of platelet transfusions (median 6 vs 10 days).

14.5 Patients with Severe Chronic Neutropenia

The safety and efficacy of filgrastim to reduce the incidence and duration of sequelae of neutropenia (that is fever, infections, oropharyngeal ulcers) in symptomatic adult and pediatric patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia was established in a randomized controlled trial conducted in patients with

severe neutropenia (Study 7).

Patients eligible for Study 7 had a history of severe chronic neutropenia documented with an ANC < 500/mm^3 on three occasions during a 6 month period, or in patients with cyclic neutropenia 5 consecutive days of ANC < 500/mm^3 per cycle. In addition patients must have experienced a clinically significant infection during the previous 12 months. Patients were randomized to a 4 month observation period followed by filgrastim treatment or immediate filgrastim treatment. The median age was 12 years (range 7 months to 76 years); 46% males; 34% idiopathic, 17% cyclic and 49% congenital neutropenia. Filgrastim was administered subcutaneously. The dose of filgrastim was determined by the category of neutropenia.

Initial dose of filgrastim:

- Idiopathic neutropenia: 3.6 mcg/kg/day
- Cyclic neutropenia: 6 mcg/kg/day
- Congenital neutropenia: 6 mcg/kg/day divided 2 times per day

The dose was increased incrementally to 12 mcg/kg/day divided 2 times per day if there was no response.

The main efficacy endpoint was response to filgrastim treatment. ANC response from baseline (< 500/mm^3) was defined as follows:

- Complete response: median ANC > 1500/mm^3
- Partial response: median ANC ≥ 500/mm^3 and ≤ 1500/mm^3 with a minimum increase of 100%
- No response: median ANC < 500/mm^3

There were 112 of 123 patients who demonstrated a complete or partial response to filgrastim treatment.

Additional efficacy endpoints included a comparison between patients randomized to 4 months of observation and patients receiving filgrastim of the following parameters:

- incidence of infection
- incidence of fever
- duration of fever
- incidence, duration, and severity of oropharyngeal ulcers
- number of days of antibiotic use

The incidence for each of these 5 clinical parameters was lower in the filgrastim arm compared to the control arm for cohorts in each of the 3 major diagnostic categories. An analysis of variance showed no significant interaction between treatment and diagnosis, suggesting that efficacy did not differ substantially in the different diseases. Although filgrastim substantially reduced neutropenia in all patient groups, in patients with cyclic neutropenia, cycling persisted but the period of neutropenia was shortened to 1 day.

16 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. Do not shake. Do not Freeze. 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.

17 PATIENT COUNSELING INFORMATION

Review the steps for direct patient administration with patients and caregivers. Training should aim to ensure that patients and caregivers can successfully perform all of the steps in the Instructions for use of ZARXIO prefilled syringe with BD UltraSafe Passive™ Needle Guard, including showing the patient or caregiver how to measure the required dose, particularly if a patient is on a dose other than the entire 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 *[see Instructions for Use]*.

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Advise patients of the following risks and potential risks with ZARXIO:

- Rupture or enlargement of the spleen may occur. Symptoms include left upper quadrant abdominal pain or left shoulder pain. Advise patients to report pain in these areas to their physician immediately *[see Warnings and Precautions (5.1)]*.
- Serious allergic reactions may occur, which may be signaled by rash, facial edema, wheezing, dyspnea, hypotension, or tachycardia. Advise patient to seek immediate medical attention if signs or symptoms of hypersensitivity reaction occur *[see Warnings and Precautions (5.2)]*.
- Dyspnea, with or without fever, progressing to Acute Respiratory Distress Syndrome, may occur. Advise patients to report dyspnea to their physician immediately *[see Warnings and Precautions (5.3)]*.
- In patients with sickle cell disease, sickle cell crisis and death have occurred. Discuss potential risks and benefits for patients with sickle cell disease prior to the administration of human granulocyte colony-stimulating factors *[see Warnings and Precautions (5.4)]*.
- Cutaneous vasculitis may occur, which may be signaled by purpura or erythema. Advise patients to report signs or symptoms of vasculitis to their physician immediately *[see Warnings and Precautions (5.10)]*.
- Advise females of reproductive potential that ZARXIO should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus *[see Use in Special Populations (8.1)]*.

ZARXIO™ (filgrastim-sndz)

ZARXIO is a trademark of Novartis AG
Manufactured by:
Sandoz Inc., Princeton, NJ 08540
US License No. 2003
At:
GP Grenzach Produktions GmbH
Grenzach-Wyhlen, Germany
Product of Austria

Patient Information
ZARXIO (zar-zee-oh)
(filgrastim-sndz) injection

What is ZARXIO?

ZARXIO is a man-made form of granulocyte colony-stimulating factor (G-CSF). G-CSF is a substance produced by the body. It stimulates the growth of neutrophils, a type of white blood cell important in the body's fight against infection.

Do not take ZARXIO if you have had a serious allergic reaction to human G-CSFs such as filgrastim or pegfilgrastim products.

Before you take ZARXIO, tell your doctor about all of your medical conditions, including if you:

- have a sickle cell disorder.
- are receiving radiation therapy.
- are allergic to latex. The needle cap on the prefilled syringe contains natural rubber (derived from latex). Do not handle the prefilled syringe if you are allergic to latex.
- are pregnant or plan to become pregnant. It is not known if ZARXIO will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if ZARXIO passes into your breast milk.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How will I receive ZARXIO?

- **ZARXIO injections can be given by a doctor or nurse by intravenous (IV) infusion or under your skin (subcutaneous injection). Your doctor may decide subcutaneous injections can be given at home by you or your caregiver. If ZARXIO is given at home, see the detailed "Instructions for Use" that comes with your ZARXIO for information on how to prepare and inject a dose of ZARXIO.**
- You and your caregiver will be shown how to prepare and inject ZARXIO before you use it.
- Your doctor will tell you how much ZARXIO to inject and when to inject it. Do not change your dose unless your doctor tells you to.
- You should not inject a dose of ZARXIO less than 0.3 mL (180 mcg) from a ZARXIO prefilled syringe. A dose less than 0.3 mL cannot be accurately measured using the ZARXIO prefilled syringe.
- If you are receiving ZARXIO because you are also receiving chemotherapy, the last dose of ZARXIO should be injected at least 24 hours before your next dose of chemotherapy.
- If you miss a dose of Zarxio, talk to your doctor about when you should give your next dose.
- Your doctor will do blood tests before and during treatment with ZARXIO to check your blood cell counts and to check you for side effects.

What are the possible side effects of ZARXIO?

ZARXIO may cause serious side effects, including:

- **Spleen rupture.** Your spleen may become enlarged and can rupture. A ruptured spleen can cause death. Call your doctor right away if you have pain in the left upper stomach (abdomen) area or your left shoulder.
- **A serious lung problem called acute respiratory distress syndrome (ARDS).** Call your doctor or get emergency medical help right away if you have shortness of breath with or without a fever, trouble breathing, or a fast rate of breathing.
- **Serious allergic reactions.** ZARXIO can cause serious allergic reactions. These reactions can cause a rash over your whole body, shortness of breath, wheezing, dizziness, swelling around your mouth or eyes, fast heart rate, and sweating. If you have any of these symptoms, stop using ZARXIO and call your doctor or get emergency medical help right away.
- **Sickle cell crises.** You may have a serious sickle cell crisis if you have a sickle cell disorder and take ZARXIO. Serious sickle cell crises has happened in people with sickle cell disorders receiving filgrastim, that has sometimes led to death. Call your doctor right away if you have symptoms of sickle cell crisis such as pain or difficulty breathing.
- **Capillary leak syndrome.** ZARXIO can cause fluid to leak from blood vessels into your body's tissues. This condition is called "Capillary Leak Syndrome" (CLS). CLS can quickly cause you to have symptoms that may become life-threatening. Get emergency medical help right away if you develop any of the following symptoms:
  - swelling or puffiness and are urinating less often
  - trouble breathing
  - swelling of your stomach-area (abdomen) and feeling of fullness
  - dizziness or feeling faint
  - a general feeling of tiredness
- **Decreased platelet count (thrombocytopenia).** Your doctor will check your blood during treatment with ZARXIO. Tell your doctor if you have unusual bleeding or bruising ZARXIO. This could mean a decrease of platelets, which

reduces the ability of blood to clot.

- **Increased white blood cell count (leukocytosis).** Your doctor will check your blood during treatment with ZARXIO.
- **Inflammation of your blood vessels (cutaneous vasculitis).** Tell your doctor if you develop purple spots or redness of your skin.

The most common side effects of ZARXIO include aching in the bones and muscles.

These are not all the possible side effects of ZARXIO. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store ZARXIO?

- Store ZARXIO in the refrigerator between 36°F to 46°F (2°C to 8°C).
- Avoid freezing ZARXIO. If frozen, thaw in the refrigerator before use. Throw away (dispose of) ZARXIO if it has been frozen more than 1 time.
- Store ZARXIO in the original pack to protect it from light.
- Do not shake ZARXIO.
- Take ZARXIO out of the refrigerator 30 minutes before use and allow it to reach room temperature before preparing an injection.
- ZARXIO may be allowed to reach room temperature for up to 24 hours. **Throw away (dispose of) any ZARXIO that has been left at room temperature for longer than 24 hours.**
- After you inject your dose, throw away (dispose of) any unused ZARXIO left in the prefilled syringe. Do not save unused ZARXIO in the prefilled syringe for later use.

Keep ZARXIO and all medicines out of the reach of children.

General information about the safe and effective use of ZARXIO:

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use ZARXIO for a condition for which it was not prescribed. Do not give ZARXIO to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or doctor for information about ZARXIO that is written for health professionals.

What are the ingredients in ZARXIO?

Active ingredient: filgrastim-sndz

Inactive ingredients: glutamic acid, polysorbate 80, sorbitol, sodium hydroxide, water for injection USP

Manufactured by: Sandoz Inc., Princeton, NJ 08540 At: GP Grenzach Produktions GmbH, Grenzach-Wyhlen, Germany, Product of Austria
For more information visit www.zarxio.com or call 1-800-525-8747.

This Patient Information has been approved by the U.S. Food and Drug Administration. Issued: March 2015

Instructions for Use

ZARXIO (zar-zee-oh)

(filgrastim-sndz) injection

Important:

- **Do not inject yourself or someone else until you have been shown how to inject ZARXIO.** Your doctor or nurse will show you how to prepare and inject ZARXIO properly using the ZARXIO prefilled syringe with UltraSafe Passive™ Needle Guard. Talk to your doctor or nurse if you have any questions.
- You should not inject a dose of ZARXIO less than 0.3 mL (180 mcg) from a ZARXIO prefilled syringe. A dose less than 0.3 mL cannot be accurately measured using the ZARXIO prefilled syringe.
- **Do not use** the ZARXIO prefilled syringe if either the seal on the outer pack or the seal of the blister are broken.
- Keep the ZARXIO prefilled syringe in the sealed pack until you are ready to use it.
- **The needle cap on the prefilled syringe contains natural rubber (derived from latex). Do not handle the prefilled syringe if you are allergic to latex.**
- The prefilled syringe has a needle guard that will be activated to cover the needle after the injection is given. The needle guard will help prevent needle stick injuries to anyone who handles the prefilled syringe.
- Avoid touching the syringe needle guard wings before use. Touching them may cause the syringe needle guard to be activated too early.
- Do not remove the needle cap until just before you give the injection.
- Throw away (dispose of) the used ZARXIO prefilled syringe right away after use. **Do not re-use a ZARXIO prefilled syringe.** See “How should I dispose of used ZARXIO prefilled syringes?” at the end of this Instructions for Use.

How should I store ZARXIO?

- Store ZARXIO in the refrigerator between 36°F to 46°F (2°C to 8°C).
- Avoid freezing ZARXIO. If frozen, thaw in the refrigerator before use. Throw away (dispose of) if it has been frozen more than 1 time.
- Store ZARXIO in the original pack to protect it from light.
- Do not shake ZARXIO.
- Take ZARXIO out of the refrigerator 30 minutes before use and allow it to reach room temperature before preparing an injection.
- ZARXIO may be allowed to reach room temperature for up to 24 hours. **Throw away (dispose of) any ZARXIO that has been left at room temperature for longer than 24 hours.**
- After you inject your dose, throw away (dispose of) any unused ZARXIO left in the prefilled syringe. Do not save unused ZARXIO in the prefilled syringe for later use.

Keep ZARXIO and all medicines out of the reach of children.

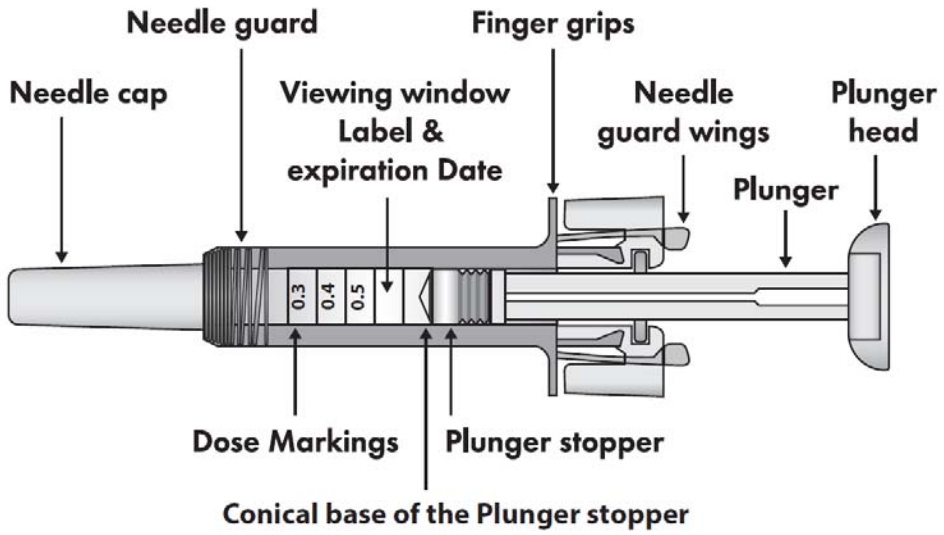
About the ZARXIO prefilled syringe:

- ZARXIO prefilled syringes come in two strengths. Depending on your prescription, you will receive ZARXIO prefilled syringes that contain 300 mcg/0.5 mL or 480 mcg/0.8 mL of medicine. Your doctor will determine the dose in milliliters (mL) that you will need to give based on your body weight.
- When you receive your ZARXIO prefilled syringes, always check to see that the:
  - name ZARXIO appears on the pack and prefilled syringe label.

- expiration date on the prefilled syringe label has not passed. **You should not use a prefilled syringe after the date on the label.**
- strength of ZARXIO (number of micrograms on the pack containing the prefilled syringe) is the same as what your doctor prescribed.

ZARXIO prefilled syringe parts (see Figure A). ZARXIO 300 mcg /0.5 mL prefilled syringe is shown as an example.

Figure A



What you need for your injection:

Included in the pack:

- A new ZARXIO prefilled syringe

Not included in the pack **(see Figure B):**

- 1 Alcohol wipe
- 1 Cotton ball or gauze
- Sharps disposal container

Figure B

See **"How should I dispose of used ZARXIO prefilled syringes?"** at the end of this Instructions for Use.

Preparing the ZARXIO prefilled syringe

Step 1. Find a clean, well-lit, flat work surface.

Step 2. Take the pack containing the ZARXIO prefilled syringe out of the refrigerator and leave it **unopened on your work surface** for about 30 minutes so that it reaches room temperature.

Step 3. Wash your hands well with soap and water.

Step 4. Remove the ZARXIO prefilled syringe from the outer pack and take it out of the blister.

Step 5. Check the expiration date. Do not use the ZARXIO prefilled syringe if the expiration date has passed.

Step 6. Look through the viewing window on the ZARXIO prefilled syringe. The liquid inside should be clear. The color may be colorless to slightly yellow. You may see a small air bubble in the liquid. This is normal. **Do not use** the prefilled syringe if the liquid contains visible particles, or if the liquid is cloudy or discolored. Return the ZARXIO prefilled syringe and the package it came in to your pharmacy.

Step 7. Do not use a ZARXIO prefilled syringe if it is broken. Return the broken prefilled syringe and the package it came in to your pharmacy.

Step 8. Check to make sure that the plastic transparent needle guard is covering the barrel of the glass syringe. If the transparent needle guard is covering the needle cap **(see Figure C)** the needle guard has already been activated. **Do not use the prefilled syringe**.

Get another prefilled syringe that has not been activated and is ready to use **(see Figure D).**

Figure C Do Not Use

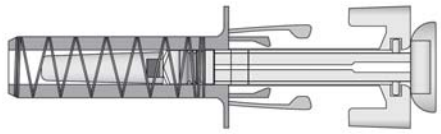


Figure C shows a needle guard that has already been activated. **Do not use a ZARXIO prefilled syringe that has been activated.**

Figure D Ready to Use

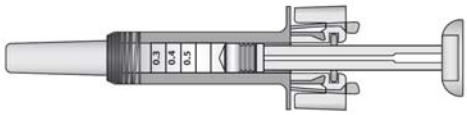


Figure D shows a needle guard that has not yet been activated. The prefilled syringe is ready for use.

Step 9: Choose the injection site:

Figure E

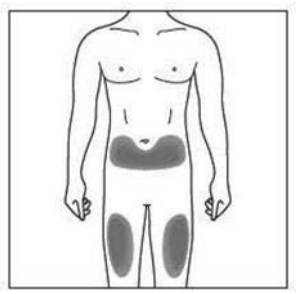
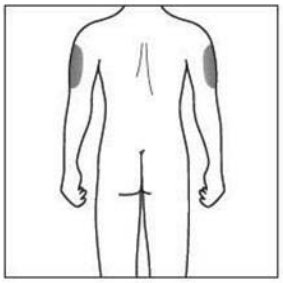


Figure F

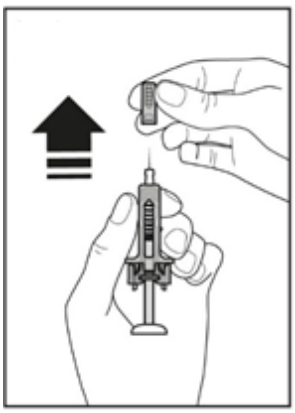


- Areas of your body that you may use as injection sites include:
  - the front of your thighs **(see Figure E)**
  - the lower stomach-area (abdomen), but not the area 2 inches around your navel (belly button) **(see figure E)**
  - upper outer arms, if a caregiver is giving you the injection **(see Figure F)**
- Choose a different site for each injection of ZARXIO.
- **Do not** inject into areas where the skin is tender, bruised, red, scaly or hard. Avoid areas with scars or stretch marks.

Step 10. Clean the injection site using a circular motion with the alcohol wipe. Leave it to dry before injecting. Do not touch the cleaned area again before injecting.

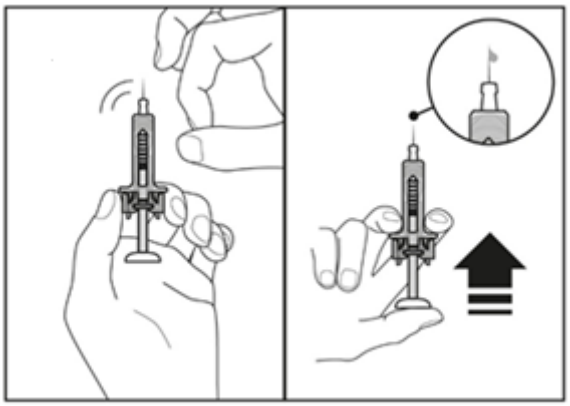
Giving your injection

Figure G



Step 11. Hold the prefilled syringe by the body (the clear plastic needle guard) with the needle pointing up **(see Figure G).** Holding the syringe with the needle pointing up helps to prevent medicine from leaking out of the needle. Carefully pull the needle cap straight off. Throw away the needle cap.

Figure H



Step 12. Check the syringe for an air bubble. Gently tap the syringe with your fingers until the air bubble rises to the top of the syringe (see Figure H). Slowly push the plunger up to push any air out of the syringe and stop when you see a small drop start to appear at the needle tip **(see Figure H).**

Step 13. Holding the syringe as shown, Press slowly on the plunger to push out the excess medicine until the edge of the conical base of the plunger stopper lines up with the syringe marking for your prescribed dose. **See Figure I,** example for a dose of 0.4 mL.

Be careful not to touch the needle guard wings before use. The needle guard may be activated too early.

Check again to make sure the correct dose of Zarxio is in the syringe.

Figure I

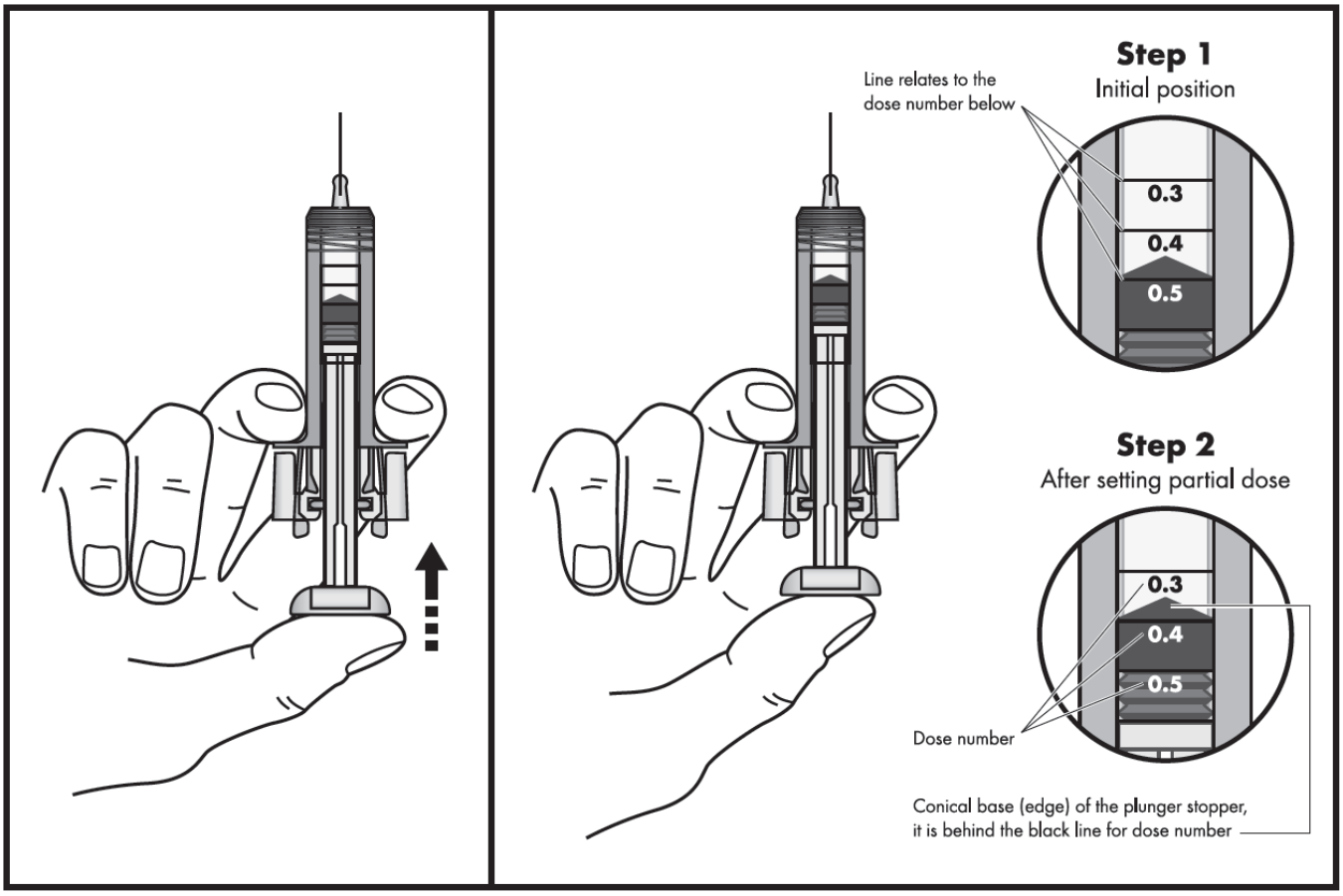
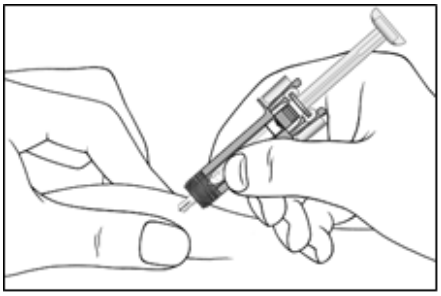
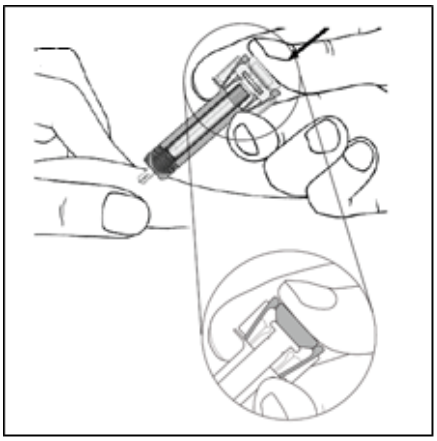


Figure J



Step 14. With one hand gently pinch the skin at the injection site. With your other hand insert the needle into your skin as shown **(see Figure J).** Push the needle all the way in to make sure that you inject your full dose.

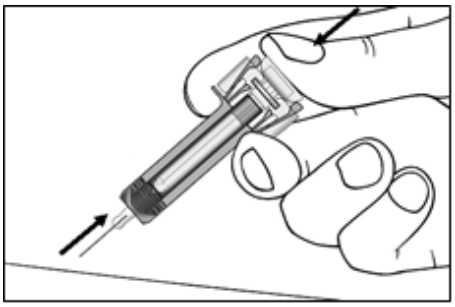
Figure K



Step 15. Hold the Zarxio prefilled syringe as shown **(see Figure K).** Slowly press down on the plunger as far as it will go so that the plunger head is completely between the needle guard wings.

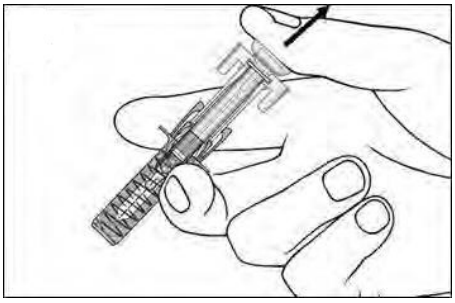
Keep the plunger pressed fully down while you hold the syringe in place for 5 seconds.

Figure L



Step 16. Keep the plunger fully pressed down while you carefully pull the needle straight out from the injection site **(see Figure L).**

Figure M



Step 17. Slowly release the plunger and allow the needle guard to automatically cover the exposed needle **(see Figure M).**

Step 18. There may be a small amount of blood at the injections site. You can press a cotton ball or gauze over the injection site and hold it for 10 seconds. Do not rub the injection site. You may cover the injection site with a small adhesive bandage, if needed.

How should I dispose of (throw away) used ZARXIO prefilled syringes?

Figure N

Put your used prefilled syringes in a FDA-cleared sharps disposal container right away after use **(see Figure N). Do not throw away (dispose of)** ZARXIO prefilled syringes in your household trash.

If you do not have an FDA-cleared sharps disposal container, you may use a household container that is:

- made of a heavy-duty plastic,
- can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
- upright and stable during use,
- leak-resistant, and
- properly labeled to warn of hazardous waste inside the container.

When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles, syringes, and prefilled syringes. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: http://www.fda.gov/safesharpsdisposal.

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Manufactured by: Sandoz Inc., Princeton, NJ 08540
At: GP Grenzach Produktions GmbH, Grenzach-Wyhlen, Germany, Product of Austria

Issued: March/2015

Each 0.5 mL prefilled syringe contains 300 mcg filgrastim-sndz, glutamic acid (0.736 mg), polysorbate 80 (0.02 mg), sorbitol (25 mg) and water for injection. Sodium hydroxide may be added to adjust pH.

Single use only. Read the full prescribing information before use.

No U.S. standard of potency.

KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.

Store in a refrigerator at 2° to 8°C (36° to 46°F). Do Not Freeze. Do Not Shake.

Keep the prefilled syringe in the outer carton in order to protect from light.

For more information visit www.zarxio.com or call 1-800-525-8747

Manufactured by:
Sandoz Inc.
Princeton, NJ 08540
US License No. 2003

At:
GP Grenzach Produktions GmbH
Grenzach-Wyhlen, Germany
Product of Austria

03-2015M

N 3 61314-304-01 8

Zarxio™ (filgrastim-sndz) Injection 300 mcg/0.5 mL

SANDOZ a Novartis company

Pharma Code

46154219

Zarxio™ (filgrastim-sndz) Injection

300 mcg/0.5 mL

NDC 61314-304-01

A recombinant Granulocyte Colony-Stimulating Factor (rG-CSF) derived from *E Coli*.

No Preservative.

Refrigerate. Do Not Freeze.

Caution: Contains Natural Rubber Latex Which May Cause Allergic Reaction.

For Subcutaneous Use or Intravenous Use Only

Single-Use Only

1 prefilled syringe with a needle guard

℞ only

SANDOZ a Novartis company

Lot
EXP

Pharma Code

Zarxio™ (filgrastim-sndz) Injection 300 mcg/0.5 mL

SANDOZ a Novartis company

46154219

61314-304-10 Carton 45625b 46154440 03-2015 Layout 1 3/4/15 10:57 AM Page 1

Each 0.5 mL prefilled syringe contains 300 mcg filgrastim-sndz, glutamic acid (0.736 mg), polysorbate 80 (0.02 mg), sorbitol (25 mg) and water for injection. Sodium hydroxide may be added to adjust pH.

Single use only. Read the full prescribing information before use.

No U.S. standard of potency.
KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.

Store in a refrigerator at 2° to 8°C (36° to 46°F). Do Not Freeze. Do Not Shake.

Keep the prefilled syringe in the outer carton in order to protect from light.

For more information visit www.zarxio.com or call 1-800-525-8747

Manufactured by:
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At:
GP Grenzach Produktions GmbH
Grenzach-Wyhlen, Germany
Product of Austria

03-2015M

N 3 61314-304-10 0

Zarxio™ 300 mcg/0.5 mL
(filgrastim-sndz)
Injection

Pharma Code

SANDOZ
a Novartis company

46154440

Zarxio™ 300 mcg/0.5 mL
(filgrastim-sndz)
Injection

46154440

Lot
Exp

Pharma Code

Zarxio™
(filgrastim-sndz)
Injection

NDC 61314-304-10

300 mcg/0.5 mL

For Subcutaneous Use or Intravenous Use Only

Single-Use Only

A recombinant Granulocyte Colony-Stimulating Factor (rG-CSF) derived from *E Coli*.

No Preservative.

Refrigerate. Do Not Freeze.

Caution: Contains Natural Rubber Latex Which May Cause Allergic Reaction.

℞ only

10 prefilled syringes with a needle guard

SANDOZ
a Novartis company

Zarxio™ 300 mcg/0.5 mL
(filgrastim-sndz)
Injection

SANDOZ
a Novartis company

Reference ID: 3711895

Each 0.8 mL prefilled syringe contains 480 mcg filgrastim-sndz, glutamic acid (1.178 mg), polysorbate 80 (0.032 mg), sorbitol (40 mg) and water for injection. Sodium hydroxide may be added to adjust pH.

Single use only. Read the full prescribing information before use.

No U.S. standard of potency.

KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.

Store in a refrigerator at 2° to 8°C (36° to 46°F). Do Not Freeze. Do Not Shake.

Keep the prefilled syringe in the outer carton in order to protect from light.

For more information visit www.zarxio.com or call 1-800-525-8747

Manufactured by:
Sandoz Inc.
Princeton, NJ 08540
US License No. 2003

At:
GP Grenzach Produktions GmbH
Grenzach-Wyhlen, Germany
Product of Austria

03-2015M

N 3 61314-312-01 3

Zarxio™ (filgrastim-sndz) Injection 480 mcg/0.8 mL

SANDOZ a Novartis company

Pharma Code

46154441

Zarxio™ (filgrastim-sndz) Injection 480 mcg/0.8 mL

46154441

Zarxio™
(filgrastim-sndz)
Injection

480 mcg/0.8 mL

NDC 61314-312-01

A recombinant Granulocyte Colony-Stimulating Factor (rG-CSF) derived from *E Coli*.

No Preservative.

Refrigerate. Do Not Freeze.

Caution: Contains Natural Rubber Latex Which May Cause Allergic Reaction.

For Subcutaneous Use or Intravenous Use Only

Single-Use Only

1 prefilled syringe with a needle guard

℞ only

SANDOZ
a Novartis company

Pharma Code

Lot
EXP

61314-312-10 Carton 45625b 46154443 03-2015 Layout 1 3/4/15 10:52 AM Page 1

Each 0.8 mL prefilled syringe contains 480 mcg filgrastim-sndz, glutamic acid (1.178 mg), polysorbate 80 (0.032 mg), sorbitol (40 mg) and water for injection. Sodium hydroxide may be added to adjust pH.

Single use only. Read the full prescribing information before use.

No U.S. standard of potency.
KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.

Store in a refrigerator at 2° to 8°C (36° to 46°F). Do Not Freeze. Do Not Shake.

Keep the prefilled syringe in the outer carton in order to protect from light.

For more information visit www.zarxio.com or call 1-800-525-8747

Manufactured by:
Sandoz Inc.
Princeton, NJ 08540
US License No. 2003

At:
GP Grenzach Produktions GmbH
Grenzach-Wyhlen, Germany
Product of Austria

03-2015M

N 3 61314-312-10 5

Zarxio™ 480 mcg/0.8 mL
(filgrastim-sndz)
Injection

SANDOZ
a Novartis company

Pharma Code

46154443

Zarxio™ 480 mcg/0.8 mL
(filgrastim-sndz)
Injection

Lot
Exp

Pharma Code

NDC 61314-312-10

Zarxio™
(filgrastim-sndz)
Injection

480 mcg/0.8 mL

For Subcutaneous Use or Intravenous Use Only

Single-Use Only

A recombinant Granulocyte Colony-Stimulating Factor (rG-CSF) derived from *E Coli*.

No Preservative.

Refrigerate. Do Not Freeze.

Caution: Contains Natural Rubber Latex Which May Cause Allergic Reaction.

℞ only

10 prefilled syringes with a needle guard

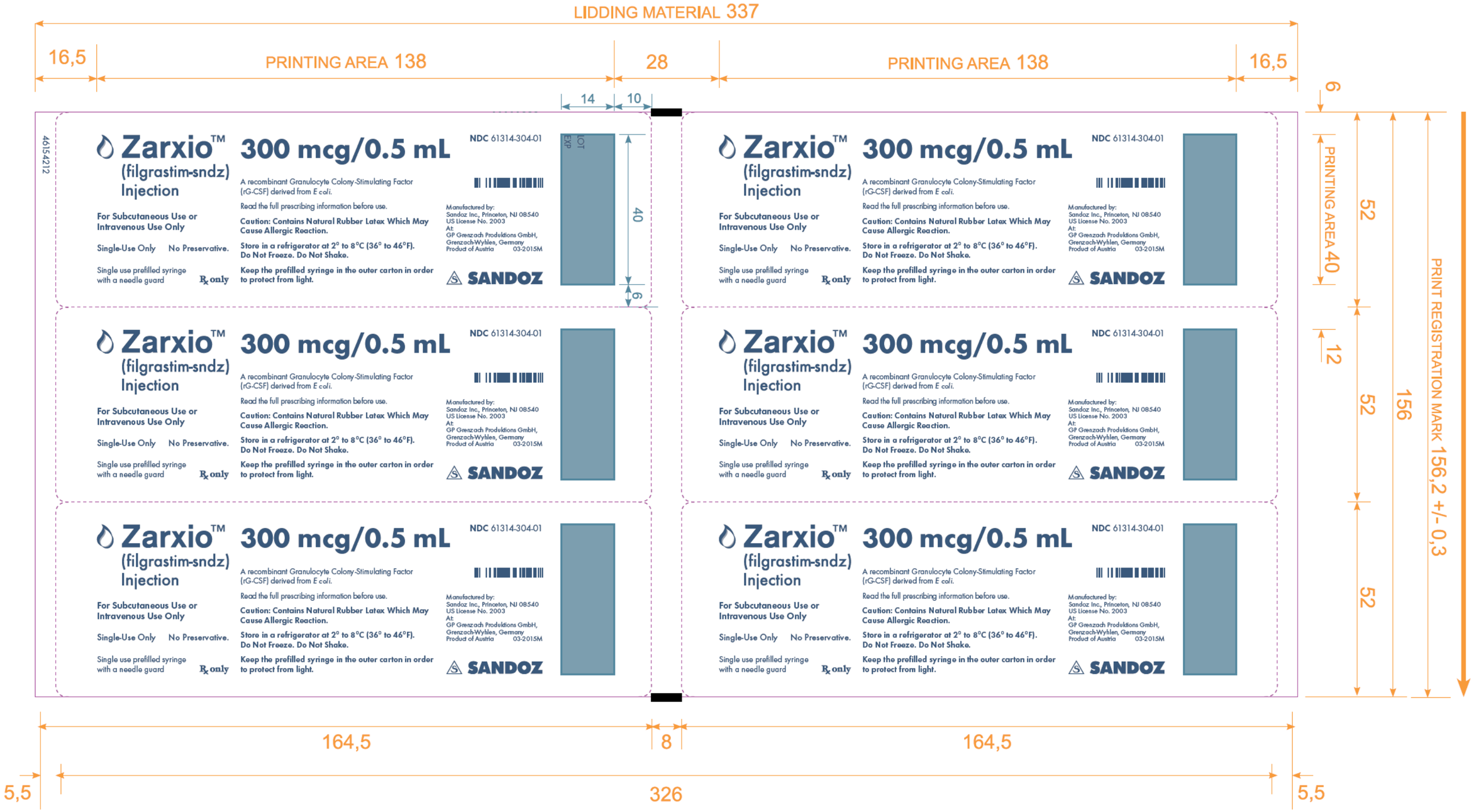
SANDOZ
a Novartis company

Zarxio™ 480 mcg/0.8 mL
(filgrastim-sndz)
Injection

SANDOZ
a Novartis company

46154443

Reference ID: 3711895



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(b) (4)

Scale: 1/1
values in mm

XXXXXXXX = Material No. GP

(b) (4)

print mark
lenght: 8 mm
width: 2 mm

Grenzach Produktions GmbH	GP Grenzach Produktions GmbH Emil-Barell-Str. 7, 79639 Grenzach-Wyhlen, Germany		
Titel:	Nov_Blister_337_Format_7_FIL_USA_V6		
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Material Nº		Country:	-
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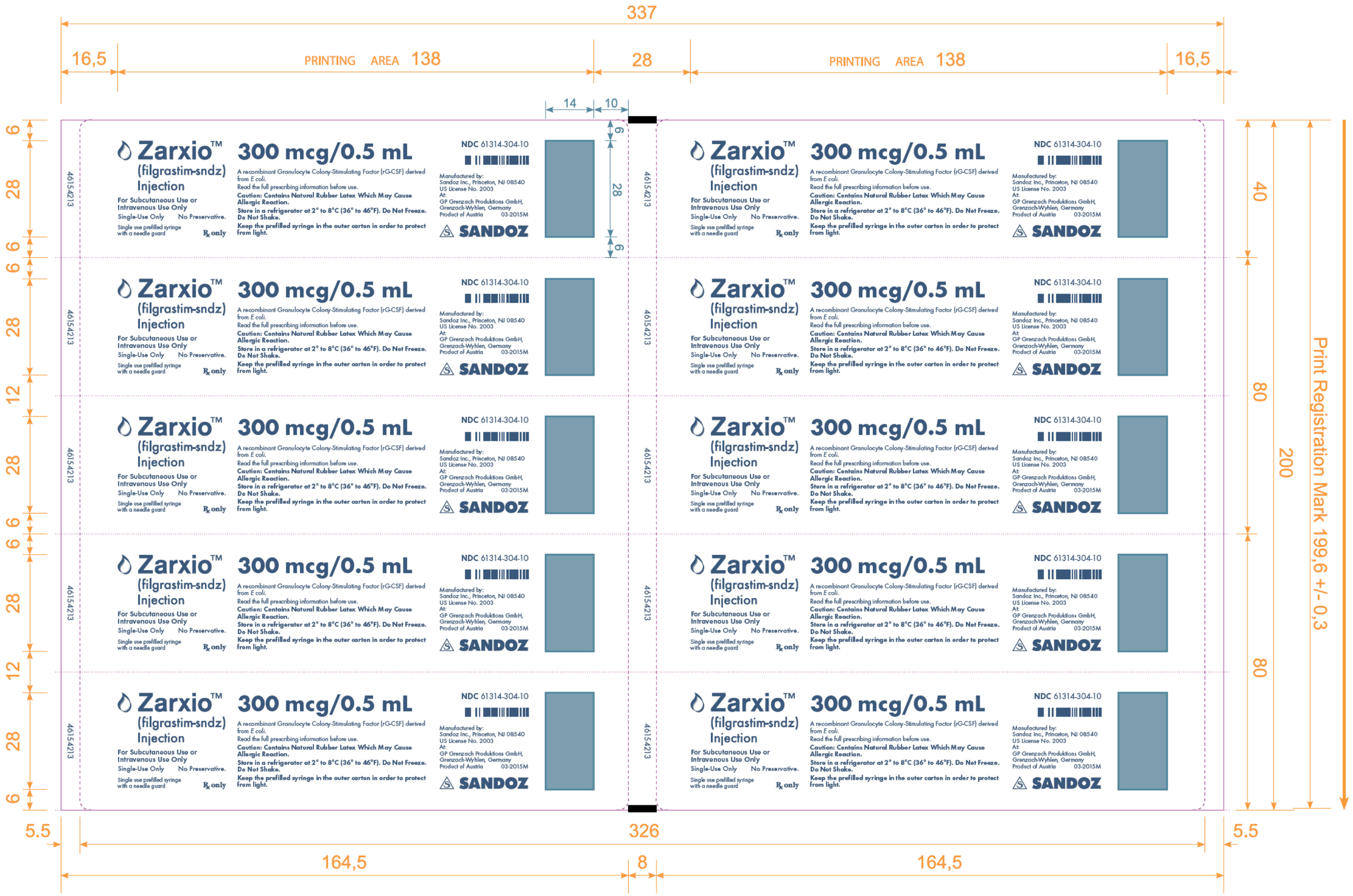
Colours:	Black		
Additional Information:	-		



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Grenzach Produktions GmbH	GP Grenzach Produktions GmbH Emil-Barell-Str. 7, 79639 Grenzach-Wyhlen, Germany		
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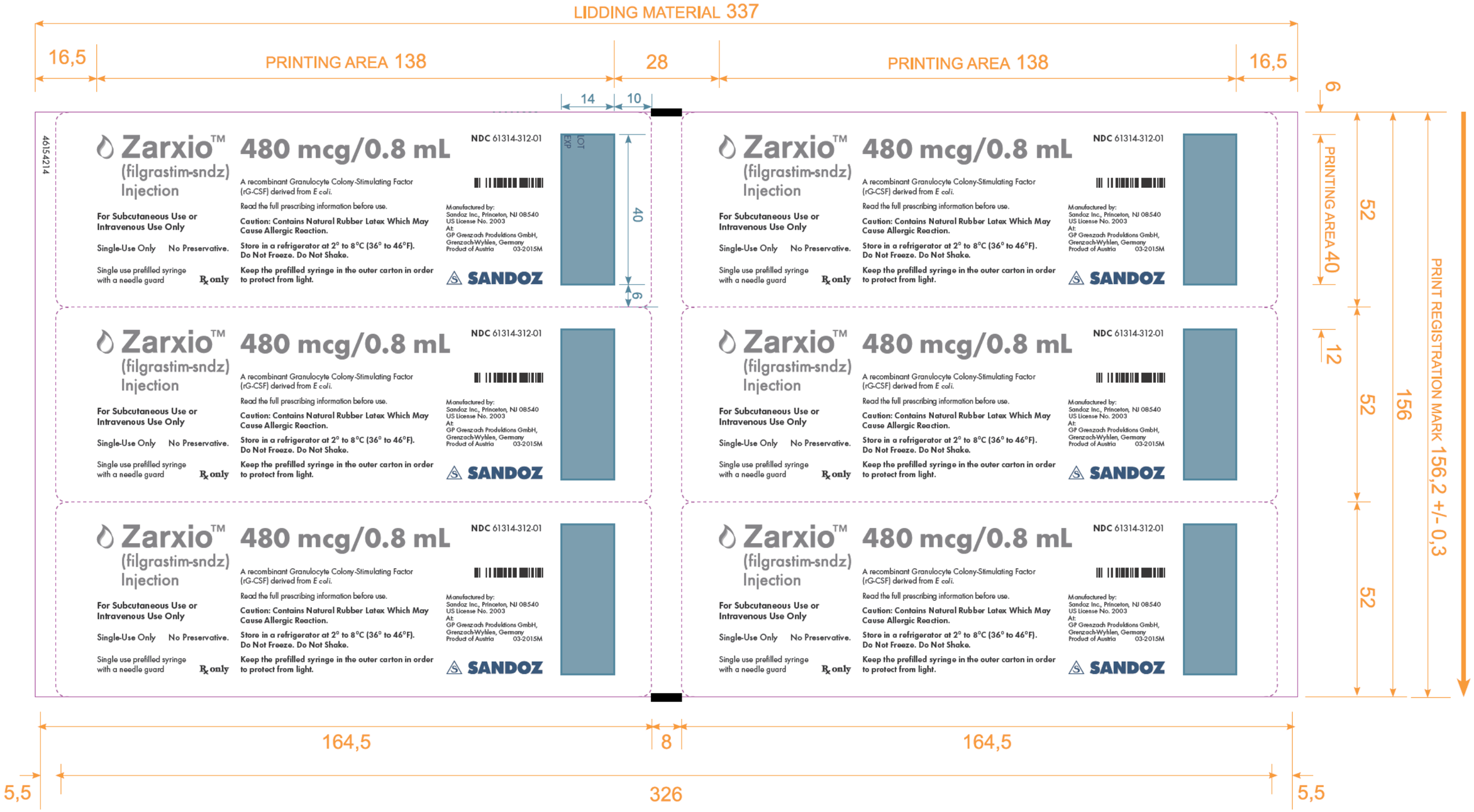
Material Nº		Country:	-
Code:	-	Edge Mark:	-
Colours:	Black		
Additional Information:	-		



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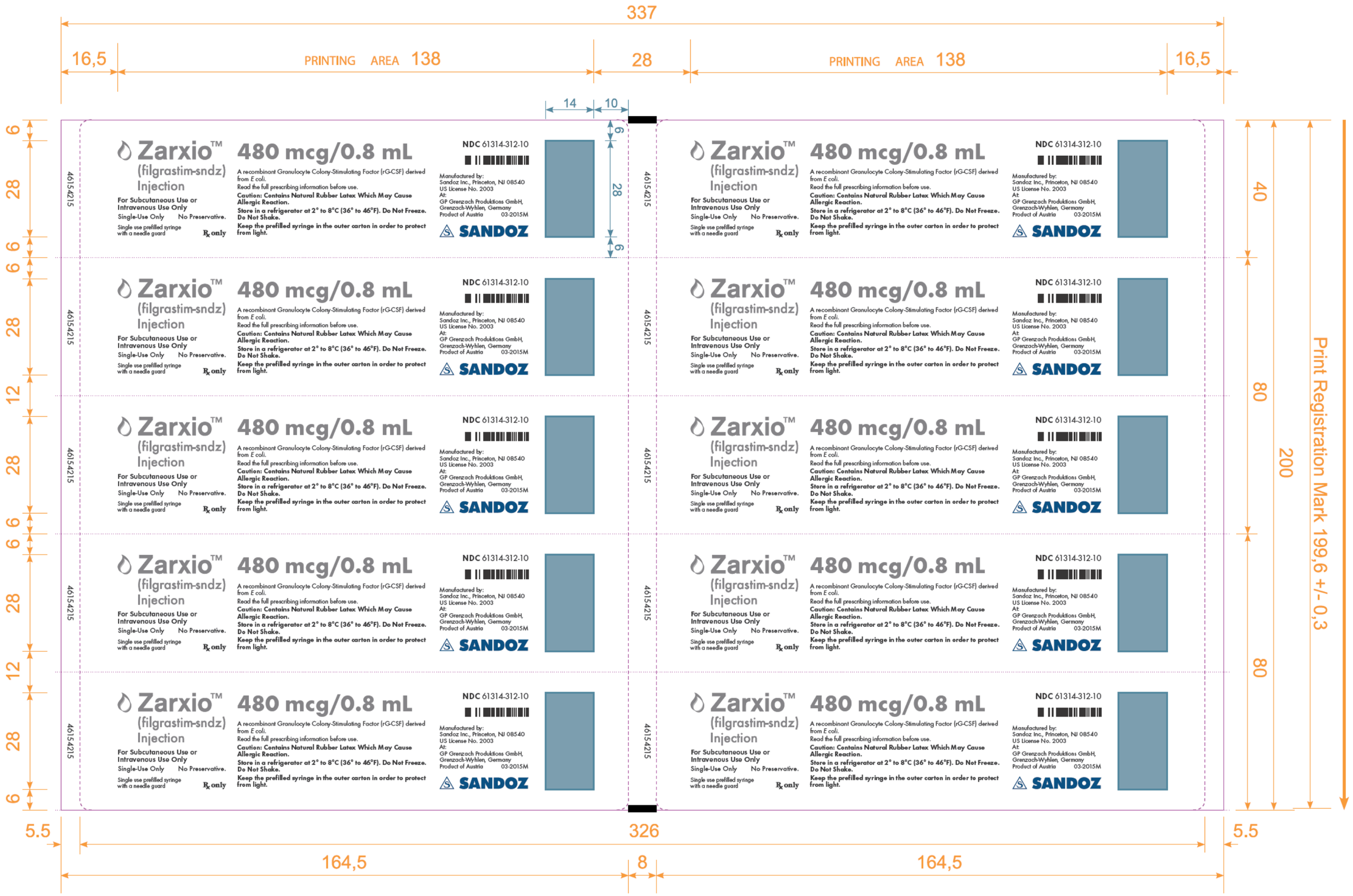
lenght: 8 mm
width: 2 mm

Grenzach Produktions GmbH	GP Grenzach Produktions GmbH Emil-Barell-Str. 7, 79639 Grenzach-Wyhlen, Germany		
Titel:	Nov_Blister_337_Format_7_FIL_USA_V6		
Product:	FIL USA	Date:	27-01-2015
Material Nº		Country:	-
Code:		Edge Mark:	-
Colours:	Black		
Additional Information:	-		



Technical colours:

(b) (4)

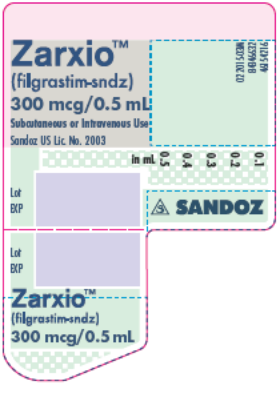
Scale: 1/1
values in mm
XXXXXXXX = Material No. GP

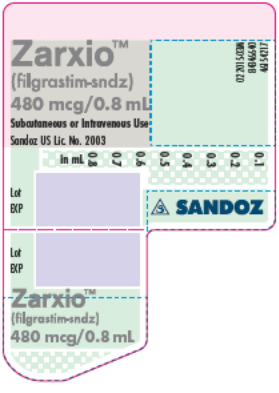
(b) (4)

print mark
lenght: 8 mm
width: 2 mm

(b) (4)

Grenzach Produktions GmbH	GP Grenzach Produktions GmbH Emil-Barell-Str. 7, 79639 Grenzach-Wyhlen, Germany		
Titel:	Nov_Blister_337_Format_9_FIL_USA_v6		
Product:	10er SD USA	Date:	27-01-2015
Material Nº		Country:	-
Code:	-	Edge Mark:	-
Colours:	Black		
Additional Information:	-		


Zarxio™
(filgrastim-sndz)
300 mcg/0.5 mL
Subcutaneous or Intravenous Use
Sandoz US Lic. No. 2003
Lot
EXP
in mL
0.5
0.4
0.3
0.2
0.1
SANDOZ
Lot
EXP
Zarxio™
(filgrastim-sndz)
300 mcg/0.5 mL
61314-304-01
LOT
EXP
46154216 02


Zarxio™
(filgrastim-sndz)
480 mcg/0.8 mL
Subcutaneous or Intravenous Use
Sandoz US Lic. No. 2003
in mL
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
Lot
EXP
SANDOZ
Lot
EXP
Zarxio™
(filgrastim-sndz)
480 mcg/0.8 mL
61314-312-01
NDC 61314-312-01

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ANN T FARRELL
03/06/2015