

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use GRANIX safely and effectively. See full prescribing information for GRANIX.

GRANIX® (tbo-filgrastim) injection, for subcutaneous use
Initial U.S. Approval: 2012

-----RECENT MAJOR CHANGES-----

Indications and Usage (1)	07/2018
Dosage and Administration (2.2)	07/2018
Warnings and Precautions, Leukocytosis (5.8)	07/2018
Warnings and Precautions, Simultaneous Use with Chemotherapy and Radiation Therapy Not Recommended (5.9)	07/2018
Warnings and Precautions, Nuclear Imaging (5.10)	07/2018
Warnings and Precautions, Aortitis (5.11)	07/2018
Warnings and Precautions, Alveolar Hemorrhage (5.12)	03/2019

-----INDICATIONS AND USAGE-----

GRANIX (tbo-filgrastim) is a leukocyte growth factor indicated in adult and pediatric patients 1 month and older for reduction in the duration of severe neutropenia in patients with non-myeloid malignancies receiving myelosuppressive anticancer drugs associated with a clinically significant incidence of febrile neutropenia. (1)

-----DOSAGE AND ADMINISTRATION-----

- Recommended dose: 5 mcg/kg per day administered as a subcutaneous injection
- Administer the first dose no earlier than 24 hours following myelosuppressive chemotherapy. Do not administer within 24 hours prior to chemotherapy (2.1)

-----DOSAGE FORMS AND STRENGTHS-----

Prefilled Syringe

- Injection: 300 mcg/0.5 mL solution in single-dose prefilled syringe (3)
- Injection: 480 mcg/0.8 mL solution in single-dose prefilled syringe (3)

Vial

- Injection: 300 mcg/1 mL solution in single-dose vials (3)
- Injection: 480 mcg/1.6 mL solution in single-dose vials (3)

-----CONTRAINDICATIONS-----

Patients with a history of serious allergic reactions to filgrastim products 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): Monitor for and manage immediately. Discontinue GRANIX if suspected (5.2)
- Serious Allergic Reactions Including Anaphylaxis: Permanently discontinue GRANIX in patients with serious allergic reactions. (5.3)
- Sickle Cell Disorders: Severe and sometimes fatal crisis can occur. Discontinue GRANIX if suspected (5.4)
- Glomerulonephritis: Evaluate and consider dose reduction or interruption of GRANIX if causality is likely (5.5)
- Capillary Leak Syndrome: Monitor if symptoms develop and administer standard symptomatic treatment (5.6)

-----ADVERSE REACTIONS-----

Most common adverse reaction ($\geq 1\%$) to GRANIX is bone pain (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Teva Pharmaceuticals at 1-866-832-8537 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

-----USE IN SPECIFIC POPULATIONS-----

GRANIX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. (8.1)

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

Revised: 03/2019

FULL PRESCRIBING INFORMATION: CONTENTS*

- 1 INDICATIONS AND USAGE**
- 2 DOSAGE AND ADMINISTRATION**
 - 2.1 Dosage
 - 2.2 General Considerations for Administration
 - 2.3 Instructions for Use of the Safety Needle Guard Device by Healthcare Professionals
- 3 DOSAGE FORMS AND STRENGTHS**
- 4 CONTRAINDICATIONS**
- 5 WARNINGS AND PRECAUTIONS**
 - 5.1 Fatal Splenic Rupture
 - 5.2 Acute Respiratory Distress Syndrome (ARDS)
 - 5.3 Serious Allergic Reactions
 - 5.4 Sickle Cell Disorders
 - 5.5 Glomerulonephritis
 - 5.6 Capillary Leak Syndrome
 - 5.7 Potential for Tumor Growth Stimulatory Effects on Malignant Cells
 - 5.8 Leukocytosis
 - 5.9 Simultaneous Use with Chemotherapy and Radiation Therapy Not Recommended
 - 5.10 Nuclear Imaging
 - 5.11 Aortitis

6 ADVERSE REACTIONS

- 6.1 Clinical Trials Experience
- 6.2 Immunogenicity
- 6.3 Postmarketing Experience

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.2 Lactation
- 8.4 Pediatric Use
- 8.5 Geriatric Use

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

GRANIX is indicated to reduce the duration of severe neutropenia in adult and pediatric patients 1 month and older with non-myeloid malignancies receiving myelosuppressive anticancer drugs associated with a clinically significant incidence of febrile neutropenia.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage

The recommended dose of GRANIX is 5 mcg/kg per day administered as a subcutaneous injection. Administer the first dose of GRANIX no earlier than 24 hours following myelosuppressive chemotherapy. Do not administer GRANIX within 24 hours prior to chemotherapy.

Daily dosing with GRANIX should continue until the expected neutrophil nadir is passed and the neutrophil count has recovered to the normal range. Monitor complete blood count (CBC) prior to chemotherapy and twice per week until recovery.

2.2 General Considerations for Administration

GRANIX may be administered by either a healthcare professional, a patient or caregiver. Before a decision is made to allow GRANIX to be administered by a patient or caregiver, ensure that the patient is an appropriate candidate for self-administration or administration by a caregiver. Proper training on storage, preparation, and administration technique should be provided. If a patient or caregiver is not an appropriate candidate for any reason, then in such patients, GRANIX should be administered by a healthcare professional.

Dispense only the prefilled syringe without a safety needle guard device to patient or caregiver. Instruct patients and caregivers to follow the Instructions for Use provided with the GRANIX prefilled syringe to properly administer an injection after training by a healthcare professional.

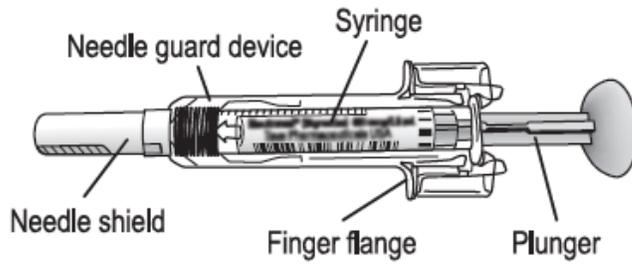
Visually inspect parenteral drug products for particulate matter and discoloration prior to administration. Do not administer GRANIX if discoloration or particulates are observed.

The prefilled syringe and vial are for single-dose only. Discard unused portions. GRANIX and all its components are not made with natural rubber latex.

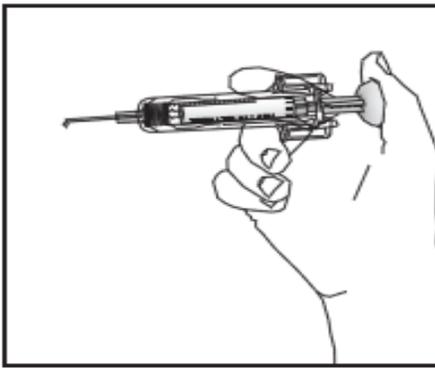
Recommended sites for subcutaneous GRANIX injections include the abdomen (except for the two-inch area around the navel), the front of the middle thighs, the upper outer areas of the buttocks, or the upper back portion of the upper arms. The injection site should be varied daily. GRANIX should not be injected into an area that is tender, red, bruised, or hard, or that has scars or stretch marks.

2.3 Instructions for Use of the Safety Needle Guard Device by Healthcare Professionals

Hold the syringe assembly by the open sides of the device and remove the needle shield.

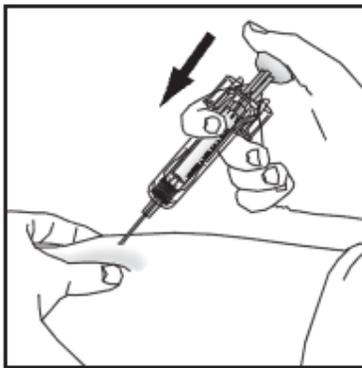


Expel any extra volume depending on dose needed.

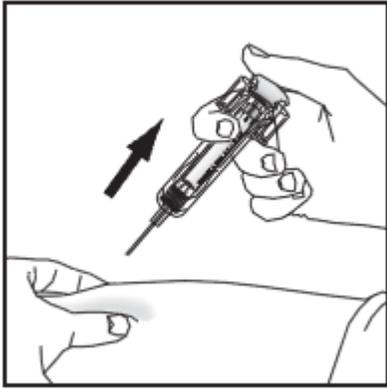


Inject GRANIX subcutaneously as recommended [*see Dosage and Administration (2.2)*].

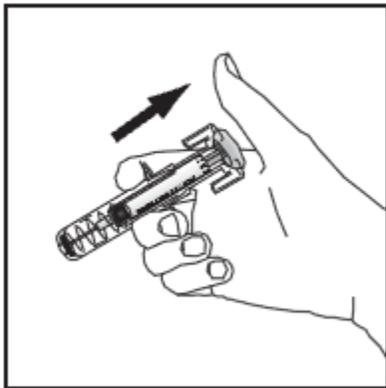
Push the plunger as far as it will go to inject all the medication. **Injection of the entire prefilled syringe contents is necessary to activate the needle guard.**



With the plunger still pressed all the way down, remove the needle from the skin.



Slowly let go of the plunger and allow the empty syringe to move up inside the device until the entire needle is guarded.



Discard the syringe assembly in approved containers.



3 DOSAGE FORMS AND STRENGTHS

GRANIX is a clear, colorless, preservative-free solution available as:

Prefilled Syringe:

Injection: 300 mcg/0.5 mL (600 mcg/mL) solution in single-dose prefilled syringe

Injection: 480 mcg/0.8 mL (600 mcg/mL) solution in single-dose prefilled syringe

Vial:

Injection: 300 mcg/1 mL solution in single-dose vial

Injection: 480 mcg/1.6 mL (300 mcg/mL) solution in single-dose vial

4 CONTRAINDICATIONS

GRANIX is contraindicated in patients with a history of serious allergic reactions to filgrastim products or pegfilgrastim products [see *Warnings and Precautions (5.3)*].

5 WARNINGS AND PRECAUTIONS

5.1 Fatal Splenic Rupture

Splenic rupture, including fatal cases, can occur following administration of filgrastim products. Evaluate patients who report upper abdominal or shoulder pain for an enlarged spleen or splenic rupture. Discontinue GRANIX if splenic rupture is suspected or confirmed.

5.2 Acute Respiratory Distress Syndrome (ARDS)

Acute respiratory distress syndrome (ARDS) can occur in patients receiving filgrastim products. Evaluate patients who develop fever and lung infiltrates or respiratory distress after receiving GRANIX, for ARDS. Discontinue GRANIX in patients with ARDS.

5.3 Serious Allergic Reactions

Serious allergic reactions, including anaphylaxis, can occur in patients receiving GRANIX. Reactions can occur on initial exposure. The administration of antihistamines, steroids, bronchodilators, and/or epinephrine may reduce the severity of the reactions. Permanently discontinue GRANIX in patients with serious allergic reactions. Do not administer GRANIX to patients with a history of serious allergic reactions to filgrastim or pegfilgrastim.

5.4 Sickle Cell Disorders

Severe and sometimes fatal sickle cell crises can occur in patients with sickle cell disorders receiving filgrastim products. Discontinue GRANIX if sickle cell crisis occurs.

5.5 Glomerulonephritis

Glomerulonephritis can occur in patients receiving filgrastim products. The diagnoses were based on azotemia, hematuria (microscopic and macroscopic), proteinuria, and renal biopsy. Generally, events of glomerulonephritis resolved after dose reduction or discontinuation of the filgrastim product. If glomerulonephritis is suspected, evaluate for cause. If causality is likely, consider dose reduction or interruption of GRANIX.

5.6 Capillary Leak Syndrome

Capillary leak syndrome (CLS) can occur in patients receiving 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 Potential for Tumor Growth Stimulatory Effects on Malignant Cells

The granulocyte colony-stimulating factor (G-CSF) receptor through which GRANIX acts has been found on tumor cell lines. The possibility that GRANIX acts as a growth factor for any tumor type, including myeloid malignancies and myelodysplasia, diseases for which GRANIX is not approved, cannot be excluded.

5.8 Leukocytosis

White blood cell counts of 100,000/mm³ or greater were observed in approximately 2% of patients receiving filgrastim products at dosages above 5 mcg/kg/day. In patients with cancer receiving GRANIX as an adjunct to myelosuppressive chemotherapy, to avoid the potential risks of excessive leukocytosis, it is recommended that GRANIX therapy be discontinued if the ANC surpasses 10,000/mm³ after the chemotherapy-induced ANC nadir has occurred. Monitor CBCs at least twice weekly during therapy. Dosages of GRANIX that increase the ANC beyond 10,000/mm³ may not result in any additional clinical benefit. In patients with cancer receiving myelosuppressive chemotherapy, discontinuation of filgrastim products 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.

5.9 Simultaneous Use with Chemotherapy and Radiation Therapy Not Recommended

The safety and efficacy of filgrastim products, including GRANIX, 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 GRANIX 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 GRANIX have not been evaluated in patients receiving concurrent radiation therapy. Avoid the simultaneous use of GRANIX with chemotherapy and radiation therapy.

5.10 Nuclear Imaging

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

5.11 Aortitis

Aortitis has been reported in patients receiving another filgrastim product. It may occur as early as the first week after start of therapy. Manifestations may include generalized signs and symptoms such as fever, abdominal pain, malaise, back pain, and increased inflammatory markers (e.g., c-reactive protein and white blood cell count). Consider aortitis in patients who develop these signs and symptoms without known etiology. Discontinue GRANIX if aortitis is suspected.

5.12 Alveolar Hemorrhage

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

6 ADVERSE REACTIONS

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

- Fatal 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)]
- Glomerulonephritis [see Warnings and Precautions (5.5)]
- Capillary Leak Syndrome [see Warnings and Precautions (5.6)]
- Potential for Tumor Growth Stimulatory Effects on Malignant Cells [see Warnings and Precautions (5.7)]
- Leukocytosis [see Warnings and Precautions (5.8)]
- Simultaneous Use with Chemotherapy and Radiation Therapy Not Recommended [see Warnings and Precautions (5.9)]
- Aortitis [see Warnings and Precautions (5.11)]

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 to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Adverse Reactions in Adult Patients

GRANIX clinical trials safety data are based upon the results of three randomized clinical trials in patients receiving myeloablative chemotherapy for breast cancer (N=348), lung cancer (N=240) and non-Hodgkin's lymphoma (N=92). In the breast cancer study, 99% of patients were female, the median age was 50 years, and 86% of patients were Caucasian. In the lung cancer study, 80% of patients were male, the median age was 58 years, and 95% of patients were Caucasian. In the non-Hodgkin's lymphoma study, 52% of patients were male, the median age was 55 years, and 88% of patients were Caucasian. In all three studies a placebo (Cycle 1 of the breast cancer study only) or a non-US-approved filgrastim product were used as controls. Both GRANIX and the non-US-approved filgrastim product were administered at 5 mcg/kg subcutaneously once daily beginning one day after chemotherapy for at least five days and continued to a maximum of 14 days or until an ANC of $\geq 10,000 \times 10^6/L$ after nadir was reached.

Bone pain was the most frequent treatment-emergent adverse reaction that occurred in at least 1% or greater in patients treated with GRANIX at the recommended dose and was numerically two times more frequent than in the placebo group. The overall incidence of bone pain in Cycle 1 of treatment was 3.4% (3.4% GRANIX, 1.4% placebo, 7.5% non-US-approved filgrastim product).

Leukocytosis

In clinical studies, leukocytosis (WBC counts $> 100,000 \times 10^6/L$) was observed in less than 1% patients with non-myeloid malignancies receiving GRANIX. No complications attributable to leukocytosis were reported in clinical studies.

Additional Adverse Reactions

Other adverse reactions known to occur following administration of filgrastim products include myalgia, headache, vomiting, cutaneous vasculitis and thrombocytopenia.

Adverse Reactions in Pediatric Patients

GRANIX clinical trials safety data in pediatric patients are based upon the results of one single-arm clinical trial in 50 pediatric patients who received myelosuppressive chemotherapy for treatment of solid tumors without marrow involvement [see *Use in Special Populations (8.4)*]. In this study, GRANIX was administered at 5 mcg/kg subcutaneously once daily beginning one day after chemotherapy. The most common (>5%) adverse reactions included thrombocytopenia (34%), pyrexia (8%), pain in extremity (6%), headache (6%) and diarrhea (6%).

6.2 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay, and the observed incidence of antibody positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to GRANIX with the incidence of antibodies to other products may be misleading.

Binding antibodies to GRANIX were detected using a validated bridging immunoassay. Anti-drug antibodies to tbo-filgrastim occurred in 1.4 % of 486 adult and pediatric patients. None of these patients had cross-reactive antibodies to the native G-CSF. All antibody responses were transient and of low titers.

6.3 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of GRANIX. 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.

Sweet's syndrome (acute febrile neutrophilic dermatosis), asthenia, diarrhea, and fatigue

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

The limited published data on filgrastim product use during pregnancy are insufficient to inform a drug-associated risk. In animal reproduction studies, administration of tbo-filgrastim to pregnant rabbits during organogenesis resulted in increased spontaneous abortion and fetal malformations at systemic exposures 50-90 times the human exposure expected at the recommended human dose (*see Data*). GRANIX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population(s) are unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Animal Data

In an embryofetal developmental study, pregnant rabbits were administered subcutaneous doses of tbo-filgrastim during the period of organogenesis at 1, 10 and 100 mcg/kg/day. Increased abortions were evident in rabbits treated with tbo-filgrastim at 100 mcg/kg/day. This dose was maternally toxic as demonstrated by reduced body weight. Other embryofetal findings at this dose level consisted of post-implantation loss, decrease in mean live litter size and fetal weight, and fetal malformations such as malformed hind limbs and cleft palate. The dose of 100 mcg/kg/day corresponds to a systemic exposure

(AUC) of approximately 50-90 times the exposures observed in patients treated with the clinical tbo-filgrastim dose of 5 mcg/kg/day.

8.2 Lactation

No data are available regarding the presence of tbo-filgrastim in human milk, the effects of the drug on the breastfed child, or the effects of the drug on milk production. Another filgrastim product was detected in human milk for up to 3 days after filgrastim administration.

8.4 Pediatric Use

The safety and effectiveness of GRANIX have been established for pediatric patients 1 month to < 17 years old (no data for the age group < 1 month old). Use of GRANIX in these age groups is supported by evidence from adequate and well-controlled studies of GRANIX in adults [see *Clinical Studies (14)*] with additional safety and pharmacokinetics data from a single-arm trial of 50 pediatric patients with solid tumors treated with GRANIX for chemotherapy-induced neutropenia. The 50 pediatric patients had a median age of 9.2 years (range, 1.4-15.9 years); 2 were infants (1 month to < 2 years old), 30 were children (2 to < 12 years old), and 18 were adolescents (12 to < 17 years old). The pharmacokinetics and safety profile of GRANIX in the pediatric population were similar to those seen in adults [see *Adverse Reactions (6.1)*, *Clinical Pharmacology (12.3)*].

8.5 Geriatric Use

Among 677 cancer patients enrolled in clinical trials of GRANIX, a total of 111 patients were 65 years of age and older, and 14 patients were 75 years and older. No overall differences in safety or effectiveness were observed between patients age 65 and older and younger patients.

11 DESCRIPTION

GRANIX (tbo-filgrastim) is a non-glycosylated recombinant methionyl human granulocyte colony-stimulating growth factor (r-metHuG-CSF) manufactured by recombinant DNA technology using the bacterium strain *E coli* K802. It has a molecular weight of approximately 18.8 kDa and is composed of 175 amino acids. The endogenous human G-CSF is glycosylated and does not have the additional methionine amino acid residue in its NH₂ terminal end.

The product is a sterile, clear, colorless, preservative-free solution containing tbo-filgrastim, glacial acetic acid, sorbitol, polysorbate 80, sodium hydroxide, and Water for Injection. The product is available in single-dose prefilled syringes that contain either 300 mcg or 480 mcg of tbo-filgrastim at a fill volume of 0.5 mL or 0.8 mL, respectively and single-dose vials that contain either 300 mcg or 480 mcg of tbo-filgrastim at a fill volume of 1 mL or 1.6 mL, respectively. See table below for product composition of each presentation.

Product Composition				
	300 mcg/0.5 mL Syringe	480 mcg/0.8 mL Syringe	300 mcg/1 mL Vial	480 mcg/1.6 mL Vial
Tbo-filgrastim	300 mcg	480 mcg	300 mcg	480 mcg
Glacial Acetic Acid	0.3 mg	0.48 mg	0.6 mg	0.96 mg
Polysorbate 80	0.0275 mg	0.044 mg	0.055 mg	0.088 mg
Sorbitol	25 mg	40 mg	50 mg	80 mg
Sodium Hydroxide	q.s. to pH 4.2	q.s. to pH 4.2	q.s. to pH 4.2	q.s. to pH 4.2
Water for Injection	q.s. to 0.5 mL	q.s. to 0.8 mL	q.s. to 1.0 mL	q.s. to 1.6 mL

q.s. = quantity sufficient to make

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Tbo-filgrastim is a human granulocyte colony-stimulating factor (G-CSF) produced by recombinant DNA technology. Tbo-filgrastim binds to G-CSF receptors and stimulates proliferation of neutrophils. G-CSF is known to stimulate differentiation commitment and some end-cell functional activation, which increases neutrophil counts and activity.

12.2 Pharmacodynamics

The time to the maximum ANC level was between 3 to 5 days and returned to baseline by 21 days following completion of chemotherapy. Doubling the tbo-filgrastim subcutaneous dose from 5 mcg/kg to 10 mcg/kg resulted in a 16% to 19% increase in the maximum ANC level and a 33% to 36% increase in the area under the effect curve for ANC.

Cardiac Electrophysiology

At an intravenous dose of 5 mcg/kg, tbo-filgrastim did not prolong the QT interval to any clinically relevant extent.

12.3 Pharmacokinetics

Tbo-filgrastim exhibits nonlinear pharmacokinetics. Increasing the dose of subcutaneous GRANIX from 5 to 10 mcg/kg resulted in an approximate 2.5-fold increase in the maximum serum concentration (C_{max}) and 3.0-fold increase in the area under the curve (AUC). In adult patients enrolled across three studies, subcutaneous GRANIX 5 mcg/kg resulted in median time to maximal serum tbo-filgrastim concentrations (T_{max}) within 4 to 6 hours. Geometric mean [coefficient of variation (CV%)] serum C_{max} was 20 to 31 ng/mL [24% to 65%] within 4 to 6 hours. Geometric mean serum tbo-filgrastim area under the curve (AUC_{0-12h}) ranged from 151 to 227 ng/mL*h [24%-60%]. No accumulation in serum tbo-filgrastim concentrations was observed after multiple dosing.

Absorption

The absolute bioavailability of 5 mcg/kg subcutaneous tbo-filgrastim was 33%.

Metabolism/Elimination

Tbo-filgrastim clearance is primarily dependent on G-CSF receptor-mediated clearance which can be saturated by high serum concentrations of tbo-filgrastim and diminished in neutropenia. The median serum elimination half-life of tbo-filgrastim (5 mcg/kg sc) was 3.0 to 3.5 hours.

Specific Populations

No sex-related differences were observed.

Pediatric Patients:

The geometric mean [coefficient of variation (CV%)] of C_{max} was 18 ng/mL (56%) and AUC_{0-12h} was 130 ng*hr/mL (52%) following subcutaneous administration of GRANIX 5 mcg/kg in 49 pediatric patients (1.4 to 15.9 years) after chemotherapy. No clinically relevant differences in the pharmacokinetics of GRANIX were observed between infants, children and adolescents.

Patients with Renal or Hepatic Impairment:

Mild renal impairment (creatinine clearance 60 to 89 mL/min by Cockcroft-Gault) had no effect on tbo-filgrastim pharmacokinetics. The pharmacokinetics in patients with moderate and severe renal impairment has not been studied. The pharmacokinetics in patients with hepatic impairment has not been studied.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity and genetic toxicology studies have not been conducted with tbo-filgrastim.

A fertility study was not conducted with tbo-filgrastim. Toxicology studies of up to 26 weeks in rats or monkeys did not reveal findings in male or female reproductive organs that would suggest impairment of fertility.

14 CLINICAL STUDIES

The efficacy of GRANIX was evaluated in a multinational, multicenter, randomized and controlled Phase 3 study in 348 chemotherapy-naïve patients with high-risk stage II, stage III, or stage IV breast cancer receiving doxorubicin (60 mg/m²) and docetaxel (75 mg/m²) comparing GRANIX to placebo and a non-US-approved filgrastim product as controls. The median age of the patients was 50 years (range 25 to 75 years) with 99% female and 86% Caucasian.

GRANIX, placebo, and the non-US-approved filgrastim product were administered at 5 mcg/kg subcutaneously once daily beginning one day after chemotherapy for at least five days and continued to a maximum of 14 days or until an ANC of $\geq 10,000 \times 10^6/L$ after nadir was reached.

GRANIX was superior to placebo in duration of severe neutropenia (DSN) with a statistically significant reduction in DSN (1.1 days vs. 3.8 days, $p < 0.0001$).

16 HOW SUPPLIED/STORAGE AND HANDLING

GRANIX solution for injection is supplied as a single-dose, preservative-free clear solution, in either a vial or, a prefilled syringe made from Type I glass which has a permanently attached stainless steel needle. The active substance is tbo-filgrastim.

Prefilled Syringes (UltraSafe Passive® Needle Guard)

GRANIX 300 mcg/0.5 mL: Each prefilled syringe contains 300 mcg of tbo-filgrastim in 0.5 mL solution with a blue plunger in:

- Pack of 1 with a safety needle guard in blister: NDC 63459-910-11
- Packs of 10 with a safety needle guard in blisters: NDC 63459-910-15

GRANIX 480 mcg/0.8 mL: Each prefilled syringe contains 480 mcg of tbo-filgrastim in 0.8 mL solution with a clear plunger in:

- Pack of 1 with a safety needle guard in blister: NDC 63459-912-11
- Packs of 10 with a safety needle guard in blisters: NDC 63459-912-15

Prefilled Syringes

GRANIX 300 mcg/0.5 mL: Each prefilled syringe contains 300 mcg of tbo-filgrastim in 0.5 mL solution with a blue plunger in:

- Pack of 1 without a safety needle guard (for patients and caregivers): NDC 63459-910-17
- Packs of 5 without a safety needle guard (for patients and caregivers): NDC 63459-910-36

GRANIX 480 mcg/0.8 mL: Each prefilled syringe contains 480 mcg of tbo-filgrastim in 0.8 mL solution with a clear plunger in:

- Pack of 1 without a safety needle guard (for patients and caregivers): NDC 63459-912-17
- Packs of 5 without a safety needle guard (for patients and caregivers): NDC 63459-912-36

Vials

GRANIX 300 mcg/1 mL: Each vial contains 300 mcg of tbo-filgrastim in 1 mL solution.

- Packs of 10 single-dose vials: (NDC 63459-918-59)

GRANIX 480 mcg/1.6 mL: Each vial contains 480 mcg of tbo-filgrastim in 1.6 mL solution.

- Packs of 10 single-dose vials: (NDC 63459-920-59)

GRANIX and all its components are not made with natural rubber latex [*see Dosage and Administration (2.2)*].

Store GRANIX in a refrigerator at 36° to 46°F (2° to 8°C). Protect from light. Within its shelf life, the product may be removed from 36° to 46°F (2° to 8°C) storage for a single period of up to 5 days between 73° to 81°F (23° to 27°C). If not used within 5 days, the product may be returned to 36° to 46°F (2° to 8°C) up to the expiration date. Dispose of syringes if stored at room temperature for more than 5 days.

Avoid shaking. The solution should be visually inspected prior to use. Only clear solutions without particles should be used. Exposure to 23° to 30°F (-1° to -5°C) for up to 72 hours and temperatures as low as 5° to -13°F (-15° to -25°C) for up to 24 hours do not adversely affect the stability of GRANIX.

Single-dose syringe and single-dose vial – discard unused portion. Any unused product or waste material should be disposed of in accordance with local requirements.

If GRANIX gets on the skin, wash the area with soap and water. If GRANIX gets in the eyes, thoroughly flush the exposed eye/eyes with water.

17 PATIENT COUNSELING INFORMATION

Availability of Patient Information and Instructions for Use

Advise all patients and/or caregivers to read the FDA-approved Patient Information. For patients that are candidates for self-administration, assist patients and caregivers in understanding the contents of the Patient Information as well as the GRANIX Instructions for Use that are included with the product, and give them the opportunity to ask questions prior to initiating therapy.

Patient Training

Once it is determined that a patient is an appropriate candidate for self-administration or administration by a caregiver, instruct the patient or caregivers on the proper storage, preparation, and administration technique for GRANIX. Patients should be advised not to skip or change their dose or stop taking GRANIX without talking to their healthcare provider first. Advise the patients to read the FDA-approved Patient Information and Instructions for Use for further information.

Bone Pain

Bone pain is common. Analgesics such as acetaminophen or NSAIDs may be necessary [*see Adverse Reactions (6.1)*].

Rupture or Enlargement of Spleen

Rupture or enlargement of the spleen may occur, which may be signaled by abdominal pain, left upper quadrant pain, or left shoulder pain. Advise patients to report onset of pain in these areas to their doctor immediately [*see Warnings and Precautions (5.1)*].

Dyspnea

Dyspnea with or without fever, progressing to Acute Respiratory Distress Syndrome, may occur. Advise patients to report dyspnea immediately to their doctor [*see Warnings and Precautions (5.2)*].

Allergic Reactions

Serious allergic reactions, including anaphylaxis, rash, and urticaria: Patients should report such reactions immediately to their doctor [*see Warnings and Precautions (5.3)*].

Sickle Cell Disorders

In patients with sickle cell disorders, sickle cell crisis and death has occurred. Discuss the potential risks and benefits for patients with sickle cell disorders prior to the administration of GRANIX [see *Warnings and Precautions (5.4)*].

Glomerulonephritis

Symptoms may include swelling of the face or ankles, dark colored urine or blood in the urine, or a decrease in urine production. Advise patients to report signs or symptoms of glomerulonephritis to their physician immediately [see *Warnings and Precautions (5.5)*].

Infections

GRANIX is used in circumstances where the risk of infection is increased. Patients should be alert for signs of infection such as fever, redness or swelling, and should report these findings to their doctor immediately.

Pregnancy

Inform patients not to become pregnant while receiving GRANIX. If pregnancy occurs, advise patients of the possibility of fetal harm [see *Use in Specific Populations (8.1)*].

Lactation

Inform lactating women that filgrastim was detected in breast milk for up to 3 days after dosing [see *Use in Specific Populations (8.2)*].

See FDA-approved Patient Labeling (Patient Information) and Instructions for Use.

TBO-00X

The logo for Teva, consisting of the word "teva" in a bold, lowercase, sans-serif font. The letter 'v' is stylized with a small gap between the two vertical strokes.

©2014-2019 Cephalon, Inc., a wholly owned subsidiary of Teva Pharmaceutical Industries Ltd. All rights reserved.

Manufactured by:
Sicor Biotech UAB
Vilnius, Lithuania
U.S. License No. 1803

Distributed by:
Teva Pharmaceuticals USA, Inc.
North Wales, PA 19454

Product of Israel