GRANIX™
(TBO-FILGRASTIM)
Injection

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

INDICATIONS AND USAGE

GRANIX (tbo-filgrastim) is a leukocyte growth factor indicated for reduction in the duration of severe neutropenia in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer 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

- 300 mcg/0.5 mL in single use prefilled syringe
- 480 mcg/0.8 mL in single use prefilled syringe (3)

CONTRAINDICATIONS

- None.

WARNINGS AND PRECAUTIONS

- Splenic Rupture: Discontinue GRANIX if suspected (5.1)
- Acute Respiratory Distress Syndrome (ARDS): Monitor for and manage immediately. Discontinue GRANIX if suspected (5.2)
- Allergic reactions (angioneurotic edema, dermatitis allergic, drug hypersensitivity, hypersensitivity, rash, pruritic rash and urticaria) (5.3)
- Sickle cell crisis: Severe and sometimes fatal crisis can occur. Discontinue GRANIX if suspected (5.4)

ADVERSE REACTIONS

- Most common adverse reaction to GRANIX is bone pain (6)

To report SUSPECTED ADVERSE REACTIONS, contact Teva 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)
- It is not known if tbo-filgrastim is excreted in human milk (8.3)
- The safety and effectiveness of GRANIX have not been established in patients under 18 years of age (8.4)

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

Revised: 07/2013

FULL PRESCRIBING INFORMATION: CONTENTS*

*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 patients with non-myeloid malignancies receiving myelosuppressive anti-cancer 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 [*see Warnings and Precautions (5)*].

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 should be administered by a healthcare professional.

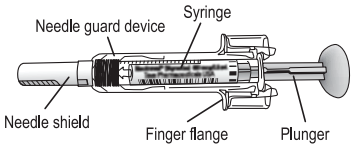
Visually inspect parenteral drug products for particulate matter and discoloration prior to administration. Do not administer GRANIX if discoloration or particulates are observed.

The prefilled syringe is for single use only. Discard unused portions.

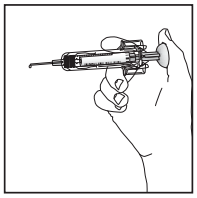
Recommended sites for subcutaneous GRANIX injections include the abdomen (except for the two-inch area around the navel), the front of the middle thighs, the upper outer areas of the buttocks, or the upper back portion of the upper arms. The injection site should be varied daily. GRANIX should not be 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

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

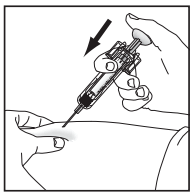


Expel any extra volume depending on dose needed.

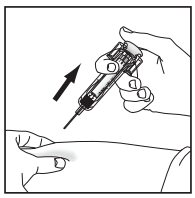


Inject GRANIX subcutaneously as recommended [*see General Considerations for Administration (2.2)*].

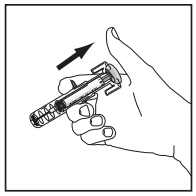
Push the plunger as far as it will go to inject all the medication. **Injection of the entire prefilled syringe contents is necessary to activate the needle guard.**



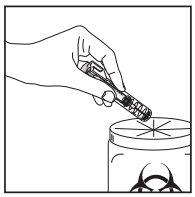
With the plunger still pressed all the way down, remove the needle from the skin.



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
300 mcg/0.5 mL injection in single-use prefilled syringe
480 mcg/0.8 mL injection in single-use prefilled syringe

4 CONTRAINDICATIONS
None.

5 WARNINGS AND PRECAUTIONS
5.1 Splenic Rupture
Splenic rupture, including fatal cases, can occur following administration of human granulocyte colony-stimulating factors. In patients who report upper abdominal or shoulder pain after receiving GRANIX, discontinue GRANIX and evaluate for an enlarged spleen or splenic rupture.
5.2 Acute Respiratory Distress Syndrome (ARDS)
Acute respiratory distress syndrome (ARDS) can occur in patients receiving human granulocyte colony-stimulating factors. Evaluate patients who develop fever and lung infiltrates or respiratory distress after receiving GRANIX, for ARDS. Discontinue GRANIX in patients with ARDS.
5.3 Allergic Reactions
Serious allergic reactions including anaphylaxis can occur in patients receiving human granulocyte colony-stimulating factors. 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 Use in Patients with Sickle Cell Disease
Severe and sometimes fatal sickle cell crises can occur in patients with sickle cell disease receiving human granulocyte colony-stimulating factors. Consider the potential risks and benefits prior to the administration of human granulocyte colony-stimulating factors in patients with sickle cell disease. Discontinue GRANIX in patients undergoing a sickle cell crisis.
5.5 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.

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6 ADVERSE REACTIONS
The following potential 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)*]
- Use in Patients with Sickle Cell Disease [*see Warnings and Precautions (5.4)*]
- Potential for Tumor Growth Stimulatory Effects on Malignant Cells [*see Warnings and Precautions (5.5)*]

The most common treatment-emergent adverse reaction that occurred at an incidence of 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 was bone pain.
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. 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 ≥10,000 x 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 x 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.
6.2 Immunogenicity
As with all therapeutic proteins, there is a potential for immunogenicity. The incidence of antibody development in patients receiving GRANIX has not been adequately determined.

7 DRUG INTERACTIONS
No formal drug interaction studies between GRANIX and other drugs have been performed.
Drugs which may potentiate the release of neutrophils, such as lithium, should be used with caution.
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.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Pregnancy Category C
There are no adequate and well-controlled studies of GRANIX in pregnant women. In an embryofetal developmental study, treatment of pregnant rabbits with tbo-filgrastim resulted in adverse embryofetal findings, including increased spontaneous abortion and fetal malformations at a maternally toxic dose. GRANIX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
In the 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 hindlimbs and cleft palate. The dose of 100 mcg/kg/day corresponds to a systemic exposure ($AUC_{0\text{-}24}$) of approximately 50-90 times the exposures observed in patients treated with the clinical tbo-filgrastim dose of 5 mcg/kg/day.
8.3 Nursing Mothers
It is not known whether tbo-filgrastim is secreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when GRANIX is administered to a nursing woman. Other recombinant G-CSF products are poorly secreted in breast milk and G-CSF is not orally absorbed by neonates.
8.4 Pediatric Use
The safety and effectiveness of GRANIX in pediatric patients have not been established.
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. No overall differences in safety or effectiveness were observed between patients age 65 and older and younger patients.
8.6 Renal Impairment
The safety and efficacy of GRANIX have not been studied in patients with moderate or severe renal impairment. No dose adjustment is recommended for patients with mild renal impairment [*see Clinical Pharmacology (12.3)*].

8.7 Hepatic Impairment
The safety and efficacy of GRANIX have not been studied in patients with hepatic impairment.

10 OVERDOSAGE
No case of overdose has been reported.

11 DESCRIPTION
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 NH_2 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-use 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. See table below for product composition of each single-use prefilled syringe.

Product Composition		
	300 mcg/0.5 mL Syringe	**480 mcg/0.8 mL Syringe**
Tbo-filgrastim	**300 mcg**	**480 mcg**
Glacial Acetic Acid	**0.3 mg**	**0.48 mg**
Sorbitol	**25 mg**	**40 mg**
Polysorbate 80	**0.0275 mg**	**0.044 mg**
Sodium Hydroxide	**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**

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
In the clinical trials of patients with cancer, the time to the ANC_{max} was between 3 to 5 days and returned to baseline by 21 days following completion of chemotherapy. In the healthy volunteer trials, doubling the tbo-filgrastim subcutaneous dose from 5 to 10 mcg/kg resulted in a 16%-19% increase in the ANC_{max} and a 33%-36% increase in the area under the effect curve for ANC.
12.3 Pharmacokinetics
In healthy subjects, the absolute bioavailability of 5 mcg/kg subcutaneous tbo-filgrastim was 33%. Increasing the dose of tbo-filgrastim from 5 to 10 mcg/kg in these healthy subjects resulted in an approximately 200% increase in both the maximum concentration (C_{max}) and the area under the curve ($AUC_{0\text{-}48h}$) of the drug.
In the clinical trials of patients with cancer, the AUC and C_{max} were greater and more variable compared to healthy volunteers receiving the same dose of tbo-filgrastim subcutaneously. The median time to maximum concentration was between 4 to 6 hours and the median elimination half-life was between 3.2 to 3.8 hours. Accumulation was not observed after repeated dosing.
Pharmacokinetics in Specific Populations
Age: Not evaluated.
Gender: No gender-related differences were observed.
Renal Impairment: Mild renal impairment (creatinine clearance 60 - 89 mL/min) had no effect on tbo-filgrastim pharmacokinetics (N=11). The pharmacokinetic profile in patients with moderate and severe renal impairment has not been assessed.
Hepatic Impairment: The pharmacokinetic profile in patients with hepatic impairment has not been assessed.
12.6 QT/QTc Prolongation
The potential effects of GRANIX on the QTc interval were not adequately evaluated in clinical trials.

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-naive patients with high-risk stage II, stage III, or stage IV breast cancer receiving doxorubicin (60 mg/m^2) and docetaxel (75 mg/m^2) 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 ≥10,000 x 10^6/L after nadir was reached.

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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-use, preservative-free, prefilled syringe of Type I glass which has a permanently attached stainless steel needle. Syringes may be supplied with or without an UltraSafe Passive® Needle Guard.
The active substance is tbo-filgrastim.
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:
- Packs of 1 with a safety needle guard in blisters: 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:
- Packs of 1 with a safety needle guard in blisters: NDC 63459-912-11
- Packs of 10 with a safety needle guard in blisters: NDC 63459-912-15

GRANIX syringes should be stored 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.
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-use syringe – discard unused portion. Any unused product or waste material should be disposed of in accordance with local requirements.

17 PATIENT COUNSELING INFORMATION
Advise patients of the following risks and potential risks with leukocyte growth factors such as GRANIX:
- Bone pain is common. Analgesics such as acetaminophen or NSAIDS may be necessary.
- 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.
- Dyspnea with or without fever, progressing to Acute Respiratory Distress Syndrome, may occur. Advise patients to report dyspnea immediately to their doctor.
- Serious allergic reactions, including anaphylaxis, rash, and urticaria: Patients should report such reactions immediately.
- In patients with sickle cell disease, sickle cell crisis and death has occurred. Discuss the potential risks and benefits for patients with sickle cell disease prior to the administration of human granulocyte colony-stimulating factors.
- 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.
- Inform patients not to become pregnant while receiving GRANIX. If pregnancy occurs, advise patients of the possibility of fetal harm.

See FDA-Approved Patient Labeling (Patient Information)

TBO-003

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

Revision 07/2013

Patient Information
GRANIX (GRAN-icks)
(tbo-filgrastim)
Injection, for subcutaneous use

Read this Patient Information before you start receiving GRANIX and before each treatment course. There may be new information. This information does not take the place of you talking with your doctor about your medical condition or treatment.

What is GRANIX?
GRANIX is a prescription medicine:
- used in people with certain types of cancer (non-myeloid malignancies), who are receiving chemotherapy that affects the bone marrow
- given to help decrease the length of time that the number of certain white blood cells (neutrophils) are very low (severe neutropenia). Neutrophils are white blood cells that are important in fighting bacterial infections.

It is not known if GRANIX is safe and effective in children under 18 years of age.

What should I tell my doctor before I receive GRANIX?
Before you receive GRANIX, tell your doctor if you:
- have sickle cell anemia or other blood problem
- plan to have bone scans or tests
- are allergic to filgrastim (Neupogen) or pegfilgrastim (Neulasta)
- have any other medical conditions
- are pregnant or plan to become pregnant. It is not known if GRANIX will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if GRANIX passes into your breast milk.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.
Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

How will I receive GRANIX?
- GRANIX is given by an injection under your skin (subcutaneous) by a doctor or nurse.
- Your first dose of GRANIX is given at least 24 hours after you receive your chemotherapy.
- GRANIX injections are usually given 1 time each day until your white blood cell count returns to normal.
- Your doctor will test your blood before your chemotherapy and during your GRANIX treatment until your white blood cell count returns to normal.
- Keep all of your appointments for your GRANIX injections and blood tests.

What are the possible side effects of GRANIX?
GRANIX can cause serious side effects, including:
- **Spleen rupture, which can cause death.** Call your doctor right away if you have pain in your left upper stomach area or left shoulder area while taking GRANIX. This pain could mean your spleen is enlarged or ruptured.
- **A serious lung problem called** Acute Respiratory Distress Syndrome (ARDS). Get medical help right away if you have any of these symptoms of Acute Respiratory Distress Syndrome (ARDS):
  - fever
  - shortness of breath
  - trouble breathing

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- **Serious allergic reactions.** If you have a serious allergic reaction during a GRANIX injection, your doctor will treat your allergic reaction and stop giving you the injections. Tell your doctor right away if you have any of these symptoms during or after your injection:
  - a rash over the whole body
  - shortness of breath
  - trouble breathing (wheezing)
  - dizziness
  - swelling around the mouth or eyes
  - fast heart rate
  - sweating
- **Severe sickle cell crisis in people with a sickle cell disease.** If you have sickle cell disease, talk to your doctor about the risks of taking GRANIX.

The most common side effect of GRANIX is bone pain.
Tell your doctor about any side effect that bothers you or that does not go away.
These are not all the possible side effects of GRANIX. For a complete list, ask your doctor or pharmacist.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General Information about GRANIX
Medicines are sometimes prescribed for purposes other than those listed in Patient Information leaflets. This Patient Information leaflet summarizes the most important information about GRANIX. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about GRANIX that is written for health professionals.
For more information, call 1-800-896-5855.

What are the ingredients in GRANIX?
Active ingredient: tbo-filgrastim
Inactive ingredient: glacial acetic acid, sorbitol, polysorbate 80, sodium hydroxide, and Water for Injection.

This Patient Information has been approved by the U.S. Food and Drug Administration.

TBO-003

TEVA Oncology

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

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