

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

Dosage and Administration (2.2) 12/2014

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

- Injection: 300 mcg/0.5 mL solution in single-use prefilled syringe
- Injection: 480 mcg/0.8 mL solution 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)
- Capillary Leak Syndrome: Monitor if symptoms develop and administer standard symptomatic treatment (5.5)

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: 12/2014

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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 may be administered by either a healthcare professional or by 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 pre-filled 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 pre-filled syringe to properly administer an injection after training by a healthcare professional.

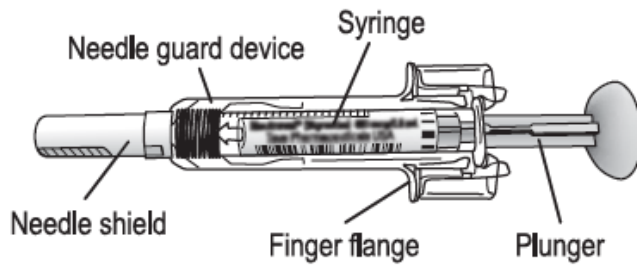
Visually inspect parenteral drug products for particulate matter and discoloration prior to administration. Do not administer GRANIX if discoloration or particulates are observed.

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

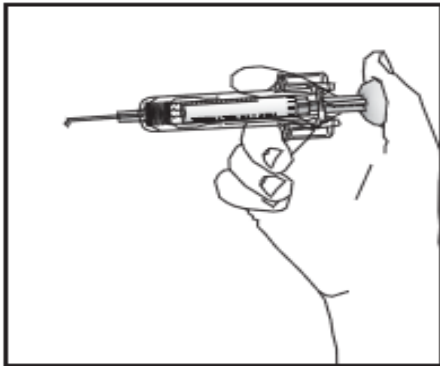
Recommended sites for subcutaneous GRANIX injections include the abdomen (except for the two-inch area around the navel), the front of the middle thighs, the upper outer areas of the buttocks, or the upper back portion of the upper arms. The injection site should be varied daily. GRANIX should not be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

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

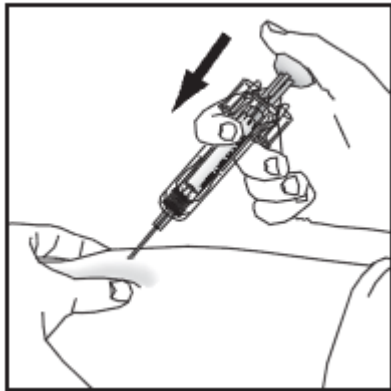


Expel any extra volume depending on dose needed.

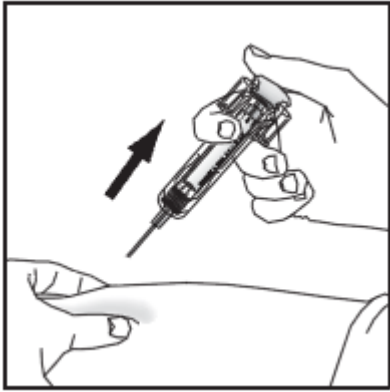


Inject GRANIX subcutaneously as recommended [see *General Considerations for Administration (2.2)*].

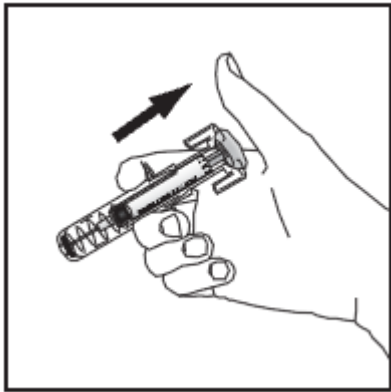
Push the plunger as far as it will go to inject all the medication. **Injection of the entire prefilled syringe contents is necessary to activate the needle guard.**



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

Injection: 300 mcg/0.5 mL solution in single-use prefilled syringe

Injection: 480 mcg/0.8 mL solution 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 Capillary Leak Syndrome

Capillary leak syndrome (CLS) can occur in patients receiving human granulocyte colony-stimulating factors 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.

5.6 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.

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)*]
- Capillary Leak Syndrome [see *Warnings and Precautions (5.5)*]
- Potential for Tumor Growth Stimulatory Effects on Malignant Cells [see *Warnings and Precautions (5.6)*]

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 $\geq 10,000 \times 10^6/L$ 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 human granulocyte colony-stimulating factors include myalgia, headache, vomiting, Sweet's syndrome (acute febrile neutrophilic dermatosis), cutaneous vasculitis and thrombocytopenia.

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

Risk Summary

There are no adequate and well-controlled studies of GRANIX in pregnant women. In animal reproduction studies, treatment of pregnant rabbits with tbo-filgrastim resulted in increased spontaneous abortion and fetal malformations at systemic exposures substantially higher than the human exposure. GRANIX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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 hindlimbs 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.

8.3 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 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-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
Polysorbate 80	0.0275 mg	0.044 mg
Sorbitol	25 mg	40 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.

Cardiac Electrophysiology

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

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_{0-48h}) 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.

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-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:

- 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

- 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 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

- 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

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

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 caregiver on the proper storage, preparation, and administration technique for GRANIX. 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.

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.

Dyspnea

Dyspnea with or without fever, progressing to Acute Respiratory Distress Syndrome, may occur. Advise patients to report dyspnea immediately to their doctor.

Allergic Reactions

Serious allergic reactions, including anaphylaxis, rash, and urticaria: Patients should report such reactions immediately to their doctor.

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 human granulocyte colony-stimulating factors.

Infections

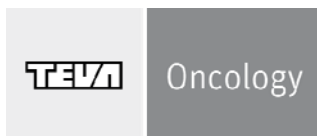
GRANIX is used in circumstances where the risk of infection is increased. Patients should be alert for signs of infection such as fever, redness or swelling, and should report these findings to their doctor immediately.

Pregnancy

Inform patients not to become pregnant while receiving GRANIX. If pregnancy occurs, advise patients of the possibility of fetal harm.

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

TBO-004



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Vilnius, Lithuania
U.S. License No. 1803

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

Product of Israel

Revision 12/2014

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).

- 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.

How should I use GRANIX?

- **GRANIX injections can be given by a doctor or nurse, or your doctor may decide that your injections can be given at home by you or your caregiver. If GRANIX is taken at home, follow the detailed Instructions for Use included with your GRANIX package for information about the right way to:**
 - **Store GRANIX**
 - **Read the syringe markings and adjust the amount of medicine**
 - **Prepare and administer an injection.**
- Your doctor will tell you how much GRANIX to inject and the timing of when to inject it. Inject GRANIX exactly as instructed.
- Do not change your dose unless your doctor tells you to.
- You or your caregiver will be shown how to prepare for an injection and how to inject GRANIX before you use it for the first time.
- Take your first dose of GRANIX at least 24 hours after you receive your chemotherapy.
- If you miss a dose or forget to take your dose of GRANIX, speak to your doctor about when to take your next dose.
- If you use too much GRANIX, call your doctor right away.
- If you or your caregiver get GRANIX on your skin, wash the area with soap and water.
- If you or your caregiver get GRANIX in your eyes, flush your eyes with water and call your doctor right away.
- Do not stop taking GRANIX without talking to your doctor.

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
- **Serious allergic reactions.** If you have a serious allergic reaction during a GRANIX injection, stop giving yourself the injections and call your doctor right away. Symptoms of serious allergic reaction can occur during or after your injection and include:
 - 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.

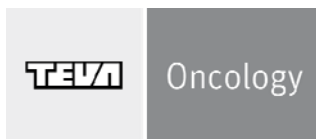
What are the ingredients in GRANIX?

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-004



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Vilnius, Lithuania
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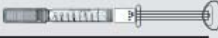


Issued: December 2014

**Instructions for Use
GRANIX (GRAN-icks)
(tbo-filgrastim)
Injection, for subcutaneous use**

Important: Keep the GRANIX syringe out of the reach of children.

About the GRANIX syringe

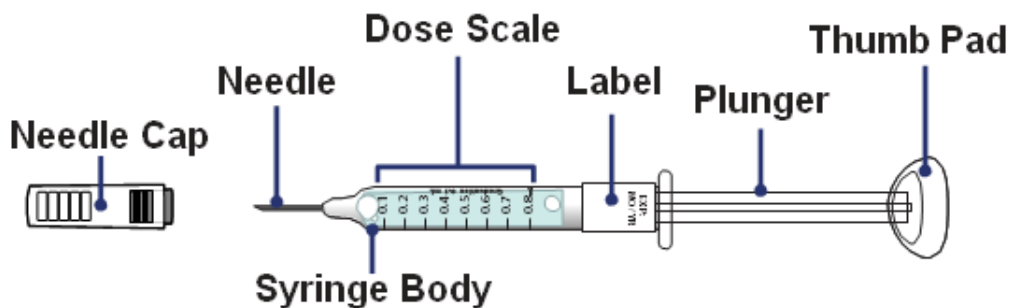
Depending on the prescription that your doctor gave you, you will receive a syringe that provides a dose of either 0.1mL to 0.5mL or 0.1mL to 0.8mL. If you are prescribed a dose over 0.8mL, two syringes will be required to reach your prescribed dose. Your doctor will determine how many syringes and the correct dose in milliliters (mL) you will need to give based on your body weight. **You should continue to give GRANIX daily until your doctor informs you that your white blood cell count has returned to normal.**

DOSE	NUMBER OF SYRINGES	
0.1mL - 0.5mL	1 Syringe	
0.1mL - 0.8mL		
0.9mL - 1.6mL	2 Syringes	

Note: Each syringe comes overfilled with medication and includes an air gap. As part of the preparation process you will need to carefully remove the air gap and some of the medication in order to match your prescribed dose.

Make sure you understand the following:

- How to store your syringes.
- How to read the syringe markings.
- How to adjust the amount of **GRANIX** in the syringe for your prescribed dose.
- How to prepare and give the injection.



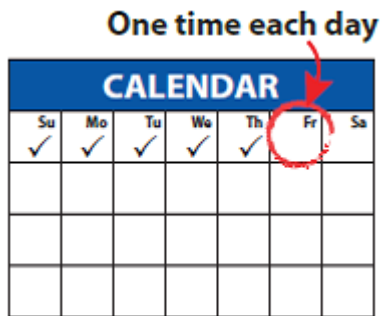
- Do not** shake syringes.
- Do not** remove the needle cap until you are ready to inject.
- Do not** re-use a syringe. The syringe is for single-use only.

Do not use earlier than 24 hours following the end of your chemotherapy cycle.

Dosing schedule

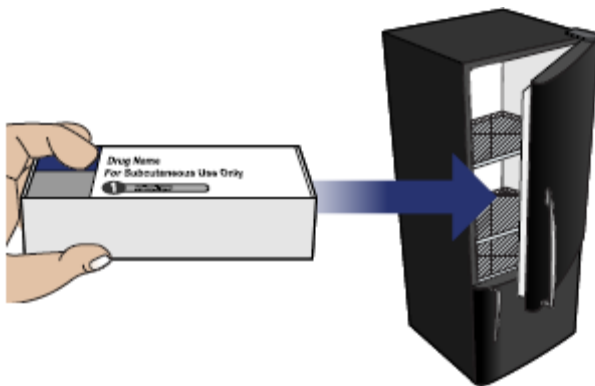
Inject your total daily dose 1 time each day as prescribed by your doctor, **starting at least 24 hours (1 day) after the end of your chemotherapy cycle.**

You should continue to give GRANIX daily until your white blood cell count returns to normal.



How to store your GRANIX syringes

- Always store the GRANIX syringes in a refrigerator at a temperature between 36°F to 46°F (2°C to 8°C).
- Always store the syringes in the carton to protect them from light.
- GRANIX syringes can be left unrefrigerated for a single period of up to 5 days, and if not used can be returned to the refrigerator.
- When preparing to inject, you will need to let the syringe(s) adjust to room temperature for 30 minutes.
- Throw away (dispose of) your syringes if stored at room temperature for more than 5 days.



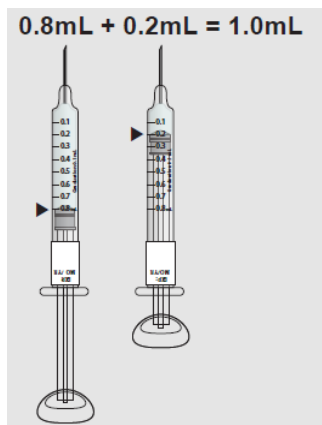
Determining how many syringes you need for your daily dose

- If your prescribed daily dose is 0.5mL or less, use 1 syringe.
- If your prescribed daily dose is 0.8mL or less, use 1 syringe.
- If your prescribed daily dose is more than 0.8mL you will need to prepare 2 syringes in order to match your prescribed dose:
 - Adjust your first syringe to 0.8mL.
 - Adjust your second syringe to the additional amount required to make up your total prescribed dose.
 - Make sure the amounts in both syringes add up to your prescribed dose (See the table to the right to determine how much medicine should be in each syringe).

Use the table below to calculate if you will need to administer one or two injections for your prescribed dose.

Dose	1 st Injection Amount	2 nd Injection Amount
0.1mL	0.1mL	
0.2mL	0.2mL	
0.3mL	0.3mL	
0.4mL	0.4mL	
0.5mL	0.5mL	
0.6mL	0.6mL	
0.7mL	0.7mL	
0.8mL	0.8mL	
0.9mL	0.8mL +	0.1mL
1.0mL	0.8mL +	0.2mL
1.1mL	0.8mL +	0.3mL
1.2mL	0.8mL +	0.4mL
1.3mL	0.8mL +	0.5mL
1.4mL	0.8mL +	0.6mL
1.5mL	0.8mL +	0.7mL
1.6mL	0.8mL +	0.8mL

For example: If your prescribed dose is 1mL you would prepare 1 syringe with 0.8mL and a second syringe with 0.2mL.



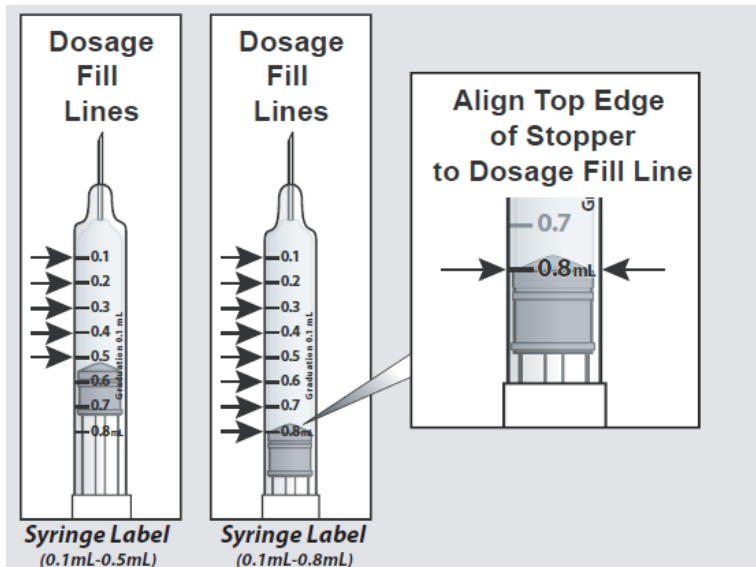
Important: When using two syringes always adjust the first syringe to 0.8mL.

How to read the syringe markings

What the markings on the syringe mean:

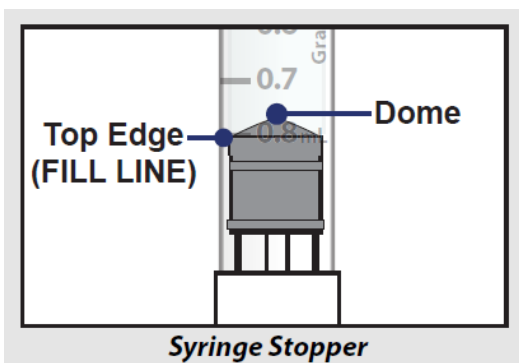
The syringe is labeled in 0.1 mL unit increments from 0.1 mL to 0.8 mL. There is a line next to each 0.1 mL unit increment.

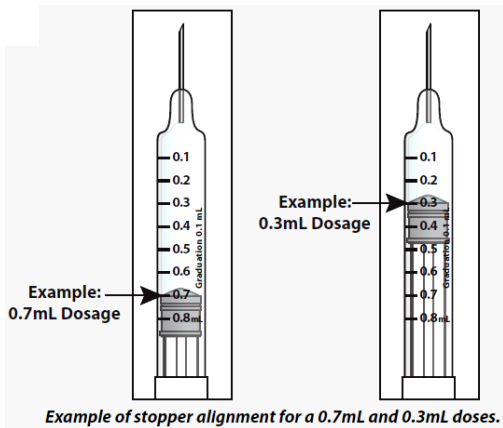
To read the dose scale always hold the syringe with the needle-end facing up so that 0.1 mL is at the top and 0.8 mL is at the bottom.



How to adjust the medicine level for your prescribed dose

- When setting your dose, (**See 2C**) you will line up the top edge of the grey rubber stopper with the line on the syringe scale that matches your prescribed dose.
- Note: The top edge of the grey rubber stopper is the edge directly below the dome at the top of the stopper.





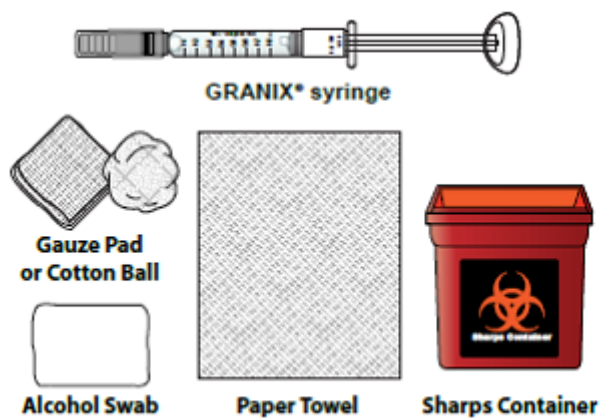
Do not use the top of the cone or the middle or lower edges of the grey stopper to measure your dose.

Injection procedure (follow the steps below for each day of dosing)

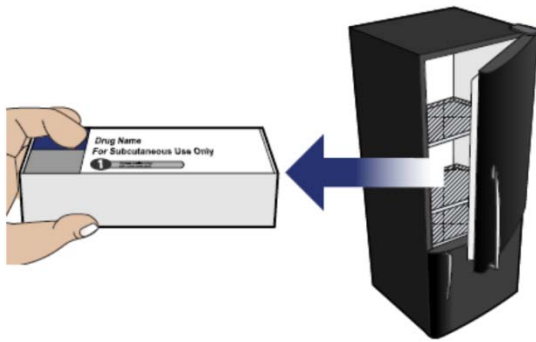
1. Prepare for injection

1A Each time you inject a dose gather the following supplies:

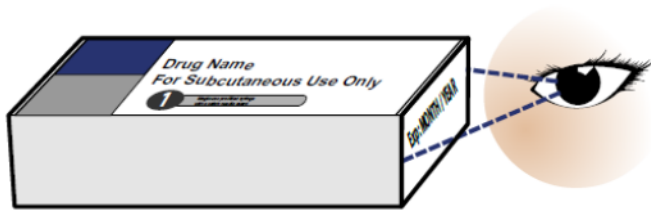
- GRANIX syringe(s)
- Alcohol swabs
- Paper towel
- Cotton ball or gauze
- Bandage (optional)
- Sharps container (hard-walled container for discarding syringes)



1B Take the carton with the syringe(s) out of the refrigerator



1C Check the label and the expiration date on the side of the carton






Important: Do not inject if:

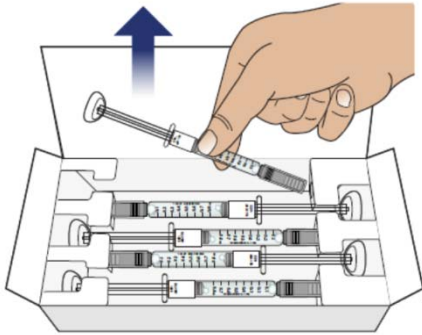
- "GRANIX[®] (tbo-filgrastim)" is not listed on the carton.
- The expiration date on the syringe label has passed.

1D Remove the syringe(s) from the carton

Open the carton by breaking the tamper proof seal and lifting the lid. Remove the number of syringes required for your daily dose by grasping each at the middle of the syringe body.

After removing your required number of syringes, place the carton back in the refrigerator.

DOSE	NUMBER OF SYRINGES
0.1mL - 0.5mL	1 Syringe 
0.1mL - 0.8mL	
0.9mL - 1.6mL	2 Syringes 

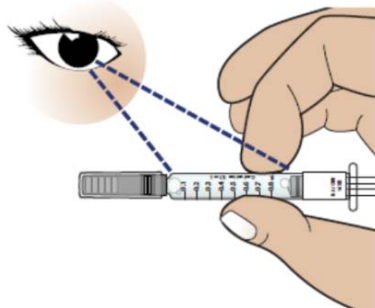


**CONTINUE TO SIDE 2 FOR
INJECTION PROCEDURE**

1E Look carefully at the syringe(s) and the medicine

Hold the syringe body and check to make sure it is not damaged.

Inspect the medicine in the syringe. GRANIX should be a clear liquid.

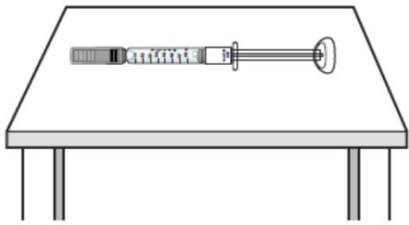


Important: Do not inject if:

- GRANIX (tbo-filgrastim) is not listed on the syringe label.
- The medicine is cloudy, discolored, or foamy.
- The medicine contains lumps, flakes, or particles.

1F Wait 30 minutes for the syringe(s) to warm to room temperature

Wait 30 minutes for GRANIX to naturally warm to room temperature. This will provide a more comfortable injection.



1G Wash your hands

When ready to inject, wash your hands with soap and warm water and dry thoroughly with a clean towel.



1H Choose an injection site

The recommended injection sites are:

If you are self-injecting:

Stomach area (abdomen): Except for a 2-inch area around the navel (belly button).

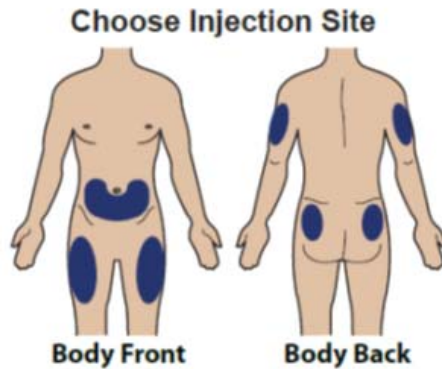
Thighs: Top or middle area of thighs.

If a caregiver is injecting GRANIX for you:

Arms: Fleishy areas on upper, back part of the arm.

Upper hip or buttock: Fleishy areas around the back of the upper hips and upper sides of the buttocks.

If 2 injections will be performed, then the second injection should be at least 1 inch away from the first injection.



Do not inject into areas that are tender, red, bruised, hard, or have scars or stretch marks.

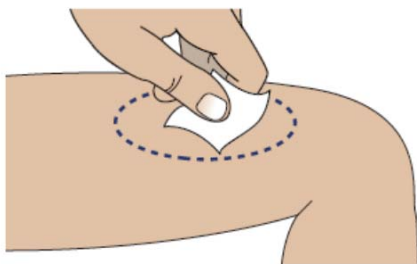
Important:

- You should select a different injection site each time you give yourself an injection.
- If you want to use the same injection site for a dose requiring 2 injections, make sure the second injection site is at least 1 inch away from the first injection site.

1I Clean the injection site using an alcohol swab

Allow site to dry for 5-10 seconds to avoid stinging.

If giving 2 injections, then the distance between the 2 injection sites should be at least 1 inch apart.



Do not touch or blow on site after cleaning.

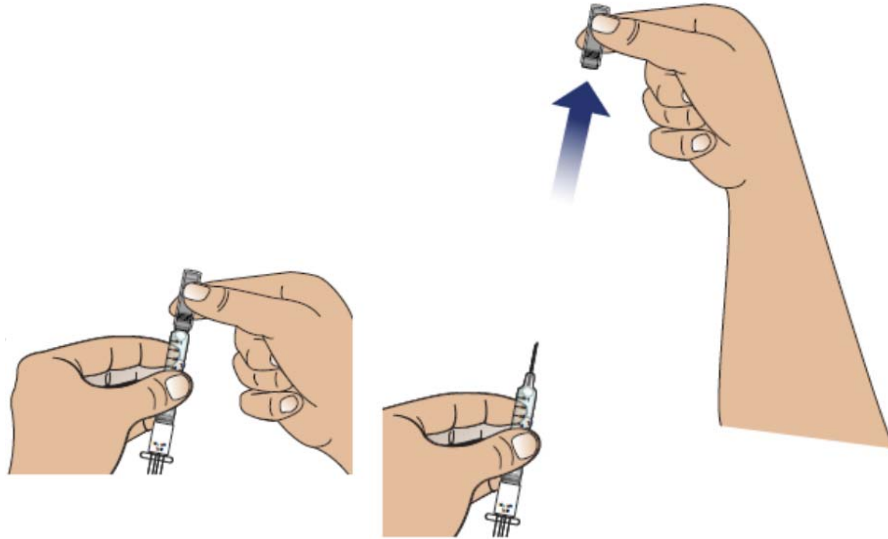
2. Adjust medicine level for your prescribed dose

2A Remove the needle cap from the syringe

Place a paper towel on the table.

To remove the needle cap, hold the body of the syringe firmly with 1 hand (with the needle facing away from you).

Pull the needle cap straight off, extending your hand away from the needle.



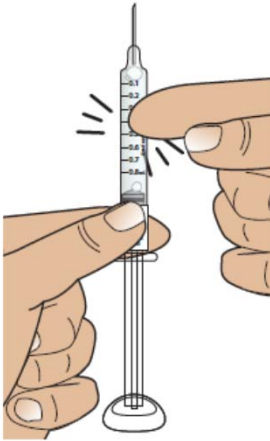
Note: Throw away the needle cap in a sharps container.

Do not recap the needle now or after the injection.

2B Hold the syringe upright and tap

Hold the syringe upright (needle pointing up), as shown.

Gently tap the barrel with your fingers to make sure any air bubbles rise to the top.

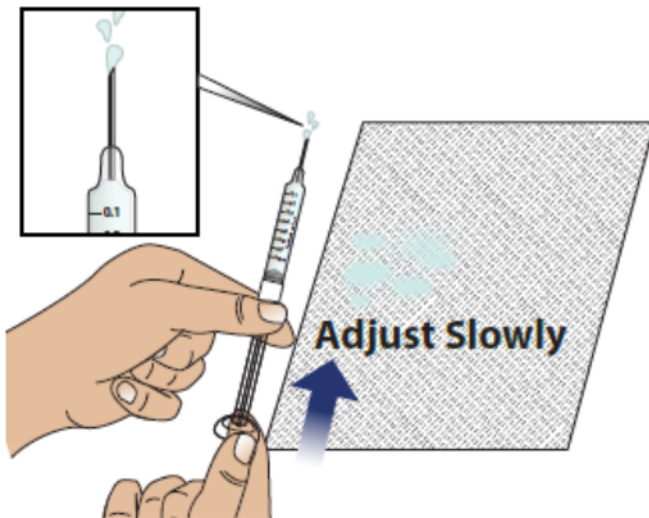


2C Slowly and Carefully adjust the medicine level

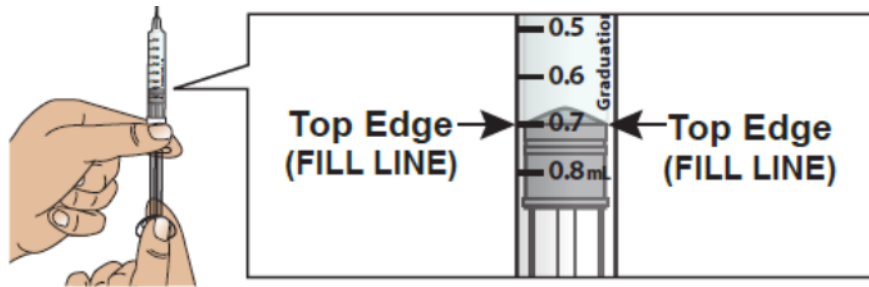
Hold the syringe with the needle pointing up and slightly away from you, as shown. Make sure you can easily see the syringe markings and numbers.

Holding the plunger as shown, **very slowly and carefully push** the plunger up until the top edge of the grey rubber stopper is even with the line that corresponds to your prescribed dose.

Note: It is OK for the medicine to make contact with your skin. Wash the area with soap and water.



Note: If you accidentally removed too much GRANIX, contact your doctor before giving your injection.



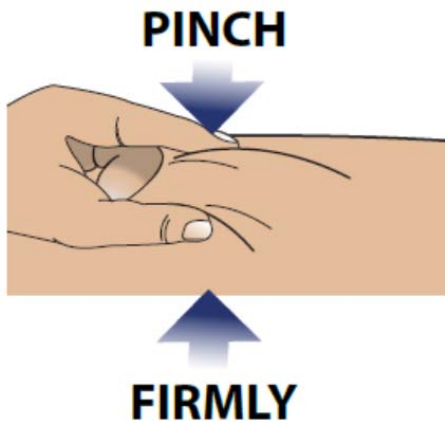
⚠ If your dose is more than 0.8mL (0.9mL – 1.6mL):

If your dose is more than 0.8mL you will need to use two (2) syringes.

- Always adjust both syringes prior to injecting to make sure you receive the correct dose.
- Adjust the first syringe to 0.8mL. Set the adjusted syringe on a clean surface, ensuring the needle does not touch anything.
- Adjust the second syringe to reach your prescribed dose, making sure the amounts in both syringes add up to your total dose. (Use the table on Side 1 to determine the amount for the second syringe).

3A Pinch skin

Use your free hand to firmly pinch the skin you previously cleaned.



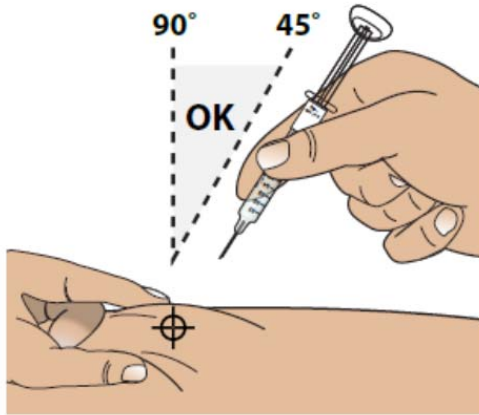
3B Insert the needle at a 45 to 90 degree angle

Hold the body of the syringe between your thumb and index finger.

Use a quick motion to fully insert the needle straight into the pinched skin at a 45 to 90 degree angle.

When the needle is inserted, you can release the pinched skin.

45-TO-90 DEGREE ANGLE

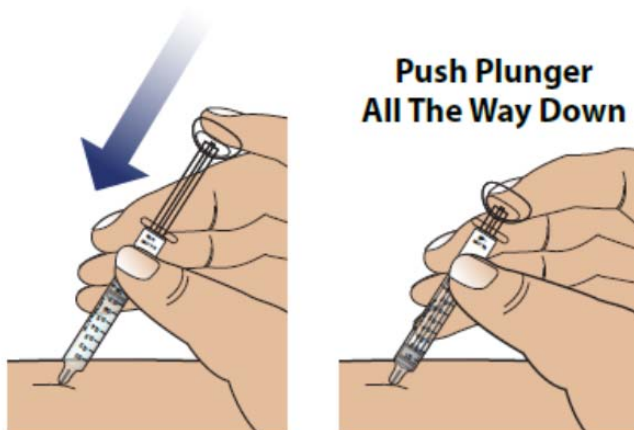


Do not hold or push on the plunger while inserting the needle into the skin.

3C Push the plunger down injecting all of the GRANIX

Use your finger to gently push down on the plunger.

When the plunger head is as far down as it will go, and all of the GRANIX has been injected, remove the needle from the skin.



3D Dispose of used syringe

Put your used needles and syringes in a FDA-cleared sharps disposal container right away after use. Do not throw away (dispose of) loose needles and syringes in your household trash.

If you do not have a 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 and 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>.

Do not dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. Do not recycle your used sharps disposal container.

3E Treat the injection site if needed and wash your hands

If you see drops of blood at the injection site, you can press a cotton ball or gauze over the injection site for several seconds to stop the bleeding.

Apply bandage, if needed.

When you are finished, wash your hands with soap and warm water and dry thoroughly with a clean towel.



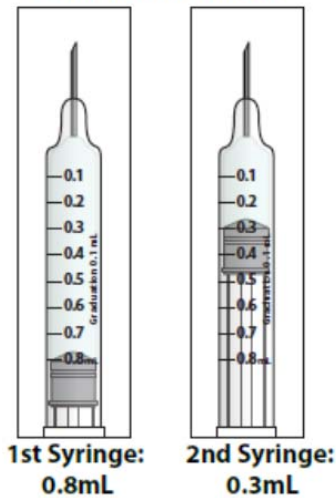
4. Repeat the procedure with the second syringe (If dose is more than 0.8mL)

If your dose is more than 0.8mL:

- Follow instructions 3A through 3E for injecting.

- Choose a different site for your second injection. If you want to use the same part of your body, make sure the second injection site is **at least 1 inch away from the first injection site.**

**Example of dosing
for a 1.1mL dose:**



TROUBLESHOOTING

If you have problems performing this procedure, please contact your healthcare professional.

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

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