MEDICAL MUTUAL®

Drug Policy

Policy:	**201825**	**Initial Effective Date: 10/30/2014**
Code(s):	**HCPCS J1447**	**Annual Review Date: 08/16/2018**
SUBJECT:	**Colony Stimulating Factors** - **Granix™ (tbo-filgrastim)**	**Last Revised Date: 08/16/2018**

Prior approval is required for some or all procedure codes listed in this Corporate Drug Policy.

Overview

Granix, a granulocyte colony stimulating factor (G-CSF), is indicated for the reduction in the duration of severe neutropenia in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer medications associated with a clinically significant incidence of febrile neutropenia.[1] The recommended dose is 5 mcg/kg per day given as a subcutaneous (SC) injection. The safety and effectiveness in Granix in pediatric patients have not been established. Granix may be administered by a healthcare professional or by a patient or caregiver. Granix is available in single-use, preservative-free, prefilled syringes in strengths of 300 mcg/0.5 mL and 480 mcg/0.8 mL intended for single use only.

Policy Statement

This policy involves the use of Granix. **This policy does not apply to Medicare or Medicare Advantage members.** Prior authorization is recommended for medical benefit coverage of Granix. Coverage is recommended for those who meet the conditions of coverage in the **Criteria, Dosing, Initial/Extended Approval, Duration of Therapy, and Labs/Diagnostics** for the diagnosis provided. The requirement that the patient meet the Criteria for coverage of the requested medication applies to the initial authorization only. **Waste Management** applies for all covered conditions. **Conditions Not Recommended for Approval** are listed following the recommended authorization criteria and Waste Management section. **Zarxio (filgrastim-sndz) is the preferred filgrastim product. Patient must have a documented failure, contraindication, intolerance, or ineffective response to Zarxio for a non-preferred filgrastim product to be considered for approval.**

Because of the specialized skills required for evaluation and diagnosis of patients treated with Granix as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Granix to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals for initial therapy are provided for the initial approval duration noted below; if reauthorization is required, a response to therapy is required for continuation of therapy.

*The site of care medical necessity criteria applies to initial therapy and reauthorizations under the medical benefit.

MEDICAL MUTUAL®

Drug Policy

FDA-Approved Indications

1. Cancer Patients Receiving Myelosuppressive Chemotherapy

Criteria. *The patient must meet the following criteria (A, B, , C and D):*

A) The agent is prescribed by, or in consultation with, an oncologist or hematologist; AND

B) The patient meets ONE of the following conditions (i, ii, iii, or iv):

i. The patient is receiving myelosuppressive anti-cancer medications that are associated with a high risk of febrile neutropenia (the risk of febrile neutropenia is at least 20% based on the chemotherapy regimen); OR

ii. The patient is receiving myelosuppressive anti-cancer medications that are associated with a risk of febrile neutropenia but the risk is less than 20% based on the chemotherapy regimen and the patient has one or more risk factors for febrile neutropenia according to the prescribing physician (e.g., aged ≥ 65 years; prior chemotherapy or radiation therapy; persistent neutropenia; bone marrow involvement by tumor; recent surgery and/or open wounds; liver and/or renal dysfunction; poor performance status; or human immunodeficiency virus [HIV] infection); OR

iii. The patient has had a neutropenic complication from prior chemotherapy and did not receive prophylaxis with a colony stimulating factor (e.g., Granix, pegfilgrastim injection, filgrastim injection, Zarxio™ [filgrastim-sndz injection], Leukine® [sargramostim injection]) and a reduced dose or frequency of chemotherapy may compromise treatment outcome; OR

iv. The patient who has received chemotherapy has febrile neutropenia and has at least one risk factor for poor clinical outcomes or for developing infection-associated complications according to the prescribing physician (e.g., sepsis syndrome; age > 65 years; severe neutropenia [absolute neutrophil count < 100 cells/mm^3]); neutropenia expected to be > 10 days in duration; invasive fungal infection; other clinically documented infections; prior episode of febrile neutropenia); AND

C) If the request is for a filgrastim product other than Zarxio, patient must have a documented failure, contraindication, intolerance or ineffective response to Zarxio; AND

D) Site of care medical necessity is met*.

Dosing in Patients with Cancer Receiving Myelosuppressive Chemotherapy.

Dosing in Adults must meet the following: The dose is 5 mcg per kg per day by SC injection.
Dosing in Pediatric Patients must meet the following: Infants ≥1 month of age, Children, and Adolescents: SubQ: 5 mcg/kg/day; continue until anticipated nadir has passed and neutrophil count has recovered to normal range.

According to the NCCN guidelines for myeloid growth factors (version 1.2017), the SC route is preferred. Granix is started the next day or up to 3 to 4 days after completion of chemotherapy and continued through post-nadir ANC recovery to normal levels.

Initial Approval/Extended Approval.

A) *Initial Approval.* Initial approval is for up to 6 months.

B) *Extended Approval.* Extended approval is for up to 6-month intervals if the patient continues to receive myelosuppressive chemotherapy.

Duration of Therapy in Adults with Cancer Receiving Myelosuppressive Chemotherapy. Therapy may be continued as long as the patient is receiving myelosuppressive chemotherapy.

Labs/Diagnostics. None required.

Other Uses with Supportive Evidence

2. Patients (Adults and Children) Undergoing Peripheral Blood Progenitor Cell (PBPC) Collection and Therapy.

Criteria. *Patient must meet the following criteria (A, B, and C):*

A. Granix is prescribed by, or in consultation with, an oncologist, a hematologist, or a physician that specializes in transplantation; AND

B. If the request is for a filgrastim product other than Zarxio, patient must have a documented failure, contraindication, intolerance or ineffective response to Zarxio; AND

C. Site of care medically necessity is met*.

Granix is not indicated in this scenario but other filgrastim products, Neupogen® (filgrastim injection for SC or intravenous [IV] use) and Zarxio® (filgrastim-sndz injection for SC or IV use) are indicated for the mobilization of hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis.[5-6] However, some data are available with Granix.[6-9] The NCCN Panel in the guidelines for the myeloid growth factors recommends tbo-filgrastim (Granix) as an alternative for allogeneic hematopoetic cell mobilization and for granulocyte transfusion (category 2B).[3] Also, tbo-filgrastim (Granix) is an alternative in the supportive care setting for post-autologous hematopoietic cell transplant (category 2A). Mobilization allows for the collection of increased numbers of progenitor cells capable of engraftment compared with collection by leukapheresis without mobilization or bone marrow harvest. After myeloablative chemotherapy, the transplantation of an increased number of progenitor cells can lead to a more rapid engraftment, which may result in a decreased need for supportive care. The scenarios where CSF is utilized includes patients with cancer or healthy donors undergoing mobilization of PBPC, as well as patients with cancer post autologous PBPC transplantation.[1-3,10-11] This criterion is recommended based on the professional opinion of specialized and other physicians.

Dosing in Patients (Adults and Children) Undergoing PBPC Collection and Therapy. *Dosing must meet ONE of the following (A, B, OR C):*

A) Patients with Cancer or Healthy Donors Undergoing Mobilization for PBPC: 10 mcg per kg per day SC for 5 to 7 days. Some patients may require up to 32 mcg per kg per day SC. Dosing can be once daily or twice daily.[3] Alternate dosing will be assessed individually on a case-by-case basis.

In the autologous setting, Granix has been given as a doage of 10 mcg/kg day SC for 3 to 4 days prior to PBPC collection. Doses up to 32 mcg/kg/day SC have been used, in daily or twice daily dosing.[2,6-9] The optimal duration has not been clearly established and some patients may require a longer duration of therapy.[9-11]

B) Patients Undergoing Mobilization of PBPC Who Are Poor Mobilizers: 12.5 to 50 mcg per kg per day SC.[11] Dosing can be once daily or twice daily.[2] Alternate dosing will be assessed individually on a case-by-case basis.

Poor mobilizers (e.g., patients who fail to mobilize an adequate number of stem cells on the first attempt; patients with Hodgkin's lymphoma, non-Hodgkin's lymphoma, and preleukemic syndromes; recent chemotherapy or radiation), may use filgrastim or use other regimens that add Leukine to filgrastim, add Mozobil® (plerixafor injection), or mobilization with chemotherapy plus filgrastim.[2,11]

C) Patients with Cancer Post Autologous PBPC Transplantation: 5 to 24 mcg per kg per day SC after reinfusion of the collected cells until a sustainable ANC is attained.[4-5] Dosing can be once daily or twice daily.[2] Alternative dosing will be assessed individually on a case-by-case basis.

In clinical trials of filgrastim, the dose given to patients was 5 to 24 mcg/kg/day after reinfusion of the collected cells until a sustainable ANC ≥ 500 cells/mm^3 was reached.[4-5] Another recommendation for supportive care in patients post autologous stem cell or cord blood transplant, is to give filgrastim 5 mcg/kg/day beginning ≥ 5 days post transplant until recovery of ANC (e.g., > 1,500 cells/mm^3 for 2 consecutive days).[2]

Initial Approval/Extended Approval.

Patients with Cancer or Healthy Donors Undergoing Mobilization of PBPC.

A) *Initial Approval.* For unrelated healthy donors, 5 days of therapy with Granix 10 mcg per kg per day are used.[9-11] For patients with cancer, 5 to 7 days of Granix 10 mcg per kg per day are usually given once daily; twice daily dosing may be used. Alternative regimens will be assessed individually on a case-by-case basis and may be extended for some patients (e.g., patients who are poor mobilizers).

B) *Extended Approval*. Not applicable.

Patients with Cancer Post Autologous PBPC Transplantation.

A) *Initial Approval*. 14 days or until the absolute neutrophil count (ANC) is > 1,500 cells/mm^3 for 3 consecutive days. Usually the duration of therapy is 9 to 11 days but has ranged from 7 to 63 days. Alternative regimens will be assessed individually on a case-by-case basis.

B) *Extended Approval*. Not applicable.

Duration of Therapy in PBPC.

Patients with Cancer or Healthy Donors Undergoing Mobilization of PBPC. 5 days of Granix. Alternative durations will be assessed individually on a case-by-case basis and may be extended for some patients (e.g., patients who are poor mobilizers).

The National Marrow Donor Program protocol gives filgrastim for 4 consecutive days (in patients weighing < 35 kg) or 5 consecutive days in unrelated donors (allogeneic transplantation).[5] In some instances, patients may require a longer duration of therapy (e.g., patients with cancer heavily pretreated with chemotherapy, healthy patients in which a higher number of cells are needed due to the type of transplantation).

Patients with Cancer Post Autologous PBPC Transplantation. 14 days of Granix. Approve for another 14 days if ANC is not at a sustainable level. Most patients have a response after 28 days of Granix. Alternative durations will be assessed individually on a case-by-case basis.

Labs/Diagnostics. None required.

Waste Management for All Indications.
Single use, preservative free syringes are in strengths of 300 mcg/0.5 mL and 480 mcg/0.5 mL. The dose is based on a mcg per kg body weight basis. Use the most efficient formulation that delivers the needed dose.

CONDITIONS NOT RECOMMENDED FOR APPROVAL
Colony Stimulating Factors have not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

1. Coverage is not recommended for circumstances *not* listed in the *Recommended Authorization Criteria*. Criteria will be updated as new published data are available.

2. **Concomitant use of Colony Stimulating Factors**: Colony Stimulating Factors are not recommended as combination therapy.

Documentation Requirements:

The Company reserves the right to request additional documentation as part of its coverage determination process. The Company may deny reimbursement when it has determined that the drugs provided or services performed were not medically necessary, investigational or experimental, not within the scope of benefits afforded to the member and/or a pattern of billing or other practice has been found to be either inappropriate or excessive. Additional documentation supporting medical necessity for the services provided must be made available upon request to the Company. Documentation requested may include patient records, test results and/or credentials of the provider ordering or performing a service. The Company also reserves the right to modify, revise, change, apply and interpret this policy at its sole discretion, and the exercise of this discretion shall be final and binding.

References

1. Granix™ injection [prescribing information]. North Wales, PA: Teva Pharmaceuticals; February 2017.
2. The NCCN Myeloid Growth Factors Clinical Practice Guidelines in Oncology (Version 1.2017). © 2017 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on July 7, 2017.
3. Smith TJ, Bohlke K, Lyman GH, Carson KR, et al. Recommendations for the use of WBC growth factors: American Society of Clinical Oncology

Clinical Practice Guideline Update. *J Clin Oncol*. 2015;33(28):3199-3212. Available at: http://jco.ascopubs.org/content/early/2015/07/08/JCO.2015.62.3488.full.pdf+html Accessed on July 7, 2017.
4. Neupogen® injection for subcutaneous or intravenous use [prescribing information]. Thousand Oaks, CA: Amgen, Inc.; June 2016.
5. Zarxio™ injection for subcutaneous or intravenous use [prescribing information]. Princeton, NJ: Sandoz; February 2017.
6. Schmitt M, Xu X, Hilgendorf I, et al. Mobilization of PBSC for allogeneic transplantation by the use of G-CSF biosimilar XM02 in healthy donors. *Bone Marrow Transplant*. 2013;48:922-925.
7. Elayan MM, Horowitz JG, Magraner JM, et al. Tbo-filgrastim versus filbrastim during mobilization and neutrophil engraftment for autologous stem cell transplantation. *Biol Blood Marrow Transplant*. 2015;21:1921-1925.
8. Trifilio S, Zough Z, Galvin J, et al. Filgrastim versus TBO-filgrastim to reduce the duration of neutropenia after autologous hematopoietic stem cell transplantation: TBO, or not TBO, that is the question. *Clin Transplant*. 2015;29:1128-1132.
9. Blair HA, Scott LJ. Tbo-filgrastim: a review in neutropenia conditions. *BioDrugs*. 2016;30:153-160.
10. Pulsipher MA, Chitphakdithai P, Miller JP, et al. Adverse events among 2408 unrelated donors of peripheral blood stem cells: results of a prospective trial from the National Marrow Donor Program. *Blood*. 2009;113:3604-3611.
11. Pusic I, DiPersio JF. The use of growth factors in hematopoietic stem cell transplantation. *Curr Pharm Des*. 2008;14(20):1950-1961.

FOR MEDICAL BENEFIT COVERAGE REQUESTS:

***MMO Site of Care Medical Necessity Criteria:**

Medications in this policy will be administered in a place of service that identifies the location to be a non-hospital facility based location (i.e., home infusion provider, provider's office, free-standing ambulatory infusion center) unless *at least one* of the following are met†:

1. Age less than 21 years; or
2. Clinically unstable based upon documented medical history (e.g., patient is hemodynamically unstable); or
3. History of a severe adverse event from previous administration of the prescribed medication; or
4. Requested medication is being administered as follows:
   - part of a chemotherapy regimen (e.g., anti-neoplastic agent, colony stimulating factor, erythropoiesis-stimulating agent, anti-emetic) for treatment of cancer; or
   - administered with dialysis; or
5. Physical or cognitive impairment and caregiver is not available to assist with safe administration of prescribed medication in the home; or
6. Experiencing adverse events that are not managed by premedication or resources available at a non-hospital facility based location.

No initial doses are allowed in a hospital based outpatient facility without other above criteria being met.

†This criterion does not apply to Medicare or Medicare Advantage members.

Prior approval is required for HCPCS Codes J1447

MEDICAL MUTUAL®

Drug Policy

HCPCS Code(s):	
J1447	Injection, tbo-filgrastim, 1 microgram