Tbo-Filgrastim (Granix)

National Drug Monograph
December 2014

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a comprehensive drug review for making formulary decisions. Updates will be made when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

FDA Approval Information

Description/Mechanism of Action	Tbo-filgrastim is a non-glycosylated recombinant human granulocyte colony-stimulating factor (G-GSF) that binds to G-CSF receptors which stimulates differentiation of neutrophils and increases neutrophil counts.
Indication(s) Under Review	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.
Dosage Form(s) Under Review	Single-use, preservative-free, prefilled glass syringes of 300 mcg/0.5ml and 480 mcg/0.8ml
REMS	☐ REMS ☒ No REMS
Pregnancy Rating	Category C

Executive Summary

Efficacy	• In the registration trial in breast cancer tbo-filgrastim was superior to placebo in cycle 1 of myelosuppressive chemotherapy for the primary endpoint of duration of severe neutropenia. • Equivalence was shown to filgrastim for the primary endpoint of duration of severe neutropenia. • Supportive trials in other cancers found similarities of outcomes for tbo-filgrastim and filgrastim. • A meta-analysis of the 3 developmental clinical trials found no significant difference in the incidence of febrile neutropenia across the trials.
Safety	• The most common adverse events were bone pain, arthralgia, back pain, and diarrhea • There were no deaths attributed to tbo-filgrastim. • Warnings for all myeloid growth factors include splenic rupture, acute respiratory distress syndrome, allergic reactions, sickle-cell crisis, and potential for stimulation of tumor growth
Other Considerations	• This is not a biosimilar and is not a generic drug.
Potential Impact	• Tbo-filgrastim may be used in place of filgrastim for primary or secondary prophylaxis to prevent febrile neutropenia. • NCCN gives both filgrastim and tbo-filgrastim a Category 1 rating for prophylaxis of febrile neutropenia. • Dosing and adherence expected to be the same as with filgrastim

Background

Purpose for review

The purposes of this monograph are to (1) evaluate the available evidence of safety, tolerability, efficacy, cost, and other pharmaceutical issues that would be relevant to evaluating tbo-filgrastim for possible addition to the VA National Formulary; (2) define its role in therapy; and (3) identify parameters for its rational use in the VA.

Issues to be determined

- ✔ Evidence of need
- ✔ Does tbo-filgrastim offer advantages over current VANF agents?
- ✔ Will tbo-filgrastim replace current VANF agents?
- ✔ What safety issues need to be considered?
- ✔ Does tbo-filgrastim have specific characteristics best managed by the non-formulary process, prior authorization, criteria for use?

Other therapeutic options

Formulary Alternatives	Other Considerations (For example efficacy, dosing regimen, safety concerns, storage limitations, etc.)
filgrastim	Additional indications for patients with myeloid leukemia receiving chemotherapy, for patients with non-myeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplant, mobilization of hematopoietic progenitor cells for collection by leukopheresis for use in peripheral stem cell transplants, and chronic neutropenia
sargramostim	Indications: Following chemotherapy for AML, mobilization and myeloid reconstitution in autologous stem cell transplants, myeloid reconstitution after autologous stem cell transplant for lymphoid malignancies, myeloid reconstitution after allogeneic bone marrow transplants, bone marrow transplant failure or engraftment delay
pegfilgrastim	Administered once after chemotherapy cycle; no indication for mobilization or for myeloid malignancies

Efficacy (FDA Approved Indications)

Literature Search Summary

A literature search was performed on PubMed/Medline (1966 to September 2014) using the search terms tbo-filgrastim and Granix and XM02. The search was limited to studies performed in humans and published in the English language. Reference lists of review articles were searched for relevant clinical trials. All randomized controlled trials published in peer-reviewed journals were included.

Review of Efficacy

Registration trial[#]
Breast Cancer[1]

Treatment Group	XM02 (N=140)	Neupogen™ (n=136)	Placebo/XM02* (n=72)
Mean DSN (days)			
Cycle 1	**1.1**	**1.1**	**3.8**
ANCOVA (95%CI)	0.028 (-0.261, 0.316)		
Cycle 4	0.7	0.7	0.7
Mean ANC nadir (10^9/L)			
Cycle 1	0.7	0.7	0.2
ANCOVA (95%CI)	-0.001 (-0.19, 0.189)		
Cycle 4	1.0	1.0	1.1
Mean time to ANC recovery (days)			
Cycle 1	8.0	7.8	14.0
ANCOVA (95%CI)	0.207 (-0.425, 0.838)		
Cycle 4	7.6	7.1	7.2
Incidence of FN (%)			
Cycle 1	12.1	12.5	36.1
Across all cycles	20.7	22.1	41.7

DSN=Duration of severe neutropenia; ANCOVA=analysis of covariance; ANC=absolute neutrophil count; FN=febrile neutropenia observed or protocol defined
# Funded by BioGeneriX
*Patients in this group received placebo cycle 1 and XM02 afterwards

- The FDA approval of tbo-filgrastim was based on the pivotal trial in breast cancer with supporting data from trials in lung cancer and non-Hodgkin's lymphoma.
- Multinational, multicenter study, randomized, controlled trial in patients with breast cancer who were chemotherapy naïve and planned or eligible to receive docetaxel/doxorubicin. ECOG PS≤2. No sites in North America.
- No double-blinding due to different volume of XM02 and Neupogen™. Investigator blinded but drugs administered by unblinded study personnel.
- Starting the day after chemotherapy (given every 3 weeks) patients received daily injection of XM02 or Neupogen™ for at least 5 days to a maximum of 14 days at 5 mcg/kg/day actual body weight.
- Superiority versus placebo: least square mean of DSN significantly shorter for XM02 versus placebo
- Equivalence of XM02 and Neupogen™ for DSN was assessed by ANCOVA and 95%CI. The CI was within the pre-specified equivalence range (-1, 1).
- Mean DSN similar in all treatment groups in cycles 2-4.
- Pharmacokinetic profiles of XM02 and Neupogen™ similar; t1/2 values correspond to published values
- Adverse event profiles similar between XM02 and Neupogen™ except for more drug-related AEs more frequent in Neupogen group™ (39.7%) vs XM02 group (25.7%) (p=0.0149)
- Immunogenicity was low and no confirmed neutralizing antibodies
- Evidence Grade: Moderate

Supporting Data

Lung Cancer[2] **Platinum based chemotherapy**	**XM02 (n=160)**	**Neupogen (n=80)**
Mean DSN (days)		
Cycle 1	0.5	0.3
Cycle 3	0.4	0.3
Mean ANC nadir (10^9/L)		
Cycle 1	2.1	2.9
Cycle 4	2.3	3.2
Mean time to ANC recovery (days)		
Cycle 1	6.3	4.5
Cycle 4	6.4	4.5
Incidence of FN (%)		
Cycle 1	15.0	8.8 (p=0.2347)
Across all cycles	33.1	23.8

No sites in North America; funded by BioGeneriX

Non-Hodgkin lymphoma[3] **CHOP/R-CHOP**	**XM02 (n=63)**	**Filgrastim/XM02* (n=29)**
Mean DSN (days)		
Cycle 1	0.5	0.9 (p=0.1055)
Cycle 4	0.2	0.7 (N.A.)
Incidence of FN (%)		
Cycle 1	11.1	20.7 (p=0.1232)
Across all cycles	31.7	41.4 (p=0.2094)
Mean ANC (10^9/L)		
Cycle 1	1.7	1.1 (P=0.1531)
Cycle 4	2.1	1.8 (N.A.)
Mean time to ANC recovery (days)		
Cycles 1	6.0	6.7 (p=0.4939)
Cycle 4	4.9	6.1 (N.A.)

*Patients received Neupogen™ cycle 1 and XM02 thereafter; N.A.=Not Assessed
No sites in North America; funded by BioGeneriX

Peripheral Blood Stem Cell Mobilization

Study	**Outcomes**
Healthy donors (HD) for Allogeneic transplant donors in hematologic malignancies[4] XM02 vs G-CSF (Amgen) n=22	• Assessed for a variety of outcomes • No differences in WBC count in peripheral blood of HD after mobilization, $CD34^+$ cell count after mobilization, $CD34^+$ absolute numbers and $CD34^+$ cells per kg body weight of patients, number of leukapherisis procedures needed, number of $CD3^+$ T lymphocytes, number of nucleated cells in the graft, and regeneration of WBC, neutrophils, and platelets in the patient • All patients engrafted • Only expected adverse events like arthralgias
Autologous transplant for multiple myeloma or lymphoma[5] Plerixafor and XM02 n=14	• All patients underwent leukapheresis and were able to collect $CD34^+$ sufficient for transplant • Bone pain was the most common AE for XM02 and diarrhea after plerixafor

	• 7 patients underwent high-dose chemotherapy with stem cell infusion; all engrafted • 7 patients are waiting for transplant in the near future

Meta-analysis[6]

- Compare the incidence of Febrile Neutropenia (FN) in cycle 1 of chemotherapy between XM02 and Neupogen™ and assess its dependence on the myelotoxic potential of the chemotherapy administered in the 3 clinical studies in the XM02 development program in breast cancer, lung cancer, and non-Hodgkin's lymphoma (see above).
- Age and other demographics similar between the studies.
- Differences with regard to gender: in the breast cancer trial 99.3% were female, in the lung cancer trial 79.6% were male.
- For FN, the estimated common risk difference of XM02 minus filgrastim was 1.7% (95%CI -3.8, 7.1). The Odds Ratio for FN was 1.08 (95%CI 0.66, 1.77).
- For Incidence by Myelotoxic Potency, the estimated common risk difference of XM02 minus filgrastim was 0.6% (95%CI -5.0%, 6.2%). The assay used in this meta-analysis was not sensitive enough to detect differences by myelotoxic potency (authors)

Potential Off-Label Use

- Patients with myeloid leukemia
- Peripheral Blood Stem Cell mobilization
- HIV-neutropenia
- Cyclic neutropenia
- Hepatitis-C treatment related neutropenia
- Radiation induced suppression of bone marrow

Safety

(for more detailed information refer to the product package insert)

	Comments
Boxed Warning	• None
Contraindications	• None
Warnings/Precautions	• Splenic rupture which can be fatal. Discontinue and evaluate patients with upper abdominal pain or shoulder pain. • Acute Respiratory Distress Syndrome (ARDS): evaluate patients who develop a fever and lung infiltrates or respiratory distress. • Allergic Reactions including anaphylaxis may occur even on initial exposure. Treat with antihistamines, steroids, bronchodilators, and/or epinephrine. Do not administer to patients with a history of allergic reactions to filgrastim or pegfilgrastim. • Use in Sickle Cell Disease may produce severe or fatal sickle cell crisis. Consider Risks/Benefits before using in patients with Sickle Cell Disease. • Potential for tumor growth stimulation: the G-CSF receptor may be found on tumor cell lines. Tbo-filgrastim may act as a growth factor for any tumor type including myeloid malignancies and myelodysplasia.

Safety Considerations

- Overall safety profile of tbo-filgrastim in the clinical trial program was similar to that of Neupogen™.
- Serious adverse events were reported in the range of 14.1% to 30.4%. Severe adverse events were reported in 17.4% to 40.1%.
- Deaths during study were not due to the study drug.

Adverse Reactions

Common adverse reactions	Bone pain, arthralgia, back pain, diarrhea
Death/Serious adverse reactions	• No deaths reported in clinical trials for tbo-filgrastim. • Deaths due to splenic rupture or fatal sickle cell crisis reported for human granulocyte colony stimulating factor.
Discontinuations due to adverse reactions	• Discontinuation due to treatment emergent adverse events ranged from 1.1% to 13.1%.

Drug Interactions

Drug-Drug Interactions

- No formal studies conducted
- Use with caution with other drugs that may potentiate the release of neutrophils, e.g. lithium.
- Increased hematopoietic activity of bone marrow may be associated with transient bone imaging changes and should be considered when interpreting bone images.

Risk Evaluation

As of November 2014

	Comments
Sentinel event advisories	• None • Sources: ISMP, FDA, TJC
Look-alike/sound-alike error potentials	• LA/SA for Granix: Granulex • LA/SA for tbo-filgrastim: filgrastim, pegfilgrastim • Sources: As part of a JCAHO standard, LASA names are assessed during the formulary selection of drugs. Based on clinical judgment and an evaluation of LASA information from three data sources (Lexi-Comp, First Databank, and ISMP Confused Drug Name List).

Other Considerations

- Supplied: pre-filled glass syringes 300 mcg/0.5mL and 480 mcg/0.8mL
- Stored in refrigerator at 36º to 46º F
- Bioequivalence trial in healthy volunteers[7]
  - XM02 versus Neupogen™ at 5 or 10 mcg/kg, 2 week washout period, then cross over to the other product
  - N=56 healthy Caucasian males
  - Primary pharmacokinetic parameters: AUC_{0-48}, $AUC_{0-\infty}$, C_{max}, ANC AUC_{0-96}, ANC $AUC_{0-\infty}$, ANC_{max}
  - Confidence intervals for pharmacokinetic parameters within 80-125%
  - ANC time profiles virtually superimposable.
- Pharmacokinetic and pharmacodynamics profile of XM02 and Neupogen for biosimilarity in Europe[8]
  - Phase 1 multicenter, single-dose, single-blind, randomized, crossover trial
  - Mean concentrations of filgrastim similar to XM02
  - ANOVA 90%Cis for primary pharmacokinetic parameter, AUC_{48h} and the secondary C_{max} and $t_{1/2}$ were within acceptance limits of 80%-125%.

Dosing and Administration

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

Special Populations (Adults)

	Comments
Elderly	• No differences in safety or efficacy observed in patients over 65 years of age versus younger patients.
Pregnancy	• Category C • No adequate or well-controlled trials in pregnant women • In pregnant rabbits, adverse embryo findings including increased spontaneous abortion. Use during pregnancy only if potential benefit justifies potential fetal risk.
Lactation	• It is not known if filgrastim is secreted in human milk although many drugs are. Use with caution in nursing mothers. Other G-CSF products are poorly secreted in breast milk and G-CSF is not orally absorbed by neonates.
Renal Impairment	• Not studied in moderate or severe renal impairment. No dose adjustments for mild impairment.
Hepatic Impairment	• Safety and efficacy not studied.
Pharmacogenetics/genomics	• None

Projected Place in Therapy

- Neutropenia is a common complication of myelosuppressive chemotherapy
- Febrile neutropenia is associated with hospitalization, serious infections, and the use of broad-spectrum antibiotics and other anti-infective agents, increased costs, decreased quality of life, and increased mortality.
- The risks associated with febrile neutropenia can be greatly reduced by colony stimulating factors when the risk for febrile neutropenia from the chemotherapy regimen without CSFs is ≥20%.
- Primary prophylaxis with CSFs is recommended by both ASCO and NCCN when the risk for development of febrile neutropenia is ≥20%. Secondary prophylaxis is recommended in some situations. Treatment of neutropenia is not routinely recommended unless the patient is at high risk for complications from infection. NCCN does not recommend use of tbo-filgrastim for treatment of neutropenia.
- NCCN currently gives both filgrastim and tbo-filgrastim a Category 1 recommendation for prophylaxis.
- Tbo-filgrastim is not a generic drug. It is not a biosimilar drug as it did not get approved in the biosimilar pathway by FDA. It was approved through an original BLA, therefore generic substitution is not allowed.
- Tbo-filgrastim could be used instead of filgrastim for primary or secondary prophylaxis in non-hematologic tumors with some caveats:
    - The registration trial used for FDA approval was in Breast Cancer with Grade of Evidence of Moderate
    - All three clinical trials submitted to the FDA as part of the tbo-filgrastim development program were done in patients outside of the US, primarily in Germany, Eastern Europe, and South America. External validity to typical VA patients is difficult to determine.
    - Across all three trials, 60.4% of patients were female.
- There is no data on use of tbo-filgrastim for stem cell mobilization. Use for stem cell mobilization is not recommended by NCCN.
- Alternatives to tbo-filgrastim include filgrastim, pegfilgrastim, and sargramostim.
- The closest formulary item is filgrastim, with many years of experience and a greatly expanded labeling for numerous indications.

References

[1] Del Gigio A, Eniu A, Ganea-Motan D, Topuzov E, Lubenau H. XM02 is superior to placebo and equivalent to Neupogen™ in reducing the duration of severe neutropenia and the incidence of febrile neutropenia in cycle 1 in breast cancer patients receiving docetaxel/doxorubicin chemotherapy. BMC Cancer 2008;8:332-339.
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[4] Schmitt M, Xu X, Higendorf I, Schneider C, Borchert, Glaser D, Freund M, Schmitt A. Mobilization of PBSC for allogeneic transplantation by the use of the G-CSF biosimilar XM02 in healthy donors. Bone Marrow Transplantation 2013;48:922-925.
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[6] Engert A, del Giglio A, Bias P, Lubenau H, Gatzmeier U, Heigener D. Incidence of febrile neutropenia and myelotoxicity of chemotherapy: a meta-analysis of biosimilar G-CSF studies in breast cancer, lung cancer, and non-Hodgkin's lymphoma. Onkologie 2009;32:599-604.
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[8] Lubenau H, Bias P, Maly A-K, Siegler KE, Mehltretter K. Pharmacokinetic and pharmacodynamics profile of new biosimilar filgrastim XM02 equivalent to marketed filgrastim Neupogen®. Biodrugs 2009;23:43-51.

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Appendix A: GRADEing the Evidence

Designations of Quality

Quality of evidence designation	Description
High	Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes (2 consistent, higher-quality randomized controlled trials or multiple, consistent observational studies with no significant methodological flaws showing large effects).
Moderate	Evidence is sufficient to determine effects on health outcomes, but the number, quality, size, or consistency of included studies; generalizability to routine practice; or indirect nature of the evidence on health outcomes (1 higher-quality trial with > 100 participants; 2 higher-quality trials with some inconsistency; 2 consistent, lower-quality trials; or multiple, consistent observational studies with no significant methodological flaws showing at least moderate effects) limits the strength of the evidence.
Low	Evidence is insufficient to assess effects on health outcomes because of limited number or power of studies, large and unexplained inconsistency between higher-quality studies, important flaws in study design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.

Please refer to Qaseem A, et al. The development of clinical practice guidelines and guidance statements of the American College of Physicians: Summary of Methods. Ann Intern Med 2010;153:194-199.

Appendix B: Approval Endpoints

Table 1. A Comparison of Important Cancer Approval Endpoints

Endpoint	Regulatory Evidence	Study Design	Advantages	Disadvantages
Overall Survival	Clinical benefit for regular approval	• Randomized studies essential • Blinding not essential	• Universally accepted direct measure of benefit • Easily measured • Precisely measured	• May involve larger studies • May be affected by crossover therapy and sequential therapy • Includes noncancer deaths
Symptom Endpoints (patient-reported outcomes)	Clinical benefit for regular approval	• Randomized blinded studies	• Patient perspective of direct clinical benefit	• Blinding is often difficult • Data are frequently missing or incomplete • Clinical significance of small changes is unknown • Multiple analyses • Lack of validated instruments
Disease-Free Survival	Surrogate for accelerated approval or regular approval*	• Randomized studies essential • Blinding preferred • Blinded review recommended	• Smaller sample size and shorter follow-up necessary compared with survival studies	• Not statistically validated as surrogate for survival in all settings • Not precisely measured; subject to assessment bias, particularly in open-label studies • Definitions vary among studies
Objective Response Rate	Surrogate for accelerated approval or regular approval*	• Single-arm or randomized studies can be used • Blinding preferred in comparative studies • Blinded review recommended	• Can be assessed in single-arm studies • Assessed earlier and in smaller studies compared with survival studies • Effect attributable to drug, not natural history	• Not a direct measure of benefit in all cases • Not a comprehensive measure of drug activity • Only a subset of patients with benefit
Complete Response	Surrogate for accelerated approval or regular approval*	• Single-arm or randomized studies can be used • Blinding preferred in comparative studies • Blinded review recommended	• Can be assessed in single-arm studies • Durable complete responses can represent clinical benefit • Assessed earlier and in smaller studies compared with survival studies	• Not a direct measure of benefit in all cases • Not a comprehensive measure of drug activity • Small subset of patients with benefit
Progression- Free Survival (includes all deaths) or Time to Progression (deaths before progression censored)	Surrogate for accelerated approval or regular approval*	• Randomized studies essential • Blinding preferred • Blinded review recommended	• Smaller sample size and shorter follow-up necessary compared with survival studies • Measurement of stable disease included • Not affected by crossover or subsequent therapies • Generally based on objective and quantitative assessment	• Not statistically validated as surrogate for survival in all settings • Not precisely measured; subject to assessment bias particularly in open-label studies • Definitions vary among studies • Frequent radiological or other assessments • Involves balanced timing of assessments among treatment arms

*Adequacy as a surrogate endpoint for accelerated approval or regular approval is highly dependent upon other factors such as effect size, effect duration, and benefits of other available therapy. See text for details.

Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), May 2007.