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Class Update with New Drug Evaluation: Colony Stimulating Factors (CSF)

Month/Year of Review: January 2015
PDL Class: Colony Stimulating Factors (CSF)
Source Document: OSU Abbreviated Class Update: Colony Stimulating Factors[1]
New Drug(s): tbo-filgrastim (Granix™)

End date of literature search: November Week 2 2014
Date of Last Review: September 2012

Manufacturer: Teva

Current Status of PDL Class: Appendix 1

Research Questions:
- Is there new evidence to change the previous recommendations regarding the efficacy, effectiveness or harms of colony stimulating factors (CSFs)?
- Is there evidence that tbo-filgrastim is superior to currently available CSFs for prevention of febrile neutropenia complications in non-myeloid malignancies following myelosuppressive chemotherapy?
- Is there evidence that tbo-filgrastim is safer than currently available CSFs?
- Are there subpopulations where tbo-filgrastim may be more effective or safer?

Conclusions:
- There is no new evidence to support changes to the previous recommendations regarding the efficacy, effectiveness or harms of CSFs.
- There is low quality evidence from 3 randomized controlled trials that tbo-filgrastim is equivalent to filgrastim for reduction in the duration of neutropenia and incidence of febrile neutropenia associated with myelosuppressive chemotherapy in chemotherapy naïve patients with breast cancer, non-Hodgkin lymphoma and lung cancer.[2,3,4]
- There is low quality evidence from 3 randomized controlled trials that tbo-filgrastim is equivalent to filgrastim for harms.[2,3,4]
- There is insufficient evidence regarding subpopulations where the use of tbo-filgrastim may be safer or more effective.

Recommendations:
- Evaluate costs in executive session for tbo-filgrastim PDL placement.
- Consider a DUE of CSFs to assess adherence to NCCN guidelines and OHP Guideline Note 11.

Reason for Review:

This class was last updated in September 2012.[1] Tbo-filgrastim was approved by the United States Food and Drug Administration (FDA) on August 29, 2012.[5] While approved in Europe as a "biosimilar," it was approved by the FDA under a standard new biological license application.[6] Additionally, new myeloid growth factors practice guidelines have been published by the National Comprehensive Cancer Network,[6] and the National Institute of Health and Care Excellence.[7]

Previous Conclusions/Recommendations (2012):

- There is moderate level evidence filgrastim and pegfilgrastim both prevent febrile neutropenia and all-cause mortality compared to placebo in patients receiving chemotherapy for solid or non-myeloid malignancies.
- There is low level evidence pegfilgrastim lowers the risk of febrile neutropenia versus filgrastim RR 0.66 (95% CI 0.44-0.98).
- There is low level evidence use of a CSF (filgrastim, pegfilgrastim, or sargramostim) lowers the risk of infection mortality versus placebo when used for prophylaxis of febrile neutropenia in patients with acute myeloid leukemia receiving chemotherapy but comparative evidence is lacking.
- There was no evidence found comparing the filgrastim, pegfilgrastim or sargramostim for the other FDA approved indications.
- There is low level evidence supporting off-label use of CSFs for hepatitis C treatment-induced neutropenia as more effective than dose reduction in improving sustained virologic response.
- Continue to list all drugs as preferred due to lack of comparative evidence for indications other than for prophylaxis of febrile neutropenia in patients receiving chemotherapy for solid or non-myeloid malignancies.

Background:

There are currently four CSFs available in the US: filgrastim, tbo-filgrastim, pegfilgrastim, and sargramostim. Sargramostim is a granulocyte macrophage-colony stimulating factor (GM-CSF) which stimulates the proliferation of neutrophil, monocyte, red-blood cell and platelet precursors.[8] Filgrastim, tbo-filgrastim and pegfilgrastim are granulocyte-colony stimulating factors (G-CSF) which induce proliferation of neutrophils.[8]

Filgrastim,[9] tbo-filgrastim[10] and pegfilgrastim[11] are all indicated to prevent febrile neutropenia, typically in patients with non-myeloid malignancies undergoing myelosuppressive chemotherapy. Febrile neutropenia can have a dose-limiting effect on chemotherapy, resulting in interruption of therapy, hospitalizations and intensive antibiotics.[6] The benefit of primary CSF prophylaxis in reducing hospitalizations, the need for antibiotics and rates of neutropenic fever in adults has been established but the impact on survival is less clear.[6] Established guidelines identify patients at highest risk for complications from chemotherapy-induced febrile neutropenia.[6] However, as much as 28% of patients are treated outside of guideline recommendations to lower risk of complications of febrile neutropenia.[12] CSFs are not used prophylactically in all patients because of safety concerns regarding the risk of developing secondary myelodysplastic syndrome or acute myeloid leukemia and rare cases of splenic rupture, even in healthy stem cell donors.[6] The most consistently observed toxicity is bone pain.[6] Treating off-label chemotherapy-induced febrile neutropenia in patients with leukemia or myelodysplastic syndrome is controversial because of the increased risk of stimulating the cancerous cell lines.[6]

Filgrastim is also indicated to speed myeloid recovery (engraftment) in harvesting of peripheral blood progenitor cells for transplant and for other neutropenias (Table 1).[9] G-CSFs are also used off-label for neutropenia induced from Hepatitis C (HCV) treatment or from AIDs, aplastic anemia, and Crohn's disease.[9,10,11]

Sargramostim is used primarily to speed engraftment after allogeneic or autologous bone marrow transplantation or following the harvesting of peripheral blood progenitor cells for transplant or graft.[13] Quick myeloid recovery (engraftment) in patients undergoing a bone marrow or peripheral blood progenitor cell transplant reduces the risk or duration of FN in both situations.[13]

Filgrastim[9] and sargramostim[13] are given daily subcutaneously (SQ) or by intravenous infusion and dosed to response for the chemotherapy cycle or transplantation. Tbo-filgrastim[10] is available as only a daily SQ formulation. Pegfilgrastim is a pegylated formulation of filgrastim and is dosed SQ one time per chemotherapy cycle.[11]

Tbo-filgrastim was approved in Europe on a biosimilar application to the reference drug filgrastim. However, in the United States it was approved on a standard biological application with clinical trials. Another drug, lipefilgrastim, is under currently review by the FDA on a biosimilar application to the reference drug pegfilgrastim.

Table 1: Colony stimulating factor indications

Drug	FDA Labeled Indications	Off-label indications
filgrastim (G-CSF)[9]	- Febrile neutropenia, In non-myeloid malignancies, in patients undergoing myeloablative chemotherapy followed by marrow transplantation; Prophylaxis - Febrile neutropenia, In non-myeloid malignancies following myelosuppressive chemotherapy; Prophylaxis - Febrile neutropenia, In patients with acute myeloid leukemia receiving chemotherapy; Prophylaxis - Harvesting of peripheral blood stem cells - Neutropenic disorder, chronic (Severe), Symptomatic	- Agranulocytosis - AIDS / Hep C- Neutropenia - Aplastic anemia - Febrile neutropenia - Febrile neutropenia, In myeloid malignancies following bone marrow transplant; Prophylaxis' - Infectious disease; Prophylaxis - Leukemia - Myelodysplastic syndrome - Neutropenia - Pre-eclampsia
tbo-filgrastim (G-CSF)[10]	- Neutropenia (Severe), In non-myeloid malignancies following myelosuppressive chemotherapy; Prophylaxis	
pegfilgrastim (G-CSF)[11]	- Febrile neutropenia, In patients with non-myeloid malignancies; Prophylaxis	- Harvesting of peripheral blood stem cells, Prior to autologous stem-cell transplantation
sargramostim (GM-CSF)[13]	- Allogeneic bone marrow transplantation, Myeloid reconstitution in HLA-matched related donors - Autologous bone marrow transplant, Myeloid reconstitution following transplant in patients with non-Hodgkin's lymphoma, Hodgkin's disease, and acute lymphoblastic lymphoma - Bone marrow transplant, Delay or failure of myeloid engraftment - Febrile neutropenia, In acute myelogenous leukemia following induction chemotherapy; Prophylaxis - Harvesting of peripheral blood stem cells - Peripheral blood stem cell graft, Autologous, myeloid reconstitution following transplant in patients mobilized with granulocyte macrophage colony stimulating factor	- Crohn's disease - Febrile neutropenia, In non-myeloid malignancies following myelosuppressive chemotherapy; Prophylaxis - Malignant melanoma - Myelodysplastic syndrome - Neutropenic disorder - Sepsis of the newborn - Pulmonary alveolar proteinosis - Wound care

Methods:
A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) from July week 2 2012 to week 2 November 2014 assessing clinically relevant outcomes of filgrastim, tbo-filgrastim, pegfilgrastim or sargramostim to placebo or active controls was conducted with limits for humans and English. Search terms included filgrastim, tbo-filgrastim, pegfilgrastim, sargramostim, XM-22, XM,-02, graulocyte colony-stimulating factor or granulocyte-macrophage colongy-stimulating factor and febrile neutropenia or peripheral blood stem cell transplantation. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, Dynamed, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts, and the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

After review of the citations from Medline and the manual searches, two updated guidelines, 2 RCTs comparing filgrastim to pegfilgrastim and 3 RCTs comparing tbo-filgrastim to placebo were included.

Systematic Reviews:
One systematic review of 3 clinical trials comparing tbo-filgrastim to filgrastim for prophylaxis of febrile neutropenia associated with myelosuppressive therapy for non-myeloid malignancy has been published but was unavailable in full-text at the time of writing this review.[14] The RCTs are reviewed individually below.

New Guidelines:
National Comprehensive Cancer Network[6] updated their consensus oncology practice guidelines for the use of myeloid growth factors (i.e. CSFs). The focus is to identify patients at high risk for febrile neutropenia for prophylactic CSF therapy. The guidelines align with Guideline Note 11 of the Prioritized List of Services (Appendix 6).[15] The guidelines identify sargramostim as having lower quality evidence for prophylaxis of febrile neutropenia in the oncology setting. It updates recommendations of timing of pegfilgrastim administration but makes no recommendation as to which of the remaining three products to use preferentially. It includes a new section on tbo-filgrastim.

The NICE pathway for prevention of neutopenic sepsis in cancer patients was updated in 2014.[7] The only mention of CSFs was “Do not routinely offer G-CSF for the prevention of neutropenic sepsis in adults receiving chemotherapy unless they are receiving G-CSF as an integral part of the chemotherapy regimen or in order to maintain dose intensity.”

Randomized Controlled Trials:

Table 2: Potentially relevant comparative trials

Study	Comparison	Population	Primary Outcome	Results
Cesaro S., et al.[16] RCT, open label, non-inferiority Δ=3 days	32 patients got pegfilgrastim 100mcg/kg x 1 dose versus 29 patients got daily filgrastim 5mcg/kg/day x 9 doses	Pediatric patients who underwent autologous peripheral blood stem cell transplant. 20% had lymphoma/leukemia and 80% had solid tumors	mean number of days to recovery of polymorphonuclear cells	filgrastim: 10.48 (SD 1.57) pegfilgrastim: 10.44 (SD 2.44) non-inferiority endpoint was reached
Shi Y-K, et al.[17] RCT, open-label, crossover, non-inferiority study (Δ not reported)	Arm 1 (n=173): single dose of pegylated filgrastim 100 µg/kg in cycle 1 and daily doses of filgrastim 5 µg/kg/day in cycle 2 Arm 2 (n=164): daily doses of filgrastim 5 µg/kg/day in cycle 1 and a single dose of pegylated filgrastim 100 µg/kg in cycle 2	Adults with malignant solid turmors, chemotherapy-naïve; life expectancy of >3 months, normal bone marrow function	rate of protection against grade 4 neutropenia after chemotherapy	"In cycle 1, the rates of protection were 89.7% (pegylated filgrastim) and 89.5% (filgrastim). In cycle 2, no episodes of grade 4 neutropenia occurred." "The protective rates of pegylated filgrastim did not differ significantly from the protective rates of filgrastim."

New Safety Alerts, Indications:

No new safety alerts or FDA indications.

New Drug Evaluation: tbo-filgrastim

The FDA approved tbo-filgrastim based upon 2 Phase I[5,18] and 3 Phase 3 studies.[2,3,4] Only del Giglio A, et al.[2] was a pivotal, equivalence study with the remaining two being primarily safety and pharmacokinetic studies that also evaluated efficacy outcomes.[3,4]

FDA approved indications: Prophylaxis of febrile neutropenia, in patients with non-myeloid malignancies following myelosuppressive chemotherapy.

Potential Off-label Use: Treatment and prevention of neutropenia from other causes, peripheral blood stem cell transplantation and other indications listed in Table 1.

Clinical Efficacy Data: Tbo-filgrastim was compared to filgrastim in patients with breast cancer,[2] non-Hodgkin lymphoma[3] and lung cancer[4] taking myelosuppressive chemotherapies. The studies were of poor to fair quality due to lack of complete blinding, no description of randomization processes and lack of power analyses. The safety studies did not identify a primary outcome and considered efficacy outcomes exploratory. Tbo-filgrastim was superior to placebo on the outcome of duration of severe neutropenia, defined as the number of days with grade 4 neutropenia with an ANC <0.5 × 109/L (1.1 days versus

3.8 days, p <0.0001). No difference was found between tbo-filgrastim and filgrastim in any of the studies for the outcomes of duration of neutropenia and incidence of febrile neutropenia.

Clinical Safety: The FDA safety review notes that 750 patients and healthy volunteers have received one dose of tbo-filgrastim. Bone pain was observed in 24% of patients on tbo-filgrastim and 31% of patients on filgrastim.[18] No new safety concerns were raised and the safety profile of tbo-filgrastim was equivalent to that of filgrastim.[18]

COMPARATIVE CLINICAL EFFICACY

Relevant Endpoints:

1) Mortality
2) Infections requiring treatment or hospitalization
3) Withdrawal due to adverse events

Primary Study Endpoint:

1) Mean duration in days of severe neutropenia in cycle 1
2) Incidence of observed febrile neutropenia

Comparative Evidence Table

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Outcomes	ARR/NNT	Safety Outcomes	ARR/NNH	Quality Rating/ Internal Validity Risk of Bias/ Applicability Concerns
del Giglio A, et al.[2] RCT; Phase 3; 52 centers; 10 countries (researchers from South America & Eastern Europe) Dec. 2004 to Sep. 2005	1. tbo-filgrastim (T): 5 mcg/kg/day 2. Neuopogen™ (N) 5 mcg/kg/day 3. placebo (P) - switched to T after cycle 1. Starting one day after chemo-therapy, patients received daily injections for 5-14 days; stopped when an ANC of ≥ 10×10^9/L after nadir was reached. Patients underwent a maximum of 4 -3 week cycles of doxorubicin 60 mg/m^2 (i.v. bolus injection) and docetaxel 75 mg/m^2 (at least 1 hour infusion).	Demographics: Female: >99% Age: 51 (25-75) Caucasian: 85% BMI: 28 kg/m^2 Cancer Stage II: ~22% II: ~53% IV: ~25% Inclusion Criteria: ≥18 years old - breast cancer high risk stage II, III or IV (per AJCC) -planned/eligible to receive treatment with docetaxel / doxorubicin - ANC ≥1.5×10^9/L -platelet count ≥100×10^9/L -adequate cardiac function (LVEF ≥ 50% as assessed by ECG <4 weeks prior to randomization) - ALT/AST <$2.5 \times$ ULN, alkaline phosphatase <$5 \times$ ULN, bilirubin <ULN, - SCr <$1.5 \times$ ULN. Exclusion Criteria: -not reported	ITT: T:140 N:136 P:72 PP: Not reported Attrition: Not reported	Primary Outcome: Mean duration of severe neutropenia (DSN) defined as the number of days with grade 4 neutropenia with an ANC <0.5×10^9/L. in cycle 1: T: 1.1 days P: 3.8 days Difference: 2.7 days p<0.0001[18] N: 1.1 days P: 3.8 days Difference: 2.7 days Least square mean: T: 1.119 days N: 1.087 days Difference: 0.032 days 95% CI (-0.262 days, 0.325 days) Secondary Outcomes: Incidence of observed febrile neutropenia T: 12.1% P: 36.1% ARR: 24%	NA T-N ARR: 0.4%	Withdrew due to Adverse Event: T: 2 (1.4%) P: 4 (5.6%) ARR: 4.2% N: 3 (2.2%) P: 4 (5.6%) ARR: 3.4%	T-N ARR: 0.8%	**Quality Rating**: Fair **Internal Validity (Risk of Bias)**: Selection: (Mod) "randomized" not described Performance: (Mod) – un-blinded because T, N formulated in different volumes. Detection: (Low) investigator/assessor blinded; used objective outcomes Attrition: (Mod); equivalence trial ITT reported in tables but text specifies PP used for primary analysis and is recommended for equivalence trials. Attrition not reported and sample size calculation not reported. **Applicability**: Patient: Patient group likely more healthy than typical patients Intervention: no description; assume same as commercially available. Comparator: Neupogen™ Outcomes: Objective, clinical outcomes but, unclear relationship to mortality. Setting: Unclear how standards of care in research sites compare to Oregon. **Analysis**: Equivalence of T and N was assessed using per protocol data. A difference of 1 day was considered to be the maximum clinically acceptable difference. The least square mean of DSN in cycle 1 was 1.119 and 1.087 days in the T and N group, respectively. ANCOVA calculated 2-sided 95% CI for "T – N" was [-0.262 days,0.325 days], which was entirely included in the pre-

				N: 12.5% P: 36.1% ARR: 23.6%				specified equivalence range [-1, 1], thus, equivalence was concluded. Results for the full analysis set were similar and confirmed equivalence of T and N.
Engert et al.[3] RCT; Phase 3 29 centers in 8 countries (researchers from Eastern Europe & South America) Dec. 2004 to Mar. 2006	1. tbo-filgrastim (T) 5 mcg/kg/day 2. Neuopogen™ 5 mcg/kg/day x 5-14 days for first cycle. All patients received T in sub-sequent cycles. Study drug had to be stopped when an ANC of $\geq$ 10 x 10^9/L after nadir was reached. Patients got a maximum of 6 – 3 week cycles of chemo.	Demographics: Female: 48% Age: 53 (18-83) Caucasian: 88% BMI: ~26 kg/m^2 Inclusion Criteria: -$\geq$18 years old -aggressive NHL - planned/eligible to receive CHOP -life expectancy >6 months - IPI score $\leq$3 - ANC $\geq$1.5x 10^9/L -platelet count $\geq$100 x 10^9/L -adequate hepatic, cardiac, and renal function for the chemotherapy regimen. Exclusion Criteria: Not reported.	ITT: T: 63 N: 29 PP: Total: 76 (17.4% non-adherence rate) Attrition: Total: 1 (0.1%)	No primary outcome designated. Mean duration of severe neutropenia defined as the number of days with grade 4 neutropenia with an ANC <0.5 × 10^9/L in cycle 1: T: 0.5 days N: 0.2 days p-value = 0.1055 Incidence of observed febrile neutropenia during first cycle: T: 11.1% N: 20.7% p-value 0.1232	NA NA	Withdrawals due to Adverse Event. Total: 5 (5.4%) not reported separately	NA	**Quality Rating**: Poor **Internal Validity (Risk of Bias)**: Selection: (Mod) "randomized" without description. >10% differences noted in gender, NHL types between groups. Performance: (Mod) administered by unblended personnel as formulations looked different. Detection: (Low) investigator/assessor blinded; objective outcomes Attrition: ITT used; multiple outcomes increases potential for α-error; small sample size increases potential for β-error for safety. No sample size calculation provided. **Applicability**: Patient: patients likely more healthy than typical NHL patient. Intervention: no description; assume same as commercially available. Comparator: Neupogen™ Outcomes: Objective, clinical outcomes but, unclear relationship to mortality. Setting: Unclear how standards of care in research sites compare to Oregon. **Analysis**: All analyses of efficacy endpoints were done without alpha adjustment and were interpreted as descriptive / exploratory analyses.
Gatzemeier et al. [4] RCT, Phase 3	1.tbo-filgrastim (T) 5 mg/kg/day 2. Neuopogen™ (N)	Demographics: Female: 22% Age: 58 (34-78)	ITT T: 160 N: 80	No primary outcome designated. Mean duration of severe		31 patients (13.1%) discontinued the		**Quality Rating**: Poor **Internal Validity (Risk of Bias)**: Selection: (Mod) "randomized" without

47 centers and 11 countries (researchers from Eastern Europe & South America) Dec. 2004 to Dec. 2005	5 mg/kg/day X 5-14 days for first cycle then all patient received T thereafter. Study drug had to be stopped when an ANC of $\geq$ 10 x 10^9/L after nadir was reached. All patient got maximum of 6 – 3 to 4 week cycles	Caucasian: 95% BMI: 24 kg/m^2 Inclusion Criteria: $\geq$18 years old -small cell or non-small cell lung cancer -planned platinum-based chemotherapy -chemotherapy naïve or no more than 1 cycle. - ANC $\geq$1.5 x 10^9/L -platelet count $\geq$100 x 10^9/L, -adequate hepatic, cardiac, and renal function for the chemotherapy regimen. Exclusion Criteria: Not reported.	PP "219 (91.3%) completed cycle 1" Attrition not reported.	neutropenia defined as the number of days with grade 4 neutropenia with an ANC <0.5 × 10^9/L in cycle 1: T: 0.5 days N: 0.3 days p-value not reported Incidence of observed febrile neutropenia during first cycle: T: 15.0% N: 8.8% p-value not reported	NA NA	study due to a adverse event (differential not reported)		description. Groups similar at baseline. Performance: (Mod) blinding not described Detection: (High) blinding not described Attrition: ITT used; multiple outcomes increases potential for α-error; small sample size increases potential for β-error. **Applicability**: Patient: patients likely more healthy than typical NHL patients; overwhelmingly Caucasian. Intervention: no description; assume same as commercially available. Comparator: Neupogen™ Outcomes: Objective, clinical outcomes but, unclear relationship to mortality. Setting: Unclear how standards of care in research sites compare to Oregon. **Analysis**: All analyses of efficacy endpoints were done without alpha adjustment and were interpreted as descriptive/exploratory analyses. The sample size of 240 has a 70% probability of detecting 1 case of AE which has an incidence rate of 0.5% or 91% for an incidence rate of 1%.

Key [alphabetical order]: AJCC = American Joint Committee on Cancer; ALT/AST = alanine and aspartate aminotransferases; ANC = absolute neutrophil count; ARR = absolute risk reduction; CHOP = cyclophosphamide, hydroxydaunorubicin, oncovin (vincristine) and prednisone; CI = confidence interval; ECG = electrocardiography; DSN = duration of severe neutropenia; IPI = international prognostic index; ITT = intention to treat; LVEF = left ventricular ejection fraction; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NHL = non-Hodgkin lymphoma; NNH = number, needed to harm; NNT = number needed to treat; PP = per protocol; RCT=Randomized Controlled Trial; RR = relative risk; SCr = serum creatinine; ULN = upper limit of normal.

References:

1. Burns A. Abbreviated Class Update: Colony Stimulating Factors. 2012. Available at: http://www.orpdl.org/durm/drug_articles/reviews/2012_09_27_CSF_CU.pdf. Accessed November 24, 2014.

2. Del Giglio 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(1):332. doi:10.1186/1471-2407-8-332.

3. Engert A, Griskevicius L, Zyuzgin Y, Lubenau H, del Giglio A. XM02, the first granulocyte colony-stimulating factor biosimilar, is safe and effective in reducing the duration of severe neutropenia and incidence of febrile neutropenia in patients with non-Hodgkin lymphoma receiving chemotherapy. *Leuk Lymphoma* 2009;50(3):374-379. doi:10.1080/10428190902756081.

4. Gatzemeier U, Ciuleanu T, Dediu M, Ganea-Motan E, Lubenau H, Del Giglio A. XM02, the first biosimilar G-CSF, is safe and effective in reducing the duration of severe neutropenia and incidence of febrile neutropenia in patients with small cell or non-small cell lung cancer receiving platinum-based chemotherapy. *Journal of Thoracic Oncology* 2009;4(6):736–740.

5. U.S. Food and Drug Administration: Drugs@ FDA. Summary Review: tbo-filgrastim (aka XM-02). 2012. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/125294Orig1s000SumR.pdf. Accessed November 24, 2014.

6. Crawford J, Armitage J, Balducci L, et al. Myeloid Growth Factors. *J Natl Compr Canc Netw* 2013;11(10):1266-1290.

7. NICE. Neutropenic sepsis: prevention and management of neutropenic sepsis in cancer patients. 2012. Available at: http://www.nice.org.uk/guidance/cg151/resources/guidance-neutropenic-sepsis-prevention-and-management-of-neutropenic-sepsis-in-cancer-patients-pdf. Accessed September 22, 2014.

8. Kaushansky K, Kipps TJ. Chapter 37. Hematopoietic Agents: Growth Factors, Minerals, and Vitamins. In: *The Pharmacological Basis of Therapeutics*. 12th ed. United States: McGraw-Hill Companies. Available at: http://accesspharmacy.mhmedical.com.liboff.ohsu.edu/content.aspx?bookid=374&sectionid=41266245&jumpsectionID=41277139&Resultclick=2. Accessed November 25, 2014.

9. Filgrastim. In: Drug Point Summary. (*Micromedex 2.0) [online database]*. United States: Truven Health Analytics; 2014. Available at: http://www.micromedexsolutions.com.liboff.ohsu.edu/micromedex2/librarian/. Accessed November 25, 2014.

10. Tbo-filgrastim In: Drug Point Summary. (*Micromedex 2.0) [online database]*. United States: Truven Health Analytics; 2014. Available at: http://www.micromedexsolutions.com.liboff.ohsu.edu/micromedex2/librarian/. Accessed November 25, 2014.

11. Pegfilgrastim In: Drug Point Summary. (*Micromedex 2.0) [online database]*. United States: Truven Health Analytics; 2014. Available at: http://www.micromedexsolutions.com.liboff.ohsu.edu/micromedex2/librarian/. Accessed November 25, 2014.

12. Freifeld A, Sankaranarayanan J, Ullrich F, Sun J. Clinical practice patterns of managing low-risk adult febrile neutropenia during cancer chemotherapy in the USA. *Support Care Cancer* 2008;16(2):181-191. doi:10.1007/s00520-007-0308-x.

13. Sargramostim In: Drug Point Summary. (*Micromedex 2.0) [online database]*. United States: Truven Health Analytics; 2014. Available at: http://www.micromedexsolutions.com.liboff.ohsu.edu/micromedex2/librarian/. Accessed November 25, 2014.

14. Engert A, del Giglio A, Bias P, Lubenau H, Gatzemeier 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(10):599-604. doi:http://dx.doi.org/10.1159/000232580.

15. Prioritized List of Health Services. 2014. Available at: http://www.oregon.gov/oha/herc/PrioritizedList/10-1-2014%20Prioritized%20List%20of%20Health%20Services.pdf. Accessed November 25, 2014.

16. Cesaro S, Nesi F, Tridello G, et al. A Randomized, Non-Inferiority Study Comparing Efficacy and Safety of a Single Dose of Pegfilgrastim versus Daily Filgrastim in Pediatric Patients after Autologous Peripheral Blood Stem Cell Transplant. Glod JW, ed. *PLoS ONE* 2013;8(1):e53252. doi:10.1371/journal.pone.0053252.

17. Shi Y, Chen Q, Zhu Y, et al. Pegylated filgrastim is comparable with filgrastim as support for commonly used chemotherapy regimens: a multicenter, randomized, crossover phase 3 study. *Anti-Cancer Drugs* 2013;24(6):641-7. doi:http://dx.doi.org/10.1097/CAD.0b013e3283610b5d.

18. FDA Oncologic Drug Advisory Committee Briefing Materials: tbo-filgrastim. 2013. Available at: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/MedicalImagingDrugsAdvisoryCommittee/UCM350157.pdf. Accessed July 3, 2014.

Appendix 1: Current Status on Preferred Drug List

Brand	Generic	PDL
NEUPOGEN	FILGRASTIM	Y
NEULASTA	PEGFILGRASTIM	Y
LEUKINE	SARGRAMOSTIM	Y
GRANIX	TBO-FILGRASTIM	N

Appendix 2: Abstracts of Clinical Trials

1) Title A randomized, non-inferiority study comparing efficacy and safety of a single dose of pegfilgrastim versus daily filgrastim in pediatric patients after autologous peripheral blood stem cell transplant.

Source PLoS ONE [Electronic Resource]. 8(1):e53252, 2013.

Abstract PURPOSE: To assess the non-inferiority of pegfilgrastim versus filgrastim in speeding the recovery of polymorphonuclear cells (PMN) in pediatric patients who underwent autologous peripheral blood stem cell transplant (PBSCT).

METHODS: The sample size of this randomized, multicenter, phase III study, was calculated assuming that a single dose of pegfilgrastim of 100 ug/kg was not inferior to 9 doses of filgrastim of 5 ug/kg/day. Randomization was performed by a computer-generated list and stored by sequentially numbered sealed envelopes.

RESULTS: Sixty-one patients, with a median age of 11.5 years, were recruited: 29 in the filgrastim arm and 32 in the pegfilgrastim arm. Twenty percent were affected by lymphoma/leukaemia and eighty percent by solid tumors. The mean time to PMN engraftment was 10.48 days (standard deviation [SD] 1.57) and 10.44 days (SD 2.44) in the filgrastim and pegfilgrastim arms, respectively. Having fixed a non-inferiority margin Delta of 3, the primary endpoint of non-inferiority was reached. No differences were observed for other secondary endpoints: platelet engraftment, mean time to platelet recovery (28 days vs. 33 days), fever of unknown origin (79% vs. 78%), proven infection (34% vs. 28%), mucositis (76% vs. 59%). After a median follow-up of 2.3 years (95% C.I.: 1.5, 3.3), 20 deaths were observed due to disease progression.

CONCLUSIONS: We conclude that pegfilgrastim was not inferior to daily filgrastim in pediatric patients who underwent PBSCT. EU CLINICAL TRIAL REGISTER

2) Title Pegylated filgrastim is comparable with filgrastim as support for commonly used chemotherapy regimens: a multicenter, randomized, crossover phase 3 study.

Source Anti-Cancer Drugs. 24(6):641-7, 2013 Jul.

Abstract The purpose of this study was to compare the efficacy and safety of a single subcutaneous injection of pegylated filgrastim with daily filgrastim as a prophylaxis for neutropenia induced by commonly used chemotherapy regimens. Fifteen centers enrolled 337 chemotherapy-naive cancer patients with normal bone marrow function. All patients randomized into AOB and BOA arms received two cycles of chemotherapy. Patients received a single dose of pegylated filgrastim 100 g/kg in cycle 1 (AOB) or cycle 2 (BOA) and daily doses of filgrastim 5 g/kg/day in cycle 1 (BOA) or cycle 2 (AOB). Efficacy and safety parameters were recorded. The primary end point was the rate of protection against grade 4 neutropenia after chemotherapy [defined as the rate at which the absolute neutrophil count (ANC) remained >0.5x10(9)/l throughout the entire cycle]. Ninety-four percent of patients receiving pegylated filgrastim or filgrastim did not develop grade 4 neutropenia. The incidence of ANC<1.0x10(9)/l was 16.0% (50/313) after support with either pegylated filgrastim or filgrastim. The incidences of febrile neutropenia and antibiotic administration were similar in both groups. Notably, faster ANC recovery was observed with pegylated filgrastim support. The ANC nadir was also earlier with pegylated filgrastim (day 7) support than with filgrastim support (day 9), although the depth of nadir was not significantly different. A single subcutaneous injection of pegylated filgrastim 100 mug/kg provided adequate and safe neutrophil support comparable with daily subcutaneous injections of unmodified filgrastim 5 mug/kg/day in patients receiving commonly used standard-dose mild-to-moderate myelosuppressive chemotherapy regimens.

3) Title 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.

Source BMC Cancer. 8:332, 2008.

Abstract BACKGROUND: Recombinant granulocyte colony-stimulating factors (G-CSFs) such as Filgrastim are used to treat chemotherapy-induced neutropenia. We investigated a new G-CSF, XM02, and compared it to Neupogen after myelotoxic chemotherapy in breast cancer (BC) patients.

METHODS: A total of 348 patients with BC receiving docetaxel/doxorubicin chemotherapy were randomised to treatment with daily injections (subcutaneous 5 microg/kg/day) for at least 5 days and a maximum of 14 days in each cycle of XM02 (n = 140), Neupogen (n = 136) or placebo (n = 72). The primary endpoint was the duration of severe neutropenia (DSN) in cycle 1.

RESULTS: The mean DSN in cycle 1 was 1.1, 1.1, and 3.9 days in the XM02, Neupogen, and placebo group, respectively. Superiority of XM02 over placebo and equivalence of XM02 with Neupogen could be demonstrated. Toxicities were similar between XM02 and Neupogen.

CONCLUSION: XM02 was superior to placebo and equivalent to Neupogen in reducing DSN after myelotoxic chemotherapy.

4) Title XM02, the first granulocyte colony-stimulating factor biosimilar, is safe and effective in reducing the duration of severe neutropenia and incidence of febrile neutropenia in patients with non-Hodgkin lymphoma receiving chemotherapy.

Source Leukemia & Lymphoma. 50(3):374-9, 2009 Mar.

Abstract Recombinant granulocyte colony-stimulating factors (G-CSFs) such as filgrastim or lenograstim are being used to treat chemotherapy-induced neutropenia. The aim of the present study was to investigate a new G-CSF, XM02, in comparison to filgrastim in terms of safety and efficacy in the prevention of chemotherapy-induced neutropenia in non-Hodgkin-lymphoma (NHL). A total of 92 patients receiving chemotherapy were randomised in cycle 1 to treatment with daily injections (subcutaneous 5 microg/kg/day) of XM02 (n = 63) or filgrastim (n = 29) for at least 5 days and a maximum of 14 days. In subsequent cycles, all patients received XM02. The mean duration of severe neutropenia (DSN) was 0.5 and 0.9 days in cycle 1 for XM02 and filgrastim, respectively (p = 0.1055). In cycle 1, the incidence of febrile neutropenia (FN) was 11.1% for XM02 and 20.7% for filgrastim (p = 0.1232). The adverse event profile was similar between XM02 and filgrastim. XM02 demonstrated equivalent efficacy and similar safety profile as the reference medication filgrastim. Treatment with XM02 is as beneficial as filgrastim in ameliorating severe neutropenia and FN in patients with NHL receiving chemotherapy. XM02 is safe and well tolerated in the doses applied in this study.

5) Title XM02, the first biosimilar G-CSF, is safe and effective in reducing the duration of severe neutropenia and incidence of febrile neutropenia in patients with small cell or non-small cell lung cancer receiving platinum-based chemotherapy.

Source Journal of Thoracic Oncology: Official Publication of the International Association for the Study of Lung Cancer. 4(6):736-40, 2009 Jun.

Abstract BACKGROUND: Recombinant granulocyte colony-stimulating factors such as Neupogen are used to treat chemotherapy-induced neutropenia. The aim of the study was to show that a new granulocyte colony-stimulating factor, XM02, is as safe and effective as Neupogen in the treatment of chemotherapy-induced neutropenia in patients with small cell or non-small cell lung cancer.

PATIENTS AND METHODS: A total of 240 patients receiving platinum-based chemotherapy were randomized in cycle 1 to treatment with daily injections (subcutaneous 5 microg/kg/d) of XM02 (n = 160) or Filgrastim Neupogen (n = 80) for at least 5 days and a maximum of 14 days. In subsequent cycles, all patients received XM02.

RESULTS: The mean duration of severe neutropenia was 0.5 and 0.3 days in cycle 1 for XM02 and Filgrastim, respectively. In the analysis of covariance for duration of severe neutropenia in cycle 1, the estimated treatment difference "XM02 minus Filgrastim" was 0.157 days, with 95% confidence level (-0.114 days, 0.428 days), which was included in the prespecified equivalence range (-1, 1). There was no statistically significant difference of the end point incidence of febrile neutropenia in cycle 1 between XM02 and Filgrastim (p = 0.2347). The adverse event profile was similar between XM02 and Filgrastim.

CONCLUSION: XM02 demonstrated similar efficacy and safety profile as the reference medication Filgrastim in cycle 1. In conclusion, treatment with XM02 is beneficial in ameliorating severe neutropenia and febrile neutropenia in lung cancer patients receiving myelosuppressive chemotherapy. XM02 is safe and well tolerated in the doses applied in this study.

Appendix 3: Highlights of Prescribing Information

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

Appendix 5: Current Prior Authorization Criteria

Preferred Drug List (PDL) – Non-Preferred Drugs in Select PDL Classes

Goal(s):

- The purpose of this prior authorization policy is to ensure that non-preferred drugs are used for an above-the-line condition.

Initiative:

- PDL: Preferred Drug List

Length of Authorization:

Up to 12 months

Requires PA:

- Non-preferred drugs

Covered Alternatives:

Preferred alternatives listed at www.orpdl.org

Note:

A complete list of PDL classes is available at www.orpdl.org .

Approval Criteria		
1. What diagnosis is being treated?	Record ICD9 code.	
2. Is this an OHP-covered diagnosis?	Yes: Go to #3.	No: Go to #4.
3. Will the prescriber consider a change to a preferred product? Message: Preferred products do not require a PA. Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Health Resource Commission (HRC).	Yes: Inform provider of covered alternatives in class.	No: Approve for 1 year or length of prescription, whichever is less.
4. RPH only; All other indications need to be evaluated as to whether they are above the line or below the line diagnosis. • If above the line and clinic provides supporting literature: Approve for length of treatment. • If below the line: Deny, (Not Covered by the OHP).		

P&T / DUR Action: *9/16/10 (KS/DO), 9/24/09(DO), 5/21/09*
Revision(s): *1/1/11, 9/16/10 (KS/DO)*
Initiated:

Appendix 6: Oregon Health Plan List of Prioritized Services: Guideline Note 11[15]

GUIDELINE NOTE 11, COLONY STIMULATING FACTOR (CSF) GUIDELINES

Lines 79,102,103,105,123-125,131,144,159,165,166,168,170,181,197,198,206-208,218,220,221,228,229,231,243,249,252,275-278,280,287,292,310-312,314,320,339-341,356,459,622

A) CSF are not indicated for primary prophylaxis of febrile neutropenia unless the primary chemotherapeutic regimen is known to produce febrile neutropenia at least 20% of the time. CSF should be considered when the primary chemotherapeutic regimen is known to produce febrile neutropenia 10-20% of the time; however, if the risk is due to the chemotherapy regimen, other alternatives such as the use of less myelosuppressive chemotherapy or dose reduction should be explored in this situation.

B) For secondary prophylaxis, dose reduction should be considered the primary therapeutic option after an episode of severe or febrile neutropenia except in the setting of curable tumors (e.g., germ cell), as no disease free or overall survival benefits have been documented using dose maintenance and CSF.

C) CSF are not indicated in patients who are acutely neutropenic but afebrile.

D) CSF are not indicated in the treatment of febrile neutropenia except in patients who received prophylactic filgrastim or sargramostim or in high risk patients who did not receive prophylactic CSF. High risk patients include those age >65 years or with sepsis, severe neutropenia with absolute neutrophil count <100/mcl, neutropenia expected to be more than 10 days in duration, pneumonia, invasive fungal infection, other clinically documented infections, hospitalization at time of fever, or prior episode of febrile neutropenia.

E) CSF are not indicated to increase chemotherapy dose-intensity or schedule, except in cases where improved outcome from such increased intensity has been documented in a clinical trial.

F) CSF (other than pegfilgrastrim) are indicated in the setting of autologous progenitor cell transplantation, to mobilize peripheral blood progenitor cells, and after their infusion.

G) CSF are NOT indicated in patients receiving concomitant chemotherapy and radiation therapy.

H) There is no evidence of clinical benefit in the routine, continuous use of CSF in myelodysplastic syndromes. CSF may be indicated for some patients with severe neutropenia and recurrent infections, but should be used only if significant response is documented.

I) CSF is indicated for treatment of cyclic, congenital and idiopathic neutropenia.