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Drug Class Literature Scan: Colony Stimulating Factors

Date of Review: October 2022

Date of Last Review: June 2021
Literature Search: 01/01/2021 – 06/09/2022

Current Status of PDL Class:
See **Appendix 1**.

Conclusions:
- Two new biosimilar products were approved by the Food and Drug Administration (FDA) since the last review.
- Guidelines from the National Cancer Care Network (NCCN) continue to recommend granulocyte colony stimulating factor (G-CSF) products for prophylaxis of febrile neutropenia, treatment of febrile neutropenia, and for mobilization of progenitor cells in cell transplant.[1]

Recommendations:
- No PDL changes recommended based on the clinical evidence.
- After evaluation of costs in executive session, tbo-filgrastim (GRANIX) was made non-preferred.

Summary of Prior Reviews and Current Policy
- Evidence for this class was last evaluated in June 2021. There are no class specific prior authorization criteria beyond preferred and non-preferred status. Non-preferred products billed through the pharmacy are required to meet nonspecific prior authorization criteria which requires validation of an FDA approved indication and funding level.
- Previous evidence summaries concluded no compelling differences in efficacy or harms between G-CSF products.[2] G-CSF products are recommended for prophylaxis of febrile neutropenia, treatment of febrile neutropenia, and for mobilization of progenitor cells in cell transplant.[2] Evidence is generally of moderate quality for these indications.
- The number of patients with claims (pharmacy or medical) for G-CSF products is relatively small in the fee-for-service only population and most products billed through medical claims where the preferred drug list (PDL) does not apply. Since 2021, utilization has shifted from use of originator products to almost exclusively biosimilar products.

Methods:
A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this literature scan is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched

for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

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.

New Systematic Reviews:
No new high quality systematic reviews were identified.

After review, 11 systematic reviews were excluded due to poor quality,[3-10] wrong study design of included trials (e.g., observational),[11] comparator (e.g., no control, comparison which was not FDA-approved),[12,13] or outcome studied (e.g., non-clinical).

New Guidelines:
No new guidelines were identified.

Guidelines from the National Cancer Care Network on the use of hematopoietic growth factors were revised in December 2021 (version 1.2022).[1] However, major recommendations regarding use of colony stimulating factors remain unchanged since the prior review.[2] Guidelines note that any FDA-approved biosimilar is an appropriate substitute for the originator. Guidelines continue to recommend prophylactic use of G-CGF in patients with high risk for febrile neutropenia (>20%) and to consider use in patients with intermediate risk (10-20%) based on individual factors.[1]

New Formulations:
Releuko® (filgrastim-ayow), a new biosimilar for filgrastim, was FDA approved in March 2022 for prophylaxis and treatment of neutropenia.[14]

Fylnetra® (pegfilgrastim-pbbk), a new biosimilar for pegfilgrastim, was FDA approved in May 2022 for prevention of febrile neutropenia in patients with non-myeloid malignancies receiving cancer treatment.[15]

Approval of these products was based on data demonstrating that they were highly similar to the reference product. Neither of these products have FDA-approval for mobilization of progenitor cells for stem cell transplant.

New FDA Safety Alerts:
None identified.

References:

1. NCCN Clinical Practice Guidelines in Oncology: Hematopoietic Growth Factors Version 1.2022. https://www.nccn.org/professionals/physician_gls/pdf/growthfactors.pdf. Accessed September 5, 2022.
2. Fletcher, S. Drug Use Research and Management. Drug Class Literature Scan: Colony Stimulating Factors. April 2022. https://www.orpdl.org/durm/meetings/meetingdocs/2021_06_03/archives/2021_06_03_CSF_LitScan.pdf. Accessed September 5, 2022. .
3. Mahtani R, Crawford J, Flannery SM, Lawrence T, Schenfeld J, Gawade PL. Prophylactic pegfilgrastim to prevent febrile neutropenia among patients receiving biweekly (Q2W) chemotherapy regimens: a systematic review of efficacy, effectiveness and safety. *BMC cancer.* 2021;21(1):621.
4. Van Belle H, Hurvitz SA, Gilbar PJ, Wildiers H. Systematic review and meta-analysis of febrile neutropenia risk with TCH(P) in HER2-positive breast cancer. *Breast cancer research and treatment.* 2021;190(3):357-372.
5. Li H, Wang G, Wen X, Zhou L. Systematic review and meta-analysis of clinical efficacy of drug therapy for acute myelogenous leukemia. *Annals of palliative medicine.* 2021;10(7):7884-7893.
6. Hoshina H, Takei H. Granulocyte-colony stimulating factor-associated aortitis in cancer: A systematic literature review. *Cancer treatment and research communications.* 2021;29:100454.
7. Lapidari P, Vaz-Luis I, Di Meglio A. Side effects of using granulocyte-colony stimulating factors as prophylaxis of febrile neutropenia in cancer patients: A systematic review. *Critical reviews in oncology/hematology.* 2021;157:103193.
8. Wang G, Zhang Y, Wang X, et al. Long-acting versus short-acting granulocyte colony-stimulating factors among cancer patients after chemotherapy in China: A systematic review and meta-analysis of randomized controlled trials. *Medicine.* 2021;100(51):e28218.
9. Shi P, Zhang J, Wu M, et al. The effects of granulocyte-colony stimulating factor on chronic liver disease: a meta-analysis. *Journal of infection in developing countries.* 2022;16(3):537-546.
10. Huang W, Ma Y, Du L, et al. Effectiveness of granulocyte colony-stimulating factor for patients with acute-on-chronic liver failure: a meta-analysis. *Annals of Saudi medicine.* 2021;41(6):383-391.
11. Muzzana M, Pedrazzoli P, Lasagna A. G-CSF and G-CSF-related vasculitis: a systematic review of the literature and intriguing future research perspectives. *Future oncology (London, England).* 2021;17(33):4619-4634.
12. Diaz-Navarro R, Urrutia G, Cleland JG, et al. Stem cell therapy for dilated cardiomyopathy. *The Cochrane database of systematic reviews.* 2021;7:CD013433.
13. Wang L, Xiang H, Yan Y, et al. Comparison of the efficiency, safety, and survival outcomes in two stem cell mobilization regimens with cyclophosphamide plus G-CSF or G-CSF alone in multiple myeloma: a meta-analysis. *Annals of hematology.* 2021;100(2):563-573.
14. Releuko (filgrastim-ayow) injection for subcutaneous or intravenous use [package labeling]. Piscataway, NJ: Kashiv BioSciences, LLC; February 2022.
15. Fylnetra (pegfilgrastim-pbbk) injection for subcutaneous use [package labeling]. Piscataway, NJ: Kashiv BioSciences, LLC; May 2022.

Appendix 1: Current Preferred Drug List

Generic	Brand	Form	Route	PDL
filgrastim	NEUPOGEN	SYRINGE	IJ	Y
filgrastim	NEUPOGEN	VIAL	IJ	Y
pegfilgrastim-apgf	NYVEPRIA	SYRINGE	SQ	Y
sargramostim	LEUKINE	VIAL	IJ	Y
tbo-filgrastim	GRANIX	SYRINGE	SQ	Y
tbo-filgrastim	GRANIX	VIAL	SQ	Y
filgrastim-aafi	NIVESTYM	SYRINGE	SQ	N
filgrastim-aafi	NIVESTYM	VIAL	IJ	N
filgrastim-ayow	RELEUKO	SYRINGE	SQ	N
filgrastim-ayow	RELEUKO	VIAL	IJ	N
filgrastim-sndz	ZARXIO	SYRINGE	IJ	N
pegfilgrastim	NEULASTA ONPRO	SYR W/ INJ	SQ	N
pegfilgrastim	NEULASTA	SYRINGE	SQ	N
pegfilgrastim-bmez	ZIEXTENZO	SYRINGE	SQ	N
pegfilgrastim-cbqv	UDENYCA	SYRINGE	SQ	N
pegfilgrastim-jmdb	FULPHILA	SYRINGE	SQ	N

Appendix 2: New Comparative Clinical Trials

A total of 111 citations were manually reviewed from the initial literature search. After further review, all citations were excluded because of wrong study design (eg, observational), comparator (eg, no control or placebo-controlled), or outcome studied (eg, non-clinical).

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) ALL 1946 to June 09, 2022

1	exp Filgrastim/	2229
2	exp Granulocyte Colony-Stimulating Factor/	16466
3	pegfilgrastim.mp.	993
4	sargramostim.mp.	240
5	tbo-filgrastim.mp.	27
6	pegfilgrastim-apgf.mp.	3
7	filgrastim-aafi.mp.	1
8	filgrastim-ayow.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	0
9	filgrastim-sndz.mp.	38
10	pegfilgrastim-bmez.mp.	1
11	pegfilgrastim-cbqv.mp.	8
12	pegfilgrastim-imdb.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	0
13	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12	16878
14	limit 13 to (english language and humans)	12968
15	limit 14 to yr="2021 -Current"	443
16	limit 15 to (clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or equivalence trial or guideline or meta analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or "systematic review")	111

Appendix 4: Key Inclusion Criteria

Population	Patients with FDA-approved indications for drugs in **Appendix 1** (e.g, neutropenia, mobilization of progenitor cells for stem cell transplant)
Intervention	Drugs in **Appendix 1**
Comparator	See **Appendix 1**
Outcomes	Febrile neutropenia, symptoms, morbidity, mortality, serious adverse events
Timing	Any study duration
Setting	Inpatient or outpatient therapy