February 4, 2015

Submission Request
National Comprehensive Cancer Network

RE: Clinical Evidence in Support of Sandoz Biosimilar Recombinant G-CSF (filgrastim) injection use as a Myeloid Growth Factor for Febrile Neutropenia and Maintenance of Scheduled Dose Delivery

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NCCN Panel:	Myeloid Growth Factors

To Whom It May Concern:

Sandoz' recombinant granulocyte colony-stimulating factor (rhG-CSF, filgrastim) application is under review by FDA. [Via the 351(k), "biosimilar" pathway] Based on the demonstrated high similarity to Neupogen® (filgrastim), Sandoz is seeking approval for the five labeled indications for Neupogen®:

- Cancer patients receiving myelosuppressive chemotherapy;
- Patients with acute myeloid leukemia receiving induction or consolidation chemotherapy;
- Cancer patients receiving bone marrow transplant;
- Patients undergoing peripheral blood progenitor cell collection and therapy;
- Patients with severe chronic neutropenia

Please consider the addition of Sandoz' rhG-CSF (EP2006) [prefilled syringes containing 300 mcg/0.5 mL or 480 mcg/0.8 mL.] in those sections where filgrastim is sited within the NCCN Guidelines, NCCN Patient Guidelines, and the associated "NCCN Drugs and Biologics Compendium™". Enclosed are data supporting the addition of Sandoz' rhG-CSF (EP2006; filgrastim) injection as a Myeloid Growth Factor for the Prophylaxis and Treatment of Febrile Neutropenia and Maintenance of Scheduled Dose Delivery.

The Sandoz rhG-CSF development program aligns with the statutory requirements and stepwise approach outlined in the draft FDA guidance for establishing biosimilarity to the reference product. The totality of the data package submitted, including analytical, functional, preclinical and clinical information allows for FDA approval of Sandoz rhG-CSF via the 351(k), "biosimilar" pathway.

Sandoz' rhG-CSF is the first drug submitted to FDA for evaluation under the biosimilar pathway and the first follow-on biologic to be reviewed by the Oncology Drug Advisory Committee (ODAC Jan 7, 2015). Data presented by the sponsor and FDA included analytical and functional data demonstrating that Sandoz' rhG-CSF was "essentially the same" drug as Neupogen® (defined as "highly similar"). After reviewing all the analytical and clinical data, ODAC voted unanimously to support approval of Sandoz' rhG-CSF for all indications of the reference product, Neupogen®.

The Sandoz rhG-CSF US clinical program focused on two pivotal studies. The PK/PD study (EP06-109) established PK and PD bioequivalence and the clinical safety and efficacy study (EP06-302) demonstrated non-inferiority to the reference product Neupogen® through comparable clinical efficacy in reduction of the duration and incidence of severe neutropenia in breast cancer patients undergoing myelosuppressive chemotherapy. As the same mode of action is evident in healthy volunteers and patients, these data provide confirmation of the high similarity between Sandoz' rhG-CSF and the reference product. Two safety and efficacy studies were conducted in a total of 388 breast cancer patients. The pivotal safety and efficacy study confirmed no treatment emergent effects or immunogenicity following repeated switches between the two products. The most frequently reported related adverse events (e.g., bone pain) were reflective of the pharmacodynamic effect of filgrastim. No subjects developed anti-rhG-CSF antibodies following drug administration. The clinical profile is also supported by a global clinical program that includes five randomized, double-blind, single and multiple dose PK/PD studies in healthy volunteers and a European non-comparative clinical safety and efficacy study. Additionally, Sandoz' rhG-CSF received European marketing authorization in 2009 and there have been over 7.5 million patient days of

exposure. There are ongoing clinical experience, pharmacovigilance, and a non-comparative post-authorization safety study.

Specific changes recommended for the Guidelines & Compendium: Please add the use of Sandoz' recombinant granulocyte colony-stimulating factor (filgrastim) injection as a Myeloid Growth Factor for Prophylaxis and Treatment of Febrile Neutropenia and Maintenance of Scheduled Dose Delivery to be used in any indication for which Neupogen® is approved.

FDA Status: Sandoz rhG-CSF (filgrastim) injection is under review and not yet FDA approved. FDA action is anticipated March 8, 2015.

Rationale for recommended change: Two pivotal studies and five supportive studies established PK and PD bioequivalence and noninferiority/comparable clinical efficacy and safety; no subject in any study developed anti-rhG-CSF antibodies following administration.

Literature support

1. FDA Briefing Materials (UCM428780) and (UCM428781) Oncologic Drugs Advisory Committee Meeting January 7, 2015. EP2006, a proposed biosimilar to Neupogen® (filgrastim) Sandoz Inc. Available from: http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/ucm428779.htm
2. Gascón P, Aapro M, et al. Prophylaxis of chemotherapy-induced febrile neutropenia with biosimilar filgrastim: Description of patients, treatment patterns and outcomes in the MONITOR-GCSF study in the breast cancer cohort. Poster 2014 San Antonio Breast Cancer Symposium, San Antonio, Texas, USA; 12 Dec 2014.
3. Tharmarajah S, Abdulaziz M, et al. Clinical efficacy and safety of Zarzio® (EP2006),a biosimilar recombinant human granulocyte colony-stimulating factor. *Biosimilars*. 2014;4:1–9.
4. Bonig H, Becker PS, et al. Biosimilar granulocyte-colony-stimulating factor for healthy donor stem cell mobilization: need we be afraid? *Transfusion*. 2014 Jun 26. [EPub]
5. Reményi P, Gopcsa L, et al. Peripheral blood stem cell mobilization and engraftment after autologous stem cell transplantation with biosimilar rhG-CSF. *Adv Ther*. 2014;31(4):451–460.
6. Gascón P, Tesch H, et al. Clinical experience with Zarzio® in Europe: what have we learned? *Support Care Cancer*. 2013;21(10):2925–2932.
7. Abraham I, Tharmarajah S, et al. Clinical safety of biosimilar recombinant human granulocyte colony-stimulating factors. *Expert Opin Drug Saf*. 2013;12(2):235–246.
8. Tesch H, Abenhardt W, et al. Non-interventional study HEXAFIL: G-CSF use in accordance to guidelines? Poster American Society Of Hematology Annual Meeting, Atlanta, Georgia, USA; 8 Dec 2012.
9. Salesi N, Di Cocco B, et al. Biosimilar medicines in oncology: single-center experience with biosimilar G-CSF. *Future Oncol*. 2012;8:625–630.
10. Aapro MS, Bohlius J, et al. 2010 update of EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphoproliferative disorders and solid tumours. *Eur J Cancer*. 2011;47(1):8–32.
11. Gascón P, Fuhr U, et al. Development of a new G-CSF product based on biosimilarity assessment. *Ann Oncol*. 2010;21(7):1419–1429.
12. Sörgel F, Lerch H, et al. Physicochemical and biologic comparability of a biosimilar granulocyte colony-stimulating factor with its reference product. *BioDrugs*. 2010 1;24(6):347–357.

We appreciate the opportunity to provide this information for consideration by the NCCN Myeloid Growth Factors Panel. If you have any questions or require additional information, please do not hesitate to contact me at (609) 627-6952 or via e-mail at matthew.frankel@sandoz.com. Thank you for your consideration.

Sincerely,

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Enclosures: Copies of referenced primary literature