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NCCN Guidelines Panel: Myeloid Growth Factor



Dear NCCN Myeloid Growth Factor panel,

On behalf of Pfizer, I respectfully request the NCCN Guideline Panel for Myeloid Growth Factor to review the enclosed information for inclusion of NIVESTYM™ (filgrastim-aafi), a biosimilar Neupogen® (filgrastim), for the treatment of patients with chemotherapy induced neutropenia and hematopoietic stem cell mobilization into the NCCN Guidelines.

Specific Changes Requested: Recommend the addition of NIVESTYM as a treatment option for patients with chemotherapy induced neutropenia and hematopoietic stem cell mobilization, similar to Neupogen.

FDA Clearance: On July 20th 2018, FDA approved NIVESTYM, a biosimilar to Neupogen, for the treatment of patients with chemotherapy induced neutropenia and hematopoietic stem cell mobilization.

Rationale: The FDA approved NIVESTYM as a biosimilar to Neupogen based upon the totality of the evidence in accordance with the FDA 351(k) pathway. The development program for NIVESTYM has been designed to demonstrate that NIVESTYM is highly similar with fingerprint-like analytical similarity to the US-licensed reference product Neupogen. The registration clinical trials included PK/PD studies in healthy volunteers (ZIN-FIL-1501; ZIN-FIL-1502) and a comparative Immunogenicity study in healthy volunteers (C1121012).

Analytical Tests and Non-clinical studies

Thirty-four state of the art analytical methods were developed to comparatively examine product attributes related to primary structure and higher order structure, post-translational modification, product-related substances and impurities, drug product characteristics and the functional activity of the filgrastim protein present in NIVESTYM and Neupogen. The structure and function of NIVESTYM were demonstrated to have fingerprint-like similarity to Neupogen in analytical studies.

Clinical Pharmacology

Two clinical pharmacology studies (ZIN-FIL-1501; ZIN-FIL-1502) in healthy volunteers demonstrated PK/PD biosimilarity between NIVESTYM and Neupogen.

In ZIN-FIL-1502 (randomized open-label, single dose, crossover study), for PK, 90% CI of the geometric mean ratios (GMR) for both AUC (1.05, 1.23) and C_{max} (1.02, 1.21) were completely contained within the pre-specified acceptance limits (0.80- 1.25) consistent with FDA guidance for industry regarding clinical pharmacology data for biosimilars. For PD, 90% CI of the GMR for ANC count for AU_{EC} (0.95, 1.02) and ANC_{max} (0.93, 1.02) were completely contained within the pre-specified acceptance limits (0.80 – 1.25).

In ZIN-FIL-1501 (randomized open-label, multiple-dose, crossover study), for PK, 90% CI for the GMR for AUC (0.97, 1.08) and C_{max} (0.95, 1.12) were both entirely contained within the pre-defined 0.80-1.25 equivalence margin. For PD, 90% CI of the GMR for AU_{EC} for CD34+ (0.98, 1.15) and CD34+_{max} (0.95, 1.19) were completely contained within the pre-specified acceptance limits (0.80-1.20).

Immunogenicity

Data from the 3 clinical studies in healthy volunteers (ZIN-FIL-1501; ZIN-FIL-1502; C1121012) were comparable between NIVESTYM and Neupogen, were without evidence for immune-modulated adverse events, and were without clinically meaningful differences. In particular immunogenicity study (C1121012-randomized, open-label, 2-period, parallel design non-inferiority study) in healthy volunteers supported the demonstration of clinical biosimilarity for NIVESTYM to Neupogen. The risk difference for developing anti-drug antibody was 2.56%. The

90% CI of the risk difference (-2.717, 8.096) was completely within the pre-specified acceptance limits (± 0.10). There was also no evidence of neutralizing Ab in any subject.

Clinical Safety

Data from the 3 clinical studies in healthy volunteers demonstrated no clinically meaningful differences in the safety profile between NIVESTYM and US-licensed Neupogen reference product.

Extrapolation

The demonstration of biosimilarity coupled with the well-characterized nature of the reference product together support extrapolation across all conditions of use for the reference product.

NIVESTYM has the same MOA (G-CSF receptor) across the approved indications for US licensed Neupogen. It is structurally and functionally similar to US-licensed Neupogen. It demonstrates PK/PD equivalence and no clinically meaningful differences in safety and immunogenicity profiles in healthy volunteers. Therefore the totality of evidence supporting biosimilarity justifies extrapolation across all indications granted by FDA except for hematopoietic syndrome of acute radiation syndrome, for which the reference product still has patent protection.

The development and manufacturing of NIVESTYM was based on our highly-related filgrastim biosimilar product in Europe, Nivestim. EU Nivestim was first approved as a biosimilar in Europe in June 2010 followed by approvals in Australia and over 50 countries around the world, and has been in the market for over 8 years with more than 8,998,540 patient-days or 24,654 patient years of treatment administered. NIVESTYM differs from EU-Nivestim in formulation preparation and minor adjustment in protein content to match the US-licensed Neupogen reference product. For US development the same drug substance is used as for the EU-approved Nivestim drug substance. However, due to differences in the protein content between EU-Nivestim and NIVESTYM, a specific US development program was required for NIVESTYM. Therefore, the efficacy and safety data of EU-Nivestim cannot be directly inferred to NIVESTYM.

The following resources are submitted in support of this requested change:

1. NIVESTYM Prescribing Information
2. FDA Scientific Considerations in Demonstrating Biosimilarity to a Reference Product (Guidance for Industry)
3. NIVESTYM CR for ZIN-FIL-1501; ZIN-FIL-1502; C1121012
4. Ottery et al (2018). Pharmacodynamics, immunogenicity, safety of single/multiple subcutaneous doses of PF-06881893 (proposed filgrastim biosimilar) vs US-licensed filgrastim reference product in healthy volunteers. Poster MASCC 2018 Jun 26-28.
5. Fruehauf et al (2016). "Compatibility of Biosimilar Filgrastim with Cytotoxic Chemotherapy during the Treatment of Malignant Diseases (VENICE): A Prospective, Multicenter, Non-Interventional, Longitudinal Study." *Adv Ther* 33(11): 1983-2000.
6. Frederic et al (2014). BIOSIMILAR FILGRASTIN THE TREATMENT AND THE PREVENTION OF CHEMOTHERAPY-INDUCED NEUTROPENIA: THE NEXT STUDY. SIOG Lisbon 2014 abstract, Vol 5, pg S1-82 (Oct)
7. Waller et al (2010). A Phase III Randomized Equivalence Study of Biosimilar Filgrastim versus Amgen Filgrastim in Patients Receiving Myelosuppressive Chemotherapy for Breast Cancer. *Onkologie* 2010;33:504–511

We appreciate the Panel's thorough consideration of Pfizer's submission for inclusion in the NCCN Guidelines of NIVESTYM for the treatment of chemotherapy induced neutropenia and hematopoietic stem cell mobilization. We welcome any questions that you may have.

Sincerely,

Dr. Selwyn Fung
Medical Director Biosimilars Oncology
Pfizer Inc.