Filgrastim-aafi (Nivestym™) Abbreviated New Drug Update (ANDU)

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OVERVIEW[1]

- Filgrastim-aafi (Nivestym), a leukocfyte growth factor approved on July 20, 2018, is the second FDA-approved biosimilar to filgrastim (Neupogen®). Filgrastim-aafi is approved for the following indications:
  - ❒ To decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a significant incidence of severe neutropenia with fever;
  - ❒ To reduce the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of patients with acute myeloid leukemia (AML);
  - ❒ To reduce the duration of neutropenia and neutropenia-related clinical sequelae (e.g., febrile neutropenia) in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplantation (BMT);
  - ❒ Mobilization of autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis; and
  - ❒ To reduce the incidence and duration of sequelae of severe neutropenia (e.g., fever, infections, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia.
- Contraindications/Warnings
  - ❒ Use in patients with a history of serious allergic reactions to human granulocyte colony-stimulating factors (CSFs), such as filgrastim or pegfilgrastim products, is contraindicated.
  - ❒ Warnings include fatal splenic rupture, acute respiratory distress syndrome (ARDS), fatal sickle cell crises, glomerulonephritis, and serious allergic reactions, including anaphylaxis.
- Availability
  - ❒ Single-dose vials containing 300 mcg/mL or 480 mcg/1.6 mL
  - ❒ Single-dose prefilled syringes containing 300 mcg/0.5 mL or 480 mcg/0.8 mL
- Dosage and Administration
  - ❒ Cancer patients receiving myelosuppressive chemotherapy or induction and/or consolidation chemotherapy for AML:
    - ❖ Initial: 5 mcg/kg/day via subcutaneous (SC) injection, short intravenous (IV) infusion (15 to 30 minutes), or continuous IV infusion
  - ❒ Cancer patients undergoing BMT:
    - ❖ 10 mcg/kg/day via IV infusion given over no longer than 24 hours; during neutrophil recovery, the daily dosage should be titrated per product labeling

- ❒ Patients undergoing autologous peripheral blood progenitor cell collection and therapy:
  - ❖ 10 mcg/kg/day via SC injection; administer for at least 4 days before first leukapheresis procedure and continue until last leukapheresis
- ❒ Congenital neutropenia:
  - ❖ Initial: 6 mcg/kg SC injection twice daily
- ❒ Cyclic or idiopathic neutropenia:
  - ❖ Initial: 5 mcg/kg SC injection as a single daily dose
- ❒ Additional information
  - ❖ Do not use prefilled syringes for doses < 0.3 mL
  - ❖ Additional details on adjustments and timing are outlined in the product labeling

- Adverse Events
  - ❒ The most common adverse events in patients with:
    - ❖ Nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs are cough, dyspnea, pyrexia, pain, and rash (≥ 2% difference in incidence compared to placebo);
    - ❖ AML are epistaxis, pain, and rash (≥ 2% difference in incidence compared to placebo);
    - ❖ Nonmyeloid malignancies undergoing myeloablative chemotherapy followed by BMT is rash (≥ 5% difference in incidence compared to placebo);Peripheral blood progenitor cell mobilization and collection (≥ 5% incidence) are bone pain, headache, and pyrexia; and
    - ❖ Severe chronic neutropenia are alopecia, anemia, diarrhea, epistaxis, hypoesthesia, and pain (≥ 5% difference in incidence compared to placebo).
- Drug Interactions
  - ❒ No drug interactions are provided in the prescribing information.
- Pregnancy
  - ❒ There are no adequate and well-controlled clinical studies in pregnant women; therefore, the potential risk to the fetus with the use of filgrastim-aafi is unknown.
- Pediatrics
  - ❒ Safety and effectiveness of filgrastim were established in pediatric patients with severe chronic neutropenia (SCN) and pharmacokinetic studies with pediatric cancer patients (aged 1.2 to 9.4 years) treated with myelosuppressive chemotherapy.

CLINICAL TRIALS[2]

- The FDA approval of filgrastim-aafi as a biosimilar is based on data demonstrating that it is highly similar to the reference product, filgrastim (Neupogen). Biosimilarity of filgrastim-aafi to filgrastim has been demonstrated for the aforementioned indications, strengths, and dosage forms and is further described in the full prescribing information.

CLINICAL CONSIDERATIONS[3,4,5,6]

- The colony-stimulating factor (CSF) filgrastim-aafi (Nivestym), by Pfizer, is the second FDA-approved biosimilar to Amgen's filgrastim (Neupogen), following filgrastim-sndz (Zarxio®). Filgrastim-aafi was approved through the 351(k) biosimilar pathway.
- Prophylactic CSF use can reduce the severity, risk, and duration of febrile neutropenia and decrease rates of infection. Additional CSFs include filgrastim (Neupogen), filgrastim-sndz (Zarxio), pegfilgrastim (Neulasta®), pegfilgrastim-jmdb (Fulphila™) and tbo-filgrastim (Granix®).
- Filgrastim-aafi carries the same indications as filgrastim, with the exception of increasing survival in patients acutely exposed to myelosuppressive doses of radiation (hematopoietic syndrome or acute radiation syndrome).
- Filgrastim (Neupogen) and filgrastim-aafi (Nivestym) are both available as single-dose vials and syringes, whereas filgrastim-sndz (Zarxio) is only available in the pre-filled syringe formulation.
- Neither filgrastim-sndz nor filgrastim-aafi prefilled syringes are recommended for direct administration of doses < 0.3 mL due to potential dosing errors. Filgrastim (Neupogen) does *not* contain this warning.
- Clinical guidelines are available for the approved indications of filgrastim-aafi, and they address the use of the reference product filgrastim and biosimilar filgrastim-sndz.
    - ❒ The American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN) Guidelines for Supportive Care – Myeloid Growth Factors support the prophylactic use of filgrastim and filgrastim-sndz, along with pegfilgrastim and tbo-filgrastim, to reduce the risk of febrile neutropenia. The NCCN guidelines recommend filgrastim and filgrastim-sndz for allogeneic hematopoietic cell mobilization and for granulocyte transfusion. NCCN states that patients should remain on the same product throughout treatment as none of the biosimilars are considered interchangeable.
        - ❖ The ASCO guidelines state that these products, and other biosimilars, as they become available, can be used for the prevention of treatment-related febrile neutropenia. The choice of agent depends on convenience, cost, and clinical situation.
        - ❖ As it was only just recently approved by the FDA, the NCCN guidelines state that there is insufficient data for consideration of filgrastim-aafi for all indications.
- Biosimilars must demonstrate that there are no clinically meaningful differences in safety or effectiveness from the reference product; however, small differences in clinically inactive compounds are permissible in biosimilar products. Currently, biosimilars are not considered interchangeable with the reference product.
- Launch date for filgrastim-aafi has not been determined, but Pfizer plans to launch it when logistically practical.

REFERENCES

1 Nivestym. [Prescribing Information]. Lake Forest, IL; Pfizer; July 2018.
2 Nivestym. [Prescribing Information]. Lake Forest, IL; Pfizer; July 2018.
3 The National Comprehensive Cancer Network practice guidelines for Myeloid Growth Factors v2.2018. Available at: https://www.nccn.org/professionals/physician_gls/pdf/myeloid_growth.pdf. Accessed August 21, 2018.
4 Neupogen [package insert]. Thousand Oaks, CA; Amgen; June 2018.
5 Smith TJ, Bohlke K, Lyman GH, et al; American Society of Clinical Oncology. Recommendations for the use of WBC growth factors: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol. 2015; 33(28):3199-3212. DOI: 10.1200/JCO.2015.62.3488. Available at: https://www.asco.org/practice-guidelines/quality-guidelines/guidelines/supportive-care-and-treatment-related-issues. Accessed August 21, 2018.
6 The National Comprehensive Cancer Network practice guidelines for myeloid growth factors v2.2018. Available at: https://www.nccn.org/professionals/physician_gls/pdf/myeloid_growth.pdf. Accessed August 21, 2018.