



David Shechter, Ph.D.
Senior Manager, Regulatory Affairs
Amgen
One Amgen Center Drive, Mail Stop 27-4-F
Thousand Oaks, CA 91320-1799

RE: BLA 125031
NEULASTA[®] (pegfilgrastim) injection, for subcutaneous use
MA 1706

Dear Dr. Shechter:

The Office of Prescription Drug Promotion (OPDP) of the U.S. Food and Drug Administration (FDA) has reviewed the promotional communication, a professional animated banner (USA-003-80637) for NEULASTA[®] (pegfilgrastim) injection, for subcutaneous use (Neulasta), submitted by Amgen Inc. (Amgen) under cover of Form FDA 2253. The FDA Bad Ad Program also received complaints regarding promotional communications with similar claims and presentations as the ones discussed in this letter. The banner makes false or misleading claims and representations about the benefit of Neulasta. Thus, the banner misbrands Neulasta within the meaning of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and makes its distribution violative. 21 U.S.C. 352(a), (n); 321(n); 331(a). See 21 CFR 202.1(e)(3)(i); 202.1(e)(5). These violations are concerning from a public health perspective because this promotional communication's misleading claims could cause healthcare providers to conclude that Neulasta delivered via the Onpro on-body injector (OBI) is more effective than Neulasta delivered via prefilled syringe (PFS) or that it is more effective than FDA-licensed biosimilar pegfilgrastim products, which are only delivered via PFS.

Background

Below are the indications and summary of the most serious and most common risks associated with the use of Neulasta.¹ According to the INDICATIONS AND USAGE section of the FDA-approved product labeling (PI) (in pertinent part):

Neulasta is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia . . .

Limitations of Use

¹ This information is for background purposes only and does not necessarily represent the risk information that should be included in the promotional piece(s) cited in this letter.

Neulasta is not indicated for the mobilization of peripheral blood progenitor cells for hematopoietic stem cell transplantation.

Neulasta is contraindicated in patients with a history of serious allergic reactions to human granulocyte colony-stimulating factors such as pegfilgrastim or filgrastim. The PI for Neulasta includes warnings and precautions regarding splenic rupture, acute respiratory distress syndrome, serious allergic reactions, allergies to acrylics, use in patients with sickle cell disorders, glomerulonephritis, leukocytosis, thrombocytopenia, capillary leak syndrome, potential for tumor growth stimulatory effects on malignant cells, myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) in patients with breast and lung cancer in conjunction with chemotherapy and/or radiotherapy, potential device failures, and aortitis. The most common adverse reactions reported with use of Neulasta include bone pain and pain in extremity.

False or Misleading Benefit Presentation

Prescription drug advertisements and labeling (promotional communications) misbrand a drug if they are false or misleading with respect to benefits. The determination of whether a promotional communication is misleading includes, among other things, not only representations made or suggested in the promotional communication, but also the extent to which the promotional communication fails to reveal facts material in light of the representations made or with respect to consequences that may result from the use of the drug as recommended or suggested in the promotional communication.

The banner includes the following claims and presentations (emphasis original):

- “In a Real-World Study with nearly 11,000 patients Pegfilgrastim **PFS resulted in a significantly higher risk of FN** vs. Onpro[®]” (frame 1)
- “Across all cycles of chemotherapy, the incidence of FN associated with prefilled syringe (PFS) was 1.7% (n = 455) vs 1.3% (n = 126) for Neulasta[®] Onpro[®]” (frame 1)
- A large presentation of an upward arrow containing the claim, “31%* *p = 0.01” (frames 1 and 2)
- “With PFS, **FN incidence increased by 31%** vs Onpro[®]” (frame 2)

These claims and presentations create a misleading impression regarding the benefit of the product by stating that there is a statistically significant higher risk of febrile neutropenia (FN) when pegfilgrastim is administered via the prefilled syringe (PFS) compared to the Onpro on-body injector (OBI). However, the multiple limitations of the cited study² preclude the drawing of such conclusions regarding the comparative risk of febrile neutropenia (FN) in patients taking pegfilgrastim depending on delivery method.

² Data on file, Amgen; 2019 – Delivering pegfilgrastim via PFS (pre-filled syringe) resulted in a significantly higher risk of FN (febrile neutropenia) vs. Onpro. The data on file was provided by Amgen in response to OPDP’s request for the information.

For example, the study was not designed to ensure that patients with FN were appropriately identified for inclusion in the analysis. Specifically, the study uses an unvalidated algorithm³ to identify study participants. This algorithm retrospectively identified patients who had FN by selecting inpatient and outpatient encounters with diagnosis codes for neutropenia **and** fever or infection. The data on file that Amgen provided to OPDP included no information about the performance characteristics (e.g., sensitivity, positive predictive value) of the algorithm or the diagnostic codes that were used. The use of an unvalidated algorithm with unknown performance characteristics is a significant limitation because of the potential for misclassification of patients at the onset of the study.⁴ We also note that the data on file does not describe any measures taken to ensure the quality and accuracy of the results generated by the algorithm. As a result, the extent of FN in this study population may be overestimated or underestimated.

In addition to the above concern, the study was not designed to ensure that the PFS and OBI patient populations were adequately balanced or controlled for potential bias. Specifically, the study did not control for factors other than the delivery device that may influence the incidence of FN in the compared groups. Eligible patients for the study had highly diverse clinical characteristics, and the study report did not include any information on the baseline comorbidity or risk factors for FN of the two exposure groups or on design or analytic strategies to minimize the risk of selection bias. Selection bias⁵ is a key concern for this study because even slight differences in populations (e.g., risk factors for FN, age, chemotherapy regimen and dosing, etc.) could substantially impact the incidence of FN and the conclusions stemming from the analysis. We note that while the size of the relative effect in this study is large (31% increased incidence of FN with PFS vs. OBI), the absolute difference is much smaller in magnitude (0.4%; 1.7% PFS vs 1.3% OBI). It cannot be ruled out that selection bias is entirely responsible for the observed risk difference. Accordingly, reporting a p-value for the claims and presentations in frames one and two of the banner is misleading.

Therefore, due to multiple limitations of design and analytic strategy, the study does not support the claims and presentations regarding the comparative FN risk when pegfilgrastim is administered via PFS compared to the OBI. We note that two limitations to the study are presented in frames seven and eight under the header “Real-World Study Limitations.” The presentation of two major deficiencies of the study design does not mitigate the misleading claims and presentations in the banner.

The above misleading claims and presentations are particularly concerning from a public health perspective because they could undermine confidence not just in Neulasta delivered via PFS but also in FDA-licensed biosimilar pegfilgrastim products, which are only delivered via PFS. The above claims prominently present “Pegfilgrastim PFS” (emphasis added) as

³ The algorithm used to identify FN in claims data for this study included several related diagnostic codes (i.e., inpatient diagnosis of neutropenia in any position AND (diagnosis of fever OR diagnosis of infection in any position); or, outpatient diagnosis of neutropenia AND (diagnosis of fever OR (diagnosis of infection AND prescription for antimicrobials))).

⁴ As noted in the cited reference, “The potential for misclassification of key variables exist, as patients are identified through diagnosis or procedure codes as opposed to medical records, and therefore are subject to data coding limitations and data entry error.”

⁵ Necessary data on potential confounding variables were unlikely to be sufficiently captured in the MarketScan® database to allow a robust analysis, increasing the likelihood of selection bias.

the comparator arm vs. “Neulasta Onpro” and “Onpro.” The use of the proper name (i.e., nonproprietary name) of Amgen’s PFS product, on the one hand, and the proprietary name of its OBI product, on the other, could result in healthcare providers failing to understand that Amgen’s Neulasta was used in both arms of the study. Healthcare providers could conclude that a biosimilar pegfilgrastim product delivered via PFS is not as effective as Amgen’s OBI product (i.e., Neulasta Onpro). As noted above, the study cited is inadequately designed and precludes the drawing of conclusions regarding the comparative risk of FN in patients taking Amgen’s pegfilgrastim products depending on delivery method. It likewise does not support conclusions about any other FDA-licensed pegfilgrastim products. OPDP notes that frame six of the banner states, less prominently and in smaller font than the claims and presentations set forth in frames one and two, that the retrospective study evaluates Neulasta Onpro vs. Neulasta PFS, but this statement is not sufficient to mitigate the more prominent presentation of Pegfilgrastim PFS vs. Neulasta Onpro and Onpro.

Conclusion and Requested Action

For the reasons discussed above, the banner misbrands Neulasta within the meaning of the FD&C Act and makes its distribution violative. 21 U.S.C. 352(a), (n); 321(n); 331(a). See 21 CFR 202.1(e)(3)(i); 202.1(e)(5).

This letter notifies you of our concerns and provides you with an opportunity to address them. OPDP requests that Amgen cease any violations of the FD&C Act. Please submit a written response to this letter within 15 working days from the date of receipt, addressing the concerns described in this letter, listing all other promotional communications (with the 2253 submission date) for Neulasta that contain representations like those described above, and explaining any plan for discontinuing use of such communications, or for ceasing distribution of Neulasta.

If you believe that your products are not in violation of the FD&C Act, please include in your submission to us your reasoning and any supporting information for our consideration within 15 working days from the date of receipt of this letter.

The concerns discussed in this letter do not necessarily constitute an exhaustive list of potential violations. It is your responsibility to ensure compliance with each applicable requirement of the FD&C Act and FDA implementing regulations.

Please direct your response to the undersigned at the **Food and Drug Administration, Center for Drug Evaluation and Research, Office of Prescription Drug Promotion, 5901-B Ammendale Road, Beltsville, Maryland 20705-1266**. A courtesy copy can be sent by facsimile to (301) 847-8444. To ensure timely delivery of your submissions, please use the full address above and include a prominent directional notation (e.g., a sticker) to indicate that the submission is intended for OPDP.

Please refer to MA 1706 in addition to the BLA number in all future correspondence relating to this particular matter. All correspondence should include a subject line that clearly identifies the submission as a Response to Untitled Letter.

Sincerely,

{See appended electronic signature page}

Rebecca Falter, PharmD, BCACP
Regulatory Review Officer
Division of Advertising & Promotion Review 1
Office of Prescription Drug Promotion

{See appended electronic signature page}

Susannah O'Donnell, MPH, RAC
Team Leader
Division of Advertising & Promotion Review 1
Office of Prescription Drug Promotion

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

REBECCA A FALTER
07/07/2021 10:33:19 AM

SUSANNAH O'DONNELL
07/07/2021 10:49:10 AM