Summary Review

Date	1 November 2018
From	Nicole Gormley, MD
Subject	Deputy Division Director Summary Review
NDA/BLA #	BLA 761039
Applicant	Coherus BioSciences, Inc.
Date of Submission	3 May 2018
BsUFA Goal Date	3 November 2018
Nonproprietary Name	Pegfilgrastim-cbqv*
Proprietary Name	UDENYCA
Dosage forms / Strength	Injection: 6 mg/0.6 mL in a single-dose prefilled syringe
Proposed Indication(s)	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.
Recommended:	Approval

* For purposes of this review, the proposed product is occasionally referred to by the Sponsor's descriptor CHS-1701. The proposed proprietary name, UDENYCA, is only conditionally accepted until the application is approved. The proposed nonproprietary name, pegfilgrastim-cbqv, was also deemed conditionally acceptable.

Material Reviewed/Consulted	**Reviewer**
Cross-Discipline Team Leader Review	Vishal Bhatnagar, MD
Clinical Review, Division of Hematology Products	Bindu Kanapuru, MD
OBP Executive Summary Review	Joel Welch, PhD; Ying-Xin Fan, PhD; Joslyn Brunelle, PhD
Division of Medication Error Prevention and Analysis (DMEPA) Consult	Nicole Garrison, Pharm.D, BCPS / Danielle Harris, PharmD, BCPS

Background

On August 9, 2016, Coherus BioSciences, Inc. (Applicant) submitted BLA 761039, for CHS-1701 as a proposed biosimilar product to US-licensed Neulasta (Amgen Inc.). BLA 761039 was submitted for the purpose of licensure of CHS-1701 under section 351(k) of the Public Health Service Act. The proposed indication for CHS-1701 is 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. This indication is approved for US-licensed Neulasta. Of note, US-licensed Neulasta also has an indication to increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Subsyndrome of Acute Radiation Syndrome). However, the acute radiation syndrome indication is not being sought by the Applicant as US-licensed Neulasta has unexpired orphan drug exclusivity for this indication.

On June 9, 2017, a Complete Response was issued due to product quality, analytical similarity, and immunogenicity deficiencies. Refer to the CR letter for a detailed description of deficiencies.

On May 3, 2018, the Applicant provided a resubmission to address the deficiencies identified in the CR letter.

Review

From an OBP perspective, the product quality and analytical similarity CR deficiencies and the additional comments described in the CR letter were adequately addressed in the resubmission. The proposed biosimilar UDENYCA has been evaluated and compared to US-licensed Neulasta using a variety of structural, physicochemical, and functional assays. A total of 13 lots of CHS-1701 Drug Product and 22 lots of US-licensed Neulasta were evaluated in the analytical similarity assessment. A tiered approach was used when comparing both products and the tier assignment was based on the criticality risk ranking and analytical method capabilities.

Coherus also provided additional information to address the differences in ADA (anti-drug antibody) incidence rates between the CHS-1701 and US-licensed Neulasta treatment arms in Study CHS-1701-04. Coherus Biosciences Inc. provided a new anti-G-CSF titer assay which was found to be acceptable. ADA were classified as anti-PEG and/or anti-G-CSF. Using the new anti-G-CSF titer assay, the majority of G-CSF titers were transient. When focusing only on the measurable G-CSF titers, there was a low absolute incidence with 2 in the CHS-1701 arm compared to 1 in the US-licensed Neulasta arm. Thus, there is no significant difference related to G-CSF titers. Overall, the difference in ADA incidence between the CHS-1701 and US-licensed Neulasta groups is driven by non-neutralizing, low titer, PEG-reactive ADA. The anti-PEG ADA are commonly present in healthy subjects. Per the product quality reviewer, “the anti-PEG antibodies found in CHS-1701 studies were at low titers, which are not clinically relevant”. As such, the immunogenicity team recommended approval.

No new clinical studies were conducted or submitted to support the resubmission other than those that were submitted in the original BLA. The resubmission included minor changes to adverse event (AE) data due to revised classification of AEs related to clinically significant laboratory abnormalities from the CHS-1701-05 study. The revised safety data did not affect the overall safety conclusions for the study. There were no major differences in the overall safety profile reported in the patients who met the ADA endpoint in the CHS-1701 arm and US-licensed Neulasta arm in the primary immunogenicity study (CHS-1701-04). As such, the clinical team recommended approval.

Regulatory Recommendation

I agree with the recommendation of the review team for approval of CHS-1701 as a biosimilar to US-licensed Neulasta for the following indication: 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.

Nicole Gormley, MD
Deputy Division Director (acting), DHP

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/s/

NICOLE J GORMLEY
11/01/2018