



BLA 761040/S-003

SUPPLEMENT APPROVAL

Wyeth Pharmaceuticals, LLC.
Attention: Brenda W. Kozan, BS
Director, Pfizer Global Regulatory Sciences
500 Arcola Road
Collegetown, PA 19426-3982

Dear Brenda Kozan:

Please refer to your supplemental biologics license application (sBLA) dated June 9, 2023, received June 9, 2023, and your amendments under section 351(a) of the Public Health Service Act for Besponsa (inotuzumab ozogamicin) lyophilized cake or powder.

We acknowledge receipt of your major amendment dated October 23, 2023, which extended the goal date by three months.

This Prior Approval supplemental biologics license application provides for the treatment of relapsed or refractory CD22-positive B-cell precursor acute lymphoblastic leukemia (ALL) in pediatric patients 1 year and older. In addition, this supplemental biologics license application provides for updates to Section 1 (Indications and Usage), Section 8.4 (Pediatric Use), Section 12.3 (Pharmacokinetics/Pediatric Patients), the addition of Section 12.6 (Immunogenicity) along with other relevant sections and editorial changes throughout the United States Prescribing Information (USPI). These changes are based on data from two studies: Study ITCC-059 (WI203581) "*A Phase 1/2, multicenter, European, multi-cohort, open-label study in pediatric patients (≥ 1 and < 18 years of age) with R/R CD22-positive ALL*", as of the study PCD on 12 September 2022 and INO-Ped-ALL-1 (WI235086) "*An open-label, multi-center Phase 1 study to assess safety and tolerability of InO in Japanese pediatric patients with R/R CD22-positive AL*".

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

WAIVER OF HIGHLIGHTS ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at FDA.gov,¹ that is identical to the enclosed labeling (text for the Prescribing Information) and include the labeling changes proposed in any pending “Changes Being Effectuated” (CBE) supplements.

Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.²

The SPL will be accessible via publicly available labeling repositories.

Also, within 14 days, amend all pending supplemental applications that include labeling changes for this BLA, including pending “Changes Being Effectuated” (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 601.12(f)] in Microsoft Word format that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

¹ <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>

² We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a known serious risk of veno-occlusive disease (VOD), and a serious potential risk of increased adverse reactions due to higher exposure in pediatric patients with lower body size.

Furthermore, the active postmarket risk identification and analysis system as available under section 505(k)(3) of the FDCA will not be sufficient to assess the serious risk.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess the known serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following trials:

- 4585-1 Conduct an integrated analysis of data from available sources, including data from Study B1931030, to support optimization of pediatric dosage(s), to assess whether lower doses of inotuzumab ozogamicin can minimize the serious risk of severe liver veno-occlusive disease (VOD) in pediatric patients and the serious potential risk of increased adverse reactions due to higher exposure in pediatric patients with lower body size. Evaluate for alternative dosing regimen(s) based on body weight to potentially minimize exposure difference between pediatric and adult patients with ALL, particularly for pediatric patients with low body surface area or weight.

The timetable you submitted on February 20, 2024, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission (Analysis Plan):	05/2024
Final Protocol Submission (Analysis Plan):	10/2024
Study Completion:	04/2025
Final Report Submission:	05/2025

Submit the datasets and model files with the final report submission.

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.³

³ See the guidance for Industry Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).
<https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

Submit clinical protocol(s) to your IND 065658 with a cross-reference letter to this BLA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final report(s) to your BLA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:

Required Postmarketing Protocol Under 505(o), Required Postmarketing Final Report Under 505(o), Required Postmarketing Correspondence Under 505(o).

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B(a)(1) of the FDCA, as well as 21 CFR 601.70 requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B(a)(1) and 21 CFR 601.70 to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 601.70. We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs*.⁴

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the Prescribing Information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.⁵ Information and Instructions for completing the form can be found at FDA.gov.⁶

All promotional materials for your drug product that include representations about your drug product must be promptly revised to make it consistent with the labeling changes approved in this supplement, including any new safety-related information [21 CFR 601.12(a)(4)]. The revisions to your promotional materials should include prominent disclosure of the important new safety-related information that appears in the revised

⁴ For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/media/128163/download>.

⁵ <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>

⁶ <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>

labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 601.12(a)(4).

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved BLA (in 21 CFR 600.80 and in 21 CFR 600.81).

If you have any questions, contact Rachel McMullen, Senior Regulatory Project Manager, at 240-402-4574.

Sincerely,

{See appended electronic signature page}

R. Angelo de Claro, MD
Division Director
Division of Hematologic Malignancies I
Office of Oncologic Diseases
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
 - Prescribing Information

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/

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