CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

761334Orig1s000

Trade Name:	Zynyz
Generic or Proper Name:	retifanlimab-dlwr
Sponsor:	Incyte Corporation
Approval Date:	March 22, 2023
Indication:	For the treatment of adult patients with metastatic or recurrent locally advanced Merkel cell carcinoma.

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CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	**X**
Other Action Letters	
Labeling	**X**
REMS	
Officer/Employee List	**X**
Multidiscipline Review(s) • **Summary Review** • **Office Director** • **Cross Discipline Team Leader** • **Clinical** • **Non-Clinical** • **Statistical** • **Clinical Pharmacology**	**X**
Product Quality Review(s)	**X**
Clinical Microbiology / Virology Review(s)	
Other Reviews	**X**
Risk Assessment and Risk Mitigation Review(s)	**X**
Proprietary Name Review(s)	**X**
Administrative/Correspondence Document(s)	**X**

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APPROVAL LETTER

BLA 761334

BLA CORRECTED APPROVAL

Incyte Corporation
Attention: Michael J. McGraw, Pharm.D., M.S.
Vice President, Global Regulatory Affairs
1801 Augustine Cut-Off
Wilmington, DE 19803

Dear Dr. McGraw:

Please refer to your biologics license application (BLA) dated August 6, 2022, received August 8, 2022, and your amendments, submitted under section 351(a) of the Public Health Service Act for Zynyz (retifanlimab-dlwr) injection, for intravenous use.

We also refer to our approval letter dated March 22, 2023, which contained the following error: The letter did not contain the new language regarding accelerated approval from the Food and Drug Omnibus Reform Act (FDORA) of 2022.

This corrected action letter incorporates the correction of the error. The effective action date will remain March 22, 2023, the date of the original letter.

LICENSING

We are issuing Department of Health and Human Services U.S. License No. 2228 to Incyte Corporation, Wilmington, Delaware, under the provisions of section 351(a) of the Public Health Service Act controlling the manufacture and sale of biological products. The license authorizes you to introduce or deliver for introduction into interstate commerce, those products for which your company has demonstrated compliance with establishment and product standards.

Under this license, you are authorized to manufacture the product Zynyz (retifanlimab-dlwr). Zynyz is indicated for the treatment of adult patients with metastatic or recurrent locally advanced Merkel cell carcinoma.

Under this license, you are approved to manufacture retifanlimab-dlwr drug substance at (b) (4) The final formulated product will be manufactured, filled, labeled, and packaged at (b) (4) You may label your product with the proprietary name Zynyz and will market it in 500 mg/20 mL single-dose vial, injection, for intravenous use.

DATING PERIOD

The dating period for Zynyz shall be 24 months from the date of manufacture when stored at 5 ± 3°C. The date of manufacture shall be defined as the date of final sterile filtration of the formulated drug product. The dating period for your drug substance shall be (b) (4) months from the date of manufacture when stored at (b) (4) °C.

Results of ongoing stability should be submitted throughout the dating period, as they become available, including the results of stability studies from the first three production lots.

We have approved the stability protocol(s) in your license application for the purpose of extending the expiration dating period of your drug substance and drug product under 21 CFR 601.12.

FDA LOT RELEASE

You are not currently required to submit samples of future lots of Zynyz to the Center for Drug Evaluation and Research (CDER) for release by the Director, CDER, under 21 CFR 610.2. We will continue to monitor compliance with 21 CFR 610.1, requiring completion of tests for conformity with standards applicable to each product prior to release of each lot.

Any changes in the manufacturing, testing, packaging, or labeling of Zynyz, or in the manufacturing facilities, will require the submission of information to your biologics license application for our review and written approval, consistent with 21 CFR 601.12.

APPROVAL AND LABELING

We have completed our review of this application, as amended. It is approved under the provisions of accelerated approval regulations (21 CFR 601.41), effective on the date of this letter, for use as recommended in the enclosed agreed-upon approved labeling. This BLA provides for the use of Zynyz for the treatment of adult patients with metastatic or recurrent locally advanced Merkel cell carcinoma.

Marketing of this drug product and related activities must adhere to the substance and procedures of the referenced accelerated approval statutory provisions and regulations.

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] Content of labeling must be identical to the enclosed labeling (text for the

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

Prescribing Information and Medication Guide). Information on submitting SPL files using eLIST may be found in the draft guidance for industry *SPL Standard for Content of Labeling Technical Qs and As* (October 2009).[2]

The SPL will be accessible via publicly available labeling repositories.

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (February 2020, Revision 7)*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved BLA 761334**". Approval of this submission by FDA is not required before the labeling is used.

ADVISORY COMMITTEE

Your application for retifanlimab-dlwr was not referred to an FDA advisory committee because the application did not raise significant safety or efficacy issues that were unexpected for a drug/biologic of this class or in the intended population for which external input was necessary.

ACCELERATED APPROVAL REQUIREMENTS

Products approved under accelerated approval pursuant to section 506(c) of the FDCA and 21 CFR 601.41 may require further adequate and well-controlled clinical trials intended to verify and describe clinical benefit. You are required to conduct such clinical trials with due diligence. If required postmarketing clinical trials fail to verify clinical benefit or are not conducted with due diligence, we may withdraw this approval. We remind you of your postmarketing requirement specified in your submission dated February 21, 2023. This requirement, along with required completion dates, is listed below.

4412-1 Conduct a multicenter clinical trial intended to confirm the clinical benefit of retifanlimab-dlwr in patients with metastatic or recurrent locally advanced Merkel cell carcinoma (MCC) who have not received prior systemic therapies for metastatic or recurrent locally advanced MCC. The trial will enroll at least 100 patients to be followed for a minimum of 12 months to establish the objective response rate and characterize the durability of response. Include an analysis of overall survival, when 70% of

[2] When final, this guidance will represent FDA's current thinking on this topic. 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.

patients have died, or all patients have been followed for at least three years.

Final Protocol Submission:	06/2023
Trial Completion:	09/2024
Final Report Submission:	03/2025

Submit clinical protocols to your IND 139181 for this product. In addition, you must submit status reports of the progress of each requirement not later than 180 days after the date of approval of this drug and every 180 days thereafter (section 506(B)(a) of the FDCA as amended by section 3210(b) of the Food and Drug Omnibus Reform Act of 2022). Under 21 CFR 601.70 you should include a status summary of each requirement in your annual report to this BLA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last report, and, for clinical trials, number of patients entered into each trial.

Submit final reports to this BLA as a supplemental application. For administrative purposes, all submissions relating to this postmarketing requirement must be clearly designated "**Subpart E Postmarketing Requirement(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.

We are waiving the pediatric study requirement for this application because this product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients and is not likely to be used in a substantial number of pediatric patients. There is no scientific rationale for pediatric patients to be enrolled in new monotherapy clinical studies of additional anti-PD-(L)1 antibodies with the same mechanism of action of agents already studied. The waiver was requested in all pediatric patients based on the rationale that there is no convincing evidence that retifanlimab-dlwr (an anti-PD-1 antibody) provides superior pharmacologic, toxicity, or activity profile to the same in class products already studied.

PROMOTIONAL MATERIALS

Under 21 CFR 601.45, you are required to submit, during the application pre-approval review period, all promotional materials, including promotional labeling and advertisements, that you intend to use in the first 120 days following marketing approval (i.e., your launch campaign). If you have not already met this requirement, you must immediately contact the Office of Prescription Drug Promotion (OPDP) at (301) 796-1200. Please ask to speak to a regulatory project manager or the appropriate reviewer to discuss this issue.

As further required by 21 CFR 601.45, submit all promotional materials that you intend to use after the 120 days following marketing approval (i.e., your post-launch materials) at least 30 days before the intended time of initial dissemination of labeling or initial publication of the advertisement. We ask that each submission include a detailed cover letter together with three copies each of the promotional materials, annotated references, and approved Prescribing Information, Medication Guide, and Patient Package Insert (as applicable).

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*.[3]

REPORTING REQUIREMENTS

You must submit adverse experience reports under the adverse experience reporting requirements for licensed biological products (21 CFR 600.80).

Prominently identify all adverse experience reports as described in 21 CFR 600.80.

You must submit distribution reports under the distribution reporting requirements for licensed biological products (21 CFR 600.81).

You must submit reports of biological product deviations under 21 CFR 600.14. You should promptly identify and investigate all manufacturing deviations, including those associated with processing, testing, packing, labeling, storage, holding and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA 3486 to:

[3] https://www.fda.gov/media/128163/download

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
5901-B Ammendale Road
Beltsville, MD 20705-1266

Biological product deviations, sent by courier or overnight mail, should be addressed to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
10903 New Hampshire Avenue, Bldg. 51, Room 4207
Silver Spring, MD 20903

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biologics qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, call Autumn Zack-Taylor, M.S., Senior Regulatory Health Project Manager, at (240) 402-5913.

Sincerely,

{See appended electronic signature page}

Paul Kluetz, M.D.
Supervisory Associate Director (Acting)
Office of Oncologic Diseases
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Medication Guide
- Carton and Container Labeling

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/

PAUL G KLUETZ
03/24/2023 09:42:11 AM