CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

761358Orig1s000

Trade Name:	Zymfentra injection, for subcutaneous use
Generic or Proper Name:	Infliximab-dyyb
Sponsor:	Celltrion, Inc.
Approval Date:	October 20, 2023
Indication:	Zymfentra is indicated in adults for maintenance treatment of: • moderately to severely active ulcerative colitis following treatment with an infliximab product administered intravenously. • moderately to severely active Crohn's disease following treatment with an infliximab product administered intravenously.

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APPLICATION NUMBER:

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APPROVAL LETTER

BLA 761358

BLA APPROVAL

CELLTRION, Inc.
c/o Parexel International, US Agent
Attention: Laya Keyvan, MS, MBA
Senior Regulatory Affairs Consultant, Parexel International
2520 Meridian Parkway, Suite 200
Durham, NC 27713

Dear Laya Keyvan:

Please refer to your biologics license application (BLA) dated and received December 22, 2022, and your amendments, submitted under section 351(a) the Public Health Service Act for Zymfentra (infliximab-dyyb) injection, for subcutaneous use.

LICENSING

We have approved your BLA for Zymfentra (infliximab-dyyb) injection effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, Zymfentra under your existing Department of Health and Human Services U.S. License No. 1996. Zymfentra is indicated for use in adults for the maintenance treatment of:

- moderately to severely active ulcerative colitis following treatment with an infliximab product administered intravenously.
- moderately to severely active Crohn's disease following treatment with an infliximab product administered intravenously.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture infliximab-dyyb drug substance at CELLTRION, Inc., Plant (b) (4) in Incheon, Republic of Korea. The final formulated drug product will be manufactured, filled, labeled, and packaged at VETTER Pharma-Fertigung GmbH & Co. KG, Ravensburg, Germany and CELLTRION Pharm, Inc. in Cheongju-si, Republic of Korea. You may label your product with the proprietary name, Zymfentra, and market it in 120 mg/mL solution in a single-dose prefilled syringe, a single-dose prefilled syringe with needle shield or a single-dose prefilled pen.

DATING PERIOD

The dating period for Zymfentra shall be 39 months from the date of manufacture when stored at 2°C to 8°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 in your license application for the purpose of extending the expiration dating period of your drug substance under 21 CFR 601.12.

FDA LOT RELEASE

You are not currently required to submit samples of future lots of Zymfentra and each kit component 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 Zymfentra, or in the manufacturing facilities, will require the submission of information to your BLA for our review and written approval, consistent with 21 CFR 601.12.

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 with minor editorial revisions listed below and reflected in the enclosed labeling.

Prescribing Information

- Revised “pre-filled” to “prefilled” throughout the document to align with the other content of labeling.
- Added “prefilled” to “pen in Section 2.3 in the second bullet.

Medication Guide

- Revised “pre-filled” to “prefilled” to align with the other content of labeling.

Instructions for Use – Single-Dose Prefilled Pen

- Corrected the spelling of ZYMFENTRA in the first paragraph.
- Revised ZYMEFTRA to all capital letters in Step 2.

Instructions for Use – Single-Dose Prefilled Syringe

- Revised format of ZYMEFTRA to all capital letters in Step 2.

Instructions for Use –Single-Dose Prefilled Syringe with Needle Shield

- Corrected spelling and format of “Single-Dose Prefilled Syringe” in the heading on the first page.
- Revised format of ZYMEFTRA to all capital letters in Step 2.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

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.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information, Instructions for Use, and Medication Guide). 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 (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 carton and container labeling submitted on October 18, 2023, 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 *SPL Standard for Content of Labeling Technical Qs & As.* For administrative purposes, designate this submission “**Final Printed Carton and Container Labeling for approved BLA 761358**.” Approval of this submission by FDA is not required before the labeling is used.

ADVISORY COMMITTEE

Your application for Zymfentra was not referred to an FDA advisory committee because this biologic is not the first in its class, evaluation of the safety data when used in the treatment of ulcerative colitis and Crohn’s disease did not raise significant safety or efficacy issues in the intended population, and outside expertise was not necessary; there were no controversial issues that would benefit from advisory committee discussion.

[1] See 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 at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

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 ages birth to less than 6 years because necessary studies are impossible or highly impracticable. This is because the incidence of ulcerative colitis and Crohn's disease in children ages birth to 2 years of age is very low. Additionally, as Zymfentra is intended to be used only after induction dosing with intravenous infliximab but there are no approved infliximab products for intravenous induction dosing in the younger age group (2 to < 6 years), designing and conducting trials that evaluate maintenance therapy with Zymfentra in this age group is deemed impossible or highly impracticable.

We are deferring submission of your pediatric study for ages 6 to < 18 years for this application because this product is ready for approval for use in adults and the pediatric study has not been completed.

Your deferred pediatric studies required under section 505B(a) of the Federal Food, Drug, and Cosmetic Act is required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 601.28 and section 505B(a)(4)(C) of the Federal Food, Drug, and Cosmetic Act. These required studies are listed below.

4492-1 Conduct a one-year, randomized trial to evaluate the safety, efficacy, and pharmacokinetics of Zymfentra (infliximab-dyyb) as maintenance treatment in pediatric patients 6 to < 18 years of age with moderately to severely active Crohn's disease.

Final Protocol Submission: 01/2024
Study Completion: 06/2027
Final Report Submission: 12/2027

4492-2 Conduct a one-year, randomized trial to evaluate the safety, efficacy, and pharmacokinetics of Zymfentra (infliximab-dyyb) as maintenance treatment in pediatric patients 6 to < 18 years of age with moderately to severely active ulcerative colitis.

Final Protocol Submission: 01/2024
Study Completion: 06/2027
Final Report Submission: 12/2027

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]

Submit the protocols to both IND 140478 and 141215, with a cross-reference letter to this BLA.

Reports of these required pediatric postmarketing studies must be submitted as a biologics license application (BLA) or as a supplement to your approved BLA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS" in large font, bolded type at the beginning of the cover letter of the submission.

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

4492-3 To perform additional method transfer exercises for IEC-HPLC, SEC-HPLC, CE-SDS (non-reduced/reduced), TNFα neutralizing assay, and TNFα binding assay on stability samples in both sending and receiving laboratories.

The timetable you submitted on August 3, 2023, states that you will conduct this study according to the following schedule:

Final Report Submission: 01/2024

4492-4 To develop and implement a comprehensive and robust control strategy to control for complement dependent cytotoxicity activity of CT-P13 SC drug substance at release. Submit the proposed specification as a Prior Approval Supplement in accordance with 21 CFR 601.12(b).

The timetable you submitted on September 19, 2023, states that you will conduct this study according to the following schedule:

Final Report Submission: 12/2024

Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this BLA. In addition, under 21 CFR 601.70 you should include a status summary of each commitment in your annual progress report of

[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.

postmarketing studies to this BLA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients/subjects entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

Requested Enhanced Pharmacovigilance

1. We request that for Zymfentra you submit all serious and non-serious domestic and foreign cases of hepatotoxicity as 15-day "Alert reports" (described under 21 CFR 600.80(c)(1)) through the 3rd year following initial U.S. approval date.

2. We request that you provide a separate narrative summary and analysis of hepatotoxicity, apart from your required analysis of 15-day "Alert reports," as part of your required periodic safety reports [e.g., periodic adverse drug experience report (PADER) required under 21 CFR 600.80(c)(2)], quarterly during the first 3 years post-approval. Your analysis should include interval and cumulative data relative to the date of approval of Zymfentra. Your analysis should provide an assessment of causality, with documentation of indication, temporal association, duration of therapy, exposure to other infliximab products, associated signs and symptoms, hepatic enzymes and liver function tests, confounders, underlying risk factors, treatment given for the event, outcome, and dechallenge/rechallenge.

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]

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at FDA.gov.[5] Information and Instructions for completing the form can be found at FDA.gov.[6]

[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

REPORTING REQUIREMENTS

You must submit adverse experience reports under the adverse experience reporting requirements at 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 at 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:

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

Your product is a combination product per 21 CFR Part 3. Therefore, you must also comply with postmarketing safety reporting requirements for an approved combination product (21 CFR 4, Subpart B). Additional information on combination product postmarketing safety reporting is available at: https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products,

POST APPROVAL FEEDBACK MEETING

New biological products 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, contact Andrew Chi, PharmD, Regulatory Project Manager, at (301) 796-8597 or email at andrew.chi@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Juli Tomaino, MD, MS
Deputy Director
Division of Gastroenterology
Office of Immunology and Inflammation
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Medication Guide
  - Instructions for Use

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/

JULI A TOMAINO
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