

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

761219Orig1s000

Trade Name: Yuflyma injection, 40 mg/0.4ml

Generic or Proper Name: Adalimumab-aaty

Sponsor: Celltrion, Inc

Approval Date: May 23, 2023

Indication: Yuflyma (adalimumab-aaty) is indicated for:

1. Rheumatoid arthritis (RA)
2. Juvenile idiopathic arthritis (JIA) (2 years of age and older)
3. Psoriatic arthritis (PsA)
4. Ankylosing spondylitis (AS)
5. Moderately to severely active Crohn's disease (CD) in adults and pediatric patients 6 years of age and older
6. Moderately to severely active ulcerative Colitis (UC) in adult patients
7. Moderate to severe Plaque Psoriasis (PsO) in adult patients who are candidates for systemic therapy or phototherapy, and when other systemic therapies are medically less appropriate.
8. Moderate to severe Hidradenitis suppurativa (HS) in adult patients.

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APPROVAL LETTER

BLA 761219

BLA APPROVAL

Celltrion, Inc.
c/o Parexel International
2520 Meridian Parkway Suite 200
Durham, NC 27713

Attention: Ryan Zettle, PharmD, MBA
Director, Regulatory Affairs

Dear Dr. Zettle:

Please refer to your biologics license application (BLA) dated and received on November 24, 2020, and your amendments, submitted under section 351(k) of the Public Health Service Act for Yuflyma (adalimumab-aaty) injection, 40 mg/0.4 mL.

We acknowledge receipt of your resubmissions dated May 27 and November 30, 2022, which constituted complete responses to our November 24, 2021, and November 23, 2022, action letters, respectively.

LICENSING

We have approved your BLA for Yuflyma (adalimumab-aaty) effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, Yuflyma under your existing Department of Health and Human Services U.S. License No. 1996.

Yuflyma (adalimumab-aaty) is indicated for:

1. Rheumatoid arthritis (RA)
2. Juvenile idiopathic arthritis (JIA) (2 years of age and older)
3. Psoriatic arthritis (PsA)
4. Ankylosing spondylitis (AS)
5. Moderately to severely active Crohn's disease (CD) in adults and pediatric patients 6 years of age and older
6. Moderately to severely active ulcerative Colitis (UC) in adult patients
7. Moderate to severe Plaque Psoriasis (PsO) in adult patients who are candidates for systemic therapy or phototherapy, and when other systemic therapies are medically less appropriate.
8. Moderate to severe Hidradenitis suppurativa (HS) in adult patients.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture adalimumab-aaty drug substance at Celltrion, Inc., (b) (4) in Yeonsu-gu, Incheon, Republic of Korea. The final formulated drug product will be manufactured, filled, labeled, and packaged at (b) (4). You may label your product with the proprietary name, Yuflyma, and market it in 40 mg/0.4 mL single-dose prefilled syringe (PFS), PFS assembled with a needle safety guard (PFS-S), and PFS assembled with an autoinjector (AI).

DATING PERIOD

The dating period for Yuflyma shall be 30 months from the date of manufacture when stored at 5 ± 3 °C, protected from light. 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.

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 Yuflyma 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 Yuflyma, 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.

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 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 *SPL Standard for Content of Labeling Technical Qs & As*. For administrative purposes, designate this submission “**Final Printed Carton and Container Labeling for approved BLA 761219**” Approval of this submission by FDA is not required before the labeling is used.

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.

The following comments pertain to Rheumatoid Arthritis indication:

We are waiving the pediatric studies requirement for the Polyarticular Juvenile Idiopathic Arthritis (pJIA) in pediatric patients 0 to less than 2 years of age

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>.

because necessary studies are impossible or highly impracticable given that the disease is rarely diagnosed in this population.

We are deferring the required pediatric assessment for patients weighing 10 kg to less than 40 kg. See Deferred Pediatric Assessments below.

The following comment pertains to Psoriatic Arthritis indication:

We are waiving the pediatric study requirements for pediatric patients 0 to 17 years of age for this indication because necessary studies are impossible or highly impracticable.

The following comment pertains to Ankylosing Spondylitis indication:

We are waiving the pediatric study requirements for pediatric patients 0 to 17 years of age for this indication because necessary studies are impossible or highly impracticable.

The following comments pertain to Crohn's Disease indication:

We are waiving the pediatric study requirements for pediatric patients with Crohn's disease less than 6 years of age because necessary studies for this product (i.e., dedicated studies limited to pediatric patients 2 years to less than 6 years of age) are impossible or highly impracticable. Additionally, this condition is rare in patients less than 2 years of age.

The following comments pertain to Ulcerative Colitis indication:

We are waiving the pediatric study requirements for pediatric patients with ulcerative colitis less than 5 years of age because necessary studies for this product (i.e., dedicated studies limited to pediatric patients 2 years to less than 5 years of age) are impossible or highly impracticable. Additionally, this condition is rare in patients less than 2 years of age.

We are deferring the required pediatric assessment for pediatric patients 5 to 17 years of age. See Deferred Pediatric Assessments below.

The following comment pertains to Plaque Psoriasis indication:

We are waiving the pediatric study requirements for pediatric patients 0 to 17 years of age for this indication because the 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.

The following comment pertains to hidradenitis suppurativa indication:

We are waiving the pediatric study requirements for pediatric patients 0 to 12 years of age for this indication because necessary studies for this product (i.e., dedicated studies limited to pediatric patients 0 to less than 12 years of age) are impossible or highly impracticable. .

We are deferring the required pediatric assessment for pediatric patients 12 to 17 years of age. See Deferred Pediatric Assessments below.

Deferred Pediatric Assessments

Your deferred pediatric studies required under section 505B(a) of the Federal Food, Drug, and Cosmetic Act are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 601.28 and section 505B(a)(3)(C) of the Federal Food, Drug, and Cosmetic Act. These required studies are listed below.

- 4433-1 Develop presentation(s) that can be used to accurately administer Yuflyma (adalimumab-aaty) to pediatric patients weighing 10 kg to less than 40 kg.

The timetable you submitted on May 17, 2023, states that you will conduct this study according to the following schedule:

Final Report Submission Date: 06/2025

- 4433-2 Assessment of Yuflyma (adalimumab-aaty) for the treatment of pediatric hidradenitis suppurativa (HS) in patients 12 years to 17 years of age.

The timetable you submitted on May 17, 2023, states that you will conduct this study according to the following schedule:

Final Report Submission Date: 10/2025

- 4433-3 Assessment of Yuflyma (adalimumab-aaty) for the treatment of pediatric ulcerative colitis (UC) in patients 5 years to 17 years of age.

The timetable you submitted on May 17, 2023, states that you will conduct this study according to the following schedule:

Final Report Submission Date: 02/2028

Submit the protocols to your IND 135944, with a cross-reference letter to this BLA.

Reports of these required pediatric postmarketing studies must be submitted as a 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.

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*.³

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.⁴ Information and Instructions for completing the form can be found at FDA.gov.⁵

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:

³ For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/media/128163/download>.

⁴ <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>

⁵ <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>

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 Part 3 combination product (21 CFR 3.2(e)); 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 FDA.gov.

If you have any questions, call Sadaf Nabavian, Senior Regulatory Project Manager, at 301-796-2777.

Sincerely,

{See appended electronic signature page}

Ozlem Belen, MD, MPH
Director (Acting)
Division of Rheumatology and Transplant Medicine
Office of Immunology and Inflammation
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE(S):

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

OZLEM A BELEN
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