CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

761420Orig1s000

Trade Name:	AVTOZMA
Generic or Proper Name:	Tocilizumab-anoh
Sponsor:	Celltrion, Inc.
Approval Date:	January 24, 2025
Indication:	AVTOZMA is indicated for the treatment of: ● Rheumatoid Arthritis (RA): Adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more Disease- Modifying Anti-Rheumatic Drugs (DMARDs). ● Giant Cell Arteritis (GCA): giant cell arteritis in adult patients. ● Polyarticular Juvenile Idiopathic Arthritis (PJIA): active polyarticular juvenile idiopathic arthritis in patients 2 years of age and older. ● Systemic Juvenile Idiopathic Arthritis (SJIA): active systemic juvenile idiopathic arthritis in patients 2 years of age and older. ● Coronavirus Disease 2019 (COVID-19): Hospitalized adult patients with coronavirus disease 2019 (COVID-19) who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).

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APPLICATION NUMBER:

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APPROVAL LETTER

BLA 761420

BLA APPROVAL

Celltrion, Inc.
c/o Parexel International
Attention: Ally Danta
Senior Associate
2520 Meridian Parkway, Suite 100
Durham, NC 27713

Dear Ally Danta:

Please refer to your biologics license application (BLA) dated and received January 26, 2024, and your amendments, submitted under section 351(k) of the Public Health Service Act for Avtozma (tocilizumab-anoh) injection, 80 mg/4 mL, 200 mg/10 mL, and 400 mg/20 mL for intravenous use, and 162 mg/0.9 mL for subcutaneous use.

This BLA seeks licensure of Avtozma (tocilizumab-anoh) injection as biosimilar to or interchangeable with US-licensed Actemra (tocilizumab) as follows:

For intravenous (IV) use:

- 80 mg/4 mL (20 mg/mL) injection in a single-dose vial as interchangeable with US-Actemra 80 mg/4 mL (20 mg/mL) injection in a single-dose vial
- 200 mg/10 mL (20 mg/mL) injection in a single-dose vial as interchangeable with US-Actemra 200 mg/10 mL (20 mg/mL) injection in a single-dose vial
- 400 mg/20 mL (20 mg/mL) injection in single-dose vial as interchangeable with US-Actemra 400 mg/20 mL (20 mg/mL) injection in a single-dose vial

For subcutaneous (SC) use:

- 162 mg/0.9 mL (180 mg/mL) injection in a single-dose pre-filled syringe as interchangeable with US-Actemra 162 mg/0.9 mL (180 mg/mL) injection in a single-dose pre-filled syringe
- 162 mg/0.9 mL (180 mg/mL) injection in a single-dose pre-filled autoinjector as biosimilar to US-Actemra 162 mg/0.9 mL (180 mg/mL) injection in a single-dose pre-filled autoinjector

BLA 761420 provides for the use of Avtozma (tocilizumab-anoh) for treatment of:

1. Rheumatoid Arthritis (RA): Adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more Disease-Modifying Anti-Rheumatic Drugs (DMARDs).

2. Giant Cell Arteritis (GCA): giant cell arteritis in adult patients.

3. Polyarticular Juvenile Idiopathic Arthritis (PJIA): active polyarticular juvenile idiopathic arthritis in patients 2 years of age and older.

4. Systemic Juvenile Idiopathic Arthritis (SJIA): active systemic juvenile idiopathic arthritis in patients 2 years of age and older.

5. Coronavirus Disease 2019 (COVID-19): Hospitalized adult patients with coronavirus disease 2019 (COVID-19) who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).

This BLA also provides for unbranded biological product labeling.

LICENSING

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

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture tocilizumab-anoh drug substance at (b) (4) The final formulated drug product in single-dose vials will be manufactured and filled at (b) (4) The final labeling and secondary packaging will be performed at Celltrion Pharm, Inc., Cheongju, Republic of Korea, Celltrion Inc., Incheon, Republic of Korea, and (b) (4) The final formulated drug products in single-dose prefilled syringe and single-dose autoinjector will be manufactured, filled, labeled, and packaged at Celltrion Pharm, Inc., Cheongju, Republic of Korea. You may label your product with the proprietary name, Avtozma, and market it in 80 mg/4 mL, 200 mg/10 mL, and 400 mg/20 mL single-dose vials, and 162 mg/0.9 mL in a single-dose prefilled syringe and single-dose prefilled autoinjector.

DATING PERIOD

The dating period for Avtozma single-dose vial shall be 24 months from the date of manufacture when stored at 5 ± 3°C. The dating period for Avtozma pre-filled syringe and autoinjector shall be 36 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.

We have approved the stability protocols in your license application for the purpose of extending the expiration dating 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 Avtozma 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 Avtozma, 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.

FIRST INTERCHANGEABLE EXCLUSIVITY

Section 351(k)(6) of the PHS Act provides:

> The Secretary shall not make approval as an interchangeable biological product effective with respect to an application submitted under this subsection that relies on the same reference product for which a prior biological product has received a determination of interchangeability for any condition of use, until the earlier of—
>
> (A) 1 year after the first commercial marketing of the first interchangeable biosimilar biological product to be approved as interchangeable for that reference product;
>
> (B) 18 months after—
>
> (i) a final court decision on all patents in suit in an action instituted under subsection (l)(6) against the applicant that submitted the application for the first approved interchangeable biosimilar biological product; or
>
> (ii) the dismissal with or without prejudice of an action instituted under

subsection (l)(6) against the applicant that submitted the application for the first approved interchangeable biosimilar biological product; or

(C)

(i) 42 months after approval of the first interchangeable biosimilar biological product if the applicant that submitted such application has been sued under subsection (l)(6) and such litigation is still ongoing within such 42-month period; or

(ii) 18 months after approval of the first interchangeable biosimilar biological product if the applicant that submitted such application has not been sued under subsection (l)(6).

For purposes of this paragraph, the term "final court decision" means a final decision of a court from which no appeal (other than a petition to the United States Supreme Court for a writ of certiorari) has been or can be taken and the term "first interchangeable biosimilar biological product" means any interchangeable biosimilar biological product that is approved on the first day on which such a product is approved as interchangeable with the reference product.

Avtozma (tocilizumab-anoh) injection, 80 mg/4 mL, 200 mg/10 mL, and 400 mg/20 mL for intravenous use, and 162 mg/0.9 mL for subcutaneous use are the first products relying on their respective reference products to receive a determination of interchangeability for any condition of use. Therefore, with this approval, these products qualify as first interchangeable biosimilar biological products for purposes of section 351(k)(6) of the PHS Act. The expiration date of any first interchangeable exclusivity has yet to be determined.

For each interchangeable biosimilar biological product approved by this letter, submit a general correspondence to this 351(k) BLA informing the Agency of the date of the first commercial marketing within 30 days of such date. Submit a duplicate copy of the correspondence via email to PurpleBook@fda.hhs.gov.

If applicable, please submit a general correspondence to this 351(k) BLA informing the Agency of the date of any final court decision (as defined in section 351(k)(6) of the PHS Act) on all patents in suit in any action implicating this BLA instituted under section 351(l)(6) of the PHS Act, or the date of dismissal with or without prejudice of any action implicating this BLA instituted under section 351(l)(6), within 30 days of such date or within 30 days of this approval if such date occurred prior to approval. If any action implicating this BLA instituted under section 351(l)(6) is still ongoing at the time of this approval, submit a general correspondence informing the Agency of this within 30 days of this approval. Submit a duplicate copy of the correspondence(s) via email to PurpleBook@fda.hhs.gov.

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 761420**." 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.

[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.

Giant Cell Arteritis, Polyarticular Juvenile Idiopathic Arthritis, and Systemic Juvenile Idiopathic Arthritis
At this time, we have determined that no pediatric assessments will be required under PREA for your BLA.

COVID-19
At this time, we have determined that, with respect to this indication in pediatric patients 0 to < 1 year of age, no pediatric assessments will be required under PREA for your BLA. We are deferring the required pediatric assessment for pediatric patients 1 to < 18 years of age. See Deferred Pediatric Assessments below.

Deferred Pediatric Assessments

Your deferred pediatric assessment required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act is a required postmarketing assessment. The status of this postmarketing assessment must be reported annually according to 21 CFR 601.28 and section 505B(a)(4)(B) of the Federal Food, Drug, and Cosmetic Act. This required assessment is listed below.

PMR 4790-1: Assessment of Avtozma (tocilizumab-anoh) for the treatment of COVID-19 in pediatric patients 1 year to 18 years of age

The timetable you submitted on January 23, 2025, states that you will conduct this assessment according to the following schedule:

Final Report Submission: 06/2026

Reports of this required pediatric postmarketing assessment 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 this assessment. 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]

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

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:

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.

[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

If you have any questions, contact Susie Choi, Regulatory Project Manager, at (240) 402-2925 or susie.choi@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Raj Nair, MD
Director
Division of Rheumatology and Transplant Medicine
Office of Immunology and Inflammation
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURES:
Branded Product Labeling

- Content of Labeling
  - Prescribing Information
  - Medication Guide
  - Instructions for Use
- Carton and Container Labeling

Unbranded Biological Product Labeling

- 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/

RAJ NAIR
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