CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761354Orig1s000

OTHER REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	August 30, 2023
To:	Susie Choi, PharmD Senior Regulatory Project Manager **Division of Rheumatology and Transplant Medicine (DRTM)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Kelly Jackson, PharmD Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Quynh-Nhu Capasso, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	TOFIDENCE (tocilizumab-bavi)
Dosage Form and Route:	injection, for intravenous use
Application Type/Number:	BLA 761354
Applicant:	Biogen Inc.

1 INTRODUCTION

On September 29, 2022, Biogen Inc. submitted for the Agency's review a 351(k) Biologics License Application (BLA) for TOFIDENCE (tocilizumab-bavi), a proposed biosimilar product to US-licensed ACTEMRA (tocilizumab).

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Division of Rheumatology and Transplant Medicine (DRTM) on January 10, 2023, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for TOFIDENCE (tocilizumab-bavi) injection, for intravenous use.

2 MATERIAL REVIEWED

- Draft TOFIDENCE (tocilizumab-bavi) MG received on September 29, 2022, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on August 1, 2023.
- Draft TOFIDENCE (tocilizumab-bavi) Prescribing Information (PI) received on September 29, 2022, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on August 1, 2023.
- Approved ACTEMRA (tocilizumab) comparator labeling dated December 21, 2022.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the MG document using the Arial font, size 10.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the PI
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

- ensured that the MG is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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QUYNH-NHU D CAPASSO
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MARCIA B WILLIAMS
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LASHAWN M GRIFFITHS
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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: August 14, 2023

To: Susie Choi, Regulatory Project Manager
Division of Regulatory Operations for Immunology and Inflammation

From: Quynh-Nhu Capasso, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Adewale Adeleye, Team Leader, OPDP
Kyle Snyder, Regulatory Review Officer, OPDP

Subject: OPDP Labeling Comments for TOFIDENCE® (tocilizumab-bavi) injection, for intravenous use

BLA: 761354

Background:
In response to DRTM's consult request dated January 10, 2023, OPDP has reviewed the proposed Prescribing Information (PI), Medication Guide (MG), and carton and container labeling for the original BLA submission for TOFIDENCE® (tocilizumab-bavi) injection, for intravenous use.

PI/MG:
OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on August 1, 2023, and our comments are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed for the proposed MG, and comments will be sent under separate cover.

Carton and Container Labeling:
OPDP's review of the proposed carton and container labeling is based on the draft labeling emailed to OPDP on August 1, 2023, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Quynh-Nhu Capasso at quynh-nhu.capasso@fda.hhs.gov.

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Clinical Inspection Summary

Date	August 4, 2023
From	Tina Chang, M.D., Medical Officer Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Stefanie Freeman, M.D., Clinical Reviewer Raj Nair, M.D., Clinical Team Leader Susie Choi, PharmD., Regulatory Project Manager Division of Rheumatology and Transplant Medicine (DRTM)
BLA #	761354
Applicant	Biogen Inc.
Drug	BAT1806 (tocilizumab-bavi)
NME (Yes/No)	No
Proposed Indication(s)	Treatment of rheumatoid arthritis (RA), systemic juvenile idiopathic arthritis (sJIA), juvenile idiopathic polyarthritis (pJIA)
Consultation Request Date	December 6, 2022
Summary Goal Date	August 23, 2023
Action Goal Date	September 29, 2023
BsUFA Date	September 29, 2023

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Drs. Agnieszka Zielinska and Slawomir Jeka were inspected in support of BLA 761354 covering one clinical study, BAT-1806-002-CR. Based on the inspection results, the study appears to have been conducted adequately, and the data generated by these clinical investigator (CI) sites appear acceptable in support of this BLA.

II. BACKGROUND

BLA 761354 was submitted in support of the use of BAT1806 (tocilizumab-bavi) for the treatment of rheumatoid arthritis (RA), systemic juvenile idiopathic arthritis (sJIA), and juvenile idiopathic polyarthritis (pJIA). According to the sponsor, BAT1806 is a recombinant human IgG2 monoclonal antibody to human IL6R and a proposed biosimilar to US-licensed Actemra (tocilizumab) and European-licensed RoActemra (tocilizumab). The sponsor is seeking some of the indications of US-licensed Actemra and will not include cytokine release syndrome and giant cell arteritis. The sponsor submitted one Phase III study, BAT-1806-CR-002-CR, to support this BLA. The following briefly describes the protocol:

> **BAT-1806-CR-002-CR,** "A Randomized, Double-Blind, Parallel-Group, Active-Control Study to Compare the Efficacy and Safety of BAT1806 to RoActemra in Rheumatoid Arthritis Patients With Inadequate Response to Methotrexate."

Protocol BAT-1806-CR-002-CR was a Phase III, multicenter, randomized, double-blind, active-controlled safety and efficacy study. The primary objective was to demonstrate equivalent efficacy of BAT1806 (tocilizumab-bavi) and RoActemra (tocilizumab) in subjects with rheumatoid arthritis (RA) that is inadequately controlled by methotrexate (MTX).

Sites: The study was conducted at 54 sites (28 in China, 7 in Ukraine, 10 in Poland, 4 in Georgia, and 5 in Bulgaria).

Subjects: A total of 621 subjects were randomized (i.e., 155 subjects received RoActemra/RoActemra, 154 subjects received RoActemra/BAT1806, and 312 received BAT1806/BAT1806) and 587 subjects completed Treatment Period 1 (i.e., 288/309 who received RoActemra and 299/312 who received BAT1806 completed TP1).

Study initiation and completion dates: 19 December 2018 (first patient, first visit); 5 January 2021 (last patient, last visit)

Database lock date: 22 April 2021

The study consisted of a ≤28-day screening period, a 24-week treatment period (TP1), a 24-week secondary treatment period (TP2), and a 4-week safety follow-up period. Day 0 was the start of TP1 (Weeks 0-24), and subjects were randomized to receive RoActemra or BAT1806 until Week 20. During TP2 (Weeks 24-44), subjects that were originally randomized to BAT1806 were to continue BAT1806 while subjects originally randomized to RoActemra were randomized 1:1 to transition to BAT1806 or to continue RoActemra.

In both TP1 and TP2, study treatment was administered at the study site every 4 weeks by 1-hour intravenous (IV) infusion at a dose of 8 mg/kg body weight. During TP1, subjects were administered a total of 6 doses of either BAT1806 or RoActemra. During TP2, subjects were administered another 6 doses of either BAT1806 or RoActemra. During the study, all subjects continued taking their regular methotrexate (MTX) therapy at a stable dose. The End-of-Study Visit was performed at Week 48 and a safety Follow-Up Visit at Week 52 or 8 weeks after the last dose of the study drug. The study duration was approximately 56 weeks.

Key inclusion criteria: Male or female subjects 18 years of age or older who fulfilled the American College of Rheumatology/European League Against Rheumatism 2010 revised classification criteria for rheumatoid arthritis (RA) diagnosis for at least 6 months before screening, based on the medical history record, presented with active RA per the prespecified criteria (≥6 out of 68 tender joints at screening and randomization AND ≥6 out of 66 swollen joints at screening and randomization AND serum C-reactive protein (CRP) > upper limit of normal value or erythrocyte sedimentation rate (ESR) ≥ 28 mm/hour at screening, received MTX therapy for ≥12 weeks before randomization, and with at least the last 4 consecutive weeks before randomization on a stable dose ranging from 10 to 25 mg/weeks. Please see protocol for full details pertaining to eligibility criteria.

Primary Efficacy Endpoint: Percentage of participants with an American College of Rheumatology 20% (ACR20) Response at Week 24.

ACR20 response is defined by at least a 20% improvement in the following components:
1) Tender joint count
2) Swollen joint count
3) Along with 20% improvement in at least 3 of the following 5 parameters:
   a) Subject's assessment of pain Visual Analogue Scale (VAS), ranging from 0 mm or "no pain" to 100 mm or "worst possible pain".
   b) Subject's Global Assessment of Disease Activity VAS, ranging from 0 mm or "very well" to 100 mm or "very poorly".
   c) Physician's Global Assessment of Disease Activity VAS, ranging from 0 mm or "very low" to 100 mm or "very high".
   d) Health Assessment Questionnaire- Disability Index (HAQ-DI) used to indicate the subject's functional ability and consists of 8 categories: 1) dressing and grooming, 2) arising, 3) eating, 4) walking, 5) hygiene, 6) reaching, 7) gripping, and 8) common daily activities. There are 2 or 3 questions for each section. Scoring within each section is on a 4-point Likert scale from 0 (without any difficulty) to 3 (unable to do). The score given to each section was the worst (highest) score within the section (i.e., if one question was scored 1 and another 2, then the score or the section was 2). The sum of the 8 scores of the 8 sections was divided by 8 to obtain the HAQ-DI. If one section was not completed by a subject, then the summed score was divided by 7. The HAQ-DI total score was calculated if 6 or more sections were available.
   e) Acute phase reactant (CRP/ESR) level.

Rationale for Site Selection

Clinical sites for BIMO inspections were selected based on risks, enrollment, and prior inspections.

III. RESULTS (by site):

1. **Dr. Agnieszka Zielinska**
   Site #POL010
   Ul. Wronia 53 Lok. B 10
   Warsaw, Poland
   BsUFA Inspection Dates: March 27-31, 2023

For Protocol BAT-1806-CR-002-CR, Dr. Zielinska screened 32 subjects and randomized 26 subjects. Out of the 26 randomized subjects, 23 subjects completed the study. Per the applicant's data line listings, one subject withdrew consent. Subject (b) (6) (randomized to RoActemra) and Subject (b) (6) (randomized to BAT1806) withdrew due to an exacerbation of rheumatoid arthritis.

An audit of the study records was conducted for 26 randomized subjects. Records reviewed

included, but were not limited to, protocol versions, protocol adherence, protocol deviations, informed consent, eligibility, case report forms, study visits, case history files, investigational drug product accountability procedures, monitoring reports, ethics committee approvals, delegation records, financial disclosures, and adverse event reporting. Source records for verification of the primary efficacy endpoint, American College of Rheumatology 20% (ACR20) Response.

There was no evidence of underreporting of adverse events. The primary efficacy data (HAQ-DI, Subject's assessment of pain VAS, Subject's Global Assessment of Disease Activity) were entered by subjects into electronic tablets supplied by the sponsor. Providers also entered primary efficacy data for the joint assessments and Physicians' Global Assessment of Disease Activity into electronic tablets supplied by the sponsor. Source data at the site consisted of printed paper copies of the data from the electronic tablets and electronic data that was saved onto a flash drive. Source records documenting the components of the ACR20 response, including the CRP/ESR levels, at Baseline and at Week 24 were compared against sponsor data line listings. No discrepancies were identified.

2. **Dr. Slawomir Jeka**
   Site #POL006
   Dr. J. Biziel University Hospital No. 2
   Department Of Rheumatology, Ujejskiego
   75 Street 85-168
   Bydgoszcz, Poland
   BsUFA Inspection Dates: March 20-24, 2023

At this site for Protocol BAT-1806-CR-002-CR, Dr. Jeka screened 46 subjects and randomized 34 subjects. Out of 34 randomized subjects, 32 subjects completed the study. Per the applicant's data line listings, Subject (b) (6) (randomized to RoActemra) withdrew due to an anaphylactic reaction. Subject (b) (6) (randomized to BAT1806) died from cardio-respiratory insufficiency. The narratives for these two subjects were submitted in the application.

An audit of the study records was conducted for 34 randomized subjects. Records reviewed included, but were not limited to, protocol versions, protocol adherence, protocol deviations, informed consent, eligibility, case report forms, study visits, case history files, investigational drug product accountability procedures, monitoring reports, ethics committee approvals, delegation records, financial disclosures, adverse event reporting, and source records for verification of the primary efficacy endpoint, ACR20 Response.

There was no evidence of underreporting of adverse events. The primary efficacy data (HAQ-DI, Subject's assessment of pain VAS, Subject's Global Assessment of Disease Activity) were entered by subjects into electronic tablets supplied by the sponsor. Providers also entered primary efficacy data (joint assessments and Physicians' Global Assessment of Disease Activity) into electronic tablets supplied by the sponsor. Source data at the site consisted of printed paper copies of the data from the electronic tablets and electronic data that was saved onto a flash drive. Source records documenting the components of the ACR20 response, including the CRP/ESR levels, at Baseline and at Week 24 were compared against sponsor

data line listings. No discrepancies were identified.

{See appended electronic signature page}

Suyoung Tina Chang, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: *{See appended electronic signature page}*

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CC:

Central Doc. Rm.
Review Division /Division Director/
Review Division /Medical Team Leader/
Review Division /Project Manager/
Review Division/MO/
OSI/Office Director/
OSI/DCCE/ Division Director/
OSI/DCCE/Branch Chief/
OSI/DCCE/Team Leader/
OSI/DCCE/GCP Reviewer/
OSI/ GCP Program Analysts/
OSI/Database PM/

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/s/

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JENN W SELLERS
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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	July 24, 2023
Requesting Office or Division:	Division of Rheumatology and Transplant Medicine (DRTM)
Application Type and Number:	BLA 761354
Product Name, Dosage Form, and Strength:	Tofidence (tocilizumab-bavi) injection, 80 mg/4 mL, 200 mg/10 mL, and 400 mg/20 mL single-dose vials
Applicant/Sponsor Name:	Biogen MA Inc.
TTT ID #:	2022-2047-1
DMEPA 1 Safety Evaluator:	Sarah K. Vee, PharmD
DMEPA 1 Team Leader:	Idalia E. Rychlik, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on July 19, 2023 for Tofidence. The Division of Rheumatology and Transplant Medicine (DRTM) requested that we review the revised container labels and carton labeling for Tofidence (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

[a] Vee, S. Label and Labeling Review for Tofidence (BLA 761354). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 JUN 29. TTT ID No.: 2022-2047.

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/s/

SARAH K VEE
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IDALIA E RYCHLIK
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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	June 29, 2023
Requesting Office or Division:	Division of Rheumatology and Transplant Medicine (DRTM)
Application Type and Number:	BLA 761354
Product Name, Dosage Form, and Strength:	Tofidence[a] (tocilizumab-xxxx) [b] injection, 80 mg/4 mL, 200 mg/10 mL, and 400 mg/20 mL single-dose vials
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Biogen MA Inc.
FDA Received Date:	September 29, 2022
TTT ID #:	2022-2047
DMEPA 1 Safety Evaluator:	Sarah K. Vee, PharmD
DMEPA 1 Team Leader:	Idalia E. Rychlik, PharmD

[a] Tofidence was reviewed by DMEPA (PNR ID# 2022-1044724789) and deemed conditionally acceptable on 12/21/2022. Of note, Biogen also refers to Tofidence as (BIIB800) throughout their submission.

[b] The non-proprietary name suffix for this product has not yet been determined; therefore, the placeholder "tocilizumab-xxxx" is used throughout this review to refer to the nonproprietary name for this product.

1 REASON FOR REVIEW

As part of the approval process for Tofidence (tocilizumab-xxxx) injection, the Division of Rheumatology and Transplant Medicine (DRTM) requested that we review the proposed Tofidence prescribing information (PI), carton labeling, and container label for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B – N/A
ISMP Newsletters*	C – N/A
FDA Adverse Event Reporting System (FAERS)*	D – N/A
Other	E – N/A
Labels and Labeling	F

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 CONCLUSION & RECOMMENDATIONS

The proposed PI and container labels are acceptable from a medication error perspective. However, container label and carton labeling may be improved to promote the safe use of this product. We provide our proposed recommendations to minimize the risk for medication error in Section 3.1 for Biogen MA.

3.1 RECOMMENDATIONS FOR BIOGEN MA INC.

We recommend the following be implemented prior to approval of this BLA:

A. General Comments (Container Label and Carton Labeling)

1. We recommend revising the route of administration and dilution instructions from, “For Intravenous Infusion Only After Dilution” to “For Intravenous Infusion After Dilution” for added clarity.

B. Container Label

1. The discard statement “Discard unused portion” is not present next to the package type term “single-dose vial”. Inclusion of this discard statement helps minimize the risk of the entire contents of the vial being given as a single dose when a dose volume less than the entire contents is intended. We recommend

revising the statement “Single-Dose Vial” to read as “Single-Dose Vial. Discard Unused Portion”.

C. Carton Labeling

1. To ensure consistency with the Prescribing Information, revise the statement, “See prescribing information for dosage, dilution, and administration information” to read “Recommended Dosage: See prescribing information.”

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Tofidence received on September 29, 2022 from Biogen MA Inc., and the listed drug (LD).

Table 2. Relevant Product Information for Tofidence and the Listed Drug		
Product Name	Tofidence	Actemra[c]
Initial Approval Date	N/A	January 08, 2010
Nonproprietary Name	tocilizumab-xxxx	tocilizumab
Indication	for 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). Polyarticular Juvenile Idiopathic Arthritis (PJIA) • Patients 2 years of age and older with active polyarticular juvenile idiopathic arthritis. Systemic Juvenile Idiopathic Arthritis (SJIA) • Patients 2 years of age and older with active systemic juvenile idiopathic arthritis.	for 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) • Adult patients with giant cell arteritis. Systemic Sclerosis-Associated Interstitial Lung Disease (SSc-ILD) • Slowing the rate of decline in pulmonary function in adult patients with systemic sclerosis-associated interstitial lung disease (SSc-ILD) Polyarticular Juvenile Idiopathic Arthritis (PJIA) • Patients 2 years of age and older with active polyarticular juvenile idiopathic arthritis. Systemic Juvenile Idiopathic Arthritis (SJIA) • Patients 2 years of age and older with active systemic juvenile idiopathic arthritis.

[c] Actemra [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. 2023 FEB 28. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/125276s138lbl.pdf

<table>
<tr><td></td><td></td><td>Cytokine Release Syndrome (CRS)
Adults and pediatric patients 2 years of age and older with chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome.
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).</td></tr>
<tr><td>Route of Administration</td><td>Intravenous infusion</td><td>Intravenous infusion and subcutaneous injection</td></tr>
<tr><td>Dosage Form</td><td>injection</td><td>injection</td></tr>
<tr><td>Strength</td><td>80 mg/4 mL, 200 mg/10 mL, and 400 mg/20 mL single-dose vials</td><td><u>Intravenous Infusion</u>
Injection: 80 mg/4 mL (20 mg/mL), 200 mg/10 mL (20 mg/mL), 400 mg/20 mL (20 mg/mL)
<u>Subcutaneous Injection</u>
Injection: 162 mg/0.9 mL in a single-dose prefilled syringe or single-dose prefilled ACTPen® autoinjector</td></tr>
<tr><td>Dose and Frequency</td><td>Rheumatoid Arthritis
Recommended Adult Intravenous Dosage:
When used in combination with DMARDs or as monotherapy the recommended starting dose is 4 mg per kg every 4 weeks followed by an increase to 8 mg per kg every 4 weeks based on clinical response.
Polyarticular Juvenile Idiopathic Arthritis<table><tr><td colspan="2">Recommended Intravenous PJIA Dosage Every 4 Weeks</td></tr><tr><td>Patients less than 30 kg weight</td><td>10 mg per kg</td></tr></table></td><td>Rheumatoid Arthritis Recommended Adult Intravenous Dosage:
When used in combination with DMARDs or as monotherapy the recommended starting dose is 4 mg per kg every 4 weeks followed by an increase to 8 mg per kg every 4 weeks based on clinical response.
Recommended Adult Subcutaneous Dosage:<table><tr><td>Patients less than 100 kg weight</td><td>162 mg administered subcutaneously every other week, followed by an increase to every week based on clinical response</td></tr><tr><td>Patients at or above 100 kg weight</td><td>162 mg administered subcutaneously every week</td></tr></table>Giant Cell Arteritis Recommended Adult Intravenous Dosage:
The recommended dose is 6 mg per kg every 4 weeks in combination with</td></tr>
</table>

Patients at or above 30 kg weight	8 mg per kg

Systemic Juvenile Idiopathic Arthritis

Recommended Intravenous SJIA Dosage Every 2 Weeks	
Patients less than 30 kg weight	12 mg per kg
Patients at or above 30 kg weight	8 mg per kg

a tapering course of glucocorticoids. ACTEMRA can be used alone following discontinuation of glucocorticoids.

- Recommended Adult Subcutaneous Dosage: The recommended dose is 162 mg given once every week as a subcutaneous injection, in combination with a tapering course of glucocorticoids.

Systemic Sclerosis-Associated Interstitial Lung Disease (SSc-ILD)

- Recommended Adult Subcutaneous Dosage: The recommended dose of ACTEMRA for adult patients with SSc-ILD is 162 mg given once every week as a subcutaneous injection.

Polyarticular Juvenile Idiopathic Arthritis (2.5)

Recommended Intravenous PJIA Dosage Every 4 Weeks	
Patients less than 30 kg weight	10 mg per kg
Patients at or above 30 kg weight	8 mg per kg

Recommended Subcutaneous PJIA Dosage	
Patients less than 30 kg weight	162 mg once every three weeks
Patients at or above 30 kg weight	162 mg once every two weeks

Systemic Juvenile Idiopathic Arthritis (2.6)

Recommended Intravenous SJIA Dosage Every 2 Weeks		
Patients less than 30 kg weight	12 mg per kg	
Patients at or above 30 kg weight	8 mg per kg	

Recommended Subcutaneous SJIA Dosage	
Patients less than 30 kg weight	162 mg every two weeks
Patients at or above 30 kg weight	162 mg every week

Cytokine Release Syndrome (2.7)

Recommended Intravenous CRS Dosage	
Patients less than 30 kg weight	12 mg per kg
Patients at or above 30 kg weight	8 mg per kg
Alone or in combination with corticosteroids.	

		Coronavirus Disease 2019 • The recommended dosage of ACTEMRA for adult patients with COVID-19 is 8 mg per kg administered by a 60-minute intravenous infusion. Administration of Intravenous formulation
How Supplied	Single-dose vials of: 80 mg/4 mL 200 mg/10 mL 400 mg/20 mL	Single-dose vials of: 80 mg/4 mL 200 mg/10 mL 400 mg/20 mL Single-dose prefilled syringe delivers 162 mg/0.9 mL Single-dose ACTPen® autoinjector delivers 162 mg/0.9 mL
Storage	Do not use beyond expiration date on the container or package. PROPRIETARY NAME must be refrigerated at 36°F to 46°F (2ºC to 8ºC). Do not freeze. Protect the vials from light by storage in the original package until time of use.	Do not use beyond expiration date on the container, package, prefilled syringe, or autoinjector. ACTEMRA must be refrigerated at 36°F to 46°F (2ºC to 8ºC). Do not freeze. Protect the vials, syringes, and autoinjectors from light by storage in the original package until time of use, and keep syringes and autoinjectors dry. Once removed from the refrigerator, the prefilled syringe and autoinjector can be stored up to 2 weeks at or below 86°F (30°C). The prefilled syringe and autoinjector must always be kept in the carton.

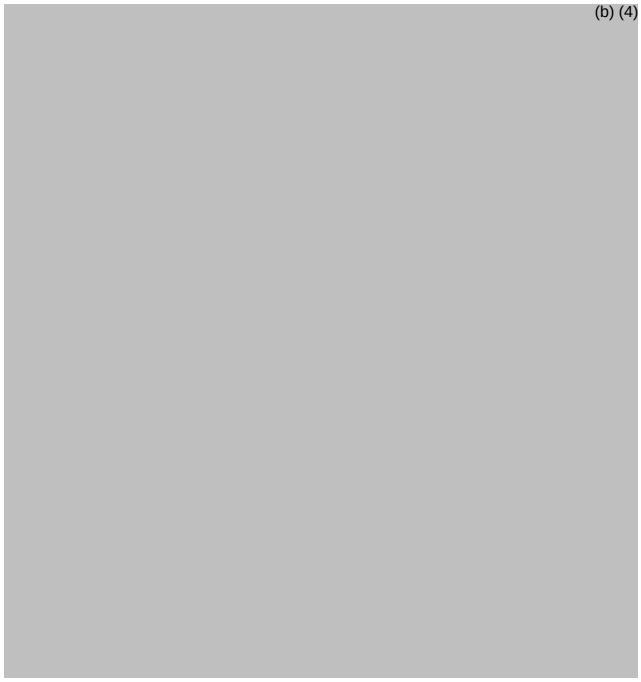
APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[d] along with postmarket medication error data, we reviewed the following Tofidence labels and labeling submitted by Biogen MA Inc..

- Container label received on September 29, 2022
- Carton labeling received on September 29, 2022
- Professional Sample container label received on September 29, 2022
- Professional Sample Carton Labeling received on September 29, 2022
- Prescribing Information (Image not shown) received on September 29, 2022, available from \\CDSESUB1\EVSPROD\bla761354\0001\m1\us\114-label\1141-draft-label\proposed1.docx

F.2 Label and Labeling Images



[d] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

4 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

SARAH K VEE
06/29/2023 11:43:44 AM

IDALIA E RYCHLIK
06/29/2023 11:52:33 AM

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 12/9/2022

TO: Division of Rheumatology and Transplant Medicine (DRTM)
Office of Immunology and Inflammation (OII)

FROM: Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct an on-site inspection**

RE: BLA 761354

The Office of Study Integrity and Surveillance (OSIS) determined that inspections are not needed at this time for the sites listed below. The rationale for this decision is noted below.

Rationale

The Office of Regulatory Affairs (ORA) conducted a Remote Regulatory Assessment (RRA) for the clinical site in August 2022, which falls within the surveillance interval. The RRA was conducted under the following submissions: ANDAs (b) (4).

The following items were discussed during the RRA close out meeting:

- (b) (4)
-

After review of the observations and the site's response, OSIS concluded that data from the reviewed studies were reliable (Final OSIS Review – October 2022).

OSIS conducted a Remote Regulatory Assessment (RRA) for the analytical site in (b) (4), which falls within the surveillance interval. The RRA was conducted under the following submission: BLA (b) (4)

The following objectionable conditions were observed:

- (b) (4)
-

After review of the objectionable conditions and the written response from the site, OSIS concluded that the RRA observations impact the reliability of data from a portion of the reviewed studies (Final OSIS Review – (b) (4).

Sites

Facility Type	Facility Name	Facility Address
Clinical	The First Hospital of JiLin University	Phase 1 Clinical Research Center, No. 71 Xinmin Street, Chaoyang District, Changchun City, Jilin Province, China
Analytical	(b) (4)	

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/s/

JOSHUA L PEREZ
12/12/2022 10:09:26 AM