Office of Therapeutic Biologics and Biosimilars
Clinical, Cross-Discipline Team Leader, and Division Memo

Date	See Electronic Stamp Date
From	Raquel Tapia, MD (Clinical Reviewer, OTBB) Thomas Herndon, MD (CTL/CDTL, OTBB) Kelly Norsworthy, MD (Division Signatory, DHM1) Banu Karimi-Shah, MD (Division Signatory, DPACC)
Subject	351(k) BLA Category D supplement to add new indications (see below for details)
BLA/Supplement Number	BLA 761354/S-009
Received Date	December 4, 2025
BsUFA Goal Date	June 4, 2026
Division/Office	Division of Pulmonology, Allergy, and Critical Care (DPACC)/Office of New Drugs (OND) Division of Hematologic Malignancies 1 (DHM1/OND)
Proprietary Name	Tofidence
Proper Name	Tocilizumab-bavi
Product Code	BAT1806 (also referred to as “BIIB800”)
Reference Product	U.S.-licensed Actemra (tocilizumab) (US-Actemra)
Pharmacologic Class	Interleukin-6 (IL-6) receptor antagonist
Applicant	Biogen MA, Inc.
Approved Indication(s)	• Rheumatoid Arthritis (RA), adult patients • Giant Cell Arteritis (GCA), adult patients • Polyarticular Juvenile Idiopathic Arthritis (PJIA), pediatric patients 2 years of age and older • Systemic Juvenile Idiopathic Arthritis (SJIA), pediatric patients 2 years of age and older • Coronavirus Disease 2019 (COVID-19), adult patients
New Indication(s) and/or Population(s)	• Coronavirus Disease 2019 (COVID-19), pediatric patients 2 years and older • Cytokine Release Syndrome (CRS), adult and pediatric patients 2 years of age and older
New Dosing Regimen(s)	Same dosing regimen as US-Actemra for the respective indications
Recommendation on Regulatory Action	Approval

1. Introduction

The Applicant, Biogen MA, Inc., submitted a supplemental biologics license application for BLA 761354 (sBLA-009) under section 351(k) of the Public Health Service (PHS) Act to expand the indications for Tofidence to include:

- Coronavirus Disease 2019 (COVID-19)

    - Hospitalized pediatric patients aged 2 years and older 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).
- 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.

The application includes scientific justification for biosimilar extrapolation along with labeling updates to include COVID-19 in pediatric patients 2 years and older and CRS in adults and pediatric patients ≥ 2 years of age.

2. Background

Tofidence (tocilizumab-bavi) is a recombinant humanized anti-human interleukin 6 (IL-6) receptor monoclonal antibody. Tofidence was approved as a biosimilar to US-Actemra on September 29, 2023, in 80 mg/4 mL (20 mg/mL), 200 mg/10 mL (20 mg/mL), and 400 mg/20 mL (20 mg/mL) single-dose vials for intravenous (IV) use.

According to the current label approved March 6, 2025, Tofidence is approved 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)
    - Adult patients with giant cell arteritis
- 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
- 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)

GCA and COVID-19 in adults were added to the Tofidence product labeling on July 19, 2024, with the approval of sBLA 761354-002. A deferred pediatric post marketing requirement (PMR) was issued under the Pediatric Research and Equity Act (PREA) to assess treatment of COVID-19 in pediatric patients 1 year to <18 years of age (PREA

PMR 4664-1) with a final report due by June 2026.

PREA requirements for COVID-19, which had been waived for pediatric patients ≤1 year and deferred for 1 to (b)(4)18 years for US-Actemra (PREA PMR 4369-1), were further waived for pediatric patients 1 to 2 years and COVID-19 was ultimately assessed in pediatric patients 2 to ≤ 18 years. The PREA PRM was fulfilled in August 2025 (refer to Cross-Discipline Team Leader (CDTL) review and Division Memo for sBLA125276-149 dated August 7, 2025 for further details).

The pediatric age group, 2 to ≤18 years for the COVID-19 indication in this supplement is consistent with US-Actemra.[1]

At the time of original Tofidence submission, Biogen did not seek the CRS indication. An orphan drug exclusivity (ODE) for this indication in adults and pediatric patients was granted to US-Actemra, which expired on February 28, 2025.

Review of the data submitted by the Applicant for the original BLA submission demonstrated that Tofidence is highly similar to US-Actemra, notwithstanding minor differences in clinically inactive components, and that there were no clinically meaningful differences between Tofidence and US-Actemra in terms of the safety, purity, and potency of the product. The Applicant also provided adequate scientific justification for extrapolation of data and information to support licensure of Tofidence in unstudied indications. A pediatric assessment for the COVID-19 and CRS indications and scientific justification for biosimilar extrapolation was resubmitted with the supplement.

3. Summary of Conclusions of Other Review Disciplines

3.1. Product Quality

No new product quality information was submitted nor required for this sBLA. There are no CMC or product quality issues that would preclude approval of this indication.

3.2. Division of Medication Error Prevention and Analysis (DMEPA)

The submission was acceptable from a medication error perspective.

4. Nonclinical Pharmacology/Toxicology

No new nonclinical pharmacology/toxicology information was submitted nor required for this supplemental BLA. There are no nonclinical pharmacology/toxicology issues that would preclude approval of the indication sought for licensure.

[1] See Actemra USPI approved December 10, 2025, BLA 125276/S-147 https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125276s147lbl.pdf

5. Clinical Pharmacology

No new clinical pharmacology information was submitted nor required for this supplemental BLA. There are no clinical pharmacology issues that would preclude approval of the indication sought for licensure.

6. Clinical Evaluation and Recommendations

6.1. Clinical/Statistical-Efficacy

Tofidence was previously evaluated in a comparative clinical study in patients with RA (BAT-1806-002-CR). The data were previously reviewed and summarized in the clinical and statistical reviews of the original BLA by the Division of Rheumatology and Transplant Medicine (DRTM), dated September 29, 2023. No new clinical/statistical efficacy information was submitted nor required for the current sBLA. There are no clinical/statistical efficacy issues that would preclude approval of the indications sought for licensure.

6.2. Safety

Tofidence was previously evaluated in a comparative clinical study in patients with RA (BAT-1806-002-CR) and in healthy subjects in a PK similarity study (BAT-1806-001-CR). The data were previously reviewed and summarized in the clinical review, dated September 29, 2023, of the original BLA by DRTM. No new safety data were submitted nor required for this sBLA. There are no clinical safety issues that would preclude approval of the indications sought for licensure.

6.3. Extrapolation

Tofidence is an approved biosimilar for the treatment of RA, GCA, and COVID-19 in adults and PJIA and SJIA in pediatric patients 2 years of age and older. In the original BLA submission, the Applicant provided data and support for biosimilarity, including extensive analytical characterization that demonstrated that tocilizumab-bavi is highly similar to US-Actemra, notwithstanding minor differences in clinically inactive components, as well as clinical data that demonstrated that there were no clinically meaningful differences between tocilizumab-bavi and US-Actemra in terms of safety, purity, and potency based on similar clinical PK in healthy subjects and similar efficacy, safety, and immunogenicity in patients with RA. The Applicant also provided scientific justification for extrapolation of data and information to support licensure of tocilizumab-bavi as a biosimilar for the non-studied indications.

With this supplement, the Applicant provided scientific justification for biosimilar extrapolation to COVID-19 in pediatric patients aged 2 years and older and CRS in adults and pediatric patients 2 years and older based on previous demonstration that Tyenne has the same known and potential mechanisms of action, similar pharmacokinetics, immunogenicity, and safety profile as US-Actemra. See Biosimilar

Multidisciplinary Evaluation and Review (BMER) dated September 29, 2023, of the original BLA.

In conclusion, the totality of evidence and scientific justification discussed above is adequate to justify extrapolating data and information submitted to this BLA to support licensure of Tofidence for the indications of:

- Coronavirus Disease 2019 (COVID-19)
  - Hospitalized pediatric patients aged 2 years and older 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).
- 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.

7. Labeling

The proposed Tofidence prescribing information (PI) incorporates relevant data and information from the Actemra USPI, with appropriate modifications. Specifically, additional language was incorporated in Section 6.2 to characterize the safety of tocilizumab observed in patients with COVID-19 and patients with CRS.

The labeling is compliant with Physician Labeling Rule (PLR) and Pregnancy and Lactation Labeling Rule (PLLR), is consistent with labeling guidance recommendations, and conveys the essential scientific information needed for safe and effective use of the product. The prescribing information incorporated relevant data and information from the US-Actemra prescribing information, with appropriate modifications.

8. Pediatrics

Under the Pediatric Research Equity Act (PREA) (section 505B of the FD&C Act), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain a pediatric assessment to support dosing, safety, and effectiveness of the product for the claimed indication unless this requirement is waived, deferred, or inapplicable. Section 505B(l) of the FD&C Act provides that a biosimilar product that has not been determined to be interchangeable with the reference product is considered to have a “new active ingredient” for purposes of PREA, and a pediatric assessment is generally required unless waived or deferred or inapplicable. Under the statute, an interchangeable product is not considered to have a “new active ingredient” for purposes of PREA.

The current supplement provides a pediatric assessment for COVID-19 and CRS in pediatric patients ≥2 years. A revised Extrapolation of Indications Report was included with the submission to support biosimilar extrapolation of both proposed indications.

The COVID-19 indication in adults was approved on February 28, 2025, under supplement-008, and PREA-PMR 4664-1 was issued for an assessment in pediatric patients 1 year to <18 years of age. However, a second waiver was granted for ages 1 to 2 years for the reference product, US-Actemra, who fulfilled its PREA PMR for COVID-19 in pediatric patients aged 2 to 18 years on August 8, 2025 (see Background section for additional information). The proposed pediatric age group for the COVID-19 indication for Tyenne is consistent with the product labeling for US- Actemra.

The U.S. product labeling for Actemra does not contain information of CRS in pediatric patients <2 years of age. US-Actemra was granted waiver in this subpopulation because necessary studies are impossible or highly impracticable. Therefore, a waiver request was not required for CRS in pediatric patients <2 years of age. For patients, 2 years and older, the proposed pediatric assessment is based on biosimilar extrapolation by having demonstrated biosimilarity to US-Actemra and providing scientific justification based on similar mechanisms of action, pharmacokinetics, immunogenicity, and toxicity as US-Actemra.

The Applicant has not developed nor is it required to develop a pediatric formulation for Tofidence.

Following review of the information submitted, this supplement addresses PREA PMR 4664-1 (Assessment of Tofidence (tocilizumab-bavi) for the treatment of COVID-19 in pediatric patients 2 year to <18 years of age) and supports an assessment of the CRS indication in pediatric patients 2 to ≤18 years of age. A Pediatric Review Committee (PeRC) meeting was held on May 12, 2026; PeRC agreed that the product is assessed for pediatric patients 2 years and older and PREA PMR 4664-1 is considered fulfilled.

9. Recommended Regulatory Action

Approval.

10. Division Director or Designated Signatory Comments

I concur with the review team’s assessment of the data and information submitted in this supplemental BLA and support the regulatory action.

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/

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