Clinical, CDTL, and Division Director Summary Review
BLA 761071/S-016

Date	See Electronic Stamp Date
From	Wiley A. Chambers, MD
Subject	Clinical, Cross-Discipline Team Leader, and Division Director Summary Review
BLA # and Supplement#	761071/S-016
Applicant	Sandoz, A Norvartis Division
Date of Submission	March 15, 2023
BSUFA Goal Date	September 15, 2023
Proprietary Name	HYRIMOZ (adalimumab-adaz)
Reference Product Proprietary Name (Proper Name)	US-Humira (adalimumab)
Dosage Form(s)	Injection
Applicant Proposed Indication	Expansion of existing indications to include: Uveitis (UV): treatment of non-infectious intermediate, posterior, and panuveitis in adults
Applicant Proposed Dosing Regimen	Same as US-Humira dosing for the respective indications
Recommendation on Regulatory Action	Approval
Recommended Indication	Uveitis: Treatment of non-infectious intermediate, posterior, and panuveitis in adults
Recommended Dosing Regimen(s)	Same as reference product dosing regimen

1. Introduction

The Applicant, Sandoz, Inc., submitted a supplemental biologics license application for BLA 761071 (sBLA-016) to expand the indication for HYRIMOZ (adalimumab-adaz) to include the treatment of non-infectious intermediate, posterior, and panuveitis in adults (UV). US-Humira's orphan-drug exclusivity for this indication expired on June 30, 2023. Subsequent to the approval of the UV indication in adult patients, US-Humira was approved to treat pediatric patients 2 years of age and older with UV. The term of orphan-drug exclusivity for US-Humira for "the treatment of non-infectious intermediate, posterior and panuveitis in pediatric patients 2 years of age and older" expires on September 28, 2025. The Applicant cross-references the original application submission under BLA 761071 and the supporting justification of extrapolation for UV in adult patients and pediatric patients 2 to 17 years of age. Only UV in adult patients, however, is currently being sought for licensure.

2. Background

HYRIMOZ (adalimumab-adaz) is a recombinant human immunoglobulin G1 (IgG1) monoclonal antibody (mAb) against tumor necrosis factor (TNF) alpha, produced by recombinant DNA technology in a mammalian cell expression system. HYRIMOZ (adalimumab-adaz) was approved as a biosimilar to US-licensed Humira (US-Humira) on October 30, 2018, under section 351(k) of the Public Health Service Act (BLA 761071). HYRIMOZ is currently supplied at 80 mg/0.8 mL (single-dose prefilled syringe and single-dose prefilled pen),40 mg/0.8 mL (single-dose prefilled syringe and single-dose prefilled pen), 40 mg/0.4 mL (single-dose prefilled syringe and single-dose prefilled pen), 20 mg/0.2 mL (single-dose prefilled syringe), 20 mg/0.4 mL (single-dose prefilled syringe) 10 mg/ 0.2 mL (single-dose prefilled syringe) and 10 mg/0.1 mL (single-dose prefilled syringe). HYRIMOZ is approved for the treatment of:

1. Rheumatoid Arthritis (RA): Reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active RA.

2. Juvenile Idiopathic Arthritis (JIA): Reducing signs and symptoms of moderately to severely active polyarticular JIA in patients 2 years of age and older.

3. Psoriatic Arthritis (PsA): Reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with PsA.

4. Ankylosing Spondylitis (AS): Reducing signs and symptoms in adult patients with active AS.

5. Crohn's Disease (CD): Treatment of moderately to severely active Crohn's disease in adults and pediatric patients 6 years of age and older.

6. Ulcerative Colitis (UC): Treatment of moderately to severely active ulcerative coltis in adult patients.

7. Plaque Psoriasis (Ps): The treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy, and when other systemic therapies are medically less appropriate.

8. Hidradenitis Suppurativa (HS): treatment of moderate to severe hidradenitis suppurativa in adult patients.

In support of the original BLA, the Applicant provided clinical study data collected from healthy subjects and patients with plaque psoriasis (Ps). The Applicant submitted two

PK similarity studies (GP17-101 and GP17-104) assessing 3-way PK similarity between GP2017, EU-approved Humira, and US-licensed Humira (based on pairwise comparisons of GP2017 to US-licensed Humira, GP2017 to EU-approved Humira, and EU-licensed Humira to US-approved Humira) in healthy subjects. In addition, the Applicant submitted the results of one comparative clinical study (GP17-301) using GP2017 and US-licensed Humira in patients with moderate to severe plaque psoriasis (Ps). Supportive PK, safety, and immunogenicity data were also provided from Study GP17-102 (a single dose study comparing GP2017 administered by an auto-injector vs. a pre-filled syringe), and Study GP17-103 (a single dose study comparing GP2017 formulations from two different drug substance production sites). In the original 351(k) BLA submission, the PK portion of the scientific bridge was established based on results of a 3-way PK similarity study (Study B5381007) comparing PF-06410293 (40 mg/0.8 mL PFS), E.U.-Humira (40 mg/0.8mL), or U.S.-Humira (40 mg/0.8mL).

In considering the totality of the evidence for the assessment of biosimilarity and the original BLA submission, review of the data submitted by the Applicant showed that HYRIMOZ (adalimumab-adaz) is highly similar to US-Humira, notwithstanding minor differences in clinically inactive components, and that there are no clinically meaningful differences between adalimumab-adaz and US-Humira 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 adalimumab-adaz for the non-studied indications sought for approval.

HYRIMOZ (adalimumab-adaz) is approved in the following strengths and presentations:

- 10 mg/0.1 mL, 10 mg/0.2 mL, 20 mg/0.4 mL and 20 mg/0.2 mL in a prefilled syringe (PFS); and
- 40 mg/0.8 mL, 40 mg/0.4 mL, and 80 mg/0.8 mL in both prefilled syringe (PFS) and autoinjector

3. CMC/Product Quality

For sBLA-016, no new product quality information was submitted nor required. There are no CMC or product quality issues that would preclude approval of the indication sought for licensure.

On April 13, 2023, Sandoz Inc. provided the estimate concentration of the drug substance at the point of entry to the aquatic environment (which is expected to be below 1 part per billion (ppb) and anticipated no extraordinary circumstances that need the preparation of environmental assessment would exist. Thus, Sandoz Inc. claimed a categorical exclusion from the requirement of an environmental assessment under 21 CFR 25.31(b). Their request for categorical exclusion from an environmental

assessment meets the criteria set forth in 21CFR §25.31(b) and is considered acceptable.

4. Nonclinical Pharmacology/Toxicology

No new nonclinical pharmacology/toxicology information was submitted nor required for this sBLA-016. There are no nonclinical pharmacology/toxicology issues that would preclude approval of the indication sought for licensure.

5. Clinical Pharmacology

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

6. Clinical/Statistical-Efficacy

Adalimumab-adaz was previously evaluated in comparative clinical studies.The data were previously reviewed and summarized above and in the clinical and statistical reviews of the original BLA and multiple sBLAs. No new clinical/statistical efficacy information was submitted nor required for this sBLA. There are no clinical/statistical efficacy issues that would preclude approval of the indication sought for licensure.

7. Safety

There are no clinical safety issues that would preclude approval of the indication sought for licensure.

8. Considerations for Extrapolation of Biosimilarity in Other Conditions of Use

HYRIMOZ (adalimumab-adaz) is an approved biosimilar for the treatment of RA, PsA, AS, CD in patients 6 years of age and older, UC, pJIA in patients 2 years of age and older, Ps and HS. In the original BLA submission the Applicant provided data and support for biosimilarity, including extensive analytical characterization that demonstrated that adalimumab-adaz is highly similar to US-Humira, notwithstanding minor differences in clinically inactive components, as well as clinical data that demonstrated that there were no clinically meaningful differences between adalimumab-adaz and US-Humira in terms of safety, purity, and potency based on similar clinical PK in healthy subjects and similar efficacy, safety, and immunogenicity.

Justification for Extrapolation to Non-studied Indications

Additional points considered in the justification for extrapolation of data and information to support licensure of adalimumab-adaz as a biosimilar for each non-studied indication for which licensure was sought and for which US-Humira was previously approved included:

- PK similarity was demonstrated between adalimumab-adaz and US-Humira. There were no product-related attributes that would increase uncertainty that the PK/biodistribution may differ between adalimumab-adaz and US-Humira in the indications sought for licensure. A similar PK profile would be expected between adalimumab-adaz and US-Humira in patients with JIA, PsA, AS, adult CD, UC, Ps, HS and UV.

- In general, immunogenicity of US-Humira was affected primarily by the dosing regimen and the use of concomitant immunosuppressive therapy across different indications, rather than by patient population, and the results were influenced by the type of assay used (per labeling for US-Humira). Similar immunogenicity was observed between adalimumab-adaz and US-Humira in patients with plaque psoriasis. Therefore, similar immunogenicity would be expected between adalimumab-adaz and US-Humira in patients with JIA, PsA, AS, adult CD, UC, Ps, HS and UV.

- There were no clinically meaningful differences between adalimumab-adaz and US-Humira in patients with plaque psoriasis nor in healthy subjects. Coupled with the demonstration of analytical and PK similarity between adalimumab-adaz, US-Humira, and EU-Humira, a similar safety profile would be expected in patients with JIA, PsA, AS, adult CD, UC, Ps, HS and UV.

- The Applicant addressed each of the known and potential mechanisms of action of US-Humira and submitted data to support the conclusion that adalimumab-adaz and US-Humira have the same mechanisms for each of the sought indications, to the extent that the mechanisms of action are known or can reasonably be determined.

Justification for Extrapolation to UV Indication

In this sBLA, the Applicant has cross-referenced the previously submitted justification for extrapolation of the data and information in support of licensure of adalimumab-adaz for this indication. The scientific justification for extrapolation to non-studied indications which was submitted with the original BLA is also applicable to UV and supports licensure of adalimumab-adaz for the treatment of adult patients with non-infectious intermediate, posterior and panuveitis.

9. Pediatrics

To address the Pediatric Research Equity Act (PREA), the Applicant confirmed on August 25, 2023, that they have submitted a pediatric assessment of the use of adalimumab-adaz for the treatment of non-infectious intermediate, posterior and panuveitis in pediatric subjects age 2 years and above. A term of orphan-drug exclusivity for US-Humira for "the treatment of non-infectious intermediate, posterior and panuveitis in pediatric subjects age 2 years and above" expires on September 28, 2025. The Applicant proposed to fulfill PREA requirements for pediatric patients 2 years and above for this indication by satisfying the statutory requirements for showing biosimilarity and providing an adequate scientific justification for extrapolating the pediatric information from US-Humira to HYRIMOZ; however, FDA cannot license HYRIMOZ for this indication in this age group until US-Humira's orphan drug exclusivity for it expires on September 28, 2025. The labeling for US-Humira does not contain adequate pediatric information for UV patients younger than 2 years of age, and no pediatric assessment will be required of the Applicant under PREA for UV patients younger than 2 years of age. The Pediatric Review Committee (PeRC) reviewed the information and considered the product to be assessed. On May 2, 2023, the Pediatric Review Committee (PeRC) reviewed the assessment and agreed with the assessment.

10. Other Relevant Regulatory Issues

Not applicable.

11. Labeling

Prescribing Information

Labeling for HYRIMOZ was updated to include the indication of adult patients with non-infectious intermediate, posterior and panuveitis. The submitted package insert, and Medication Guide have been reviewed and found to be acceptable. The final label will be included in the approval letter.

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

12. Postmarketing Recommendations

There are no new safety or efficacy issues identified in this review that warrant further assessment with a postmarketing requirement or commitment.

13. Risk Evaluation and Mitigation Strategies

The review team did not identify a need for Risk Evaluation and Mitigation Strategies (REMS) to ensure the safe use of adalimumab-adaz.

14. Recommended Regulatory Action

Approval.

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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