Clinical, Cross-Discipline Team Leader, and Division Director Summary Review for BLA 761059 Supplement 8

Date	See Electronic Stamp Date
From	Carol Kim, Pharm.D, Clinical Reviewer (OTBB) Nina Brahme, Ph.D., M.P.H., Clinical Reviewer (OTBB) William M. Boyd, MD, CDTL (DO) Wiley A. Chambers, MD, Division Director (DO)
Subject	Clinical Review Summary Review
sBLA # and Supplement#	761059/S-008
Applicant	Samsung Bioepis Co., Ltd (Samsung)
Date of Submission	September 16, 2022
BSUFA Goal Date	July 16, 2023
Proprietary Name (Proper Name)	Hadlima (adalimumab-bwwd)
Product Code Name	SB5
Reference Product Proprietary Name (Proper Name)	Humira (adalimumab)
Dosage Form	Injection
Applicant Proposed Indication(s)/Population(s)	Expansion of existing indications to include the following: • Uveitis (UV): Treatment of non-infectious intermediate, posterior, and panuveitis in adult patients
Applicant Proposed Dosing Regimen(s)	Same as US-Humira dosing for UV in adult patients
Regulatory Action	**Approval**

1. Introduction

The Applicant, Samsung, submitted this supplement 008 to expand the indications of Hadlima (adalimumab-bwwd) to include "the treatment of non-infectious intermediate, posterior and panuveitis in adult patients." US-Humira's orphan-drug exclusivity for this indication expires 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 761059 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

The Applicant originally submitted a BLA under section 351(k) of the Public Health Service Act (PHS Act) for adalimumab-bwwd on July 23, 2018. Adalimumab-bwwd (Hadlima) is biosimilar to US-Humira. Hadlima was approved on July 23, 2019, under

section 351(k) of the Public Health Service Act (PHS Act). It is currently approved for the treatment of:

1) Rheumatoid Arthritis (RA)
2) Juvenile Idiopathic Arthritis (JIA) in patients 2 years of age and older
3) Psoriatic Arthritis (PsA)
4) Ankylosing Spondylitis (AS)
5) Crohn's Disease (CD) in patients 6 years of age and older
6) Ulcerative Colitis (UC) in adult patients
7) Plaque Psoriasis (Ps)
8) Hidradentitis Suppurativa (HS) in adult patients

The original application included the following:

- A comprehensive comparative analytical assessment of adalimumab-bwwd, US-Humira, and EU-approved Humira (EU-Humira). These included comparative characterization of physicochemical attributes and comparative functional assessments.
- Nonclinical studies including a 7-week pharmacology study in Tg197 mice and a 4-week repeat-dose toxicology study in monkeys to compare the effects of adalimumab-bwwd to those of EU-Humira.
- A PK similarity study (SB5-G11-NHV) in healthy subjects following a single subcutaneous (SC) 40 mg dose of adalimumab-bwwd, EU-Humira, or US-Humira.
- A comparative clinical study (SB5-G31-RA) evaluating comparative efficacy, safety, and immunogenicity of adalimumab-bwwd and EU-Humira in combination with methotrexate in patients with moderately to severely active RA who have had an inadequate response to methotrexate.
- A scientific justification (based on mechanism of action, PK, immunogenicity, and toxicity) for extrapolation of data and information submitted in the application to support licensure of adalimumab-bwwd for each of the additional indications for which Samsung was seeking licensure and for which US-Humira had been previously licensed.

In considering the totality of the evidence for the original BLA submission, review of the data submitted by the Applicant showed that adalimumab-bwwd is highly similar to US-Humira, notwithstanding minor differences in clinically inactive components, and that there are no clinically meaningful differences between adalimumab-bwwd 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-bwwd for the non-studied indications being sought. Review of the information submitted by the Applicant demonstrated that adalimumab-bwwd is biosimilar to US-Humira for each of the following indications for which US-Humira has been previously approved and the Applicant was seeking licensure for adalimumab-bwwd: RA, JIA (b) (4) PsA, AS, Ps, Adult CD, and Adult UC. Refer to the Biosimilar Multi-Disciplinary Evaluation and Review (dated July 23, 2019).

Under supplement 4, the approved indications were expanded to include the following: treatment of moderately to severely active polyarticular juvenile idiopathic arthritis (JIA) in patients 2 years of age and older and treatment of moderately to severely active Crohn's disease in pediatric patients ages 6 years of age and older. Refer to Cross-Discipline Team Leader review dated June 16, 2022, for additional details.

Under supplement 6, the approved indications were expanded to include treatment of moderate to severe HS in adult patients. Refer to Clinical, Cross-Discipline Team Leader, and Division Summary Review dated June 20, 2023.

3. Product Quality

There are no proposed changes in the product's composition or presentation with this supplement, 008. There are no CMC or product quality issues that would preclude approval of the indication sought for licensure.

According to the OBP review dated October 14, 2022, the Applicant's claim for categorical exclusion from the preparation of an environmental assessment under 21 CFR Part 25 is considered appropriate and acceptable.

4. Nonclinical Pharmacology/Toxicology

There are no nonclinical pharmacology/toxicology issues that would preclude approval of the indication sought for licensure.

5. Clinical Pharmacology

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

6. Clinical/Statistical- Efficacy

Adalimumab-bwwd was previously studied in patients with RA in the comparative clinical study (SB5-G31-RA). The data were previously reviewed and summarized in the BMER dated July 23, 2019, for the original application. There are no clinical/statistical efficacy issues that would preclude approval of the indication sought for licensure.

7. Safety

Adalimumab-bwwd was previously studied in patients with RA in the comparative clinical study (SB5-G31-RA) and in healthy subjects in the PK similarity study (SB5-G11-NHV). The data were previously reviewed and summarized in the BMER dated July 23, 2019, for the original application. There are no clinical safety issues that would preclude approval of the indications sought for licensure.

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

Adalimumab-bwwd is an approved biosimilar for the treatment of RA, PsA, AS, CD in patients 6 years of age and older, UC, Ps, HS in adult patients, and JIA in patients 2 years of age and older. The Applicant submitted justification for extrapolation for UV in adults and pediatric patients 2 to 17 years of age. Only UV in adult patients, however, is currently being sought for licensure.

Scientific considerations for the extrapolation of data and information to support licensure for UV in adults and pediatric patients 2 to 17 years of age are outlined below:

1. Biosimilarity has previously been established between adalimumab-bwwd and the reference product, US-Humira based on extensive analytical characterization, comparative PK study, comparative clinical study, safety and immunogenicity data.
2. Adequate scientific justification supporting extrapolation of scientific information and data (based on mechanism of action, PK and immunogenicity, safety and toxicities) from the original BLA submission (761059) allowed licensure of non-studied indications for which the reference product has been approved.
3. Similar extrapolation of scientific information and data from the original application applies to the indication that is subject of this supplement. Therefore, in adult and pediatric patients 2 to 17 years of age with Uveitis:
    a. a similar PK profile would be expected between adalimumab-bwwd and US-Humira
    b. similar immunogenicity would be expected between adalimumab-bwwd and US-Humira
    c. similar safety profile would be expected between adalimumab-bwwd and US-Humira
    d. The applicant addressed each of the known and potential mechanisms of action of US-Humira and submitted data to support the conclusion that adalimumab-bwwd and US---Humira have the same mechanisms for Uveitis, to the extent that the mechanisms of action are known or can reasonably be determined

In terms of safety and toxicity, the same safety data which supported approval of the extrapolated indications, including pediatric JIA in patients 2 years of age and older are applicable and relevant to support safety in adults and pediatric patients 2 to 17 years of age with UV.

In conclusion, the totality of evidence and scientific justification discussed above is adequate to justify extrapolating the data and information submitted to the BLA to support licensure of adalimumab-bwwd (b) (4) Currently, however, only licensure for "treatment of non-infectious intermediate, posterior and panuveitis in adult patients" is being sought.

Note that while the Applicant has also submitted acceptable extrapolation justification for UV in pediatric patients 2 to 17 years of age, FDA has recognized orphan-drug exclusive approval for US-Humira for UV for the "treatment of non-infectious intermediate, posterior, and panuveitis in pediatric patients 2 years of age and older." FDA therefore cannot license adalimumab-bwwd for this patient population prior to the expiration of the period of orphan-drug exclusivity, which is September 28, 2025.

9. Pediatrics

A 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 proposed to fulfill PREA requirements for pediatric patients 2 years of age and older for this indication by satisfying the statutory requirements for showing biosimilarity and providing an adequate scientific justification for extrapolation of data and information to support licensure of adalimumab-bwwd for this population; however, FDA cannot license adalimumab-bwwd 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 pediatric information for the UV indication in pediatric patients less than 2 years of age, and no pediatric assessment will be required of the Applicant under PREA for the UV indication in pediatric patients less than 2 years of age.

On May 2, 2023, the Pediatric Review Committee (PeRC) reviewed the pediatric assessment and considers the product to be assessed.

10. Other Relevant Regulatory Issues

None

11. Labeling

It was determined that the proposed labeling is compliant with Physician Labeling Rule (PLR) and Pregnancy and Lactation Labeling Rule (PLLR) and is consistent with labeling guidance recommendations, and conveys the essential scientific information needed for safe and effective use of the product. The proposed Hadlima labeling incorporated relevant data and information from the U.S.-Humira labeling, with appropriate modifications.

12. Post-marketing Recommendations

None.

13. Risk Evaluation and Mitigation Strategies

None.

14. 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/

WILEY A CHAMBERS
07/11/2023 08:34:48 AM

CAROL Y KIM
07/11/2023 08:49:46 AM

NINA N BRAHME
07/11/2023 08:51:51 AM

WILLIAM M BOYD
07/11/2023 08:56:52 AM