EDA Assessment Report for Biological Medicinal Product

(Scientific Discussion)

Adalimab

Date: November 2024

Unit: Technical Assessment Unit

Assessment report

Adalimab 40mg

Administrative information:

Trade name of the medicinal product:	Adalimab
INN (or common name) of the active substance(s):	Adalimumab 40 mg
Manufacturer of the finished product	Reliance Life Sciences Pvt. Ltd., Dhirubhai Ambani life science center, Plant- 2, R-282 TTC area of MIDC, Thane- Belapur Road, Rabale Navi Mumbai, 400 701, Maharashtra, India
Marketing Authorization holder	Egyptian International Pharmaceutical Industries Company, EIPICO, Industrial Zone B1, Tenth of Ramadan City, Egypt
Applied Indication(s):	**1.1 Rheumatoid Arthritis** **Adalimab** is indicated for 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 rheumatoid arthritis. **Adalimab** can be used alone or in combination with methotrexate or other non-biologic disease-modifying anti-rheumatic drugs (DMARDs). **1.2 Juvenile Idiopathic Arthritis** **Adalimab** is indicated for reducing signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis in patients 2 years of age and older. **Adalimab** can be used alone or in combination with methotrexate.

	1.3 Psoriatic Arthritis **Adalimab** is indicated for reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with active psoriatic arthritis. **Adalimab** can be used alone or in combination with non-biologic DMARDs. **1.4 Ankylosing Spondylitis** **Adalimab** is indicated for reducing signs and symptoms in adult patients with active ankylosing spondylitis. **1.5 Adult Crohn's Disease** **Adalimab** is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy. **Adalimab** is indicated for reducing signs and symptoms and inducing clinical remission in these patients if they have also lost response to or are intolerant to infliximab. **1.6 Pediatric Crohn's Disease** **Adalimab** is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients 6 years of age and older with moderately to severely active Crohn's disease who have had an inadequate response to corticosteroids or immunomodulators such as azathioprine, 6-mercaptopurine, or methotrexate. **1.7 Ulcerative Colitis** **Adalimab** is indicated for inducing and sustaining clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to

	immunosuppressants such as corticosteroids, azathioprine or 6-mercaptopurine (6-MP). The effectiveness of **Adalimab** has not been established in patients who have lost response to or were intolerant to TNF blockers. **1.8 Plaque Psoriasis** **Adalimab** is indicated for 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. **Adalimab** should only be administered to patients who will be closely monitored and have regular follow-up visits with a physician. **1.9 Hidradenitis Suppurativa** **Adalimab** is indicated for the treatment of moderate to severe hidradenitis suppurativa in patients 12 years of age and older. **1.10 Uveitis** **Adalimab** is indicated for the treatment of non-infectious intermediate, posterior, and panuveitis in adults and pediatric patients 2 years of age and older.
Pharmaceutical form(s) and strength(s):	Solution for S.C injection Adalimumab 40 mg/0.8mL
Route of administration	subcutaneous
Approved pack	single-dose (Type I) glass Pre-filled Syringe of 0.8ml

List of abbreviations:

µg/mL	Microgram per milliliter
ACR	American College of Rheumatology
AEs	Adverse Events
AS	ankylosing spondylitis

AUC0-∞	Area under the plasma concentration time curve from drug administration to infinity
AUC0-t	Area under the plasma concentration time curve from drug administration to concentration at Time (1200) hr
CHO	Chinese hamster ovary
CI	Confidence Interval
Cmax	Maximum Measurable Plasma Concentration
DAS	Disease Activity Score
EMA	European medicines agency
FDA :	Food and Drug Administration
GLP	Good laboratory practice
HAQ-DI	Health Assessment Questionnaire Disability Index
hr.	hours
Humira®	reference adalimumab
lnCmax	log transformation of the Cmax data
R-TPR 021	Test product- adalimumab
SAEs	Serious adverse events
T/R	Test/reference
T1/2	Elimination Half Life
TEAE	Treatment Emergent Adverse Event
Tmax	Time to reach Maximum Plasma Concentration

Dossier initial submission and evaluation process:

- The product was submitted for registration via normal track
- The dossier was initially received by the registration administration units on 24.8.2022 after providing Full CTD for the product

Table of contents

1. General introduction about the product including brief description of the AI, its mode of action and indications

Adalimumab is a humanized monoclonal antibody that binds specifically to TNF-α. TNF is a naturally occurring cytokine that is involved in normal inflammatory and immune responses TNF-α normally binds to TNF-α receptors, which leads to the inflammatory response of autoimmune diseases. By binding to TNF-α, Adalimumab reduces this inflammatory response. RLS Adalimumab is being developed as a biosimilar to Humira.

2. Quality aspects:

2.1 Introduction

2.2 Drug Substance (Active ingredient)

International non-proprietary name (INN**):** Adalimumab

Company or Laboratory Code: R-TPR-021

Drug Substance is a Clear and colorless liquid free of Particulates contains Adalimumab at a concentration of 50-85 mg/ml in a buffer that has the same components as in the final product of Humira®.

- **Manufacture, process controls and characterization:**

Manufacturer:

Reliance Life Sciences Pvt. Ltd., Dhirubhai Ambani life science center, Plant- 2, R- 282, TTC Area of MIDC, Thane - Belapur Road, Rabale, Navi Mumbai, 400701 Maharashtra, India.

Description of Manufacturing Process and Process Controls.

- The description of each stage in manufacturing process of Adalimumab drug substance, flow chart, quantity of used material, operating parameter, in process control and the percentage yield had been submitted in the file

- The flow chart for each stage represent the in process control and typical yield ranges is also illustrated in the file.

Control of Materials

-Sufficient information on raw materials used in the active substance manufacturing process has been submitted.

-All raw materials are sourced from qualified suppliers. Raw materials are received, identified, tested and released according to written Standard Operating Procedures (SOPs) as required by cGMP.

- Chemicals used for Adalimumab drug substance manufacturing are of compendial grade with exception of five raw materials. Specifications for these raw materials are provided and found satisfactory

-Materials used in the manufacture of drug substance are tested internally and accepted on the basis of relevant pharmacopeia testing methods & Supplier's Certificate of Analysis with reference to internal specifications.

Controls of Critical Steps and Intermediates

Process parameter and the Critical quality attribute for the manufacturing process stages had been identified. Information on the quality control of the intermediate had been submitted with description of the acceptance criteria of tests and process parameter.

All the critical process parameters monitored during the manufacturing runs in fermentation, cell harvest and purification steps were found to be consistent and reproducible, as evidenced by the results obtained at each stage of manufacturing process.

Process Validation

The consistency of the drug substance manufacturing process was assessed to demonstrate the ability of the process to deliver a product that meets all the key product quality attribute specifications.

Manufacturing Process Development.

Adalimab product was developed as a biosimilar to innovators product Humira
Applicant provided information regarding the development efforts related to protein production in the bioreactor and subsequent downstream processing related to protein purification and formulation of drug substance.

Characterization

• Adalimumab is a glycosylated monoclonal antibody produced in genetically modified CHO cells. The drug substance produced was characterized in a comprehensive test program that employed orthogonal tests to provide information regarding the primary, secondary and tertiary structure of the protein.

•Applicant provided the analysis method used to characterize the molecule different CQAs.

•A complete report on the characterization study of Adalimumab was provided with the details regarding the batches used in each test

Impurities

Applicant provided a complete comparative characterization report regarding the Impurity Contamination

Specification

The recombinant Adalimumab specifications are in accordance to the ICH Q6B guidelines. The specifications established include the assays which determine the physicochemical properties, biological activity, immunochemical properties, purity and impurities. Specifications are chosen to confirm the quality of the drug Substance and focus on those molecular and biological characteristics found to be useful in ensuring the safety and efficacy of the product.

Analytical Procedures

All analytical procedures were in-house developed, the applicant provided detailed analytical procedures and detailed validation reports for each of them, they were reviewed and found satisfactory except for system suitability criteria for Identification and purity by WCX-HPLC and for bioassay test using L929 cytotoxicity inhibition assay

Batch analysis

-Batch analyses for three consecutive commercial scale batches were provided. Results of the batches were all within pre-set specifications and reflected that the process is under control.

-Updated batch analysis for three batches was requested by the assessor to reflect the new specifications of bacterial endotoxin. Applicant provided them and the results indicated that the process is under control with the new specifications and test method.

Reference Standards or Materials

-Information regarding the reference standards used is sufficient. With respect to method validation, sufficient validation data for methods have been provided.

-Applicant used innovator batch (Humira) as a reference standard in the early stages of product development to assess the similarity of RLS product with the innovator.

Applicant developed the first internal reference standard

Container closure system

At the end of the downstream processing, Adalimumab drug substance is filtered through a 0.1µ filter and the filtrate is collected in a pre-sterilized multilayer plastic bottle or sterile storage (Flexboy) bags depending upon batch size to produce drug substance.

Stability of drug substance

Approved Shelf Life: 2 years

Approved storage condition: Store in an airtight container, protected from direct sunlight, at or below temperature of -20°C.

2.3 Drug product:

-Description and Composition of the Drug Product:

The composition of Reliance produced Adalimab drug product is identical to the innovator's product, Humira®

Pharmaceutical Development

Components of drug product

Adalimab consists of two heavy and two light chains covalently linked by disulfide bonds. The heavy and light chains have 450 and 214 amino acids respectively. Adalimumab production occurs in genetically modified Chinese Hamster Ovary (CHO) cells cultured in bioreactors.

Excipients

-Adalimumab drug substance and drug product have an identical formulation. The formulation is not modified during finished product manufacturing. The excipients composition in Adalimab is exactly similar to that of the innovator product.

All excipients are well-known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation..

- Formulation Development

The composition of produced Adalimab was kept identical to that of innovator's product Humira® in all aspects Rationale for choice of Excipients: Adalimab drug product is a biosimilar to the innovator's product Humira®. Hence the excipient composition of Adalimab® is kept exactly similar to that of the innovator's product.

- Manufacturing Process Development

The drug product manufacturing primarily involves dilution of drug substance with formulation buffer to required drug product concentration. This dilution is carried out in two stages, primary dilution and final dilution. At each stage, product is mixed for fixed time interval to achieve the target concentration. The concentration of the drug product is verified by A280nm-

Microbiological Attributes

Adalimab is sterile product. No preservatives are used in the product at any stage of manufacture

- Compatibility

Compatibility of primary packaging of drug product is being continuously evaluated with an ongoing stability program, data for which have been described in section P.8 stability of drug product which involves use of sensitive techniques such CEX-HPLC for monitoring drug product quality. Other changes such as increase in product related species content, precipitates, and discoloration, which may
cause degradation of drug product are also being evaluated in an ongoing stability program. Results from stability batches indicates compatibility of container closure system with Adalimumab formulation..

Manufacture of the drug product:

Description of manufacturing process and process controls along with manufacturers and responsibilities.

Manufacturer:

-The finished product manufacturing take place Reliance Life Sciences Pvt. Ltd., Dhirubhai Ambani life science center, Plant- 2, R-282 TTC area of MIDC, Thane- Belapur Road, Rabale Navi Mumbai, 400 701, Maharashtra, India

- Control of critical steps and intermediates

The critical process step for manufacture is mentioned in details in file

- Process validation and / or evaluation

Validation data demonstrates that the process is controlled and reproducible while consistently producing active substance and finished product having the required quality when manufactured within the defined operating ranges

Product specification:

-Raw materials used in the formulation of Adalimab meets specifications as per European Pharmacopoeia. The suppliers of all these materials produce these under GMP and as part of release testing, all the tests outlined in EP monograph are carried out and are mentioned in the Certificate of Analysis accompanying the product shipment. On arrival, these raw materials are retested as per as internal standard testing procedure prior to be used in drug product formulation of Adalimumab.

- The recombinant Adalimumab specifications are in accordance to the ICH Q6B guidelines. The specifications established include the assays which determine the physicochemical properties, biological activity, immunochemical properties, purity and impurities. Specifications are chosen to confirm the quality of the drug product and focus on those molecular and biological characteristics found to be useful in ensuring the safety and efficacy of the product.

- **Reference Standards or Materials.**

Applicant used innovator batch (Humira) as a reference standard in the early stages of product development to assess the similarity of RLS product with the innovator**.**
All reference standards used are mentioned in the file**.**

Container closure system

Adalimab manufactured at RLS is presented as sterile solution for injection in 1 ml syringes. The composition of Adalimab drug product is similar to that of the innovator product in the drug product composition and formulation. The container-closure system for syringe made up of USP Type I glass and coated bromobutyl rubber stopper. The syringes are purchased as ready to use as they are sterilized using ethylene oxide while the rubber stoppers are purchased from approved vendors as ready-to-sterilize and used after autoclaving.

Stability of Drug Product

Approved Shelf Life: 36 months

Approved Storage Condition: Store in a refrigerator (2 – 8 °C). Do Not freeze. Store in original carton box till time of administration

Non-clinical aspect and clinical aspect

- **Non-clinical aspects**

Adalimab is a biosimilar to the innovator's product Humira®. Adalimab is a glycosylated monoclonal antibody produced in genetically modified CHO cells. It consists of two heavy and two light chains covalently linked by disulfide bonds. It is indicated for the management of some autoimmune diseases such as Rheumatoid arthritis, Juvenile idiopathic arthritis, Ankylosing spondylitis, Psoriatic arthritis, Crohn's disease, Ulcerative colitis, Plaque psoriasis and Hidradenitis suppurativa Uveitis. This product was not granted either EMEA or FDA approvals.

Pharmacology: The similarity of Adalimab to reference product Humira® was addressed by a series of head-to-head in vitro comparative studies including receptor binding studies and cell-based assays for the characterization of Fab and Fc-related effects. From a non-clinical point of view, the biological function parameters were found to be similar between Adalimab and Humira®.

Pharmacokinetics: Pharmacokinetic studies are not formally requested for biosimilars. Additionally, the absence of studies evaluating the distribution, metabolism, excretion and pharmacokinetic drug interactions is consistent with CHMP guidance (Guideline on similar biological medicinal products containing monoclonal antibodies, EMA/CHMP/BMWP/403543/2010).

Toxicology: The quality comparability exercise and in vitro biological potential of Adalimab have shown high similarity between Adalimab and Humira®, leaving no gaps that require additional in vivo studies. Thus, additional repeated dose toxicity studies were

not considered necessary (Guideline for Registration of Biosimilar Products in Egypt, 2020). However, the applicant submitted a series of GLP-compliant single and repeated dose toxicity studies that were conducted in toxicologically non-relevant species (rats, mice and rabbits) and thus considered supportive to assess general toxicity. Adalimab and the comparator product Humira® elicited similar toxicological profiles in rats and rabbits at the low dose exposure level though it was either statistically or clinically insignificant. This suggests that Adalimab was well tolerated at the highest technically feasible doses in both species.

Overall conclusion: the nonclinical biosimilarity and safety data demonstrate that Adalimab is similar to the reference product Humira®

- **Clinical Aspects**

Pharmacokinetics

After subcutaneous administration of a single 40 mg dose, the absorption and distribution of Adalimumab was slow and reached the peak serum concentrations about 5 days after administration.

The average absolute bioavailability of Adalimumab estimated was 64%, the maximum serum concentration (Cmax) and the time to reach the maximum concentration (Tmax) were 4.7 ± 1.6 µg/mL and 131 ± 56 hours following the administration of adalimumab to healthy adult subjects.

the median half-life (T1/2) observed is approximately 402.07 hrs.

No pharmacokinetic data are available for patients with renal or hepatic impairment.

- **Pharmacodynamics**

PD Properties

After treatment with **Adalimab**, a decrease in levels of acute phase reactants of inflammation (C- reactive protein [CRP] and erythrocyte sedimentation rate [ESR]) and serum cytokines (IL-6) was observed compared to baseline in patients with rheumatoid arthritis. A decrease in CRP levels was also observed in patients with Crohn's disease, ulcerative colitis and hidradenitis suppurativa. Serum levels of matrix metalloproteinases (MMP-1 and MMP-3) that produce tissue remodeling responsible for cartilage destruction were also decreased after **Adalimab** administration.

- **Clinical Efficacy conclusion**

In pivotal study no. RLS/TP/2013/02 phase III (efficacy and safety study)

The total number of responders achieving clinical response as per ACR20 criteria as primary endpoint was (90.48%) in R-TPR-021 arm and (90.00%) at 16 weeks in the Humira® arm in the PP population ($p>0.05$)

For the secondary endpoints, the total number of responders at Week 24 achieving clinical response as per ACR50 criteria and ACR70 criteria was (70.24%) vs. (70.00%) and (28.57)

vs. (35.00) in R- TPR-021 arm vs. in the Humira® arm in the PP population with (p= 0.2706) and (p=0.7907)
there was no significant difference observed for reduction of HAQ-DI scores and reduction of mean of DAS28 scores between R-TPR-021 and Humira® arm.
In study no. 1409044 Phase I (bioequivalence study)
the ratios of the mean of the ln-transformed data (T/R ratio) for ln-Cmax, ln-AUC0-t and lnAUC0-∞ were 99.48% [90% CI 93.02 - 106.38)], 95.92% [90%CI (84.40 - 109.02)], and 94.85% [90% CI (80.92 - 111.19)] for Adalimumab that occurred the 90% confidence with the acceptance bioequivalence window (80%-125%)

- **Clinical Safety conclusion**

In pivotal study no. RLS/TP/2013/02 phase III (efficacy and safety study)
In the double-blind phase, there were 83 adverse events were reported 62 were reported in the R-TPR-021 arm and 21 were reported in the Humira® arm that occurred in 34 (40.48%) subjects in the R-TPR-021arm and 10 (50.00%) subjects in the Humira® arm
The most commonly TEAEs reported adverse events according to System Organ Class (SOC) reported was infection and infestation occurred in (17.86%) vs. 5 (25.00%) followed by General disorders and administration site conditions (8.33%) vs. (5.00%), Metabolism and nutrition disorders (5.95%) vs. (10.00%)], Gastrointestinal disorders (4.76%) vs. (5.00%), and investigations and Blood and lymphatic system disorders (3.57%) vs. (50.00%) of subjects in the R-TPR-021 arm vs. in the Humira® arm
In the open label phase, there were 18 adverse events were reported that included 13 were reported in the R-TPR-021 arm and 5 in the Humira® arm that occurred in 9 (9.68%) subjects in the R-TPR-021 arm and 3 (3.23%) subjects in the Humira® armThe most commonly reported TEAEs were related to infection and infestations
(6.67%). that reported as Gastroenteritis (1.33%), Herpes zoster (1.33%)], Respiratory tract infection [1 (1.33%), Tuberculosis (1.33%), Upper respiratory tract infection (1.33%) SOC followed by Cardiac disorders (4.00%) In the R-TPR-021 arm vs. (0.00%) In the Humira® armthere were16 SAE reported in R-TPR-021 arm and 3 SAEs reported in Humira® arm during the study, the most common reported SAEs were infections and infestations
In Double blinded phase There were 15 subjects reported (SAEs)that included 12 (14.29%) subjects in the R-TPR-021 arm and 3(15.00%) subjects in the Humira® arm.
In Open label phase There were three (3.23%) subjects in the R-TPR 021 arm and zero (00.00%) subjects in the Humira® arm Death One death was reported in the study in R-TPR-021 arm that reported neurogenic sepsis shock which was possibly related to study medication In study no. 1409044 Phase I (bioequivalence study)
Overall, A total of 17 Adverse Events (AEs) were reported in the study that occurred in 10 (16.67%) AEs were reported in the Test arm (2 were possibly related) and 7(11.67%) AEs were reported in the reference arm (1 was possibly related) There were 2 (3.33%) vs. 1

(1.67%) AEs reported from Blood and lymphatic system disorders, 2 (3.33%) vs. 0(0%) were reported from Infections and infestations and 6(10.00%) vs. 5(8.33%) were reported from Investigations System Organ Class There was one SAE was reported in the study in the Test arm, his diagnosis was Amoebic Liver abscess with reactive pleural effusion that classified possibly related to test product and there were no deaths cases

➢ **Clinical Immunogenicity conclusion**

Overall, the Immunogenicity testing in the pivotal study showed presence of antibodies only in one subject in the R TPR-021 arm, However, this subject was a clinical responder at week 16. Thus, the immunogenicity profiling did not indicate any clinically significant concerns. In study no. 1409044, all samples were found to be negative for the presence of anti-Adalimumab antibodies.

➢ **Benefit/ Risk discussion:**

In conclusion the overall benefit/risk of Adalimab is favorable in the treatment of rheumatoid arthritis, Juvenile idiopathic arthritis, ankylosing spondylitis (AS), Psoriatic arthritis, adult Crohn's disease, pediatrics Crohn's disease, Ulcerative colitis, plaque psoriasis, Hidradenitis suppurativa and adult intermediate, posterior and panuveitis and pediatric anterior uveitis

Assessor Input:

The was a concern regarding small sample size of phase 3 study applied on only 106 patients although phase 3 for other biosimilar to Humira applied on minimum 300 patients according EMA assessment reports:

However, by reviewing the submitted data in accordance with international guidelines it was found that a total of 106 subjects were randomized ratio 4:1 which include 85 subjects in R-TPR-021 arm "test product" and 21 subjects in Humira arm "reference product" that was reasonable for acceptance of conduction phase III study on small sample size.

Risk Management plan (RMP)

Detailed plans for monitoring the safety profile of Adalimab, including the collection, assessment and reporting of adverse events that outlines strategies to identify, characterize and minimize risks associated with Adalimab

● **Compliance Monitoring and Reporting**

Through timely submission of periodic safety update reports (PSURs) to pharmacovigilance department of EDA.

- **General Conclusion and Recommendations if any:**
  A post-marketing plan for conforming the long-term safety and efficacy of Adalimab that should include:

Benefit/ Risk discussion:

In conclusion the overall benefit/risk of Adalimab is favorable in the treatment of rheumatoid arthritis, Juvenile idiopathic arthritis, ankylosing spondylitis (AS), Psoriatic arthritis, adult Crohn's disease, pediatrics Crohn's disease, Ulcerative colitis, plaque psoriasis, Hidradenitis suppurativa and adult intermediate, posterior and panuveitis and pediatric anterior uveitis