Unit: Technical Assessment Unit

Public assessment report for biological products

Nepexto

Administrative information:

Trade name of the medicinal product:	**Nepexto 25 mg/0.5ml pre-filled syringe** **Nepexto 50 mg/ml pre-filled syringe** **Nepexto 50 mg/ml pre-filled pen**
INN (or common name) of the active substance(s):	ETANERCEPT
Manufacturer of the finished product	Lupin Limited (Biotech Division), Gat No. 1156 - 1160 Village Ghotawade, Taluka Mulshi, Dist. Pune – 412115, Maharashtra, India. Lupin Limited Unit 2 Plot No. 6B Sector 17, Special Economic Zone, Mihan, Nagpur – 441108, Maharashtra, India.
Marketing Authorization holder	Biosimilar Collaborations Ireland limited (BCIL), 35/36, grange parade, Baldoyle industrial estate, Dublin 13 - Ireland.
Applied Indication(s):	Rehumatoid Arthritis Juvenile Idiopathic Arthritis Psoriatic Arthritis Axial Spondylarthritis Plaque Psoriasis Pediatric Plaque Psoriasis
Pharmaceutical form(s) and strength(s):	- Solution for injection in pre-filled syringe or pre-filled pen - 25 mg/0.5ml pre-filled syringe - 50 mg/ml pre-filled syringe - 50 mg/ml pre-filled pen
Route of administration	Subcutaneous injection
Registration track	EMA approved

(Nepexto 25 mg/0.5ml PFS & 50 mg/ml PFS & PFP)

List of abbreviations

ADA: Antidrug antibody
Ab: Antibody
ADCC: Antibody Dependent Cell mediated Cytotoxicity
AUC: Area Under the Curve
AUC0-t: Area Under the Curve from time zero to last measurable concentration
AUC0-inf: Area Under the Curve from time zero extrapolated to infinity
AUC%exp: Percentage of AUC extrapolated
AUCt: Area Under the Plasma Concentration-Time Curve at time t.
CHO: Chinese hamster ovary
EMA: European Medicines Agency
Fc: Fragment crystallizable region
IBD: Inflammatory bowel disease
IgG: Immunoglobulin G
PK: Pharmacokinetic
PFS: Prefilled syringe
PFP: Prefilled pen
PsA: psoriatic arthritis
PS: Psoriasis
PD: Pharmacodynamic(s)
PD-DI: Pharmacodynamic drug interaction
PK: Pharmacokinetic(s)
RA: Rheumatoid arthritis
RMP: Risk management product
SC: Subcutaneous(ly).
TNF: Tumor necrosis factor
TNFR: Tumor necrosis factor receptor
TK: Toxicokinetic(s)
YLB113: Lupin Etanercept, Nepexto.

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1. Introduction

The file evaluated according to EDA Reliance Model & the company submitted data which are the following:

1. Quality module-3 from the CTD file.
2. EMA Unredacted Assessment.

2. <u>Quality aspects:</u>

- **Manufacturer(s):**

- **Drug Substance**

The Active substance is manufactured at:

- Lupin Limited (Biotech division), Gat No. 1156 - 1160, Village Ghotawade, Taluka Mulshi, Dist. Pune – 412 115, Maharashtra, India.

- **Drug product**

The Finished product is manufactured at:

- Lupin Limited (Biotech Division), Gat No. 1156 - 1160 Village Ghotawade, Taluka Mulshi, Dist. Pune – 412115, Maharashtra, India.
- Lupin Limited Unit 2 Plot No. 6B Sector 17, Special Economic Zone, Mihan, Nagpur – 441108, Maharashtra, India.

- **Stability**

Drug substance:

- Approved shelf life for the active substance: 24 months

- Approved Storage Conditions of the active substance: store at (2- 8°C)

Drug product:

- Approved shelf life for the finished product: 3 years

- Approved Storage Conditions of the finished product:

- Store in a refrigerator (2°C - 8°C).

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- Do not freeze.
- Keep the pre-filled syringes in the outer carton in order to protect from light.
- Nepexto may be stored at temperatures up to a maximum of 25°C for a single period of up to four weeks; after which, it should not be refrigerated again.
- Nepexto should be discarded if not used within four weeks of removal from refrigeration.

3. Non –clinical aspect:

- **Lupin Etanercept (YLB113)** is a fully human, recombinant dimeric fusion protein consisting of two soluble molecules of the extracellular ligand-binding portion of human TNF receptor 2 (sTNFR2) coupled to the Fc fragment of human IgG1 antibody (Ab). The recombinant protein is expressed in Chinese Hamster Ovary (CHO) cells. It is a potent competitive inhibitor of TNF binding to its cellular receptors and indicated for the treatment of pathological complications such as rheumatoid arthritis (RA), inflammatory bowel disease (IBD), psoriatic arthritis (PsA) and psoriasis (PS). This product was granted EMA approval on 20 May 2020.

- **Pharmacology:** In-vitro PD studies of YLB113 showed comparable activity with Enbrel® (the reference product) in the receptor binding, neutralization and Fc effector functions. Higher ADCC activity of YLB113 than Enbrel® was observed. However, it is considered to be a clinically non relevant mechanism of action for TNF antagonists in patients with inflammatory diseases and did not turn into clinically meaningful differences. In the collagen induced arthritic mouse model, with respect to arthritic score, paw swelling and reduced joint damage during the treatment period, YLB113 showed distinct/ well-documented ant-arthritic activity when compared with arthritic control group. Its anti-arthritic activity was also comparable with the RMP Enbrel®. No *in vivo* studies evaluating secondary PD, safety pharmacology or PD-DIs were deemed necessary in accordance with EMA guideline on biosimilars.

- **Pharmacokinetics:** In conclusion, no significant differences in exposure were noted for Lupin Etanercept and Enbrel following SC administration. The observed results of the PK program are consistent with previously published nonclinical PK data for Enbrel®.

- **Toxicology:** Toxicity evaluations were mostly performed comparatively with the biosimilar investigational product YLB113 and the reference product Enbrel®. Acute and repeated dose toxicity studies, including the investigation of local and systemic tolerance, TK and immune response, resulted in similar results for both products. Both were well tolerated by study animals, and no mortality occurred. No difference was observed in the clinical signs, body weight, food and water consumption, blood and urine analysis, ophthalmological and auditory examination and necropsy between animals of the control

group, animals receiving YLB113 and animals receiving Enbrel®. No significant injection site reactions were observed. No accumulation of Etanercept was observed under dosage regimens used. As there was no dose related trend in ADA incidence with YLB113 treated animals, intergroup differences in ADA incidence were considered reflective of inter-animal variability. The immunogenicity of YLB113 was considered low.

- **Overall conclusion:** Etanercept is expected to be safe at therapeutic doses and indeed has been demonstrated safe and effective during the past many years of clinical use. Taken together, the submitted non-clinical data (in particular the in vitro TNF binding and Fc effector functional assay data) support the biosimilarity between Nepexto and Enbrel®.

4. Clinical aspect:

- **Clinical Overview**

The clinical program for Nepexto (YLB113) comprised a pivotal Phase 1 pharmacokinetic (PK) study in healthy male subjects and a pivotal Phase 3 study in patients with moderate to severe rheumatoid arthritis (RA). Two earlier PK studies (YLB113-001 and LBC-14-155) were conducted at an informative stage but were not considered representative of the commercial product due to differences in the manufacturing process.

Overview of Key Clinical Studies

- **Pivotal Phase I (ETA.50/334)**: Single-dose, open-label, randomized, two-period crossover study comparing Nepexto 50 mg SC and Enbrel 50 mg SC in healthy adult male subjects. The study assessed PK bioavailability as the primary objective and safety/tolerability as secondary objectives. Duration was approximately 50 days, including a 28-day washout period.
- **Pivotal Phase III (YLB113-002)**: Randomized, double-blind, parallel-group study in patients with moderate to severe RA receiving stable methotrexate therapy. The study evaluated efficacy, safety, and immunogenicity of Nepexto 50 mg SC weekly versus Enbrel 50 mg SC weekly over multiple stages (Stage A: 24 weeks, Stage B: 28 weeks, Stage C: 28 weeks) with a total treatment and follow-up duration of 56 weeks.

- **Clinical Efficacy and Immunogenicity**

Efficacy
The pivotal Phase III trial (YLB113-002) demonstrated therapeutic equivalence between Nepexto and Enbrel:

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- **Primary Endpoint:** ACR20 response at Week 24 was 81.3% for Nepexto vs. 87.1% for Enbrel; difference -5.8% (95% CI: -11.8, 0.2), within the predefined equivalence margin of ±15%.
- **Secondary Endpoints:** ACR50, ACR70, and DAS28 scores were comparable over time. A statistically significant difference in ACR50 at Week 24 was isolated and not reflected in other endpoints.
- **Sustainability:** Stage C (crossover) confirmed maintenance of efficacy after treatment switch.

Immunogenicity
Immunogenicity was low and transient for both products:

- Week 24: 2 ADA-positive cases in Nepexto, none neutralizing; 21 ADA-positive cases in Enbrel, 2 neutralizing.
- Long-term (Stage B & C): No neutralizing ADAs in Nepexto; 3 ADA-positive cases without neutralizing potential in Enbrel.

The overall immunogenicity profile supports biosimilarity.

➢ **Clinical Safety**

Phase I Study (ETA.50/334)

- TEAEs occurred in 29.8% (Nepexto) vs. 34.0% (Enbrel).
- No serious adverse events (SAEs) or deaths reported.

Phase III Study (YLB113-002)

- TEAEs were consistent across Stage A, B, and C. Overall incidence: 55.5% (Nepexto) vs. 65.7% (Enbrel).
- Injection site reactions were 10% lower in Nepexto, likely due to latex-free syringe components.
- Most frequent TEAEs: infections (nasopharyngitis) and administration site conditions.
- SAEs were infrequent (<5%) and comparable between groups; all resolved.
- Discontinuations due to AEs were rare and similar between treatment arms.

Conclusion on Safety: Nepexto exhibits a comparable safety profile to Enbrel, with no new safety signals identified.

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- **Overall Conclusion**
  - PK/PD: Bioequivalence demonstrated between Nepexto and Enbrel (Cmax, AUC0-t, AUC0-∞ within 80–125% acceptance range).
  - Efficacy: Therapeutic equivalence confirmed in RA patients, with consistent results across primary and secondary endpoints.
  - Safety & Immunogenicity: Comparable safety and immunogenicity profiles, with low and non-neutralizing ADA formation in Nepexto.

- **Benefit–Risk Analysis**

The totality of clinical data supports that Nepexto is highly similar to Enbrel in terms of pharmacokinetics, efficacy, safety, and immunogenicity:

- **Benefits:** Effective management of moderate to severe RA, once-weekly dosing, comparable clinical outcomes to the reference product.
- **Risks:** Safety profile consistent with known etanercept class effects; no new or unexpected risks identified.
- **Overall Assessment:** The benefit-risk balance is favorable, supporting Nepexto as a biosimilar to Enbrel for the treatment of RA.

5. General Conclusion and Recommendations if any:

Based on the review of CTD modules and other supplementary documents, the product is approved

For more information, please visit EMA published assessment report link:

https://www.ema.europa.eu/system/files/documents/assessment-report/h-4711-par_en.pdf