Unit: Technical Assessment Unit

Public assessment report for biological products

(Trastuza)

Administrative information:

Trade name of the medicinal product:	Trastuza, Lyophilized Powder for Concentrate for solution for IV Infusion
INN (or common name) of the active substance(s):	Trastuzumab 440 mg
Manufacturer of the finished product	Reliance life sciences Pvt. Ltd - INDIA ;
Marketing Authorization holder	Egyptian International Pharmaceutical Industries Company (EIPICO) - EGYPT ;
Applied Indication(s):	-HER2-positive Adjuvant Breast Cancer and Metastatic Breast Cancer. - HER2-positive Metastatic Gastric Cancer.
Pharmaceutical form(s) and strength(s):	1 multidose vial of Trastuza 440 mg lyophilized Powder + 20 ml clear glass vial of WFI
Route of administration	I.V \ Infusion
Type of registration (EMA/FDA – Local)	Local

List of abbreviations

DNA: Deoxyribonucleic Acid
CHO: Chinese Hamster Ovary Cells
INN: International Nonproprietary Name
MCB: Master Cell Bank
WCB: Working Cell Bank
EOP: End of Production cell
DS: Drug substance
IPCs: In-Process Control
API: Active Pharmaceutical Ingredient
RLS: Reliance Life Sciences
MA: Marketing autherization
IRS: Internal Reference Standard
IWS: Internal Working Standard
CTD: Common Technical Document
IV: Intravenous

WFI: Water for injection
HER2: Human epidermal growth factor-2 protein
C1q: A subcomponent of complement C1, involved in immunoglobulin initiation of complement activation via the classical pathway
FcRn: Neonatal FC receptor
FcγR1: FC gamma receptor I (CD64)
FcγRIIa: FC gamma receptor 2a (CD32a)
FcγRIIb: FC gamma receptor 2b (CD32b)
FcγRIIIa (F type): FC gamma receptor 3a F type (CDI 6a-F)
FcγRIIIa (V type): FC gamma receptor 3a V type (CD16a-V)
FcγRIIIb: FC gamma receptor 3b (CD 16b)
ADCC: Antibody-dependent cellular cytotoxicity
BT474 cells: Human mammary gland, ductal carcinoma cell line which overexpress HER-2 antigen on the surface
NZW: New Zealand White
RMP: Reference medicinal product
PK: Pharmacokinetics

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1. **General introduction about the product including brief description of the AI, its mode of action and indications:**
   - Trastuzumab has been produced by recombinant DNA technology using genetically engineered Chinese Hamster ovary cells (CHO).
   - **General information**
   - Drug Substance contains Trastuzumab at a concentration of 37-65 mg/ml in a buffer that has the same components as in the final Drug Product of RMP. To conduct bio-comparability exercise, Herclon®/Herceptin® (manufactured by M/s Roche) is used by Reliance Life Science Pvt Limited. Both are manufactured from the same manufacturer but sold under two different brand names. Herclon® is the brand name of Innovator product in India.
     - **Nomenclature**:

     - Recommended International Nonproprietary Name (INN): Trastuzumab
   - **Manufacture, process controls and characterization:**

Name and address of the manufacturers of the biological active substance:

Reliance life sciences Pvt. Ltd - INDIA

- **Description of Manufacturing Process and Process Controls.**
  The Manufacturing Process of RLS Trastuzumab Drug Substance is discussed in details in the MA file and the comparability exercise is performed and fulfill the requirement.
  Control of Materials.
  A summary of tests, specifications for the API "RLS Trastuzumab drug substance" is provided in MA file.
- **Controls of Critical Steps and Intermediates.**
  The critical steps of RLS Trastuzumab drug substance are identified and suitably controlled during manufacturing process.

Process Validation

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.

- **Manufacturing Process Development.**
- The development efforts with respect to protein production in the bioreactor and downstream processing for protein purification and formulation of drug substance is well described.
- Risk Assessment report for initiation of Trastuzumab drug substance manufacturing in addition to the process control strategy are provided in the file.
- **Specification**

- Specifications sheet of the RLS Trastuzumab drug substance is provided and 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.**

Details of the test methods are provided.

- **Reference Standards or Materials.**

The manufacturer submit detailed qualification report of Trastuzumab internal reference standard along with COA of IRS and IWS.

- **Container closure system**
  - Compatibility test of these sterile bags was conducted to identify and quantify the leachable that could migrate from the components when exposed to Trastuzumab. This study was carried out on RLS trastuzumab drug substance stored in disposable Flexboy bags for a period of 24 months at -20±5ºC.

Stability of the drug Substance.

-Based on available stability data, For DS plant 2 and DS plant 7:

approved Shelf Life: 24 months.

approved Storage Conditions: -20°±5°

2.2.3 Drug product:

- **Manufacture of the drug product:**

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

Manufacturer:

Reliance life sciences Pvt. Ltd - INDIA

- Control of critical steps and intermediates

In-process specification and standard testing procedure are attached in CTD.

- Process validation and / or evaluation.

The consistency of the overall Drug Product manufacturing process as well as reproducibility of key product quality attributes were evaluated as part of process validation.

Product specification:

Details of the test methods are provided.

The applicant described in details all types of product and process related impurities. The level of impurities found to be controlled to their accepted range.

- **Reference Standards or Materials.**

The Reference Standard used in DP is the same as ones that used in DS part.

- **Container closure system.**
- RLS Trastuzumab Drug Product 440 is presented as sterile lyophilized powder for intravenous infusion in 50R glass vial

Stability of the drug product.

-Based on available stability data:

approved Shelf Life: 36 months
approved Storage Conditions: 2-8 °.
And for solvent:
approved Shelf Life: 36 months
storage condition 20°C to 25°C (68° to 77°F).

3. **Non –clinical aspect:**

- **Pharmacodynamics**

In vitro characterization of comparative binding affinity assays of HER2 binding, cell based HER2 binding affinity, FcRn binding, FcγRI, FcγRIIa, FcγRIIb, FcγRIIIa (F type and V type), FcγRIIIb and C1q binding have been found to be highly similar. To confirm corresponding effects, in vitro bioactivity based on the proliferation of cancerous cells (BT-474) and ADCC has also been performed, demonstrating similarity in the mode of action. The applicant used the local brand Herclon 440 mg as an RMP instead of Herceptin, this was endorsed.
One In vivo study was submitted and demonstrated the comparable tumor regression potential of the candidate product compared with Herclon in NOD. SClD mice. This study is considered supportive due to the intrinsic high level of variability in the In vivo studies that makes it difficult to capture the possibly existing minor differences between biosimilars.

- **Pharmacokinetics:**

Specific non-clinical studies on absorption, distribution, metabolism, excretion, or drug interactions were not required. This approach is fully aligned with the Guideline for Registration of Biosimilar Products in Egypt (2023), which allows reliance on advanced analytical and clinical comparability data instead of traditional PK studies in animals.

Toxicology:
Single and repeated toxicity studies on mice, rats and NZW rabbits showed no toxicological findings. The selected dose levels for repeated dose toxicity were 1, 2.5, and 5 times more than the human intended exposure in rats and rabbits (considering human dose as 8 mg/kg). The studies for genotoxicity, carcinogenicity, reproduction and development and local tolerance are not required for the assessment of biosimilar products according to national and international guidelines. Thus, the skin sensitization study on Guinea pigs is considered supportive.
Overall, the non-clinical data support the conclusion that the R-TPR-016 (trastuzumab) is highly similar to the reference (Herclon™) and does not raise any new safety concerns.

4. **Clinical aspect:**

R-TPR-016 (trastuzumab) is a proposed biosimilar to Herceptin® (Herclon™) developed for the treatment of metastatic HER2-overexpressing breast cancer. Its clinical development included a large, multi-centre, randomized, active-controlled Phase III study (RLS/TP/2011/05). The study evaluated **pharmacokinetics, efficacy, safety, and immunogenicity** of R-TPR-016 compared with Herceptin®.

A total of **148 female patients** were enrolled across two study stages:

- **Stage I:** PK comparability in 42 patients (1:1 randomization).
- **Stage II:** Efficacy & safety in 106 patients (4:1 randomization; 84 R-TPR-016 vs 22 Herceptin®).

Both products were administered intravenously with the same dosing regimen (loading 8 mg/kg followed by 6 mg/kg every 3 weeks).

The comprehensive clinical dataset demonstrates that **R-TPR-016 behaves similarly to Herceptin® in pharmacokinetic exposure, therapeutic effect, and safety profile**.

- **Clinical Efficacy and Immunogenicity:**

Efficacy was assessed mainly through **Objective Response Rate (ORR)** at Week 25 using RECIST 1.1.

Primary Endpoint ORR at Week 25

- **R-TPR-016:** 48.44% (CR 10.94%; PR 37.50%)
- **Herceptin®:** 44.44% (CR 11.11%; PR 33.33%)

The difference was **not statistically significant**, confirming comparable anti-tumor activity.

Secondary Endpoints

- **Progression-Free Survival (PFS):**
  - Median PFS: 11.67 months (R-TPR-016) vs 8.02 months (Herceptin®)
  - Differences were **not statistically significant**.

- **Overall Survival (OS):**
  - At 2 years: 15.92 months (R-TPR-016) vs 15.33 months (Herceptin®)
  - At 5 years: 16.28 months vs 15.33 months
  - No statistically significant differences.

- **Radiological Tumor Response (52 weeks & 2 years):**
  - Comparable CR and PR rates between groups at both timepoints.

Immunogenicity

Immunogenicity was assessed at Week 25 in 52 patients.

- **No anti-drug antibodies were detected** in either treatment arm.
- No immunologically mediated safety concerns were observed.

Conclusion:

R-TPR-016 demonstrates **equivalent efficacy and immunogenicity** to Herceptin® across all measured endpoints.

- **Clinical Safety conclusion:**

Overall Exposure

- 82 patients received R-TPR-016 and 22 patients received Herceptin®.
- Both groups received comparable cumulative doses.

Adverse Events

- Total AEs: 206 (R-TPR-016) vs 60 (Herceptin®)
- Incidence of ≥1 AE: 71.95% vs 59.09%
- Most frequent AE categories were similar between groups and reflected the **established trastuzumab safety profile**, including:
  - General disorders (e.g., fatigue, pyrexia)
  - Nervous system disorders
  - Musculoskeletal disorders
  - Hematologic abnormalities (e.g., neutropenia)
  - Gastrointestinal symptoms

Serious Adverse Events (SAEs)

- SAEs: 9 patients (R-TPR-016) vs 2 patients (Herceptin®)
- Most common SAEs: neutropenia, anemia, infections
- **Two SAEs** were considered related to study drug (distributed across both arms).

Deaths

- 4 deaths in R-TPR-016 arm vs 2 in Herceptin® arm.
- All deaths were consistent with disease progression and known drug-related risks.

Infusion-related Reactions

- None were formally reported; potential infusion-related symptoms showed **no statistically significant difference** between groups.

Laboratory & Organ Function

- No clinically meaningful differences from baseline in hematology, liver, kidney, or metabolic parameters.

Post-marketing (India)

- Post-marketing data for the same product (TrastuRel®) showed **no new safety concerns**, supporting a stable long-term safety profile.

Conclusion:
R-TPR-016 demonstrates a **safety profile comparable** to Herceptin® with no unexpected adverse effects or concerns.

- **Overall Conclusion:**

R-TPR-016 has demonstrated **biosimilarity to Herceptin®** based on comprehensive pharmacokinetic, efficacy, safety, and immunogenicity data derived from a robust Phase III comparative clinical trial. The findings confirm that:

- Clinical outcomes (ORR, PFS, OS) are **equivalent**.
- Safety and tolerability are **consistent** with the established trastuzumab profile.
- No immunogenicity concerns are present.
- Pharmacokinetic exposure matches the reference product within regulatory acceptance criteria.

R-TPR-016 provides an effective and safe therapeutic option for patients with metastatic HER2-positive breast cancer, offering comparable clinical performance to Herceptin®.

- **Benefit/ Risk discussion:**

Benefits

- Equivalent ORR, PFS, OS, and radiological outcomes relative to Herceptin®.
- No detected immunogenicity.
- Pharmacokinetic parameters fall within accepted bio similarity limits (90% CI within 80–125%).

Risks

- Adverse events consistent with known trastuzumab safety profile.
- No increase in serious toxicity or infusion reactions.
- No immune-mediated risk identified.

Overall Benefit–Risk Balance
The totality of evidence including PK comparability, comparable clinical efficacy, aligned safety patterns, and absence of immunogenicity supports a **positive benefit–risk profile** for R-TPR-016 equivalent to Herceptin®.

5. General Conclusion and Recommendations if any:

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