LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Liraglutide Reddy
(liraglutide (synthetic))

SE/H/2576/01/DC

This module reflects the scientific discussion for the approval of Liraglutide Reddy. The procedure was finalised at 2026-01-21. For information on changes after this date please refer to the module 'Steps taken after the finalisation of the initial procedure - Summary'.

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.lakemedelsverket.se E-mail: registrator@lakemedelsverket.se

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have agreed to grant a marketing authorisation for Liraglutide Reddy, 6 mg/ml, Solution for injection in pre-filled pen.

The active substance is liraglutide (synthetic). A comprehensive description of the indication and posology is given in the SmPC.

II. EXECUTIVE SUMMARY

II.1 About the product

Indications and posology
Liraglutide Reddy is indicated for treatment of adults, adolescents and children aged 10 years and above with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise.

- as monotherapy when metformin is considered inappropriate due to intolerance or contraindications
- in addition to other medicinal products for the treatment of diabetes

Liraglutide Reddy is administered once daily as a subcutaneous injection, with a starting dose of 0.6 mg, which can be increased after at least one week to 1.2 mg. The maximum daily dose is 1.8 mg. To improve gastro-intestinal tolerability, the starting dose is 0.6 mg liraglutide daily.

Mode of action
Liraglutide is an analog of human GLP-1 and acts as a GLP-1 receptor agonist. The peptide precursor of liraglutide, has been engineered to be 97% homologous to native human GLP-1 by substituting arginine for lysine at position 34. Liraglutide is made by attaching a C-16 fatty acid (palmitic acid) with a glutamic acid spacer on the remaining lysine residue at position 26 of the peptide precursor. Liraglutide has thereby obtained pharmacokinetic properties that are suitable for once-daily dosing.

By binding to the GLP-1 receptor, Liraglutide potentiates glucose-dependent insulin secretion from the pancreatic beta cells. Thus, when blood glucose is high, insulin secretion is stimulated, and glucagon secretion is inhibited.

Special aspects
The reference product, Victoza, is a biological medicinal product with the active substance liraglutide derived from Saccharomyces cerevisiae, whereas Liraglutide Reddy is manufactured synthetically.

The drug product is a solution for subcutaneous injection in pre-filled pen, 6.0 mg/mL of the drug substance presented in a pre-filled, multi-dose pen-injector. The proposed generic product composition is qualitatively equivalent to the reference product's composition.

Pharmacological classification
The ATC Code is A10BJ02, Pharmacotherapeutic group: Drugs used in diabetes, glucagon-like peptide-1 (GLP-1) analogues.

II.2 General comments on the submitted dossier

The application for Liraglutide Reddy, 6 mg/ml, Solution for injection in pre-filled pen, is a Hybrid Art. 10(3) application submitted according to Directive 2001/83/EC. The applicant applies through the

Decentralised Procedure with Sweden acting as reference member state (RMS) and AT, DE, ES, FR, IT, RO as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Victoza, 6 mg/ml, Solution for injection in pre-filled pen, authorised in the Union since 2009, with Novo Nordisk A/S as marketing authorisation holder.

The reference product used in the bioequivalence study is Victoza, 6 mg/ml, Solution for injection in pre-filled pen from Czech Republic with Novo Nordisk A/S as marketing authorisation holder.

Potential similarity with orphan medicinal products
According to the application form and a check of the Community Register of orphan medicinal products there is no medicinal product designated as an orphan medicinal product for a condition relating to the indication proposed in this application

II.3 General comments on compliance with GMP, GLP, GCP and agreed ethical principles

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, 'close-out letters' or 'exchange of information' issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

GMP active substance
Regarding the statement on GMP for the active substance a statement/declaration is provided from the manufacturer(s) responsible for manufacture of the finished product and batch release situated in the EU.

GCP
A statement on the application of appropriate GCP standards in the submitted study has been provided. No issues regarding GCP have been identified. No inspection of the submitted bioequivalence study is needed.

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

Drug substance
The structure of the drug substance has been adequately proven, and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described, and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

Drug Product
The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III.2 Non-clinical aspects

Pharmacology/Pharmacokinetics/Toxicology
The application procedure refers to Article 10(3) hybrid application. In line with this type of procedure, in the non-clinical part of the dossier the applicant submitted bibliographical data plus results from in-vitro studies (comparison of biological activity, GLP-1 receptor binding and immunogenicity) aimed at demonstrating the similarity between synthetically derived Liraglutide Reddy and biotechnology derived Victoza (reference product).

Pharmacodynamic, pharmacokinetic and toxicological properties of liraglutide are well known. As liraglutide is a widely used, well-known active substance, no further studies are required and bridging non-clinical data using bibliographical data together with in-vitro studies is acceptable for this generic application.

The non-clinical overview dated 19th of September 2024, was written by Navakanth Bondalapati Global Medical Affairs, Dr. Reddy's Laboratories Limited, Hyderabad, India. The report refers to 38 publications, the most recent from year 2024.

Non-clinical sections of the SmPC are in accordance with the SmPC of the reference product Victoza.

A short description and main results of the submitted studies are given below.

Relative Potency Estimation by *In vitro* cell-based cAMP Bioassay
Results from a comparative *in vitro* cell-based cAMP bioassay showed that the average relative potency (cAMP induction) was comparable to that of reference product Victoza. The results support that Liraglutide Reddy is expected to have similar biological activity as the reference product.

Potency Estimation by *In vitro* GLP-1 receptor binding assays
The applicant provided a comparative receptor binding study using the Tag-Lite Glucagon GLP1 Receptor Cells cell system, The result showed no significant differences when comparing Liraglutide Reddy to Victoza.

In vitro Beta-cell proliferation assay
The applicant performed an in vitro beta-cell proliferation assay to further support the comparability

with the reference product Victoza. The assay was performed in compliance with OECD Principles of GLP and compared six batches of Liraglutide Reddy with the reference product Victoza (three batches).

The results from the *in vitro* beta-cell proliferation study did not indicate any significant difference between Liraglutide Reddy and the reference product Victoza supporting similar functional activity between the two products.

In silico immunogenicity risk assessment

The applicant conducted an *in silico* immunogenicity evaluation of Liraglutide Reddy and peptide related impurities using the Insilco methods/tools to screen for the presence or absence of T-cell epitopes. Using this approach, the immunogenic risk of Liraglutide Reddy and its peptide related impurities were categorized as “acceptable” or “insignificant”. The relevance of *in silico* T-cell activation predictions are uncertain and *in silico* data are not considered predictive of clinical immunogenicity.

In vitro human PBMC T cell proliferation studies
To determine the relative antigenicity of Liraglutide Reddy and its impurities compared to the reference product Victoza, the applicant isolated human PBMCs from healthy donors and measured T-cell proliferation in vitro.

While the overall data indicated that Liraglutide Reddy performed comparable to the reference product with low potential immunogenicity. While it is unclear how well results from this *in vitro* assay can predict clinical immunogenicity, the results indicate the Liraglutide Reddy has a similar *in vitro* T-cell proliferation profile as the reference product Victoza.

In vitro Innate immnunogenicity
The applicant conducted a human whole blood-based cytokine release assay. Samples from healthy donors were analysed. Altough the cytokine release assay results do not appear to differ significantly from the reference product results, the *in vitro* data are not considered predictive for clinical outcomes.

Environmental Risk Assessment (ERA)
Liraglutide Reddy is a synthetic human GLP-1 analogue with 97% sequence homology to human GLP-1. Since Liraglutide Reddy is a generic product, it will not lead to an increased exposure to the environment.

The applicant calculated $PEC_{surface\ water}$ value which was found to be below the action limit of 0.01 μg/L (0.0090 μg/L).

Based on the above, Liraglutide Reddy is unlikely to pose a significant risk to the environment and no further ecotoxicological assessment is required.

Conclusions on studies:
The active substance is a synthetic human GLP-1 analogue with 97% sequence homology to human GLP-1, a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, Liraglutide Reddy is not expected to pose a risk to the environment.

There are no objections to approval of Liraglutide Reddy from a non-clinical point of view.

III.3 Clinical aspects

Pharmacokinetics
To support the marketing authorisation application the applicant has conducted one bioequivalence study in the fasted state, comparing Liraglutide Reddy with the reference product Victoza.

Pharmacokinetic properties of the active substance
Absorption:
The absorption of liraglutide following subcutaneous administration was slow, reaching maximum concentration approximately 11 hours post dosing. The average liraglutide steady state concentration ($AUC_{\tau/24}$) reached approximately 31 nmol/L in obese (BMI 30–40 kg/m^2) patients following administration of 3 mg liraglutide. Liraglutide exposure increased proportionally with dose. Absolute bioavailability of liraglutide following subcutaneous administration is approximately 55%.

Elimination:
The mean clearance following subcutaneous administration of liraglutide is approximately 0.9–1.4 l/h with an elimination half-life of approximately 13 hours.

Study 075-24 - FASTING
Methods
This was a single-dose, two-way crossover study conducted in 48 healthy volunteers (46 completed), comparing Liraglutide Reddy, injection, 6 mg/ml, solution for injection in pre-filled pen with Victoza, 6 mg/ml, solution for injection in pre-filled pen, under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 72 hours post-dose. Plasma concentrations of liraglutide were determined with an LC-MS/MS method. Analysis of variance (ANOVA) was performed on the ln-transformed data for AUC_{0-t} and C_{max}.

Results

The results from the pharmacokinetic and statistical analysis are presented in Table 1 below.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for liraglutide, n=46.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**1516.75 ±391.52**	**59.52 ±16.48**	**11.75 (4.00-16.00)**
Reference	**1550.54 ±357.54**	**61.38 ±15.68**	**12.00 (8.02 - 24.00)**
***Ratio (90% CI)**	**97.30 (94.03-100.68)**	**96.35 (92.67-100.17)**	**-**

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum plasma concentration

**calculated based on ln-transformed data*

For AUC_{0-t} and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00 %.

Discussion and overall conclusion

The bioequivalence study and its statistical evaluation were in accordance with accepted standards for bioequivalence testing, as stated in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr). The bioanalytical methods were adequately validated.

Based on the submitted bioequivalence study, Liraglutide Reddy could be considered bioequivalent with Victoza.

Pharmacodynamics/Clinical efficacy/Clinical safety

A bioequivalence study (study 075-24) was performed to compare single dose (0.6 mg) of Liraglutide Reddy 6 mg/ml solution with single dose (0.6 mg) of Victoza (liraglutide) 6 mg/ml in 48 healthy adult male subjects, under fasting conditions. The study was a randomised, two-treatment, two-period, two-sequence single-dose crossover study. Two subjects did not complete the study. Based on this study, the test product is considered bioequivalent with the reference product Victoza®.

Furthermore, the BE study generated safety data. In the BE Study 075-24, subjects were monitored for adverse events throughout the study. At the end of the study, post study safety evaluation was done which included hematology and clinical biochemistry. Eight AEs were reported by 5 (10.4%) subjects among 48 enrolled in the study. The study performed in healthy individuals and not in individuals belonging to the target population, resulted in safety data which generally were not considered alarming. No SAEs were reported, and no injection-site reactions were reported.

All AEs were classified as ‘Mild’. Headache, fever and elevated liver enzymes were reported by 2, 1 and 2 subjects, respectively. The frequency observed (common) for headache is in accordance with the listed AE frequency for the reference drug Victoza (Victoza SmPC sect 4.8). Two subjects were observed to have elevated aspartate aminotransferase (AST) and Alanine transaminase (ALT), with possible relationship with the drug. For both subjects, all measurements were back to normal levels at the repeat post study samples. The data shown are not considered alarming.

Post study samples showed serum potassium above reference interval (3,5-5,1 mmol/L) for eleven of 48 subjects (23 %). For the subject with the highest potassium level, the potassium level was noted as an AE with relationship with the drug noted as ‘unlikely’. A repeated post-study sample showed

normalised level of potassium. For one subject, elevated potassium was noted both in screening and post-study samples, and for one subject, elevated potassium was noted in screening sample, but not post-study.

The Applicant provided a general discussion of elevated potassium, and a discussion of the incidence rate of 23% in their study. Hyperkalemia is present in the healthy population, and that confounding factors exist. Already published data on liraglutide do not support an association between elevated potassium and liraglutide, and the method of action does not support such an association.

For the subject with elevated potassium with 'unlikely' relationship with the drug, it is agreed that elevated potassium post-study lowers the probability of a causal relationship. The transient nature does not exclude a causal relationship, neither does the fact that the subject was asymptomatic. Nevertheless, it is agreed that the elevated potassium observed in the study is not considered an issue alarming for the B/R balance of the test product.

Bioequivalence is considered proven, see conditions above. Therefore, the clinical efficacy and clinical safety can be assumed to be similar to that of the reference product. Since 'sameness' compared to the reference product is considered proven, and no quality issues, e.g. concerning fibril formation, are remaining, immunogenicity studies *in vivo* are not required.

The drug product consists of pharmaceutical product and medical device. The medical device is a non-refillable pen injector (pre-filled pen), similar to the injection device of the reference product. A notified body opinion is received confirming compliance with relevant GSPRs for the pre-filled pen device. No new user-related risks are identified. Therefore, a usability study is not considered necessary.

Pharmacovigilance system

Proposed MAH: Reddy Holding GmbH, betapharm Arzneimittel GmbH, Dr. Reddy's S.r.l., Dr. Reddys Laboratories Romania S.R.L., Reddy Pharma Iberia S.A. Reddy Pharma S.A.S.,
The Applicant has submitted a signed Summary of the Applicant's/Proposed Future MAH's Pharmacovigilance System together with an annex listing all relevant subsidiaries. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module, the RMS considers the Summary acceptable.

Risk Management Plan
The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Liraglutide Reddy.

Part II Safety specification

Summary of safety concerns	
Important identified risks	None
Important potential risks	• Neoplasms (including melanoma) • Medullary thyroid cancer (C-cell carcinogenicity) • Pancreatic cancer
Missing information	None

The proposed safety concerns are based on the RMP for Victoza (v.33 dated 1st of December 2022). It is considered correct to harmonise with the safety concerns of the originator. After the DLP of the Applicant´s RMP, a new version of liraglutide RMP has been approved (version 34.1), but the update of the originator´s RMP from v.33 to v.34.1 is not considered to influence the Applicant´s RMP.

Part III Pharmacovigilance Plan

Routine pharmacovigilance is suggested, and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Part V Risk minimisation measures

The safety information in the proposed product information is aligned to the reference medicinal product. Routine RMMs are stated in tables in section V for T2D but is not stated for weight management since the proposed indication is T2D not weight management. This is acknowledged.

Part VI Summary of the RMP

General information on Liraglutide Reddy and Summary of risk management plan for … (liraglutide in T2D) is included in Part VI.

Conclusion RMP assessment

The submitted Risk Management Plan, version 0,3 signed 25th of November 2025 is considered acceptable.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

Periodic Safety Update Report (PSUR)

Active substance is currently listed in the published EURD list

With regard to PSUR submission, the MAH should take the following into account:

- PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.

- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.

- In case the active substance will be removed in the future from the EURD list because the MAs have been withdrawn in all but one MS, the MAH shall contact that MS and propose DLP and frequency for further PSUR submissions together with a justification.

Common renewal date
The common renewal date will be 5 years after closure of the DCP

IV. BENEFIT RISK ASSESSMENT

The quality of the generic product, Liraglutide Reddy, is found adequate. There are no objections to approval of Liraglutide Reddy, from a non-clinical and clinical point of view. Bioequivalence between the test and reference product has been adequately demonstrated. The product information is acceptable. The benefit/risk is considered positive, and the application is therefore recommended for approval.

V. RECOMMENDATIONS AND CONDITIONS FOR MARKETING AUTHORISATION AND PRODUCT INFORMATION

V.1 List of recommendations not falling under Article 21a/22 of Directive 2001/83/EC

Post approval commitments
N/A

V.2 List of conditions pursuant to Article 21a or specific obligations pursuant to Article 22 of Directive 2001/83/EC

- **Additional risk minimisation measures (including educational material)**
  N/A

- **Obligation to conduct post-authorisation measures in accordance with Article 21a of Directive 2001/83/EC**
  N/A

- **Specific obligation to complete post-authorisation measures for the marketing authorisation under Exceptional circumstances in accordance with Article 22 of Directive 2001/83/EC**
  N/A

V.3 Summary of Product Characteristics (SmPC)

The approved SmPC is available in the MRI Product Index.

V.4 Package Leaflet (PL)

V.4.1 Package Leaflet

The approved PL is available in the MRI Product Index.

V.4.2 Assessment of User Testing

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PL was English.
The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
-	-	-	-	-	-