Public Assessment Report
Scientific discussion

Ejulir
(liraglutide)

SE/H/2572/001/DC

This module reflects the scientific discussion for the approval of Ejulir. The procedure was finalised at 2025-10-09. For information on changes after this date please refer to the module 'Update'.

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

TABLE OF CONTENTS

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have agreed to grant a marketing authorisation for Ejulir, 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
Adults
is indicated as an adjunct to a reduced-calorie diet and increased physical activity for weight management in adult patients with an initial Body Mass Index (BMI) of:
• ≥30 kg/m² (obesity), or
• ≥27 kg/m² to <30 kg/m² (overweight) in the presence of at least one weight-related comorbidity such as dysglycaemia (prediabetes or type 2 diabetes mellitus), hypertension, dyslipidaemia or obstructive sleep apnoea.
Treatment with [Invented name] should be discontinued after 12 weeks on the 3.0 mg/day dose if patients have not lost at least 5% of their initial body weight.

Adolescents (≥12 years)
Ejulir can be used as an adjunct to a healthy nutrition and increased physical activity for weight management in adolescent patients from the age of 12 years and above with:
• obesity (BMI corresponding to ≥30 kg/m2 for adults by international cut-off points)* and
• body weight above 60 kg.

Treatment with Ejulir should be discontinued and re-evaluated if patients have not lost at least 4% of their BMI or BMI z score after 12 weeks on the 3.0 mg/day or maximum tolerated dose,

Mode of action
Liraglutide is an acylated human glucagon-like peptide-1 (GLP-1) analogue with 97% amino acid sequence homology to endogenous human GLP-1. Liraglutide binds to and activates the GLP-1 receptor (GLP-1R).

GLP-1 is a physiological regulator of appetite and food intake, but the exact mechanism of action is not entirely clear. In animal studies, peripheral administration of liraglutide led to uptake in specific brain regions involved in regulation of appetite, where liraglutide, via specific activation of the GLP-1R, increased key satiety and decreased key hunger signals, thereby leading to lower body weight.

GLP-1 receptors are also expressed in specific locations in the heart, vasculature, immune system and kidneys. In mouse models of atherosclerosis, liraglutide prevented aortic plaque progression and reduced inflammation in the plaque. In addition, liraglutide had a beneficial effect on plasma lipids. Liraglutide did not reduce the plaque size of already established plaques.

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

The drug product is a solution for subcutaneous injection in a pre-filled pen.

Pharmacological classification
The ATC code is A10BJ02

II.2 General comments on the submitted dossier

The application for Ejulir, 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, CZ, DE, DK, ES, FR, IE, IT, NL, PL, RO, SK as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Saxenda, 6 mg/ml, Solution for injection in pre-filled pen authorised in Union since 2015, with Novo Nordisk A/S of the originator product as marketing authorisation holder.

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

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 aspects
A statement on the application of appropriate GCP standards in the submitted study has been provided. No issues regarding GCP have been identified. The clinical and bioanalytical facilities were inspected by the WHO in 2023, by FDA in 2022 and by Austrian authority (AGES) in 2019, without any critical findings. 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, the applicant submitted bibliographical data plus results from in-vitro studies (comparison of biological activity and immunogenicity) aimed at demonstrating the similarity between synthetically derived liraglutide (Ejulir) and biotechnology derived Saxenda® (reference product).

Pharmacodynamic, pharmacokinetic and toxicological properties of liraglutide are well known. As liraglutide is a widely used, well-known active substance, apart from the in silico/in vitro comparability studies, the applicant has not provided additional non-clinical studies.

The non-clinical overview dated 29th of April 2024, was written by Dr. Shifa Farhan Shaikh Global Medical Affairs, Dr. Reddy's Laboratories Limited, Hyderabad, India. The report refers to 34 publications, the most recent from year 2023.

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

In the innate immunogenicity in vitro studies, no relevant difference was observed between the Liraglutide test product and Saxenda®.

Biological Evaluation:

a) Summary of comparative in vitro Biological Activity- Potency Estimation by In vitro cell based Bioassay

To support comparability with the reference product, the Applicant has analyzed the relative biological activity of Liraglutide test and reference items on the stimulation of adenylate cyclase accumulation in the CHO-K1 GLP1R cell line using a Hit hunter cAMP kit.

The relative potency value was measured for each determinant, combined mean relative potency and corrected % combined mean relative potency. Results from the in vitro cAMP assay demonstarated similarity between the tested Liraglutide product and the reference Liraglutide product Saxenda® with a mean relative potency within the acceptability criteria.

b) Summary of Comparison of in vitro GLP-1 receptor binding assay, Study AD-G2320

In-vitro characterization of the biological action and comparison between the Liraglutide test product 6 mg/mL and the reference product Saxenda® 6 mg/mL was performed by determination of Ki (Competitive binding) and IC50.

Validation of the method for GLP1 receptor binding affinity was performed in accordance with the OECD Principles of Good Laboratory Practice.

Three batches of Liraglutide 6 mg/mL test product and three batches of Saxenda® EU RMP were tested in triplicates. The Ki and IC50 values were recorded for each test product and EU RMP and compared with the reference RMP data. The relative potency of the test products and EU RMP was calculated using IC50 values.

The relative potency (RP) of the test product comparable to reference product.

As the obtained relative potency percentage values of test products and RMP were within the acceptance limits, , Liraglutide test product 6 mg/mL and EU RMP Saxenda® 6 mg/mL can be considered as similar to the reference RMP batch of Saxenda®.

Immunogenicity studies

In silico immunogenicity evaluation

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” by the applicant.

In the *in silico* immunogenicity evaluation, Liraglutide Reddy was compared to its reference product Viconza®. An *in silico* immunogenicity evaluation of Ejulir and its reference product Saxenda® has not been conducted. Since Applicant has changed manufacturer for Liraglutide between the two products, i.e. Liraglutide Reddy and Ejulir, the impurity profile may differ between the products, but not the amino acid sequence.

Nevertheless, the relevance of *in silico* T-cell activation predictions are uncertain and *in silico* data are not considered predictive of clinical immunogenicity.

In vitro Innate Immunogenicity test

A cytokine release assay was performed on pooled whole blood from 20 healthy donors for assessing the innate immune activation in three bathes of Liraglutide test product for comparison with three Saxenda® batches. No relevant difference was observed between Liraglutide test product and Saxenda®.

Similarity in immunogenicity profiles between the reference product Victoza and Liraglutide Reddy have been based on comparative quality exercises. The quality concerns has been addressed satisfactory.

Environmental Risk Assessment (ERA)

The applicant has provided a Phase I Environmental Risk Assessment. The $PEC_{surface\ water}$ value calculated using refined Fpen (based on API consumption) was found to be below the action limit of 0.01 µg/L. No further ecotoxicological assessment is therefore required.

Since Liraglutide Reddy is a generic product, it will not lead to an increased exposure to the environment. Furthermore, as indicated in the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use, peptides are due to their nature unlikely to result in a significant risk to the environment. An environmental risk assessment is therefore not deemed necessary.

III.3 Clinical aspects

Pharmacokinetics

To support the marketing authorisation application the applicant has conducted one bioequivalence study comparing Ejulir (Liraglutide Injection) with the reference product Saxenda.

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 059-23

Methods

This was a single-dose, two-way crossover study conducted in 48 healthy volunteers (47 completed), comparing Liraglutide Injection, 6 mg/ml, solution for injection in pre-filled pen with Saxenda, 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 a 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=47.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**2082.76 ± 489.39**	**80.81 ± 25.12**	**12.000 (8.500-16.000)**
Reference	**2152.79 ± 481.43**	**83.54 ± 26.06**	**11.500 (8.000-16.000)**
***Ratio (90% CI)**	**96.24 (92.54-100.09)**	**96.42 (91.22-101.92)**	**-**
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 method was adequately validated.

Based on the submitted bioequivalence study, Ejulir is considered bioequivalent with Saxenda.

Pharmacodynamics

No new data have been submitted. No data are required for an abridged application provided bioequivalence has been satisfactorily demonstrated.

Clinical efficacy

No new data on clinical efficacy has been submitted.

Clinical safety

8 AEs were reported by 7 subjects in the study (Table 1). Incidence was balanced between the test and reference product groups (2 vs. 1 AE, respectively) whereas 5 cases were reported during the post study safety assessment. No SAEs were reported. Abdominal pain was reported by one subject in each treatment group. Abdominal pain is listed as an adverse reaction under section 4.8 of the SmPC for the reference product Saxenda (frequency common). Three cases of elevated serum cholesterol were registered in the post study safety assessment and could not be attributed to a particular study group. These patients had cholesterol values in the upper range already at the screening visit. Furthermore, in the post study sample data, two cases of elevated potassium were noted One of the patients had high serum potassium already at the screening visit (6 mEq). Thus, the summarized data do not indicate a different safety profile for the test product compared to the reference product Saxenda.

Table 1. Incidence of Adverse Events.

Body System / Adverse Event	**Reported Incidence by Treatment Groups**		
	Test Product (A)	**Reference Product (B)**	**Post Study Safety lab abnormality / Safety population**
N	**47**	**48**	**48***
GIT			
Abdominal pain	01 (2.13%)	01 (2.08%)	-
Body as whole			
Fever	01 (2.13%)	-	-
Post study safety			
Total cholesterol	-	-	03 (6.25%)
Serum potassium	-	-	02 (4.17%)
Total	**02 (4.26%)**	**01 (2.08%)**	**05 (10.42%)**
Note: Post study evaluation was performed for 48 subjects hence the number of subjects considered for safety population was 48. * Post-study safety abnormal laboratory values, which cannot be ascribed to any treatment, the N was considered 48 (Safety population).			

Pharmacovigilance system

Proposed MAH:

RMS, CMS: AT, CZ, DK, IE, NL, PL, RO, ES, SK - Viatris Limited
CMS: DE - Viatris Healthcare GmbH
CMS: FR - Viatris Sante
CMS: IT: Mylan S.p.A.

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 Ejulir.

Part II Safety specification

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	• Neoplasms (including melanoma) • Medullary thyroid cancer (C-cell carcinogenicity) • Pancreatic cancer
Missing information	• Patients with a history of major depression or other severe psychiatric disorders • Concomitant use of other weight lowering products

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

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

The safety information in the proposed product information is aligned to the reference medicinal Product which is sufficient according to GVP module V guideline.

Part VI Summary of the RMP
The Summary of the RMP is endorsed.

Conclusion RMP assessment
The submitted Risk Management Plans (version 0.2 signed 19 August 2025 for Ejulir 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, Ejulir, is found adequate. There are no objections to approval of Ejulir, 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

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
-	-	-	-	-	-