LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Glanux,
(liraglutide (synthetic))

SE/H/2747/001/DC

This module reflects the scientific discussion for the approval of Glanux. The procedure was finalised at 2026-05-12. For information on changes after this date please refer to the module 'Steps taken after the finalisation of the initial procedure - Summary'.

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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 Glanux, 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
Glanux 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

Glanux 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 a GLP-1 analogue with 97% sequence homology to human GLP-1 that binds to and activates the GLP-1 receptor. The GLP-1 receptor is the target for native GLP-1, an endogenous incretin hormone that potentiates glucose-dependent insulin secretion from the pancreatic beta cells.
Unlike native GLP-1, liraglutide has a pharmacokinetic and pharmacodynamic profile in humans suitable for once daily administration. Following subcutaneous administration, the protracted action profile is based on three mechanisms: self-association, which results in slow absorption; binding to albumin; and higher enzymatic stability towards the dipeptidyl peptidase -4 (DPP-4) and neutral endopeptidase (NEP) enzymes, resulting in a long plasma half-life.
Liraglutide action is mediated via a specific interaction with GLP-1 receptors, leading to an increase in cyclic adenosine monophosphate (cAMP). Liraglutide stimulates insulin secretion in a glucose-dependent manner. Simultaneously, liraglutide lowers inappropriately high glucagon secretion, also in a glucose-dependent manner. Thus, when blood glucose is high, insulin secretion is stimulated, and glucagon secretion is inhibited. Conversely, during hypoglycaemia liraglutide diminishes insulin secretion and does not impair glucagon secretion. The mechanism of blood glucose lowering also involves a minor delay in gastric emptying. Liraglutide reduces body weight and body fat mass through mechanisms involving reduced hunger and lowered energy intake, GLP-1 is a physiological regulator of appetite and food intake, but the exact mechanism of action is not entirely clear.

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

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 applications for Glanux, 6 mg/ml, Solution for injection in pre-filled pen, and its six duplicate applications are Hybrid Art. 10(3) applications submitted according to Directive 2001/83/EC. The applicant applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and with the following concerned member states (CMS):

Procedure	CMS
SE/H/2747/001/DC	IT

*W*ithdrawn from the procedure at Day 160*

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, 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
A statement on the application of appropriate GCP standards in the submitted study has been provided. The Applicant provided outcomes from inspections conducted around the time the study was performed. No critical 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, the applicant submitted a non-clinical overview based on bibliographical data. The applicant has also conducted two GLP in vivo studies (14-days repeat toxicology studies in rats and rabbits), aimed to demonstrate the safety of liraglutide 6 mg/mL solution for injection and included these studies in the overview.

The non-clinical overview dated December 2024 refers to 63 publications, the most recent from year 2024.

Pharmacodynamic, pharmacokinetic and toxicological properties of liraglutide are well known. As liraglutide is a widely used, well-known active substance, apart from the toxicology studies, the applicant has not provided additional studies.

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

The following non-clinical in vivo studies were submitted:

- 14-day repeated dose subcutaneous toxicity study of liraglutide 6 mg/mL solution for injection in Sprague Dawley rats
- 14-day repeated dose subcutaneous toxicity study of liraglutide 6 mg/mL solution for injection in New Zealand white rabbits ()

In the provided in vivo studies (which are not a requirement in the EU; conducted to meet local legislation from Medicines Agency), liraglutide was well tolerated and showed effects on body weight

and food consumption in both species which are expected to occur due to the pharmacological activity of liraglutide. In rabbits, moderate dose-related vacuolation of hepatocytes in the liver were noted with unclear relevance.

Environmental Risk Assessment (ERA)
Glanux is a hybrid product with an approved reference medicinal product Victoza.

The provided ERA is based on the assumption that Glanux is a non-natural substance/peptide. This is not agreed, since Liraglutide is a human GLP-1 analogue modified by a substitution of natural amino acids (lysine by arginine), and an incorporation of a natural fatty acid (palmitic acid). Liraglutide could therefore be considered as a natural peptide and a justification for not performing an ERA would have been acceptable.

According to the applicant the provided environmental risk assessment (ERA) document for liraglutide that has been conducted in line with the 2024 CHMP ERA Guideline. The provided log pow value of liraglutide is approx. 0.4 estimated at pH 7.9 for aqueous solution, taken from read-across data (reference to ECHA, 2024) and therefore the applicant considers that liraglutide is readily biodegradable and does not present a bioaccumulation risk and an assessment for PBT is not necessary. The applicant does not present any calculations of the PECsw value. Based on studies with reference product Victoza the applicant states that the PECsw value is below the threshold limit of 0.01.

Liraglutide is excreted in low amounts (< 10%) and thus there is no need for further ERA studies. It is considered unlikely that Liraglutide is to pose a risk to the environment.

III.3 Clinical aspects

Pharmacokinetics
To support the marketing authorisation applications the applicant has conducted one (1) bioequivalence study in the fed state, comparing Liraglutide with the reference product Victoza.

Pharmacokinetic properties of the active substance
Absorption: Liraglutide has an absolute bioavailability of (approximately) 55% after subcutaneous administration. The maximal plasma concentration after subcutaneous administration of 0.6 mg, was 9.4 nmol/l (for mean body weight of approximately 73 kg) and occur at around 8-12 hours.

The liraglutide can be administered independently of food intake, and therefore there are no restrictions with respect to food in the SmPC of the originator.

Linearity: The pharmacokinetics of liraglutide is linear, with a proportional increase in exposure with dose.

Elimination: The elimination half-life is approximately 13 hours.

Bioequivalence Study

Methods
This was a single-dose, two-way crossover study conducted in 48 healthy volunteers, comparing Liraglutide, 6 mg/ml, solution for subcutaneous injection in pre-filled pen, with Victoza, 6 mg/ml, solution for subcutaneous injection in pre-filled pen, under fed conditions. Blood samples for concentration analysis were collected pre-dose and 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}, $AUC_{0-\infty}$ 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 median, range) for liraglutide,

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	$AUC_{0-\infty}$ ng*h/ml	t_{max} h
***Ratio (90% CI)**	**103.09 (97.63- 108.86)**	**104.41 (97.45- 111.87)**	**102.50 (97.30- 107.98)**	**-**

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
C_{max} maximum plasma concentration

**calculated based on ln-transformed data*

For AUC_{0-t}, $AUC_{0-\infty}$ 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) and ICH M13A Guideline on bioequivalence for immediate-release solid oral dosage forms (EMA/CHMP/ICH/953493/2022). The bioanalytical methods were adequately validated.

The testing dose of 0.6 mg is seen as acceptable considering that the pharmacokinetics are dose-proportional, and higher doses without careful up-titration can lead to tolerability issues.

From a pharmacokinetic point of view, based on the submitted bioequivalence study, Liraglutide could be considered bioequivalent with Victoza.

Pharmacodynamics/Clinical efficacy/Clinical safety
No new studies on pharmacodynamics, clinical efficacy or clinical safety have been submitted.
If bioequivalence is proven, see conditions above, the clinical efficacy and clinical safety can be assumed to be similar to that of the reference product, provided that the quality issues (see the list of questions in section V), are resolved.

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

Efficacy
An adequate literature review has been performed and is acknowledged to support efficacy.

Safety
An adequate literature review has been performed and is acknowledged to support safety.

Furthermore, the BE study generated safety data. In this study, 8.7% of participants in the test product group (Liraglutide STADA Arzneimittel AG) reported 6 AEs and 11% of participants reported 6 AEs in the reference (Victoza) group. Most of the reported AEs were gastrointestinal events, known as very common or common for liraglutide. Overall, the safety results from study do not give rise to any concerns regarding safety not identified for the reference product.

Immunogenicity
No immunogenicity studies have been submitted. As ‘sameness’ compared to the reference product is considered proven, immunogenicity studies in vivo are not required.

Usability
The drug product consists of pharmaceutical product and medical device. The medical device is a non-refillable pen injector (pre-filled pen). The Applicant has submitted two similarity /comparison reports for comparison between the pen used with reference product and the one used with the applied product. The first report, i.e. Victoza and Liraglutide 6mg/ml and pen injector Use Comparison report compared the Instructions for use, design dimensions, force of use and performance. The second one, i.e., Victoza EU and Liraglutide 6mg/ml pen injector container closure system and performance comparison addressed primary packaging, subassemblies, dimensions, design, and performance parameters such as dose dispensing force and dose accuracy. Based on the data presented it is agreed with the Applicant that the pre-filled pen for the Applied product is similar to the injection device of the reference product.

Pharmacovigilance system
Proposed MAH: S.F. Group Srl (SE/H/2747)
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 (version 4.0; DLP 23-Mar-2026), in accordance with the requirements of Directive 2001/83/EC.

Part II Safety specification

The proposed safety concerns are aligned with those of the reference product Victoza (RMP version 34.1).

Table SVIII.1: 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

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.

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

Conclusion RMP assessment
The submitted Risk Management Plan, version 4.0 signed 23-Mar-2026 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 hybrid product Glanux is found adequate. There are no objections to approval of Glanux 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 applications are 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

A user consultation with target patient groups on the package information leaflet (PL) has been performed on the basis of a bridging report making reference to Victoza 6 mg/ml solution for injection in pre-filled pen, EMEA/H/C/1026.

Content
The applicant has proposed a bridging to a user test carried out on the product Victoza 6 mg/ml solution for injection in pre-filled pen. The user test of the Victoza leaflet was assessed and accepted in EMEA/H/C/1026. A comparison between the parent PL and the daughter PL together with a critical discussion hereof has been provided. The proposed bridging regarding content is considered acceptable.

Layout
The applicant has proposed a bridging to a user test carried out on a previously accepted user-tested leaflet material [Design/layout]. The proposed bridging regarding layout is considered acceptable. The bridging report submitted by the applicant has been found acceptable.

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
-	-	-	-	-	-