LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Triglyva
(liraglutide (synthetic))

SE/H/2347/01/DC

This module reflects the scientific discussion for the approval of Triglyva. The procedure was finalised on 2025-02-19. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Triglyva, 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.

For recommendations to the marketing authorisation not falling under Article 21a/22a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a/22a/ 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

The application for Triglyva, 6 mg/ml, Solution for injection in pre-filled pen, is a Hybrid 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 DE, ES, FI, IT, NO and PL 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 the Union since 2015, with Novo Nordisk A/S as marketing authorisation holder.

II. QUALITY ASPECTS

II.1 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.

II.2 Medicinal 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. 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 immunogenicity) aimed at demonstrating the similarity between synthetically derived Triglyva 6 mg/ml injection and biotechnology derived Saxenda.

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

Non-clinical section of the SmPC is in accordance with the innovator's SmPC.

The applicant has conducted comparative in-vitro studies between test product Triglyva and reference product Saxenda at three levels to compare the receptor binding, receptor activation and biological function. The studies utilized well-known and validated assays (SPR and cAMP based receptor activation method) and included testing of 3 test batches and 3 reference product batches.
The comparative in-vitro studies regarding target binding and biological characterization show similar pharmacodynamic activity between the test item and the reference product.

In the provided in-vitro immunogenicity studies Liraglutide DP and RLD batches were tested at a suitable concentration to evaluate the innate immune response. In the following screening study it was shown that Liraglutide DP show no increased immunogenicity compared with the two reference listed drugs Victoza -EU and -US towards a panel of cytokines/chemokines over the 20 PBMC donors tested. However, it is uncertain how these in vitro data are predictive of a clinical immunogenicity risk.

Environmental Risk Assessment (ERA)
Since Triglyva is a generic product, it will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

IV. CLINICAL ASPECTS

Pharmacokinetics
No bioequivalence study has been submitted. The applicant claims that a bioequivalence study is not necessary according to the Guideline on the investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1) since the product is an aqueous parenteral solution.

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%.

Distribution:
The mean apparent volume of distribution after subcutaneous administration is 20–25 L (for a person weighing approximately 100 kg). Liraglutide is extensively bound to plasma protein (>98%).

Biotransformation:
During 24 hours following administration of a single [^{3}H]-liraglutide dose to healthy subjects, the major component in plasma was intact liraglutide. Two minor plasma metabolites were detected (≤9% and ≤5% of total plasma radioactivity exposure).

Elimination:
Liraglutide is endogenously metabolised in a similar manner to large proteins without a specific organ as major route of elimination. Following a [^{3}H]-liraglutide dose, intact liraglutide was not detected in urine or faeces. Only a minor part of the administered radioactivity was excreted as liraglutide-related metabolites in urine or faeces (6% and 5%, respectively). The urine and faeces radioactivity was mainly excreted during the first 6–8 days and corresponded to three minor metabolites, respectively. 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.

Applicant's justification:
Bioequivalence study:
A bioequivalence waiver approach was adopted for the proposed medicinal product being a Solution for injection for subcutaneous injection basis the comparative physicochemical testing performed to evaluate the similarity between the proposed medicinal product and EU Reference Product, Saxenda. The comparative testing data indicates that the proposed medicinal product is comparable to both reference products and indicates that both reference products are of same quality/standard.

The proposed medicinal product is a parenteral solution intended solely for administration by injection, therefore, the bioequivalence is self-evident. Reference is made to the CHMP's "*Guideline on the Investigation of Bioequivalence*". Appendix II of the guideline highlights the bioequivalence study requirements for different dosage forms. This guidance describes the bioequivalence study requirements for parenteral solutions that intended for subcutaneous injection, when the test product is of the same type of solution (i.e., aqueous), contains the same concentration of the same active substance and the same excipients in similar amounts as the medicinal product currently approved, bioequivalence studies are not required.
Moreover, a bioequivalence study is not required for an aqueous parenteral solution with comparable excipients in similar amounts, if it can be demonstrated that the excipients have no impact on the viscosity.

Additionally, a comparative threshold analysis has been performed between the test product device v/s the reference product device wherein it was concluded that the proposed applicant's pen device is essentially same as the reference product pen device in terms of design, user interface, function, and the instructions for use. The comparative analysis include:

- Physical comparison of the delivery device constituent part by visual examination and tactile examination of the physical features of Test product v/s reference product
- Comparative task analysis of test product v/s reference product
- Instructions for use (IFU) comparison, by performing side-by-side, line-by-line comparison of instructions for use, and descriptions of the delivery device constituent parts of the test product and its reference product.

The outcomes of threshold analysis performed has confirmed that there are no design differences identified between the user interface of test product v/s Reference product.
Accordingly, the usability (human factor) studies are not warranted for proposed generic pen device.

Discussion and overall conclusion
The applicant has provided updated comparative sameness data of test compared to the reference product. The comparative physicochemical properties, higher order structure, its oligomerization state, biological assay, its fibrillation/aggregation propensity, receptor binding, receptor activation and albumin binding properties of liraglutide were evaluated to demonstrate the similarity between the test and reference product.

The applicant has evaluated the quality attributes (e.g. that may change oligomerisation, albumin binding or fibrillation) that might affect the absorption and elimination of liraglutide and justified that these properties can by fully be characterised by analytical methods. It is agreed that similarity to the

reference product in all quality attributes that may influence liraglutide pharmacokinetics has been demonstrated based on a comprehensive analytical comparability exercise (see Quality assessment report). The justification for biowaiver is acceptable.

In general, considering the relatively small size of the liraglutide structure, it is assumed that full characterisation on the quality level is possible, and that complex tertiary structures are not relevant. Thus, it is concluded that the test and reference liraglutide can be fully characterised and compared with currently available analytical methods, and it is agreed that the methods presented in the current application now are sufficient to conclude full sameness. Bioequivalence data would in any case not be sufficient to justify any substantial differences in quality attributes.
The applied product is a solution for subcutaneous injection and contains the same excipients in similar amounts as the medicinal product currently approved. In line with the Guideline on the investigation of bioequivalence, no bioequivalence study is required for this kind of products. Given that sameness has been shown on a quality level between test and reference, the justification for a biowaiver approach is considered acceptable by the RMS (see Quality assessment report).

Pharmacodynamics/Clinical efficacy/Clinical safety
No new studies on pharmacodynamics, clinical efficacy or clinical safety have been submitted. Sufficient similarity regarding quality aspects between the test and reference product is shown and bioequivalence with the originator product is proven, thus additional data is not necessary.

The summary of literature supporting clinical efficacy and safety of liraglutide in weight management seems somewhat incomplete and contains references that are considered less relevant. But this is not further pursued by the assessor because the literature part is not considered pivotal for this application.

The injection pen for the test product was designed based on the reference product's pen. A comparative threshold analysis was performed between the test product device vs the reference product device. The conclusion of the threshold analysis was that the two pens were nearly identical, and that the use-related risks were identical for the two pens. No new risks were identified for the test product's pen. The applicant concludes that a usability study is not necessary, which is agreed upon.

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 Triglyva.

Part II Safety specification
The proposed safety concerns are aligned with those of the reference product Saxenda (latest version v. 33.0), see table below.

Table SVIII.1: Summary of safety concerns [2]

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.

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

Conclusion RMP assessment
The MAH has satisfactorily responded to the questions raised and updated the RMP accordingly.

The submitted Risk Management Plan, version 0.2 signed 29th of February 2024 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.

Conclusion RMP assessment
The MAH has satisfactorily responded to the questions raised and updated the RMP accordingly.

V. USER CONSULTATION

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. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the product, Triglyva, is found adequate. There are no objections to approval of Triglyva, from a non-clinical and clinical point of view. The absence of bioequivalence studies is acceptable. The product information is acceptable. The benefit/risk is considered positive, and the application is therefore recommended for approval.

List of recommendations not falling under Article 21a/22a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a/22a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

The decentralised procedure for Triglyva, 6 mg/ml, Solution for injection in pre-filled pen was positively finalised on 2025-02-19.

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Public Assessment Report – Update

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

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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