

Public Assessment Report

Scientific discussion

Linagliptin Pharmazac (linagliptin)

SE/H/2368/01/DC

This module reflects the scientific discussion for the approval of Linagliptin Pharmazac. The procedure was finalised at 2025-10-09. 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, the Member States have agreed to grant a marketing authorisation for Linagliptin Pharmazac, 5 mg, Film-coated tablet.

The active substance is linagliptin. A comprehensive description of the indication and posology is given in the SmPC.

II. EXECUTIVE SUMMARY

II.1 About the product

Pharmacotherapeutic group: Drugs used in diabetes, dipeptidyl peptidase 4 (DPP-4) inhibitors, ATC code: A10BH05

Mechanism of action

Linagliptin is an inhibitor of the enzyme DPP-4 (dipeptidyl peptidase 4, EC 3.4.14.5) an enzyme which is involved in the inactivation of the incretin hormones GLP-1 and GIP (glucagon-like peptide1, glucose-dependent insulinotropic polypeptide). These hormones are rapidly degraded by the enzyme DPP-4. Both incretin hormones are involved in the physiological regulation of glucose homeostasis.

Incretins are secreted at a low basal level throughout the day and levels rise immediately after meal intake. GLP-1 and GIP increase insulin biosynthesis and secretion from pancreatic beta cells in the presence of normal and elevated blood glucose levels. Furthermore GLP-1 also reduces glucagon secretion from pancreatic alpha cells, resulting in a reduction in hepatic glucose output. Linagliptin binds very effectively to DPP-4 in a reversible manner and thus leads to a sustained increase and a prolongation of active incretin levels. Linagliptin glucose-dependently increases insulin secretion and lowers glucagon secretion thus resulting in an overall improvement in the glucose homeostasis. Linagliptin binds selectively to DPP-4 and exhibits a > 10 000 fold selectivity versus DPP-8 or DPP-9 activity in vitro.

II.2 General comments on the submitted dossier

The application for Linagliptin Pharmazac, 5 mg, Film-coated tablet, is a Generic Art. 10(1) application submitted according to Directive 2001/83/EC. The applicant applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and CY, EE, EL, LV and LT as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Trajenta, 5 mg, film-coated tablet, authorised in the Union since 2011, with Boehringer Ingelheim International GmbH as marketing authorisation holder.

The reference product used in the bioequivalence study is Trajenta, 5 mg, film-coated tablet from Portugal with Boehringer Ingelheim International GmbH 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.

GMP active substance

Regarding the statement on GMP for the active substance declarations are provided from the manufacturers 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. An inspection of the submitted bioequivalence study is not considered necessary.

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

Pharmacodynamic, pharmacokinetic and toxicological properties of linagliptin are well known. As linagliptin is a widely used, well-known active substance, no further studies are required, nor does the applicant provide any. Overview based on literature review is, thus, appropriate.

Environmental Risk Assessment (ERA)

Since Linagliptin Pharmazac is a generic product, it will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

There are no objections to approval of Linagliptin Pharmazac from a non-clinical point of view.

III.3 Clinical aspects

Pharmacokinetics

To support the marketing authorisation application the applicant has conducted one single-dose bioequivalence study in the fasting state, comparing Linagliptin Pharmazac, 5 mg, film-coated tablet, with the reference product Trajenta, 5 mg, film-coated tablet.

Pharmacokinetic properties of the active substance

Absorption: The absolute bioavailability of linagliptin is approximately 30 %. After oral administration of a 5 mg dose to healthy volunteers or patients, linagliptin was rapidly absorbed, with peak plasma concentrations (median T_{max}) occurring 1.5 hours post-dose.

Co-administration of a high-fat meal with linagliptin prolonged the time to reach C_{max} by 2 hours and lowered C_{max} by 15% but no influence on AUC_{0-72h} was observed. No clinically relevant effect of C_{max} and T_{max} changes is expected; therefore, linagliptin may be administered with or without food.

Elimination: Plasma concentrations of linagliptin decline in a triphasic manner with a long terminal half-life (terminal half-life for linagliptin more than 100 hours), that is mostly related to the saturable, tight binding of linagliptin to DPP-4 and does not contribute to the accumulation of the medicinal product. The effective half-life for accumulation of linagliptin, as determined from oral administration of multiple doses of 5 mg linagliptin, is approximately 12 hours.

Study 23-VIN-0587 - FASTED

Methods

This was a single-dose, two-way crossover study conducted in 42 healthy volunteers, comparing Linagliptin Pharmazac, 5 mg, film-coated tablet, with Trajenta, 5 mg, film-coated tablet, under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 72 hours post-dose. Plasma concentrations of linagliptin were determined with an LC-MS/MS method. Analysis of variance (ANOVA) was performed on the ln-transformed data for AUC_{0-72} and C_{max} . The study was conducted between 2024-01-23 and 2024-04-07.

Results

The results from the pharmacokinetic and statistical analysis are presented in Table 1 below. 33 subjects completed both the periods of study and were included in pharmacokinetic analyses. However, statistical analysis was performed on 31 subjects as pre-dose concentration of > 5% of C_{max} was observed for subject no. 16 in period 02 and subject no. 29 for period 02. Hence, these subjects were excluded from the statistical analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean $\pm$ SD, $t_{\max}$ median, range) for linagliptin, n=33.

Treatment	AUC₀₋₇₂ ng*h/ml	C_{max} ng/ml	t_{max} h
Test	175.97 $\pm$ 28.42	4.99 $\pm$ 1.14	2.670 (1.00 - 5.00)
Reference	177.88 $\pm$ 30.04	5.12 $\pm$ 1.06	2.670 (1.02 - 18.00)
*Ratio (90% CI) (n=31)	98.92 (95.04 - 102.95)	96.80 (91.50 - 102.41)	-
AUC ₀₋₇₂ area under the plasma concentration-time curve from time zero to 72 hours C _{max} maximum plasma concentration t _{max} time for maximum plasma concentration			

**calculated based on ln-transformed data*

For AUC₀₋₇₂ 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, Linagliptin Pharmazac can be considered bioequivalent with Trajenta.

Pharmacodynamics/Clinical efficacy/Clinical safety

No new studies on pharmacodynamics, clinical efficacy or clinical safety have been submitted. Provided that bioequivalence with the originator product is demonstrated, additional data is not necessary.

Pharmacovigilance system

Proposed MAH: PHARMAZAC S.A.

The Applicant has submitted a signed Summary of the Applicant's/Proposed Future MAH's Pharmacovigilance System. 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 Linagliptin Pharmazac.

Part II Safety specification

The MAH has submitted the version 0.2 RMP dated 18.07.2024 and proposed the following summary of safety concerns:

Summary of safety concerns	
Important identified risks	- Pancreatitis
Important potential risks	- Pancreatic cancer
Missing information	- Pregnancy/breast-feeding

Part III Pharmacovigilance Plan

Routine pharmacovigilance is suggested and in accordance with the reference product. The applicant has proposed a follow-up questionnaire concerning pancreatic cancer (malignancy/neoplasm) which is acknowledged. No additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

The reference product also has non-conditioned follow-up questionnaire involving pancreatitis. This ongoing application does not have the corresponding questionnaire in the RMP, which can be agreed for a generic application.

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 0.2 signed 18.07.2024 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.

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, Linagliptin Pharmazac, is found adequate. There are no objections to approval of Linagliptin Pharmazac, 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
-	-	-	-	-	-