



HUNGARIAN NATIONAL CENTER FOR PUBLIC HEALTH AND PHARMACY

Public Assessment Report

Scientific discussion

Linagliptin Sandoz 5 mg filmtabletta

(linagliptin)

HU/H/0904/001/DC

Date: 23.07.2026

This module reflects the scientific discussion for the approval of Linagliptin Sandoz 5 mg filmtabletta. The procedures were finalised on 03-09-2024. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Linagliptin Sandoz 5 mg filmtabletta from Pharos Pharmaceutical Oriented Services Ltd.

The products are indicated in adults with type 2 diabetes mellitus as an adjunct to diet and exercise to improve glycaemic control as:

monotherapy

- when metformin is inappropriate due to intolerance, or contraindicated due to renal impairment.

combination therapy

- in combination with other medicinal products for the treatment of diabetes, including insulin, when these do not provide adequate glycaemic control (see sections 4.4, 4.5 and 5.1 for available data on different combinations).

A comprehensive description of the indications and posology is given in the SmPCs.

These decentralised applications concern a generic version of Linagliptin, under Linagliptin Sandoz 5 mg filmtabletta trade name. The originator product is Trajenta 5 mg film-coated tablet by Boehringer Ingelheim International GmbH, registered since 23-08-2011.

The applications are made according to the provisions of Article 10(1) of Dir 2001/83/EC, as amended and therefore does not include the results of pharmacological or toxicological tests or clinical trials.

No scientific advice has been given to the Applicant with respect to this product.

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.

Type 2 diabetes (formerly called non-insulin-dependent, or adult-onset) results from the body's ineffective use of insulin. Over 90% of diabetes mellitus cases are type 2 diabetes mellitus (T2DM). Symptoms may be similar to those of type 1 diabetes, but are often less marked. As a result, the disease may be diagnosed several years after onset, once complications have already arisen. Until recently, this type of diabetes was seen only in adults but it is now also occurring increasingly frequently in children.

Dipeptidyl peptidase-4 (DPP-4) is the serine dipeptidase that is responsible for the initial rapid cleavage of the endogenous incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulintropic polypeptide (GIP) *in vivo*. DPP-4 inhibitors act to lower blood glucose levels by inhibiting the enzyme DPP-4, thereby preventing the degradation of the incretin hormones GLP-1 and GIP and attenuating postprandial glucose excursions. These two hormones are important for the normal regulation of glucose homeostasis and have been shown to play a key role in enhancing glucose-stimulated insulin secretion and maintaining normal glucose tolerance. They have diverse effects to improve b-cell function, as assessed using various surrogate markers, and the potential to maintain b-cell mass (so far, only shown in isolated b-cells and human islets *in vitro* and in animal studies), while GLP-1 also suppresses glucagon secretion, delays gastric emptying and reduces appetite.

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

II. QUALITY ASPECTS

II.1 Introduction

The chemical-pharmaceutical assessment report concerns the application of Linagliptin Sandoz 5 mg film-coated tablets via a decentralized procedure according to Article 10(1) of Directive 2001/83/EC (i.e a generic application).

Reference product is Trajenta 5 mg film-coated tablets (containing 5 mg of linagliptin as active ingredient) which was the original product of Boehringer Ingelheim International GmbH.

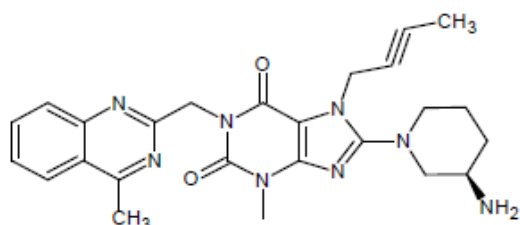
II.2 Drug Substance

Data on the quality and manufacture of the active substance were provided in the applicant's submission using the Active Substance Master File (ASMF) procedure with additional data in the marketing authorization dossier. The Quality Overall Summary is adequate.

INN name: Linagliptin

Chemical name: 8-[(3R)-3-Amino-1-piperidinyl]-7-(2-butyln-1-yl)-3,7-dihydro-3-methyl-1-[(4-methyl-2-quinazolinyl) methyl]-1H-purine-2,6-dione.

Structure:



The active substance is creamish or yellow powder, soluble in methanol and N, N-dimethylformamide, practically insoluble in hexane, isopropyl ether and water. It shows polymorphism, it simultaneously exists in two polymorphic forms, the manufacturer consistently produces the correct isomer and the same polymorphic form.

The ASMF holder presented complete details of the manufacturing process. Description of the manufacturing process of the active pharmaceutical ingredient (API) is adequate.

Evidence of the structure has been confirmed by elemental analysis, UV, FT-IR, NMR (¹H, ¹³C) spectroscopy and MS technique. The impurity profile of the API contains detailed information about genotoxic impurities, residual solvents and catalysts.

Linagliptin is not official in the Ph. Eur. Therefore, an in-house specification has been set for the active substance, which includes the following tests: description, identification by IR and HPLC, solubility, water content, sulphated ash, enantiomeric purity, related substances, residual solvents, assay, and microbiological purity.

The presented specification is in accordance with the Ph. Eur. general monograph on *Substances for Pharmaceutical Use* and the ICH Q6A guideline. The specifications reflect all relevant quality attributes of the active substance and were found to be adequate to control the quality of the drug substance. The limits set are properly justified.

Testing methods not described in details in the Pharmacopoeia are adequately drawn up and sufficiently validated. Reference materials used by the active substance manufacturer and the drug product manufacturer for the control of the substance are adequately characterised.

The substance complies with the requirements of the EMA guideline on genotoxic impurities.

Batch analysis data justify the limits, indicate the good performance of testing methods and demonstrate the batch to batch consistency of the production.

Stability studies have been performed with the drug substance. According to the presented stability data the proposed re-test period of is acceptable if stored in tight container under nitrogen atmosphere protected from light and moisture at temperature NMT 30°C.

Good Manufacturing Practice (GMP) compliance of the API manufacture is demonstrated by the applicant.

II.3 Medicinal Product

The aim was to develop film-coated tablets containing linagliptin as drug substance in 5 mg doses, bioequivalent and pharmaceutically equivalent to the reference medicinal product Trajenta 5 mg film-coated tablets, the branded original product of Boehringer Ingelheim.

A satisfactory package of data on development pharmaceuticals has been presented. Brief discussion on reasons for inclusion and quantity of excipients has been provided.

As regards dissolution and impurity profile the product is shown to be similar to the reference product.

The compositions and the pharmaceutical tests evaluated during development of the final formulation are included in the documentation. As a result of development studies product with the following appearance, composition and packaging was obtained.

Light pink, round, biconvex film-coated tablet debossed with '5' on one side. The diameter of the tablet is 8.1 mm $\pm$ 5% (7.7-8.5) mm.

The excipients used in the finished product are mannitol, crospovidone types A and B, hypromellose, colloidal anhydrous silica, magnesium stearate; the coating consists of hypromellose, titanium dioxide, talc, macrogol 6000 and red iron oxide. All excipients used comply with their respective European Pharmacopoeia monograph, except for red iron oxide, which complies with Commission Regulation (EU) 231/2012. Compliance of the product with the general monograph of the European Pharmacopoeia *on the Products with the risk of TSE* has been demonstrated by the applicant.

A description and flow chart of the manufacturing method has been provided. Appropriate in-process controls are included in the manufacturing process. Satisfactory batch formulae were also presented. GMP compliance of the manufacturing site has been demonstrated.

The finished product specification is satisfactory. Acceptance criteria have been justified with respect to conventional pharmaceutical requirements as prescribed in the relevant dosage form monograph of the Ph. Eur. and the ICH Q6A guideline. Appropriate control strategy was selected. The test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and complied with the specification. Certificates of analysis for the batches involved in the bioequivalence study are presented.

The container closure systems of the product are Aluminium-OPA/Alu/PVC blisters or High Density Polyethylene (HDPE) bottles, closed with a white, polypropylene (PP), child resistant cap. Specifications and quality certificates for all packaging components are enclosed.

Finished product stability studies have been conducted in accordance with the current guidelines. Based on the results, a **shelf-life of 3 years with no special storage conditions** is approved.

The Summary of Product Characteristics, patient Information Leaflet and label texts are pharmaceutically acceptable.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Conclusion: The product has been shown to meet the current regulatory requirements with regards to its quality and content of the active substance as well as dosage-form characteristics until the end of the approved shelf-life consistently. The manufacture and the quality standards applied adequately support the safe use and efficacy of the product.

III. NON-CLINICAL ASPECTS

Pharmacodynamic, pharmacokinetic and toxicological properties of Linagliptin are well known. As Linagliptin is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate.

The non-clinical overview (NCO) on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate.

The NCO details the efficacy, primary and secondary pharmacodynamic properties of Linagliptin, includes relevant data regarding safety, interactions, pharmacokinetic and toxicity attributes in the pre-clinical phase based on literature data.

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Linagliptin Sandoz 5 mg filmdablette is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

IV. CLINICAL ASPECTS

IV.1 Introduction

By selectively targeting DPP-4, the gliptins potentially cause a more physiologically based control of glucose-dependent postprandial glucose excursions and of fasting blood glucose, both of which are mediated by effects of glucose on insulin and glucagon secretion. An advantage of DPP-4 inhibition is that since incretin-stimulated release of insulin is glucose dependent, these agents are associated with a low incidence of hypoglycaemia. Moreover, DPP-4 inhibitors have a low potential for drug-drug interactions (with the exception of saxagliptin, which is metabolized by cytochrome P450 [CYP] 3A4/5), are generally well tolerated and have minimal or neutral effects on bodyweight.

Most of the currently licensed DPP-4 inhibitors are all eliminated primarily via the renal route and are not recommended for use in patients with renal impairment and/or dosage adjustment is required in those with renal impairment; thus, there is a niche amongst this class of antihyperglycaemic agents for a drug eliminated primarily via a non-renal route. Linagliptin has a potential advantage over currently approved gliptins in that it primarily undergoes non-renal elimination.

Linagliptin has a low dissociation rate from the DPP-4 enzyme, is more potent than other DPP-4 inhibitors, and is therefore expected to be effective at low therapeutic doses. Its long duration of action means it has the potential to be the first truly once-a-day DPP-4 inhibitor for the treatment of type 2 diabetes, providing full 24-h DPP-4 inhibition coverage and a rise in basal GLP-1 levels.

IV.2 Pharmacokinetics

GCP

The submitted bioequivalence study was conducted in compliance with GCP and GLP requirements. Quality Assurance Statement and monitoring reports were provided. Clinical, Bioanalytical, PK and Statistical sites had been inspected by competent regulatory agencies.

Pivotal bioequivalence study

Open-label, randomized, two-treatment, two period, two-sequence, single-dose, crossover, oral bioequivalence study in healthy, adult, human, male subjects under fasting conditions was performed. 54 subjects participated in the study were healthy, adult, male, humans between 18 and 45 years of age. All subjects having met all the inclusion criteria and none of the exclusion criteria as described in the protocol were judged eligible for enrollment in this study.

Linagliptin in human plasma was determined using high performance liquid chromatography with tandem mass spectrometry method.

Pharmacokinetic parameters were calculated using Phoenix® WinNonlin® Version 8.3.

Primary pharmacokinetic parameters were C_{max} and AUC₇₂ and secondary pharmacokinetic parameter was T_{max}.

The statistics is described adequately, and the methods are acceptable. The randomisation scheme was provided. There was no significant treatment effect according to the ANOVA model in the study.

Bioequivalence evaluation:

Parameter	Least square Geo Means		T/R Ratio (%)	90% Confidence Intervals		Power (%)	Intra subject CV (%)
	Test (T)	Reference (R)		Lower (%)	Upper (%)		
C _{max} (pg/mL)	5023.5464	4916.1941	97.86	89.08	107.51	98.7	29.5
AUC ₇₂ (hr*pg/mL)	146241.0881	143028.2043	97.80	94.74	100.96	100.0	9.7
AUC _{inf} (hr*pg/mL)	266335.4539	259395.7243	97.39	93.75	101.18	100.0	11.6

Safety results

No death or serious adverse event occurred during the study. The test and reference products were well tolerated and were found to be safe.

IV.3 Pharmacodynamics

A comprehensive description of Pharmacodynamics is given in the SmPC.

Type 2 Diabetes Mellitus (T2DM) is a chronic metabolic disorder principally characterised by hyperglycaemia. Its incidence and prevalence is increasing in developed countries, associated with a parallel increase in obesity contributed to by excessive and qualitatively inappropriate food intake and reduced physical activity. The pathogenesis of T2DM includes insulin resistance together with a relative impairment of insulin secretion which tends to progress over time. Part of the insulin deficiency is represented by a diminution in the "incretin effect", the physiological mechanism by which post-prandial insulin secretion is enhanced as a result of insulin secretagogues (incretins) being released into the circulation from the upper gastrointestinal tract following feeding. Linagliptin is an inhibitor of DPP-4, the enzymatic activity of which includes as substrates the incretin hormones GLP-1 and GIP. Levels of these incretins are therefore increased following administration of linagliptin, which thus lowers blood glucose by enhancing insulin response to feeding.

This action of linagliptin and other DPP-4 inhibitors in improving post-prandial insulin secretion is different from and is complementary to the actions of other oral hypoglycaemic agents (OHA) currently in use and mentioned in the current and proposed indications for Trajenta. Metformin improves glucose disposal by mechanisms which are not entirely clear but which are not dependent on insulin, and can be regarded as improving insulin sensitivity. Sulphonylureas (SU) stimulate insulin secretion more directly and can do so in the fasting state or at normal blood glucose levels, hence being more prone than other OHA to cause hypoglycaemia. Thiazolidinediones (TZD) counter insulin resistance by improving response to insulin at the post-receptor level. Combinations of these classes of OHA, including DPP-4 inhibitors such as linagliptin, are therefore rational as their various actions are all directed at improving the quantum of insulin action on its target metabolic pathways; as is the

supplementary administration of insulin itself, hence combination of any OHA class with insulin also is a hypothetically rational basis for therapy.

IV.4 Clinical efficacy

Due to the increasing number of individuals with diabetes and diabetic complications, a high demand for novel and effective therapeutic strategies with the primary aim of delaying and/or ameliorating diabetic complications including renal impairment has emerged. All patients with diabetes and impaired renal function require dose adjustment of the administered antidiabetic drug.

Linagliptin is a pharmacologically unique, orally active, once-daily dipeptidyl peptidase-4 inhibitor which compared with other dipeptidyl peptidase-4 inhibitors, has a favorable pharmacokinetic profile with a primarily nonrenal route of elimination that avoids the need for dose adjustment in patients with renal impairment. This is an advantage of linagliptin in patients with moderate to severe renal insufficiency. Thus, linagliptin is the drug most frequently chosen to treat type 2 diabetes mellitus patients with renal failure

When administered as monotherapy or in combination with other antihyperglycemic drugs, linagliptin treatment leads to clinically meaningful reductions in glycated hemoglobin, fasting plasma glucose and postprandial plasma glucose levels. In addition, pancreatic β -cell function is enhanced.

Linagliptin is protective for both macrovascular and microvascular complications of diabetes in preclinical models, as well as clinical models. Linagliptin treatment was associated with a significantly reduced risk of cardiovascular events in clinical trials of ≤ 2 years. Linagliptin exerts beneficial CV effects through glycemic control, as well as effects beyond glycemic control and beyond class effects. Linagliptin modulation of endothelial and immune cell responses appear to be key mechanisms for ameliorating the progression of CVD

Overall, oral linagliptin, 5 mg once daily, is an effective, well-tolerated DPP-4 inhibitor, suitable for use in a wide range of patients with T2DM. Clinical studies demonstrate an overall favorable safety profile, low risk for hypoglycemia, weight neutrality, primarily nonrenal clearance, and efficacy for glycosylated hemoglobin reduction.

However Linagliptin's additive effect to non-responders to SU derivatives is currently questionable. The effect on HbA1c was -0.29% in the European population. This is considered too small for justifying an indication.

IV.5 Clinical safety

No major difference in AE incidence between the linagliptin and the placebo group was observed in general. The finding of a lower number of hypoglycaemic events with linagliptin compared to glimepiride is an advantage and expected from the known mechanisms of action of these drugs. However, the beneficial effect of linagliptin may be overestimated considering the apparently smaller glucose-lowering effect of linagliptin (leading to smaller HbA1c and FPG reduction). Due to the presence of insulin resistance, hypoglycaemia, especially severe hypoglycaemia is usually not a major problem in patients with T2DM. However, (very) elderly patients are generally more prone to experiencing hypoglycaemia. Due to its mechanism of action, linagliptin is not associated with hypoglycaemia except when used in combination with a SU but the enhancement of SU-associated hypoglycaemia is also known for other antihyperglycaemic drugs and is therefore not unique to linagliptin. The low propensity of linagliptin to cause hypoglycaemia is an advantage that may be relevant in patients more prone to hypoglycaemic events.

Treatment safety is an important consideration for patients with T2DM and comorbidities, and the findings of CARMELINA indicate that linagliptin is an appropriate choice to use in addition to other agents across a range of patient populations. The results of CAROLINA support the findings of

CARMELINA in a complementary population of patients with T2DM of shorter duration and without CKD, together demonstrating the long-term CV and renal safety of linagliptin in T2DM across a broad range of patients at elevated CV risk. When additional glucose-lowering is required, these two trials reaffirm treatment guidelines for choosing additional therapies for high-risk patients with T2DM at high CV and/or renal risk, and further enhance our understanding of how linagliptin and DPP-4 inhibitors fit into evolving treatment approaches for patients with T2DM.

Add-on treatment to pioglitazone has not been appropriately investigated. CHMP guidance for add-on trials, requests that the new antidiabetic agent should be added in non-responders to the established antidiabetic agent. In this trial 50% of patients were drug-naïve, and therefore not non-responders. Considering the relatively small effect size (-0.37% decrease in HbA1c) and the increased weight gain the B/R ratio of this dual combination therapy appears unfavourable.

Patients and clinicians should be aware of the risk for hypoglycemia when linagliptin is prescribed as a treatment adjunctive to a regimen of an insulin secretagogue. An initial dose decrease in the secretagogue should be considered to prevent hypoglycemic events. Additionally, the efficacy of linagliptin may be limited in patients receiving concomitant inducers of CYP3A4 or P-gp (eg, rifampin).

The use of linagliptin whether in monotherapy or not, is associated with important AEs, and their occurrence and frequency are varied, being of mild to moderate intensity. The most frequent AEs were nasopharyngitis with linagliptin in monotherapy and gastrointestinal AEs with linagliptin in combination.

IV.6 Discussion on the clinical aspects

Pharmacodynamic, pharmacokinetic and toxicological properties of Linagliptin are well known. As Linagliptin, are widely used, well-known active substances, the applicant has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate.

The Clinical Overview (CO) on the pharmacology, pharmacokinetics and toxicology is adequate. The CO details efficacy, primary and secondary pharmacodynamic properties of Linagliptin, includes relevant data regarding safety, interactions, pharmacokinetic and toxicity attributes based on literature data.

IV.7 Pharmacovigilance

Product's name: LINAGLIPTIN SANDOZ 5 mg filmdabletta

Active substance: linagliptin;

MAH: SANDOZ Hungária Kereskedelmi Kft.

Reference number: HU/H/0904/001/DC

1. Summary of Pharmacovigilance System

The Applicant has submitted a signed Summary of the Applicant's Pharmacovigilance System (version: 10.0, dated on 06 July 2023).

Provided that the Pharmacovigilance System Master File fully complies with the legal requirements as set out in the Commission Implementing Regulation 520/2012 and as detailed in the relevant GVP module, the Summary is considered acceptable.

2. Risk Management Plan

The MAH has submitted an updated risk management plan (version number: 2.1, Date of final sign off: 24.01.2024), 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 Sandoz 5 mg film-coated tablets in the HU/H/0904/001/DC procedure, 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 the above mentioned product containing linagliptin as active substance.

Safety specification

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

The list of safety concerns proposed by the Applicant is full in line with latest version of the originator's RMP (Version 13.1; Date of final sign off: 14-Aug-2019). Summary of this RMP is published on the EMA website on 10.12.2019.

(https://www.ema.europa.eu/en/documents/rmp-summary/trajenta-epar-risk-management-plan-summary_en.pdf).

Pharmacovigilance Plan

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

As routine pharmacovigilance activities, specific adverse reaction follow-up questionnaires are in place for the risk of "Pancreatitis" and "Pancreatic cancer", appended in Annex 4 of the RMP.

Risk minimisation measures

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

Conclusion on the RMP

The submitted updated Risk Management Plan, version 2.1 signed on 24/01/2024, 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.

3. Periodic Safety Update Report (PSUR)

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.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The characteristics of linagliptin are adequately reflected in the SmPC and the indications and precautions for the use of this drug are justified by its pharmacological properties.

Overall, the available clinical information provides adequate evidence that the benefit-risk ratio for linagliptin is **favourable**. Its efficacy and safety profile indicate that it is an effective therapeutic agent for the treatment of type 2 diabetes mellitus. As for all drugs, the benefits and risks of treatment should be evaluated carefully for each patient.

Modul 6

Steps taken after the initial procedure with an influence on the Public Assessment Report

Procedure number	Type of modification ¹	Date of start of the procedure	Date of end of procedure	Approval/non approval
HU/H/0904/001/IA/001/G	A.1.Change in the name and/or address of the marketing authorisation holder	2025.03.18	2025.04.17	Positive
HU/H/0904/001/IA/002/G	The change in the name and/or address concerns the marketing authorisation holder	2026.04.29	2026.05.29	Positive