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Public Assessment Report

Scientific discussion

Linagliptin Kern Pharma 5 mg film-coated tablets (linagliptin)

ES/H/0977/001/DC

Date: 21 August 2025

This module reflects the scientific discussion for the approval of Linagliptin Kern Pharma 5 mg film-coated tablets. The procedure was finalised at 13 July 2025. 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 Kern Pharma 5 mg film-coated tablets, from Kern Pharma S.L.

The product is indicated for the treatment of type 2 diabetes mellitus as an adjunct to diet and exercise to improve glycemic control as: monotherapy when metformin is not suitable due to intolerance or is contraindicated due to renal impairment; or treatment in combination with other medications for the treatment of diabetes, including insulin, when these do not provide adequate glycemic control

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

The marketing authorisation has been granted pursuant to Article 10.1 of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

The product Linagliptin Kern Pharma 5 mg film-coated tablets, from Kern Pharma S.L. consists on film-coated tablets containing 5 mg of linagliptin.
The maximum daily dose is 5 mg of Linagliptin.
Linagliptin Kern Pharma 5 mg film-coated tablets are packaged in blister with PA/Alu/PVC 25/45/60 µm film, heat-sealed to an aluminum foil of 20 µm.

II.2 Drug Substance

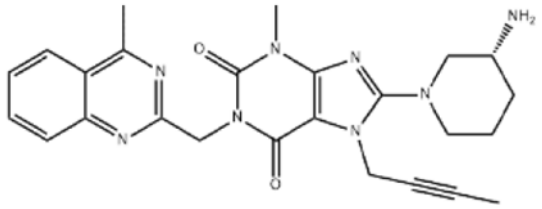
The ASMF procedure is used to support the quality of the drug substance.

General Information

Nomenclature:

INN: Linagliptin
Chemical name: 8-[(3R)-3-aminopiperidin-1-yl]-7-(but-2-yn-1-yl)-3-methyl-1-[(4-methylquinazolin-2-yl) methyl]-3, 7-dihydro-1H-purine-2,6-dione
CAS: 668270-12-0

Chemical structure:



Empirical Formula: $C_{25}H_{28}N_8O_2$
Molecular weight: 472.74

General Properties:

Appearance: Off-white to yellowish powder.
Solubility: Highly soluble over a pH range of 1.2 to 7.4.
Hygroscopicity: Slightly hygroscopic.
Stereochemistry and isomerism: The drug substance contain one chiral center.
Polymorphism: It exhibits polymorphism such as Form-A, B, C, D and E.
Melting range: 206.5 ºC.

Manufacture, process controls and characterisation

The description of the manufacturing process is properly detailed. The specifications of the materials used in the synthesis are sufficient and adequate. The profile of impurities, including residual solvents, of these materials which can influence the quality of the active substance are well defined and controlled. The acceptance criteria for the critical stages and the information on the quality and control of intermediates are adequate.

Specification, analytical procedures, batch analysis

Active substance specifications are considered appropriate and limits justified. Analytical methods are correctly described and validation carried out according to ICH. Batch results support consistent production.

Container closure system

The choice of the container closure system is properly justified. Compliance with the relevant requirements and/or regulations is confirmed.

Stability

Stability studies have been performed in accordance with current guidelines. Protocol, controlled parameters and test methods are considered adequate. The packaging material is similar to that proposed for storage. Proposed re-test period and storage conditions are justified.

II.3 Medicinal Product

Description of the product

The drug product is a light-red, 8 mm, round film-coated tablet containing 5 mg of linagliptin. The qualitative composition of the finished product is as follows:

Tablet core

Linagliptin
Mannitol
Pregelatinized starch (maize)
Copovidone
Crospovidone
Glycerol dibehenate

Film coating

Polyvinyl alcohol partially hydrolyzed
Titanium dioxide (E171)
Macrogol
Talc
Iron oxide red (E172)

The packaging material intended for the commercial use consists in a PA/Alu/PVC 25/45/60 //Aluminum 20 µm blister.

Pharmaceutical Development

The development of the product has been described, the choice of excipients is justified and their functions explained.
The physicochemical characteristics of the active substance that may affect the pharmaceutical form are identified and their control strategy is justified.

Manufacture of the product

The manufacturing process is fully described and in-process controls are appropriate considering the nature of the product and the manufacturing process. The industrial batch size is well-defined.
Sufficient validation data are provided.

Excipients

Excipients used are well known and of appropriate quality.
None of the excipients is of animal origin.

Product specification, analytical procedures, batch analysis

The finished product specifications are adequate to control the finished product. Provided description and validation data for the analytical methods are adequate. Batch analysis data have been submitted and the results show that the finished product meets the proposed release specification.

Container closure system

The finished product is packaged in a PA/Alu/PVC 25/45/60 //Aluminum 20 µm blister. The choice of the container closure system is justified considering the nature of the finished product. Compliance with the relevant requirements and/or regulations is confirmed.

Stability

Stability studies have been performed in accordance with current guidelines. The proposed protocol is considered adequate. The packaging material is the same as that intended for marketing. Proposed shelf-life and storage conditions are properly established.

Shelf-life: 30 months.

Storage conditions: This medicinal product does not require any special storage conditions.

III. NON-CLINICAL ASPECTS

III.1 Critical evaluation of the Non-Clinical Overview

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.

III.2 Ecotoxicity/environmental risk assessment (ERA)

Since Linagliptin Kern Pharma 5 mg film-coated tablets is intended for generic substitution, this will not lead to an increased exposure to the environment. Therefore, additional ERA testing is not deemed necessary.

IV. CLINICAL ASPECTS

IV.1 Introduction

Linagliptin is a well-known active substance with established efficacy and safety. A clinical overview has been provided, which is based on scientific literature. The clinical overview justifies that there no need to generate additional clinical data.

For this generic application of an immediate release formulation, the MAH has submitted one bioequivalence study with the 5 mg strength under fasting condition according to the Guideline on the investigation of bioequivalence, which is discussed below.

IV.2 Pharmacokinetics

Biowaiver

As only a single strength is being submitted, a biowaiver is not applicable.

Bioequivalence study

Study code
KP-LNG-115; CRO code: LINA23010

GCP compliance
The study was conducted in accordance with Good Clinical Practice (GCP) standards. Monitoring reports and certificates of audits carried out by the Quality Assurance Unit are presented. The sites have been previously inspected by EU regulatory authorities.

Clinical and Bioanalytical Study Sites
Arab Pharmaceutical Industry Consulting/Pharmaceutical Research Unit19, Yajooz Street, Al-jubaiha P.O Box 1084 Sweileh 11910 Jordan

Design
The study was a randomised, two-treatment, two-period, two-sequence single-dose crossover study conducted in 46 healthy volunteers under fasting conditions.
All subjects received the same dose of study medication on dosing day in the morning between 08:00 and 08:22 in Period I and Period II in the fasting state orally, with 240 ml of water in sitting position to healthy subjects after an overnight fast of at least 10 hours in the morning of study dosing day of the two study periods.
The study periods were separated by a wash-out period of 45 days.

The total of 20 blood samples were collected at each period according to the following sample collection schedule: (8 mL) at pre-dosing (-1.00) and at 0.25, 0.50, 0.75, 1.00, 1.25, 1.50, 1.75, 2.00, 2.50, 3.00, 4.00, 6.00, 8.00, 10.00, 12.00, 16.00, 24.00, 48.00 and 72.00 hours after dosing. Samples received from clinical and stored in the analytical department at freezer -70°C until assay.
No adverse events occurred during Period I and two adverse events (headache) occurred in subjects 29 and 30 after receiving reference and test respectively. Rest of AEs occurred during the washout and follow up periods (lab abnormalities). No serious adverse events occurred in the study.

Analytical and statistical methods
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples.
The 90% confidence interval (90% CI) of the ratio of the test formulation to the reference formulation for the log-transformed values of Cmax and AUC was calculated using an ANOVA model. This model included the covariates sequence, period, formulation and subject nested to sequence.
Bioequivalence was defined when the 90% CI of the ratios (test/reference) for Cmax and AUC was in the range 80.00 -125.00%.
The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
46+4 subjects were included in the study. 46 subjects were treated; 46 subjects completed the study and were used in the statistical analysis according to the protocol.
Four subjects withdrew from the study before receiving any treatment. There were no dropouts among subjects who received study medications.
The inclusion and exclusion criteria are considered acceptable for a bioequivalence study.

Summary of assessment bioequivalence study.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range)

Treatment	**AUC_{0-72}** **pg/ml/h**	**C_{max}** **pg/ml**	**t_{max}** **h**
Test	143677.76 ± 28368.26	5318.77 ± 2.950.84	1.75 (0.25–6.00)
Reference	140243.70 ± 29869.70	5260.46 ± 4.139.88	1.75 (0.5–24.00)
***Ratio (90% CI)**	102.91% (98.70–107.30)	104.40% (91.44–119.19)	

**ln-transformed values*

Conclusion on bioequivalence study:

Based on the submitted bioequivalence study **LINA23010; KP-LNG-115**, Linagliptin Kern 5 mg film coated tablets is considered bioequivalent with Trajenta 5 mg film coated tablets.

IV.3 Pharmacodynamics/ Clinical efficacy/ Clinical safety

No original studies were submitted. This is acceptable in the context of a generic application, and no additional PD, efficacy or safety studies are deemed necessary. The efficacy and safety of linagliptin have been demonstrated in several clinical trials conducted with the reference product and during post-marketing experience. Therapeutic indication proposed for Linagliptin Kern 5 mg film coated tablets is the same as that authorized for the reference product, Trajenta 5 mg film-coated tablets.

IV.4 Risk Management Plan

The MAH has submitted a risk management plan (version 0.3, 31 May 2025), 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 Kern Pharma 5 mg film-coated tablets (linagliptin).

There are neither proposed additional pharmacovigilance activities nor proposed additional risk minimisation measures planned for Linagliptin Kern Pharma 5 mg film-coated tablets.

IV.5 Discussion on the clinical aspects

Please refer to section IV.2.

V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Trajenta 5 mg film coated tablets. The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product Linagliptin Kern is found adequate. There are no objections to the approval of Linagliptin Kern 5 mg film coated tablets 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.