CMDh/223/2005
February 2014

Public Assessment Report

Scientific discussion

Linagliptin Viatris/Ilinpru
linagliptin

SK/H/0302-0303/001/DC

Date: 04/2024

This module reflects the scientific discussion for the approval of Linagliptin Viatris/Ilinpru. The procedure was finalised at 29 December 2023. 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 Viatris/Ilinpru, film-coated tablets, 5 mg from Viatris Limited, Ireland.
The product is 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 SmPC.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC, so called generic application.

II. QUALITY ASPECTS

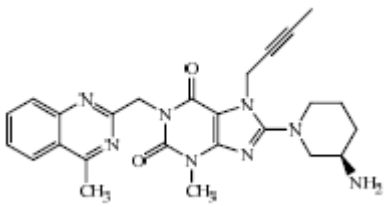
II.1 Introduction

Linagliptin Viatris/Ilinpru are pink film-coated, round, biconvex tablet, debossed with “M” on one side of the tablet and “LI” on the other side with a diameter of approximately 8 mm. Drug substance linagliptin is present in the drug product with a strength of 5 mg. Excipients used in the drug product (mannitol, maize starch, copovidone, magnesium stearate in tablet´s core and hypromellose type 2910, titanium dioxide, nacrogol 3350, talc, iron oxide red in film-coating) are well known and widely used as pharmaceutical excipients. Medicinal product is available in:

PVC/OPA/Alu blister packs containing 14, 28, 30, 90 and 100 film-coated tablets.
Perforated PVC/OPA/Alu unit dose blister packs containing 10 x 1, 30 x 1 and 90 x 1 film-coated tablets.
HDPE bottle with a polypropylene (PP) screw cap closure and a silica gel desiccant, pack sizes of 30, 90, 100 and 120 film-coated tablets placed in an outer cardboard carton or provided without a carton.

II.2 Drug Substance

Linagliptin structural formula:



Chemical names:
1H-Purine-2, 6-dione, 8-[(3R)-3-amino-1-piperidinyl]-7-(2-butyn-1-yl)-3, 7-dihydro-3-methyl-1-[(4-methyl-2-quinazolinyl) methyl]-[Source: FDA Label]
or

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

Appearance: White to yellowish powder

Solubility: Soluble in methanol, sparingly soluble in ethanol, very slightly soluble in acetone and water.

Chirality: Linagliptin contains one asymmetric carbon and exhibits optical isomerism with a possibility for a pair of optical isomers. The ASM manufactures the R-isomer. The S-Isomer is controlled in the drug substance specifications with a limit of not more than 0.15% by a chiral HPLC method.

Manufacturing: Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory. The synthesis of linagliptin involves seven stages having six isolated intermediates. Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented and are satisfactory.

Specifications: The active substance specification, includes tests for: description, solubility, identification (IR and HPLC), water content (KFR), residue on ignition/sulphated ash, related substances (HPLC), chiral purity (HPLC), assay (HPLC), residual solvents (GC), polymorphic identification (PXRD).

Stability: Stability studies were carried out under ICH conditions. Re-test period is 60 months if prereserved in double clear and black LDPE bags enclosed by a triple laminated bag in a HDPE container at controlled room temperature between 20°C and 25°C (excursions allowed between 15°C and 30°C).

II.3 Medicinal Product

Pharmaceutical development: The aim of the pharmaceutical development work was to develop a stable formulation of linagliptin 5 mg film-coated tablet which would be bioequivalent to the reference medicinal product Trajenta 5 mg film-coated tablet, manufactured by Boehringer Ingelheim International GmbH. The following drug substance attributes were considered during the development of linagliptin 5 mg film-coated tablets: particle size distribution, bulk density, tapped density, compressibility index and hausner ratio.

Manufacturing: The manufacturing process consists of following steps: granulation, drying, milling, blending, and compression.

Product specification: The proposed specification for the finished product is in line with ICH Q6A. The finished product release and shelf life specifications include appropriate tests and limits for description (in house), dimensions (in-house), identification (HPLC), dissolution (HPLC), uniformity of dosage units (in-house), assay (HPLC), related substances (HPLC), water (Ph.Eur.), microbiological test (Ph.Eur.), and colour identification (in-house).

Stability: The conditions used in the stability studies are according to the ICH stability guideline. The control tests and specifications for drug product are adequately drawn up. Stability data were provided for three batches under long-term and accelerated conditions which were packed in cold form blister pack / high density polyethylene (HDPE) bottle pack (primary packaging) and low-density polyethylene (LDPE) bag (bulk packaging). The proposed shelf-life of 24 months without storage conditions to be specified for the drug product was acceptable.

II.4 Discussion on chemical, pharmaceutical and biological aspects

From a quality point of view the dossier was adequately presented.

III. NON-CLINICAL ASPECTS

III.1 Introduction

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 were not required. Overview was based on literature review which was considered appropriate.

The excipients contained in Linagliptin Viatris/Ilinpru are similar to those in the reference product Trajenta. There are no novel excipients used in the formulation of Linagliptin Viatris/Ilinpru. The drug substance contains few identified impurities that are controlled to levels below the respective qualification thresholds.

The non-clinical safety data contained in the proposed SmPC reflects the characteristics of the drug substance and is in line with the reference product´s SmPC Trajenta.

III.2 Ecotoxicity/environmental risk assessment (ERA)

Considering the provided data, it was concluded that linagliptin´s logKow is not expected to exceed the PBT screening threshold, and thus, there was no need for further PBT assessment.

The calculation of PECsw of 0.025 µg/L demonstrated that the action value of 0.01 µg/L was exceeded following the use of the default market penetration factor.

The applicant therefore chose to refine the Fpen value using the annual consumption data of linagliptin (2017–2021 in 24 EU countries).

Given the provided data, the fact that linagliptin is used as a second-line medication when metformin is contraindicated or in combination with other antidiabetic drugs, and to follow 3R principles, an additional PECsw recalculation or Phase II screening was not deemed necessary, and the use of the product containing linagliptin was considered unlikely to pose environmental risks.

III.3 Discussion on the non-clinical aspects

As linagliptin is a widely used, well-known active substance, the applicant has not provided additional studies and further non-clinical studies were not required. This approach is acceptable for generic applications.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

Bioequivalence study

To support the applications, the applicant has submitted as a report one bioequivalence study conducted under fasting conditions as a single-dose, randomization blinded, two-period, two-sequence, two-treatment, crossover study to investigate the oral bioequivalence of test product, linagliptin tablets 5 mg, to Trajenta 5 mg film-coated tablets.

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

PARAMETER	Unit	REFERENCE LEAST SQUARE MEANS Ln DATA	TEST LEAST SQUARE MEANS Ln DATA	REFERENCE GEOMETRIC MEANS	TEST GEOMETRIC MEANS
Cmax	(ng/mL)	1.550	1.605	4.712	4.976
AUC72	(ng/mL)*(hr)	5.155	5.161	173.224	174.421

PARAMETER	Unit	INTRA-SUBJECT CV(%)	RATIO OF GEOMETRIC MEANS	90% CONFIDENCE INTERVAL	Bioequivalence
Cmax	(ng/mL)	17.974	105.58%	(98.23%; 113.48%)	Yes
AUC72	(ng/mL)*(hr)	9.712	100.69%	(96.82%; 104.72%)	Yes

C_{max}: Maximum measured plasma concentration over the time span specified.
AUC_{72}: The area under the curve (AUC – calculated by the linear trapezoidal rule) from time zero to 72 hours.
Note: AUC_{72} were calculated using partial AUC method.

Secondary Pharmacokinetic Parameters
T_{max}: Time of the maximum measured plasma concentration. If the maximum plasma concentration occurs at more than one time point, the first was chosen as T_{max}.

Conclusion on bioequivalence study
Based on the submitted bioequivalence study Linagliptin Viatris/Ilinpru was considered bioequivalent with Trajenta.

IV.2 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 Viatris/Ilinpru.

- Summary table of safety concerns as approved in RMP

Important identified risks	Pancreatitis
Important potential risks	Pancreatic cancer
Missing information	Pregnancy/breast-feeding

IV.3 Discussion on the clinical aspects

Submitted clinical dossier was of sufficient quality. Submitted data supported the chosen legal basis "generic application". Bioequivalence between the test product Linagliptin Viatris/Ilinpru with the reference medicinal product Trajenta has been demonstrated based on provided data.

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, EMEA/H/C/002110 with regard to content and Paracetamol Mylan 1000 mg tablets, PT/H/2077/001-002/DC with regard to design/layout. The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

These were the applications for a marketing authorisation of a medicinal product for human use as it is defined in Article 10(1) (generic application) of the European Directive 2001/83/EC as amended. Decentralised procedure according to Article 28(3) of Directive 2001/83/EC as amended with Slovak Republic acting as RMS. The Applicant Viatris Limited, Ireland, has submitted these duplicate MAAs under procedural numbers SK/H/0302-0303/001/DC.
CMS were:

SK/H/0302/001/DC: Bulgaria, Czech Republic, Denmark, Finland, Ireland, Italy, Netherlands, Norway, Portugal, and Sweden
SK/H/0303/001/DC: Austria, Cyprus, Greece, Spain, and Malta

As a reference medicinal product Trajenta 5 mg film-coated tablets (MAA No: EU/1/11/707/001-011) from Boehringer Ingelheim International GmbH, Germany, was chosen.

Quality aspects of the dossier were adequately described; specifications of linagliptin were adequately drawn up and that of finished medicinal product were in line with ICH Q6A.

As linagliptin is a widely used, well-known active substance, the applicant has not provided additional studies and further non-clinical studies were not required.

To support the applications, the applicant has submitted as report one bioequivalence study conducted under fasting conditions as a single-dose, randomization blinded, two-period, two-sequence, two-treatment, crossover study to investigate the oral bioequivalence test product, linagliptin tablets 5 mg, to Trajenta 5 mg film-coated tablets. Based on the submitted bioequivalence study, test product Linagliptin Viatris/Ilinpru was considered bioequivalent with the reference medicinal product Trajenta.