COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Linagliptin 5 mg film-coated tablets (linagliptin)

NL/H/4958/001/DC

Date: 8 June 2021

This module reflects the scientific discussion for the approval of linagliptin Intas. The procedure was finalised at 10 February 2021. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Linagliptin Intas 5 mg film-coated tablets, from Intas Third Party Sales 2005, S.L.

The product is indicated for 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.

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

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Trajenta 5 mg film-coated tablets (NL RVG 107883) which has been centrally registered by Boehringer Ingelheim International GmbH (Germany) since 24 August 2011 (original product) via procedure EMEA/H/C/002110 and has MA number EU/1/11/707.

The concerned member states (CMS) involved in this procedure were Greece, Spain, Italy, Malta and Poland.

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

II. QUALITY ASPECTS

II.1 Introduction

Linagliptin Intas is a round, light red, biconvex, bevel-edged film coated tablet debossed with "L5" on one side and plain on the other side.

Each film-coated tablet contains as active substance 5 mg of linagliptin.

The tablets are packed in perforated Alu-Alu, triple laminated (OPA/Aluminium/PVC) foil as forming foil and hard tampered aluminium foil with heat seal lacquer (HSL) coating as lidding foil unit dose blisters in cartons.

The excipients are:

Tablet core - mannitol (E421), maize starch, copovidone and magnesium stearate (E470b).

Film coating - hypromellose 2910 - 5 mPa.s (E464), titanium dioxide (E171), talc (E553b), macrogol (6000) and iron oxide red (E172).

II.2 Drug Substance

The active substance is linagliptin, a well-known active substance not described in the Ph. Eur., BP or USP. Linagliptin is a crystalline powder and is very slightly soluble in water. The active substance corresponds to the R-isomer. The S-isomer is controlled as an impurity. The active substance exhibits polymorphism. The ASM manufactures a mixture of anhydrous form A and anhydrous form B. It is known from the public assessment report of the reference product Trajenta that the two polymorphic forms are enantiotropically related, reversibly convert into each other approximately at room temperature, and that they do not differ with regard to biopharmaceutical properties. It is therefore not necessary to define the exact ratio of the two polymorphic forms.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process

The proposed manufacturing process includes six synthetic steps and one purification step. The proposed starting materials are considered acceptable. The proposed manufacturing process does not include metal catalysts. The solvents used in the last step of the manufacturing process are acceptable as well. Up to date, one batch was reprocessed. The batch analysis and stability data of this batch demonstrate compliance with the drug substance specification.

There are no reworking and recovery procedures. The ASMF will be updated if recovery procedures have been established.

Quality control of drug substance

The active substance specification of the active substance manufacturer includes tests for description, solubility, identification, water content, sulphated ash, related substances, chiral purity, assay, residual solvents, and polymorphic identification. The active substance specification of the drug product manufacturer is in accordance with the specification of the active substance manufacturer with additional requirements for particle size and microbial examination. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data is provided for two batches by the MAH and for five batches by the ASMF holder.

Stability of drug substance

Stability data on the active substance has been provided for five pilot scale batches stored at 25°C/60% RH (60 months) and 40°C/75% RH (6 months). No significant changes or any trends were observed at both storage conditions. A re-test period of 60 months with no specific storage conditions is claimed. This is justified.

II.3 Medicinal Product

Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained. The MAH varied the concentration of the excipients to obtain the most suitable composition. The dissolution profile of the reference product was compared with the biobatch and was found to be not similar. The MAH varied the hardness of the tablet, the compression speed, the lubrication time and determined the segregation during compression during the manufacturing development. The pharmaceutical development of the product has been adequately performed.

Manufacturing process

The tablets are manufactured by granulation, milling, blending and compression after which the tablets are coated. The manufacturing process has been adequately described according to relevant European guidelines. Process validation data on the product has been presented for three batches with the minimum commercial batch size. The product is manufactured using conventional manufacturing techniques. Process validation for full scaled batches will be performed post authorisation which is acceptable since it is a standard process.

Control of excipients

The excipients (except the Opadry coating) comply with Ph. Eur. requirements. The specifications are acceptable. The in-house specification for the Opadry coating is acceptable as well.

Quality control of drug product

The product specification includes tests for description, average weight, identification (API and colorant), loss on drying, dissolution, uniformity of dosage units, related substances, assay and microbial examination. The release and shelf-life limits are identical. The drug product specification is acceptable. The analytical methods have been adequately described and validated.

Batch analytical data from the proposed production site have been provided on three batches with the minimum commercial batch size.

Stability of drug product

Stability data on the product has been provided on three batches with the minimum commercial batch size stored at 25°C/60% RH (36 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches

were stored in Alu/Alu blisters. Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light.

No significant changes were observed at both storage conditions. The claimed shelf life of three years (with no specific storage conditions) is justified.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Linagliptin Intas has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Linagliptin Intas 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.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Trajenta 5 mg film-coated tablets which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Linagliptin Intas is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted one bioequivalence study which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Linagliptin Intas (Intas Third Party Sales 2005, S.L., Spain) is compared with the pharmacokinetic profile of the reference product Trajenta 5 mg film-coated tablets (Boehringer Ingelheim International GmbH, Germany).

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and composition of Trajenta 5 mg film-coated tablets. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Bioequivalence study

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 30 healthy male subjects, aged 30.8 +/- 7.99 years. Each subject received a single dose (5 mg) of one of the two linagliptin formulations (test or reference product). The tablet was orally administered with 240 ml water after 10 hours of fasting. There were two dosing periods, separated by a washout period of 41 days.

Blood samples were collected pre-dose and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.3, 2.7, 3, 3.5, 4, 5, 6, 8, 10, 12, 14, 16, 20, 24, 36, 48 and 72 after administration of the products.

The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

The wash-out period of 41 days is theoretically long enough, as the terminal half-life is more than 100 hours. The sampling period is sufficient enough, and the sampling scheme is adequate to estimate PK parameters. Although the wash-out period should be sufficient, many subjects had a pre-dose linagliptin level at the start of the second period. Only in one case the pre-dose level was over 5% of the C_{max}. Therefore, no influence on the bioequivalence

outcome is expected. Sufficient sampling was performed around the T_{max} (1,5 hours). A single dose, crossover study to assess bioequivalence is considered adequate.

Fasting conditions has been applied as the product can be taken with or without food. Subjects were dosed with glucose throughout the study for safety reasons. This is not expected to influence bioequivalence outcome as food does not influence linagliptin pharmacokinetics significantly.

Taken together, it is concluded that the study design is acceptable.

Results
Out of a total of 30, 27 subjects were eligible for pharmacokinetic analysis. Two subjects discontinued from the study on their own accord in period-II. One subject was withdrawn from the study on medical grounds in period- II (diarrhea, reference treatment).

Table 1. Pharmacokinetic parameters of linagliptin (non-transformed values; arithmetic mean ± SD, t_{max} (median, range))of linagliptin under fasting conditions. (Excluding subject whose pre-dose concentration was >5% of C_{max} in Period II)

Treatment N=26	**AUC_{0-72} (ng.h/ml)**	**C_{max} (ng/ml)**	**t_{max} (h)**
Test	264 ± 53	7.5 ± 2.9	3.5 (0.8-12.0)
Reference	260 ± 53	6.6 ± 1.6	4.0 (1.0-14.0)
***Ratio (90% CI)**	1.02 (0.98 -1.05)	1.10 (1.03- 1.18)	--
CV (%)	8.4	13.8	--

AUC_{0-72h} area under the plasma concentration-time curve from time zero to 72 hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life
CV coefficient of variation

**ln-transformed values*

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of linagliptin under fasted conditions. (Including subject whose pre-dose concentration was >5% of C_{max} in Period II)

Treatment N=27	**AUC_{0-72} ng/ml/h**	**C_{max} ng/ml**
Test	264 ± 52	7.4 ± 2.8
Reference	260 ± 52	6.6 ± 1.6
***Ratio (90% CI)**	1.02 (0.98-1.06)	1.1 (1.04-1.17)
CV%	7.9	13.5
AUC_{0-72h} area under the plasma concentration-time curve from time zero to 72 hours **C_{max}** maximum plasma concentration		

**ln-transformed values*

What can be concluded from both table 1 and 2 is that including or excluding the subject whose pre-dose concentration was >5% of C_{max} in period II had no influence on the results for the bioequivalence of both linagliptin formulations.

Conclusion on bioequivalence study

The 90% confidence intervals calculated for AUC_{0-72h} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study, Linagliptin 5 mg film-coated tablets is considered bioequivalent with Trajenta 5 mg film-coated tablets.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

IV.3 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 Intas.

Table 3. Summary table of safety concerns as approved in RMP

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

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information. In line with the innovator, specific questionnaires are in place to obtain structured information on reported suspected adverse reactions pancreatitis and pancreatic cancer.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Trajenta. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to the PL of Trajenta (for content) and Zoledronic Acid Accord 4 mg/5 ml concentrate for solution for infusion (for design and lay-out). The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet. The package leaflet meets the criteria set out in Art 59(3) of Directive 2001/83/EC and is regarded acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Linagliptin 5 mg film-coated tablets has a proven chemical-pharmaceutical quality and is a generic form of Trajenta 5 mg film-coated tablets. Trajenta is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Linagliptin Intas with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 10 February 2021.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse