**IPAR**

**Public Assessment Report for a**
**Medicinal Product for Human Use**

Scientific Discussion

Sitagliptin Pinewood 50 mg film-coated tablets
Sitagliptin Hydrochloride
PA0281/219/002

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

**CONTENTS**

## I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Sitagliptin Pinewood 25mg, 50mg and 100mg film-coated tablets, from Pinewood Laboratories Ltd on 8th April 2022. This medicine is indicated in adult patients with type 2 diabetes mellitus to

improve glycaemic control: as monotherapy

- in patients inadequately controlled by diet and exercise alone and for whom metformin is inappropriate due to contraindications or intolerance.

as dual oral therapy in combination with

- metformin when diet and exercise plus metformin alone do not provide adequate glycaemic control.
- a sulphonylurea when diet and exercise plus maximal tolerated dose of a sulphonylurea alone do not provide adequate glycaemic control and when metformin is inappropriate due to contraindications or intolerance.
- a peroxisome proliferator-activated receptor gamma (PPARγ) agonist (i.e. a thiazolidinedione) when use of a PPARγ agonist is appropriate and when diet and exercise plus the PPARγ agonist alone do not provide adequate glycaemic control.

as triple oral therapy in combination with

- a sulphonylurea and metformin when diet and exercise plus dual therapy with these medicinal products do not provide adequate glycaemic control.
- a PPARγ agonist and metformin when use of a PPARγ agonist is appropriate and when diet and exercise plus dual therapy with these medicinal products do not provide adequate glycaemic control.

Sitagliptin Pinewood 25mg, 50mg and 100 mg is also indicated as add-on to insulin (with or without metformin) when diet and exercise plus stable dose of insulin do not provide adequate glycaemic control.

This application is being made under Directive 2001/83/EC, Article 10.1 as amended. The generic immediate release tablets are claimed to be essentially similar to the reference product, marketed as Januvia by Merck Sharpe & Dohme Ltd on 21 March 2007. To support the application, a pivotal bioequivalence study was submitted.

These products are subject to prescription which may be renewed. The Summary of Product Characteristics for (SmPC) for this medicinal product is available on the HPRA's website at https://www.hpra.ie/homepage/medicines

| | |
|---|---|
| Name of the product | Sitagliptin Pinewood 25mg, 50mg, 100 mg |
| Name(s) of the active substance(s) (INN) | Sitagliptin |
| Pharmacotherapeutic classification (ATC code) | A10BH01 |
| Pharmaceutical form and strength(s) | 25mg, 50mg and 100mg film-coated tablets |
| Marketing Authorisation Number(s) in Ireland (PA) | PA0281/219/001-003 |
| Marketing Authorisation Holder | Pinewood Laboratories Ltd |

## II. QUALITY ASPECTS

### II.1. Introduction

This application is for Sitagliptin Pinewood 25mg, 50mg and 100 mg film-coated tablets.

### II.2 Drug substance

The active substance is sitagliptin hydrochloride monohydrate, an established active substance, and is manufactured in accordance with the principles of Good Manufacturing Practice (GMP)

The active substance specification is considered adequate to control the quality and meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with this specification has been provided.

### II.3 Medicinal product

P.1 Composition

25 mg tablet: each tablet contains sitagliptin hydrochloride monohydrate equivalent to 25 mg of Sitagliptin.
50 mg tablet: each tablet contains sitagliptin hydrochloride monohydrate equivalent to 50 mg of Sitagliptin.
100 mg tablet: each tablet contains sitagliptin hydrochloride monohydrate equivalent to 100 mg of Sitagliptin.

The excipients in the medicinal product are listed in section 6.1 of the SmPC.
A visual description of the product is included in section 3 of the SmPC.

P.2 Pharmaceutical Development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.

The manufacturing process has been validated according to relevant European/ICH guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients/*Ancillary Substances*)

All ingredients comply with Ph. Eur. or are adequately controlled by the manufacturer's specifications.

P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopoeial monograph for coated tablets, and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production sites have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material

The approved packaging for this product is described in section 6.5 of the SmPC.

Evidence has been provided that the packaging complies with Ph. Eur./EU legislation for use with foodstuffs requirements.

P.7 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines and support the shelf-life and storage conditions listed in sections 6.3 and 6.4 of the SmPC.

Adventitious Agent Safety

For excipient lactose monohydrate compliance with the Note For Guidance on Minimising the Risk if Transmitting Animal Spongiform Encephalopathy Agents via Medicinal Products has been satisfactorily demonstrated.

**II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects**

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Sitagliptin Pinewood 25mg, 50mg and 100 mg film-coated tablets.

## III. NON-CLINICAL ASPECTS

**III.1 Introduction**

This active substance, sitagliptin, is a generic formulation of Januvia (Merck Sharpe & Dohme Ltd) on the European market since 2007. No new preclinical data have been submitted.
As such, no pre-clinical assessment has been made on the application. This is acceptable for this type of application.

**III.5 Ecotoxicity/environmental risk assessment**

An Environmental Risk Assessment (ERA) for sitagliptin was submitted by the applicant. The ERA indicates a log $K_{ow}$ of 0.6 and a log $K_{ow}$ of -0.03 at pH 7, therefore indicating no bioaccumulation potential for stagliptin. The calculated PECsurfacewater is 0.5 µg/L, which is above the trigger value of 0.01 µg/L indicating that a Phase II assessment is required. Sitagliptin is not a PBT substance.
Considering the above data, stagliptin is not expected to pose a risk to the environment.

**III.6 Discussion on the non-clinical aspects**

The pharmacodynamic, pharmacokinetic and toxicological properties of sitagliptin are well known. As this is a generic application, the applicant has not provided additional nonclinical studies and further studies are not required. The overview provided based on literature review is thus appropriate. Sitagliptin is not a PBT substance and is not expected to pose a risk to the environment.

## IV. CLINICAL ASPECTS

**IV.1 Introduction**

Sitagliptin is a well-known active substance with established efficacy and tolerability.

The content of the SmPC approved during the national procedure is in accordance with that accepted for the reference product Januvia marketed by Merck Sharpe & Dohme Ltd.

For this generic application, the applicant has submitted one bioequivalence study in which the pharmacokinetic profile of the test product Sitagliptin 100 mg Tablet is compared with the pharmacokinetic profile of the reference product Januvia (SITAGLIPTIN) 100 mg film-coated tablet.

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out. Sitagliptin 100mg tablet, Laboratorios Liconsa, S.A, Poligono Industrial, Spain was compared to the reference product Januvia 100 mg Film-coated tablet, Merck Sharp and Dohme Ltd. Based on the pharmacokinetic parameters of active substance, the reference tablet Januvia 100 mg Film-coated tablet marketed by Merck Sharp and Dohme Ltd and test tablet Sitagliptin 100mg tablet are bioequivalent with extent to the rate and extent of absorption and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

A biowaiver for an in-vivo bioequivalence study was requested for Sitagliptin 25 mg and 50 mg film-coated tablets meeting the requirements as per Guideline CPMP/QWP/EWP/1401/98 Rev. 1/Corr**.

Pharmacodynamic, pharmacokinetic and efficacy/safety data of the active substance are well known. This is a generic application and no new indications have been applied for.

- *Risk Management Plan (usual pharmacovigilance requirements and/or additional requirements)*
- *The proposed schedule for submission of PSURs should be addressed.*

The HPRA has been assured that GCP standards were followed in an appropriate manner in the studies conducted.

**IV.2 Pharmacokinetics**

For this generic application, one bioequivalence study in which the pharmacokinetic profile of the test product Sitagliptin 100 mg Tablet is compared with the pharmacokinetic profile of the reference product Januvia (SITAGLIPTIN) 100 mg film-coated tablet has been submitted.

An open label, balanced, randomized, two-treatment, two-period, two-sequence, single oral dose, crossover, bioequivalence study of sitagliptin 100mg tablets of laboratorios liconsa, S.A. Espana versus Januvia® (Sitagliptin) 100 mg film-coated tablets of Merck Sharp & Dohme Ltd. In normal, healthy, adult, human subjects under fasting conditions.

In this study, 38 healthy subjects were enrolled (Gender: males and females, age 20-44 years, weight: 50.4-83.3 kg, BMI: 18.65-29.83 kg/m2). The numbers of dosed subjects were 38 and 32 for period I and II respectively. The reasons for withdrawal were based on medical grounds, in accordance with the protocol and are well documented.

**Results**

The intra-subject variability of this study was 13.3%; therefore, the standard accepted limits of between 80.00-125.00% are used.

All pre-dose concentrations were below LLOQ and the residual area was < 20% for all subjects during each period, demonstrating no carryover effect. The 90% confidence intervals for $C_{max}$ and $AUC_{0-t}$ were 94.63-106.02% and 99.71-102.48% respectively; all of which are within the accepted ranges of 80.00-125.00%.

**Relative Bioavailability Results for Sitagliptin (N = 32)**

| Parameters | Geometric Least Squares Means | | | 90% Confidence Interval | Intra Subject CV (%) | Power (%) |
|---|---|---|---|---|---|---|
| | Test Product-T | Reference Product-R | Ratio (T/R)% | | | |
| $lnC_{max}$ | 488.585 | 487.779 | 100.2 | 94.63 - 106.02 | 13.3 | 100.0 |
| $lnAUC_{0-t}$ | 4355.153 | 4308.382 | 101.1 | 99.71 - 102.48 | 3.2 | 100.0 |
| $lnAUC_{0-\infty}$ | 4418.189 | 4378.194 | 100.9 | 99.59 - 102.26 | 3.1 | 100.0 |

**Table 3.3 Bioequivalence Evaluation of Sitagliptin in Project No. 0205-18**

| Pharmacokinetic Parameter | Geometric Mean Ratio Test/Reference | 90% Confidence Intervals | CV%[1] |
|---|---|---|---|
| $AUC_{(0-t)}$ | 101.1 | 99.71 - 102.48 | 3.2 |
| $C_{max}$ | 100.2 | 94.63 - 106.02 | 13.3 |

[1]Estimated from the Residual Mean Squares.

6 adverse events were recorded (upper respiratory tract infection, n=3; vomiting, n=1; hyperchlorhydria, n=1; and thrombophlebitis superficial, n=1). One AE was recorded as not related, while the remaining 5 AEs were recorded as unlikely related to the study treatment. The applicant classified all 6 AEs as mild in nature. All of the AEs resolved, with majority of the AEs requiring treatment with medication. No serious adverse events (SAEs) or death were reported during this study.

**IV.3 Pharmacodynamics**

The applicant has not conducted any new pharmacokinetic studies to support this application.

**IV.4 Clinical Efficacy**

No additional efficacy studies were conducted which is acceptable for this application type.

**IV.5 Clinical Safety**

No new safety findings were noted during the bioequivalence studies and no additional safety studies were conducted which is acceptable for this application type.

A Risk Management Plan, version 0.2, dated 26th March 2021 has been submitted, 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 Sitagliptin Pinewood 25mg, 50mg and 100mg film-coated tablets. It is concluded that routine pharmacovigilance and risk minimisation measures are sufficient.

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.

**IV.6 Discussion on the clinical aspects**

For this marketing authorisation, no new clinical or non-clinical studies were conducted. A biowaiver for an in-vivo bioequivalence study was submitted in support of Sitagliptin 25 mg and 50 mg film-coated tablets. The MAH demonstrated bioequivalence between the test product Sitagliptin 100 mg Tablet and the reference product Januvia (SITAGLIPTIN) 100 mg film-coated tablet, in accordance with the Bioequivalence Guideline CPMP/QWP/EWP/1401/98 Rev. 1/Corr**.

The safety and efficacy profiles for this medicinal product are well-established over many years. There were no new or unexpected safety concerns noted during assessment of this procedure.

There is extensive clinical experience with Sitagliptin in the management of adult patients with type 2 diabetes mellitus, which has demonstrated a positive benefit risk profile.

## V. OVERALL CONCLUSIONS

Sitagliptin Pinewood 25mg, 50mg and 100mg film-coated tablets are a generic form of product Januvia (SITAGLIPTIN) 100 mg film-coated tablet. Januvia 100 mg film-coated tablet is a well-known medicinal product with a proven chemical-pharmaceutical quality and an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the CHMP guidance documents. The SmPC is consistent with that of the reference product.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The HPRA, on the basis of the data submitted considered that Sitagliptin Pinewood 25mg, 50mg and 100mg film-coated tablets demonstrated bioequivalence with the reference product as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

## VI. REVISION DATE

## VII. UPDATES

This section reflects the significant changes following finalisation of the initial procedure.

| SCOPE | PROCEDURE NUMBER | PRODUCT INFORMATION AFFECTED | DATE OF START OF PROCEDURE | DATE OF END OF PROCEDURE |
|---|---|---|---|---|
| | | | | |