IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Sitagliptin/Metformin Hydrochloride Pinewood 50 mg/850 mg film-coated tablets
Sitagliptin Hydrochloride
Metformin Hydrochloride
PA0281/220/001

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/Metformin Hydrochloride Pinewood 50 mg/850 mg film-coated tablets and Sitagliptin/Metformin Hydrochloride Pinewood 50 mg/1000 mg film-coated tablets, from Pinewood Laboratories Limited on 23rd of June 2023 indicated as follows:
For adult patients with type 2 diabetes mellitus:
Sitagliptin/Metformin Hydrochloride Pinewood is indicated as an adjunct to diet and exercise to improve glycaemic control in patients inadequately controlled on their maximal tolerated dose of metformin alone or those already being treated with the combination of sitagliptin and metformin.
Sitagliptin/Metformin Hydrochloride Pinewood is indicated in combination with a sulphonylurea (i.e., triple combination therapy) as an adjunct to diet and exercise in patients inadequately controlled on their maximal tolerated dose of metformin and a sulphonylurea.
Sitagliptin/Metformin Hydrochloride Pinewood is indicated as triple combination therapy with a peroxisome proliferator-activated receptor gamma (PPARγ) agonist (i.e., a thiazolidinedione) as an adjunct to diet and exercise in patients inadequately controlled on their maximal tolerated dose of metformin and a PPARγ agonist.
Sitagliptin/Metformin Hydrochloride Pinewood is also indicated as add-on to insulin (i.e., triple combination therapy) as an adjunct to diet and exercise to improve glycaemic control in patients when stable dose of insulin and metformin alone do not provide adequate glycaemic control.

This application for a marketing authorisation was submitted under Article 10(1) of Directive 2001/83/EC as amended and via national application.

The reference products Janumet 50 mg/850 mg film-coated tablets and Janumet 50 mg/1000 mg film-coated tablets developed by Merck Sharp & Dohme B.V. have been authorised in the European Economic Area since 2008.

The applicant's products are of the same indication, strength and route of administration as that of the reference medicinal product Janumet 50 mg/850 mg film-coated tablets and Janumet 50 mg/1000 mg film-coated tablets.

Sitagliptin/Metformin Hydrochloride Pinewood 50 mg/850 mg film-coated tablets and Sitagliptin/Metformin Hydrochloride Pinewood 50 mg/1000 mg film-coated tablets 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 www.hpra.ie.

Name of the product	Sitagliptin/Metformin Hydrochloride Pinewood 50 mg/850 mg film-coated tablets
Name(s) of the active substance(s) (INN)	Sitagliptin Hydrochloride, Metformin Hydrochloride
Pharmacotherapeutic classification (ATC code)	A10BD07 -metformin and sitagliptin
Pharmaceutical form and strength(s)	Film-coated tablet 50/850 milligrams
Marketing Authorisation Number(s) in Ireland (PA)	PA0281/220/001
Marketing Authorisation Holder	Pinewood Laboratories Ltd
Case Reference Number	CRN009TNH

II. QUALITY ASPECTS

II.1. Introduction

This application is for Sitagliptin/Metformin Hydrochloride Pinewood 50mg/850mg and 50mg/1000mg film coated tablets.

II.2 Drug substance

The active substances are Sitagliptin, an established active substance, and Metformin Hydrochloride, an established active substance described in the European Pharmacopoeia, and are manufactured in accordance with the principles of Good Manufacturing Practice (GMP)

The active substances specifications are 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

Each film-coated tablet contains sitagliptin hydrochloride monohydrate, equivalent to 50 mg of sitagliptin and 850 mg or 1000 mg of metformin hydrochloride.

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 site(s) 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.

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 the medicinal product.

III. NON-CLINICAL ASPECTS

III.1 Introduction

These active substances, sitagliptin and metformin, is a generic formulation of Janumet (Merck Sharpe & Dohme Ltd) on the European market since 2008. 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.2 Ecotoxicity/environmental risk assessment

An Environmental Risk Assessment (ERA) for sitagliptin and metformin was submitted by the applicant.

Sitagliptin
The ERA indicates a log K_{ow} of 0.6 and a log K_{ow} of -0.03 at pH 7, therefore indicating low bioaccumulation potential for stagliptin. Sitagliptin is not a PBT substance. 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. Based on the NOEC for the most sensitive chronic test organism and the PECsw, the PECsw/PNEC <1, indicating stagliptin is not expected to pose a risk to the environment.

Metformin
The ERA indicates a log K_{ow} of -1.43 to -2.64, therefore indicating low bioaccumulation potential for metformin.
The calculated PECsurfacewater is 10 µg/L, which is above the trigger value of 0.01 µg/L indicating that a Phase II assessment is required. Based on the NOEC for the most sensitive chronic test organism and the PECsw, the PECsw/PNEC <1, indicating metformin is not expected to pose a risk to the environment.

Considering the above data, the combination of sitagliptin and metformin is not expected to pose a risk to the environment.

III.3 Discussion on the non-clinical aspects

The pharmacodynamic, pharmacokinetic and toxicological properties of sitagliptin and metformin 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. Neither sitagliptin nor metformin are PBT substances and the combination is not expected to pose a risk to the environment.

IV. CLINICAL ASPECTS

IV.1 Introduction

This is a generic application submitted under article 10(1) of Directive 2001/83/EC.

Sitagliptin and metformin are well-known active substances with established efficacy and tolerability.

The content of the SmPCs approved during the decentralised procedure is in accordance with that accepted for the reference product Janumet 50 mg/850 mg film-coated tablets and Janumet 50 mg/1000 mg film-coated tablets marketed by Merck Sharp & Dohme B.V.

For this generic application, the applicant has submitted 2 bioequivalence studies in which the pharmacokinetic profile of the test product is compared with the pharmacokinetic profile of the reference product.

In the first study, a single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out. Sitagliptin/Metformin Hydrochloride Pinewood 50 mg/850 mg film-coated tablets, was compared to the reference product Janumet 50 mg/850 mg film-coated tablets, Merck Sharp & Dohme B.V. Based on the pharmacokinetic parameters of the active substances sitagliptin and metformin, the reference tablet Janumet 50 mg/850 mg film-coated tablets, Merck Sharp & Dohme B.V and test tablet Sitagliptin/Metformin Hydrochloride Pinewood 50 mg/850 mg film-coated tablets are bioequivalent with extent to the rate and extent of absorption and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

In the second study, a single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out. Sitagliptin/Metformin Hydrochloride Pinewood 50 mg/1000 mg film-coated tablets, was compared to the reference product Janumet 50 mg/1000 mg film-coated tablets, Merck Sharp & Dohme B.V. Based on the pharmacokinetic

parameters of the active substances sitagliptin and metformin, the reference tablet Janumet 50 mg/1000 mg film-coated tablets, Merck Sharp & Dohme B.V and test tablet Sitagliptin/Metformin Hydrochloride Pinewood 50 mg/1000 mg film-coated tablets are bioequivalent with extent to the rate and extent of absorption and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

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

IV.2 Pharmacokinetics

Sitagliptin
Absorption: Following oral administration of a 100-mg dose to healthy subjects, sitagliptin was rapidly absorbed, with peak plasma concentrations (median Tmax) occurring 1 to 4 hours post-dose, mean plasma AUC of sitagliptin was 8.52 μM•hr, Cmax was 950 nM. The absolute bioavailability of sitagliptin is approximately 87 %.

Since co-administration of a high-fat meal with sitagliptin had no effect on the pharmacokinetics, sitagliptin may be administered with or without food.

Linearity: Plasma AUC of sitagliptin increased in a dose-proportional manner. Dose-proportionality was not established for Cmax and C24hr (Cmax increased in a greater than dose-proportional manner and C24hr increased in a less than dose-proportional manner).

Elimination
The apparent terminal t½ following a 100-mg oral dose of sitagliptin was approximately 12.4 hours.

Metformin
Absorption: After an oral dose of metformin, Tmax is reached in 2.5 h. Absolute bioavailability of a 500 mg metformin tablet is approximately 50-60 % in healthy subjects.

Food decreases the extent and slightly delays the absorption of metformin. Following administration of a dose of 850 mg, a 40% lower plasma peak concentration, a 25 % decrease in AUC and a 35 min prolongation of time to peak plasma concentration was observed. The clinical relevance of this decrease is unknown.

Linearity: After oral administration, metformin absorption is saturable and incomplete. It is assumed that the pharmacokinetics of metformin absorption is non-linear. At the usual metformin doses and dosing schedules, steady state plasma concentrations are reached within 24-48 h and are generally less than 1 μg/mL. In controlled clinical trials, maximum metformin plasma levels (Cmax) did not exceed 5 μg/mL, even at maximum doses.

Elimination: Following an oral dose, the apparent terminal elimination half-life is approximately 6.5 h.

IV.3 Pharmacodynamics

Metformin is a biguanide with antihyperglycaemic effects, lowering both basal and postprandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce hypoglycaemia.
Sitagliptin phosphate is an orally-active, potent, and highly selective inhibitor of the dipeptidyl peptidase 4 (DPP-4) enzyme for the treatment of type 2 diabetes.

Sitagliptin/Metformin Pinewood combines two antihyperglycaemic medicinal products with complementary mechanisms of action to improve glycaemic control in patients with type 2 diabetes: sitagliptin phosphate, a dipeptidyl peptidase 4 (DPP-4) inhibitor, and metformin hydrochloride, a member of the biguanide class.
Pharmacotherapeutic group: Drugs used in diabetes, Combinations of oral blood glucose lowering drugs, ATC code: A10BD07

IV.4 Clinical Efficacy
The efficacy of sitagliptin/metformin in the proposed indications is established in clinical use. No new clinical efficacy studies are provided and none are required.

IV.5 Clinical Safety

The overall safety profile of sitagliptin/metformin is established and generally known. No new safety studies are provided and none are required.

The safety information in the SmPC and Package Leaflet are in line with those of the reference product.

A Risk Management Plan, version 0.2, dated 27th April 2022 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/Metformin 50mg/850mg and 50 mg/1000mg film coated tablets. It is concluded that routine pharmacovigilance and risk minimisation measures are sufficient.

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.

IV.6 Discussion on the clinical aspects

As this is a generic application under Article 10(1) of Directive 2001/83/EC, additional non-clinical and clinical studies to demonstrate efficacy and safety are not required.
The applicant has submitted the results of 2 suitable bioequivalence studies, which has demonstrated the similarity of the test product Sitagliptin/Metformin Hydrochloride Pinewood 50 mg/850 mg film-coated tablets of Pinewood Laboratories Limited against the reference product Janumet 50 mg/850 mg film-coated tablets of Merck Sharp & Dohme Ltd., and test product Sitagliptin/Metformin Hydrochloride Pinewood 50 mg/1000 mg film-coated tablets of Pinewood Laboratories Limited against the reference product Janumet 50 mg/1000 mg film-coated tablets of Merck Sharp & Dohme Ltd., in accordance with the relevant guidance.
The applicant has also submitted a clinical overview and summary of the evidence demonstrating the efficacy and safety of this product in clinical practice.

V. OVERALL CONCLUSIONS

Sitagliptin/Metformin Hydrochloride Pinewood 50 mg/850 mg film-coated tablets and Sitagliptin/Metformin Hydrochloride Pinewood 50 mg/1000 mg film-coated tablets of Pinewood Laboratories Limited are generic forms of Janumet 50 mg/850 mg film-coated tablets and Janumet 50 mg/1000 mg film-coated tablets of Merck Sharp & Dohme Ltd S.A.. Janumet 50 mg/850 mg film-coated tablets and Janumet 50 mg/1000 mg film-coated tablets are well-known medicinal products with a proven chemical-pharmaceutical quality and 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/Metformin Hydrochloride Pinewood 50 mg/850 mg film-coated tablets and Sitagliptin/Metformin Hydrochloride Pinewood 50 mg/1000 mg film-coated tablets demonstrated bioequivalence with the reference product Janumet 50 mg/850 mg film-coated tablets and Janumet 50 mg/1000 mg film-coated tablets respectively as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

VI. REVISION DATE

5 years from the finalisation of the procedure.

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
New National	N/A	SmPC sections 1-9	23rd June 2023	22nd June 2028