

IPAR



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

Scientific Discussion

Sitagliptin and Metformin hydrochloride Ascend 50 mg/1000 mg film-coated tablets
Sitagliptin phosphate
Metformin Hydrochloride
PA23429/002/002

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.

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I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Sitagliptin and Metformin hydrochloride Ascend 50mg/850mg & 50mg/1000mg Film-coated Tablets, from Ascend GmbH, on 4th April 2025 in adult patients with type 2 diabetes mellitus:

- 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,
- 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,
- as triple combination therapy with a peroxisome proliferator-activated receptor gamma (PPAR γ) 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 PPAR γ agonist,
- 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 via a decentralised procedure in accordance with Article 10(1) of Directive 2001/83/EC and is referred to as an 'generic' application.

Ireland was the Reference Member State (RMS) and the only Concerned Member States (CMS) was Germany.

These are prescription-only medicinal products.

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 and Metformin hydrochloride Ascend 50mg/850mg & 50mg/1000mg Film-coated Tablets
Name(s) of the active substance(s) (INN)	Sitagliptin phosphate, Metformin Hydrochloride
Pharmacotherapeutic classification (ATC code)	A10BD07
Pharmaceutical form and strength(s)	50mg/850mg & 50mg/1000mg Film-coated Tablets
Marketing Authorisation Number(s) in Ireland (PA)	PA23429/002/001-002
Marketing Authorisation Holder	Ascend GmbH
MRP/DCP No.	IE/H/1247/001-002/DC
Reference Member State	IE
Concerned Member State	DE

II. QUALITY ASPECTS

II.1. Introduction

This application is for Sitagliptin and Metformin hydrochloride Ascend 50mg/850mg & 50mg/1000mg Film-coated Tablets.

II.2 Drug substance

The active substances are sitagliptin phosphate and metformin hydrochloride, which are both established active substances. Sitagliptin phosphate is supported by an ASMF while metformin hydrochloride is described in the European Pharmacopoeia, and are manufactured in accordance with the principles of Good Manufacturing Practice (GMP)

The active substance specifications are considered adequate to control the quality and meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with the specifications have been provided.

II.3 Medicinal product

P.1 Composition

The finished products are film-coated tablets containing 50 mg of sitagliptin (as phosphate) 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 guideline and the process is considered to be sufficiently validated.

P.4 Control of Other 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 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 Sitagliptin and Metformin hydrochloride Ascend 50mg/850mg & 50mg/1000mg Film-coated Tablets.

III. NON-CLINICAL ASPECTS

III.1 Introduction

This active substance is a generic formulation of Janumet (50 mg/850 mg and 50 mg/1000 mg) tablets on the European market. No new preclinical data have been submitted. This is acceptable for this type of application.

III.2 Pharmacology

N/A

III.3 Pharmacokinetics

N/A

III.4 Toxicology

N/A

III.5 Ecotoxicity/environmental risk assessment

Since sitagliptin and metformin hydrochloride 50mg/850mg & 50mg/1000mg film-coated tablets are generic products, it will not lead to an increased exposure to the environment. Further environmental risk assessment is therefore not deemed necessary

III.6 Discussion on the non-clinical aspects

Pharmacodynamic, pharmacokinetic and toxicological properties of sitagliptin and metformin are well known. As sitagliptin and metformin are widely used and well-known active substances the applicant has not provided additional studies, and further studies are not required. Overview based on literature review was provided and is acceptable for this type of generic application.

IV. CLINICAL ASPECTS

IV.1 Introduction

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

The content of the SmPC approved during the decentralised procedure is in accordance with that accepted for the reference product Janumet marketed by MAH.

For this generic application, the applicant has submitted two bioequivalence studies in which the pharmacokinetic profile of the test product Sitagliptin and Metformin hydrochloride Ascend 50mg/850mg & 50mg/1000mg Film-coated Tablets is compared with the pharmacokinetic profile of the reference product Janumet.

For each strength, a single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out. Sitagliptin and Metformin hydrochloride Ascend 50mg/850mg & 50mg/1000mg Film-coated Tablets, was compared to the reference product Janumet, Merck Sharp & Dohme B.V..Based on the pharmacokinetic parameters of active substances, the reference tablet and test 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.

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

IV.2 Pharmacokinetics

Sitagliptin

The active substance sitagliptin is rapidly absorbed and the absolute bioavailability of is approximately 87 %. Sitagliptin may be administered with or without food and it is primarily eliminated unchanged in urine, metabolism is a minor pathway. Plasma AUC of sitagliptin increased in a dose-proportional manner. Dose-proportionality was not established for C_{max} and C_{24hr} (C_{max} increased in a greater than dose-proportional manner and C_{24hr} increased in a less than dose-proportional manner). Approximately 79 % of sitagliptin is excreted unchanged in the urine. The apparent terminal t_{1/2} following a 100-mg oral dose of sitagliptin was approximately 12.4 hours. Sitagliptin accumulates only minimally with multiple doses. Compared to normal

healthy control subjects, plasma AUC of sitagliptin was increased by approximately 1.2-fold and 1.6-fold in patients with mild renal impairment (GFR \geq 60 to $<$ 90 mL/min) and patients with moderate renal impairment (GFR \geq 45 to $<$ 60 mL/min), respectively.

Metformin

After an oral dose of metformin, T_{max} is reached in 2.5 h. Absolute bioavailability of a 500 mg metformin tablet is approximately 50-60 % in healthy subjects. After an oral dose, the non-absorbed fraction recovered in faeces was 20-30 %. After oral administration, metformin absorption is saturable and incomplete. It is assumed that the pharmacokinetics of metformin absorption is non-linear. Food decreases the extent and slightly delays the absorption of metformin. Metformin is excreted unchanged in the urine.

No metabolites have been identified in humans. Following an oral dose, the apparent terminal elimination half-life is approximately 6.5 h. When renal function is impaired, elimination half-life is prolonged.

IV.3 Pharmacodynamics

The finished products combine 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.

IV.4 Clinical Efficacy

No additional efficacy clinical studies to demonstrate efficacy have been included in the application. This is appropriate for this type of application.

IV.5 Clinical Safety

The overall safety profile of sitagliptin/metformin is established and generally known. No additional safety clinical studies to demonstrate safety have been included in the application and none are required.

A Risk Management Plan, version 0.2, dated 17th May 2023 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 and Metformin hydrochloride Ascend 50mg/850mg & 50mg/1000mg Film-coated Tablets. It is concluded that routine pharmacovigilance and risk minimisation measures are sufficient. However, in line with the reference medicinal product, the RMP includes a Specific Adverse Reaction Follow-Up Questionnaire for Lactic acidosis.

Summary table of safety concerns as approved in RMP:

Important identified risks	Lactic acidosis
Important potential risks	Pancreatic Cancer
Missing information	Exposure during pregnancy and lactation

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.
- In case the active substance will be removed in the future from the EURD list because the MAs have been withdrawn in all but one MS, the MAH shall contact that MS and propose DLP and frequency for further PSUR submissions together with a justification.

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 suitable bioequivalence studies, which have demonstrated the similarity of the test products against the reference products, in accordance with the relevant

guidance. No additional tests are required for this application.

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 and Metformin hydrochloride Ascend 50mg/850mg & 50mg/1000mg Film-coated Tablets are a generic form of Janumet. Janumet 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 and Metformin hydrochloride Ascend 50mg/850mg & 50mg/1000mg 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

08.02.2030