COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Vildagliptin/Metformin hydrochloride Intas 50 mg/850 mg and 50 mg/1000 mg film-coated tablets (vildagliptin/metformin)

NL/H/5291/001-002/DC

Date: 29 July 2022

This module reflects the scientific discussion for the approval of Vildagliptin/Metformin hydrochloride Intas 50 mg/850 mg and 50 mg/1000 mg film-coated tablets. The procedure was finalised at 4 May 2022. 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 Vildagliptin/Metformin hydrochloride Intas 50 mg/850 mg and 50 mg/1000 mg film-coated tablets, from Intas Third Party Sales 2005, S.L.

The products are indicated as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus:

- in patients who are inadequately controlled with metformin hydrochloride alone,
- in patients who are being treated with the combination of vildagliptin and metformin hydrochloride as separate tablets,
- 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 of the SmPC for available data on different combinations).

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 products Eucreas 50 mg/850 mg and 50 mg/1000 mg film-coated tablets (EMEA/H/C/000807) which have been registered in the European Union by Novartis Europharm Limited since 2007.

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

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

II. QUALITY ASPECTS

II.1 Introduction

Vildagliptin/Metformin hydrochloride Intas 50 mg/850 mg tablets are yellow coloured, oval shaped, biconvex, and debossed with “GG2” on one side and plain on the other side. Each tablet contains as active substances 50 mg of vildagliptin and 850 mg of metformin hydrochloride (corresponding to 660 mg of metformin).

Vildagliptin/Metformin hydrochloride Intas 50 mg/1000 mg tablets are dark yellow coloured, oval shaped, biconvex, and debossed with “GG3” on one side and plain on the other side. Each tablet contains as active substances 50 mg of vildagliptin and 1000 mg of metformin hydrochloride (corresponding to 780 mg of metformin).

The film-coated tablets of both strengths are packed in aluminium blisters.

The excipients of both tablet strengths are:
Tablet core - hydroxypropylcellulose (E463), magnesium stearate (E470b) and microcrystalline cellulose (E460).
Film-coating - hypromellose (E464), titanium dioxide (E171), yellow iron oxide (E172), macrogol 4000 (E1521) and talc (E553b).

II.2 Drug Substance

Vildagliptin
Vildagliptin is an established active substance not described in the European Pharmacopoeia (Ph.Eur.). The active substance is a crystalline powder and is freely soluble in water. The active substance has one chiral centre, chirality is adequately controlled in the drug substance specification. The MAH has adequately addressed the control of polymorphic forms of the drug substance and it can be concluded there is no change in the polymorphic form of Vildagliptin "form A" during manufacturing as well as during shelf life storage of the product.

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 (Intas Third Party Sales 2005, S.L.) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities 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 manufacturing process consists of four steps to form vildagliptin from starting materials, the process is described in sufficient detail. Adequate specifications have been adopted for starting materials, solvents and reagents. The active substance has been adequately characterised.

Quality control of drug substance
The active substance specification is established in-house by the applicant and is considered adequate to control the quality by European guidelines. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance
Stability data on the active substance have been provided for three batches in accordance with applicable European guidelines. Based on the data submitted, a retest period could be granted of three years.

Metformin hydrochloride

Metformin hydrochloride is an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a crystalline powder and is freely soluble in water. The polymorphic form is acceptably controlled as shown by the provided data and it is shown that after six months storage at accelerated stability conditions the polymorphic forms are not altered, hence polymorphism is adequately controlled.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process

A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance

The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. with additional requirements for control of residual solvents. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance

The active substance is stable at 25±2°C/60±5% RH or at 30±2°C/65±5% RH or at 30±2°C/75±5% RH (72 months) and at 40±2°C/75±5% RH (6 months). No changes are seen in the long term or accelerated stability studies and the proposed retest period of three years is accepted. Storage conditions “Store in the original package (blister) in order to protect from moisture. This medicinal product does not require any special temperature storage conditions” are acceptable. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The development of the product has been described, the choice of excipients is justified, and their functions explained. Development trials to optimise the granulation process have been described. Comparative dissolution at three pHs has been successfully studied in support of two bioequivalence studies. The Quality Control method has been sufficiently justified. The optimal composition and manufacturing process parameters have been adequately

investigated. Overall, the pharmaceutical development of the product has been adequately performed.

Manufacturing process

The drug product is manufactured by a wet granulation process, which consists of mixing, granulation, drying and sizing, followed by blending, lubrication, compression and film-coating. The manufacturing process has been validated according to relevant European guidelines. Process validation data on the product have been presented for three full scaled batches in accordance with the relevant European guidelines.

Control of excipients

The excipients comply with the Ph.Eur. and in-house requirements and the specifications are acceptable.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for description, average weight of tablets, identification, loss on drying, dissolution, uniformity of dosage units, related substances, assay, residual solvents and microbial examination. Release and shelf life requirements are identical, except for vildagliptin related substances. The specification is acceptable. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from six batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for six full scaled batches in accordance with applicable European guidelines demonstrating the stability of the product at 25°C/60% (6 months) and at 40°C/75% RH (6 months). The batches were stored in Alu-Alu blisters. Stability data for six batches bulk product packed in triple laminated aluminium bags stored at 25°C/60% RH (6 months) were also provided. Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light. An increase in vildagliptin impurities was observed during accelerated stability studies and a similar trend was seen under long term conditions. All tested parameters remained within shelf-life limits. On basis of the data submitted, a shelf life was granted of 24 months. The labelled storage conditions are: “Store in the original package (blister) in order to protect from moisture. This medicinal product does not require any special temperature storage conditions.”.

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 Vildagliptin/Metformin hydrochloride Intas has proven chemical-pharmaceutical qualities. Sufficient controls have been laid down for the active substances and finished products. No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Vildagliptin/Metformin hydrochloride 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 Eucreas which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. 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

Vildagliptin and metformin hydrochloride are well-known active substances with established pharmacology, efficacy and safety. 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 two bioequivalence studies, which are discussed below.

IV.2 Pharmacokinetics

The MAH conducted two bioequivalence studies. In study 1, the pharmacokinetic profile of the test product Vildagliptin/Metformin hydrochloride Intas 50 mg/850 mg film-coated

tablets (Intas Pharmaceuticals Limited, India) is compared with the reference product Eucreas 50 mg/850 mg (Novartis Pharma). In study 2, the pharmacokinetic profile of the test product Vildagliptin/Metformin hydrochloride Intas 50 mg/1000 mg film-coated tablets (Intas Pharmaceuticals Limited, India) is compared with the pharmacokinetic profile of the reference product Eucreas 50 mg/1000 mg film-coated tablets (Novartis Pharma).

The choice of the reference products in the bioequivalence studies have been justified by comparison of dissolution results and compositions with the EU reference products. The formulas and preparations of the bioequivalence batches are identical to the formulas proposed for marketing.

Bioequivalence studies

Study 1 - Vildagliptin/Metformin hydrochloride Intas 50 mg/850 mg vs. reference product Eucreas 50 mg/850 mg under fed conditions

Design

An open label, balanced, randomized, two-sequence, two-treatment, two-period, single oral dose crossover bioequivalence study was carried out under fed conditions in 56 healthy male subjects, aged 20 - 44 years. For each subject there were two dosing periods in which they received a single dose (50 mg/850 mg) of the test and the reference formulations, separated by a washout period of 4 days. The tablets were orally administered with 240 ml of a 20% glucose solution in water, 30 minutes after the start of intake of a high fat, high caloric meal (consisting of bread, butter, chana, onions, peanuts, oil, potatoes, cheese, paneer, milk and sugar). Subjects were provided 60 ml of drinking water containing 20% glucose at every 15 minutes for the first 4 hours post dose to prevent hypoglycaemia. According to the SmPC, it is recommended to take the tablets with food. As such, the fed condition applied in the study is considered adequate.
Blood samples were collected pre-dose and at 0.33, 0.67, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 4.33, 4.67, 5, 5.5, 6, 6.5 (for vildagliptin only), 7, 8, 10, 12, 16, 20, 24 and 36 hours (the last 3 samples for metformin only) after administration of the products. The design of the study is acceptable.

Analytical/statistical methods

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.

Results

One subject was withdrawn from the study on the grounds of emesis in Period I and one subject was withdrawn from the study on medical grounds (pyrexia) in Period I. Fifty-four subjects were eligible for pharmacokinetic analysis.

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

Treatment N=54	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)	$t_{1/2}$ (h)
Test	1144 ± 209	1199 ± 224	180 ± 52	5.0 (0.68– 8.0)	2.7 ± 0.7
Reference	1114 ± 244	1162 ± 260	183 ± 65	4.33 (0.68 – 8.0)	2.7 ± 0.8
***Ratio (90% CI)**	1.04 (0.99 – 1.09)	--	1.00 (0.93 - 1.07)	--	--
CV (%)	15.0	--	22.5	--	--

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t 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 metformin under fed conditions.

Treatment N=54	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)	$t_{1/2}$ (h)
Test	16377 ± 3308	16479 ± 3335	1622 ± 415	4.69 (1.33– 10.0)	4.4 ± 0.5
Reference	15807 ± 3435	15900 ± 3456	1618 ± 400	4.0 (1.33 – 8.0)	4.4 ± 0.6
***Ratio (90% CI)**	1.04 (1.00 – 1.08)	--	1.00 (0.96 - 1.05)	--	--
CV (%)	11.5	--	15.1	--	--

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

**ln-transformed values*

Study 2 - Vildagliptin/Metformin hydrochloride Intas 50 mg/1000 mg vs. reference product Eucreas 50 mg/1000 mg under fed conditions

Design

An open label, balanced, randomized, two-sequence, two-treatment, two-period, single oral dose crossover bioequivalence study was carried out under fed conditions in 56 healthy male subjects, aged 22 - 43 years. For each subject there were two dosing periods in which they received a single dose (50 mg/1000 mg) of the test and the reference formulations, separated by a washout period of 4 days. The tablet was orally administered with 240 ml of a 20% glucose solution in water 30 minutes after the start of intake of a high fat, high caloric meal (consisting of bread, butter, chana, onions, peanuts, oil, potatoes, cheese, paneer, milk and sugar), which was consumed within 30 minutes. Subjects were provided 60 ml of drinking water containing 20% glucose at every 15 minutes for the first four hours post dose to prevent hypoglycaemia. According to the SmPC, it is recommended to take the tablets with food. As such, the fed condition applied in the study is considered adequate.
Blood samples were collected taken pre-dose and at 0.33, 0.67, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 4.33, 4.67, 5, 5.5, 6, 6.5 (for vildagliptin only), 7, 8, 10, 12, 16, 20, 24 and 36 hours (the last 3 samples for metformin only) after administration of the products. The design of the study is acceptable.

Analytical/statistical methods

The analytical methods proved to be accurate and precise for analysis of vildagliptin and metformin in plasma and are considered acceptable. Long term stability of vildagliptin in plasma and metformin in plasma was shown for 22 and 26 days, respectively. Incurred sample reanalysis showed that the method analysis was reproducible for vildagliptin as well as for metformin. Therefore, the methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results

One subject was withdrawn from the study on his own accord in Period II, another subject was withdrawn from the study due to non-protocol compliance in Period II. This resulted in 54 subjects who completed the study and were eligible for pharmacokinetic analysis.

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of vildagliptin under fed conditions.

Treatment N=54	**AUC_{0-t} (ng.h/ml)**	**$AUC_{0-\infty}$ (ng.h/ml)**	**C_{max} (ng/ml)**	**t_{max} (h)**	**$t_{1/2}$ (h)**
Test	1030 ± 233	1069 ± 233	154 ± 45	5.75 (1.33– 10.0)	2.7 ± 0.6
Reference	1016 ± 225	1064 ± 218	147 ± 42	5.0 (1.0 – 10.0)	3.1 ± 2.1
***Ratio (90% CI)**	1.02 (0.99 – 1.05)	--	1.05 (0.99 - 1.12)	--	--
CV (%)	9.4	--	20.6	--	--

$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t}	area under the plasma concentration-time curve from time zero to t 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 4. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of metformin under fed conditions.

Treatment N=54	**AUC_{0-t} (ng.h/ml)**	**$AUC_{0-\infty}$ (ng.h/ml)**	**C_{max} (ng/ml)**	**t_{max} (h)**	**$t_{1/2}$ (h)**
Test	17230 ± 3505	17339 ± 3538	1587 ± 445	6.0 (2.0– 10.0)	4.2 ± 0.5
Reference	17504 ± 3897	17615 ± 3928	1695 ± 582	5.5 (1.0 – 10.0)	4.3 ± 0.5
***Ratio (90% CI)**	0.99 (0.96 – 1.02)	--	0.96 (0.91 - 1.01)	--	--
CV (%)	9.8	--	16.5	--	--

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

**ln-transformed values*

Conclusion on bioequivalence studies

In both studies, the 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence studies, Vildagliptin/Metformin hydrochloride Intas 50 mg/850 mg tablets is considered bioequivalent with Eucreas 50 mg/850 mg tablets and Vildagliptin/Metformin hydrochloride Intas 50/1000 mg tablets is considered bioequivalent with Eucreas 50/1000 mg tablets.

The MEB has been assured that both bioequivalence studies have 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 Vildagliptin/Metformin hydrochloride Intas.

Table 5. Summary table of safety concerns as approved in RMP

Important identified risks	• Drug induced liver injury • Acute pancreatitis • Lactic acidosis
Important potential risks	• Muscle events/ myopathy/ rhabdomyolysis, in particular with current statin use (events of myalgia excluded)
Missing information	• None

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Eucreas. No new clinical studies were conducted. The MAH demonstrated through two bioequivalence studies 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 Eucreas film-coated tablets and Solifenacin succinate 5/10 mg film-coated tablets (DK/H/2339/001-002/DC). The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Vildagliptin/Metformin hydrochloride Intas 50 mg/850 mg and 50 mg/1000 mg film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Eucreas 50 mg/850 mg and 50 mg/1000 mg film-coated tablets. Eucreas 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 Vildagliptin/Metformin hydrochloride Intas with the reference products, and have therefore granted a marketing authorisation. The decentralized procedure was finalised with a positive outcome on 4 May 2022.

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