LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Vilbaco
(vildagliptin, metformin hydrochloride)

SE/H/2053/01-02/DC

This module reflects the scientific discussion for the approval of Vilbaco. The procedure was finalised on 2021-08-10. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Vilbaco, 50 mg/850 mg, 50 mg/1000 mg, film-coated tablet.

The active substances are vildagliptin and metformin hydrochloride. A comprehensive description of the indication and posology is given in the SmPC.

For recommendations to the marketing authorisation not falling under Article 21a/22a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a/22a/ 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

The application for Vilbaco, 50 mg/850 mg and 50 mg/1000 mg, film-coated tablet, is a generic application made according to Article 10(1) of Directive 2001/83/EC. The applicant, STADA Arzneimittel AG, applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and with EL and HR as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Eucreas, 50 mg/850 mg and 50 mg/1000 mg, film-coated tablet, authorised in the Union since 2007, with Novartis Europharm Limited as marketing authorisation holder.

The reference product used in the bioequivalence studies is Eucreas, 50 mg/850 mg and 50 mg/1000 mg, film-coated tablet, from Germany with Novartis Europharm Limited as marketing authorisation holder.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

Pharmacodynamic, pharmacokinetic and toxicological properties of vildagliptin, metformin hydrochloride are well known. As vildagliptin, metformin hydrochloride is a widely used, well-known active substance, no further studies are required, and the applicant provides none. Overview based on literature review is, thus, appropriate.

Impurities related to vildagliptin, e.g. cyclo imidamide impurity, and cyclic impurity, has been discussed. The amide impurity is considered toxicologically qualified.

Environmental Risk Assessment (ERA)
Since Vilbaco is a generic product, it will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

There are no objections to approval of Vilbaco from a non-clinical point of view.

IV. CLINICAL ASPECTS

Pharmacokinetics
To support the marketing authorisation application the applicant has conducted two bioequivalence studies comparing Vildagliptin/Metformin with the reference product Eucreas.

Pharmacokinetic properties of the active substances

Vildagliptin/Metformin (combined formulation - reference product)
Food effect: Food does not affect the extent and rate of absorption of vildagliptin from the combined formulation. The rate and extent of absorption of metformin from the combined formulation 50 mg/1000 mg were decreased when given with food as reflected by the decrease in C_{max} by 26%, AUC by 7% and delayed T_{max} (2.0 to 4.0 h).

Vildagliptin
Absorption: Food slightly delays the time to peak plasma concentration to 2.5 hours.

Elimination: The elimination half-life after oral administration is approximately 3 hours.

Linearity: The C_{max} for vildagliptin and the area under the plasma concentrations versus time curves (AUC) increased in an approximately dose proportional manner over the therapeutic dose range.

Metformin
Absorption: After an oral dose of metformin, the maximum plasma concentration (C_{max}) is achieved after about 2.5 h.

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

Linearity: After oral administration, metformin absorption is saturable and incomplete. It is assumed that the pharmacokinetics of metformin absorption are non-linear.

Study 060B18
Methods
This was a single-dose, two-way crossover study conducted in 30 healthy volunteers, comparing Vildagliptin/Metformin, 50 mg/850 mg, film-coated tablet with Eucreas, 50 mg/850 mg, film-coated tablet under fed conditions. Blood samples for concentration analysis were collected pre-dose and up

to 16 hours (vildagliptin) and 24 hours (metformin) post-dose. Plasma concentrations of vildagliptin and metformin were determined with LC-MS/MS methods. Analysis of variance (ANOVA) was performed on the log-transformed data for AUC_{0-t} and C_{max}. The study was conducted between 2019.04.08 and 2019.04.29.

Results
The results from the pharmacokinetic and statistical analysis are presented in Table 1 and 2 below.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for vildagliptin, n=30.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**1062.38 ± 216.21**	**226.86 ± 59.02**	**2.33 (0.67-4.50)**
Reference	**1045.05 ± 183.21**	**221.67 ± 48.61**	**2.00 (0.67-5.00)**
***Ratio (90% CI)**	**101.17 (98.73-103.66)**	**101.45 (94.64-108.75)**	**-**
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 plasma concentration			

**calculated based on ln-transformed data*

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for metformin, n=30.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**11618.20 ± 2350.79**	**1433.32 ± 257.67**	**4.00 (1.00-6.00)**
Reference	**11475.65 ± 2417.24**	**1392.66 ± 267.11**	**4.00 (2.33-5.00)**
***Ratio (90% CI)**	**101.43 (98.20-104.76)**	**103.14 (98.51-107.98)**	**-**
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 plasma concentration			

**calculated based on ln-transformed data*

For vildagliptin and metformin AUC_{0-t} and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

Study CT-37754-20-0228
Methods
This was a single-dose, two-way crossover study conducted in 21 healthy volunteers, comparing Vildagliptin/Metformin, 50 mg/1000 mg, film-coated tablet with Eucreas, 50 mg/1000 mg, film-coated tablet under fed conditions. Blood samples for concentration analysis were collected pre-dose and up to 16 hours (vildagliptin) and 24 hours (metformin) post-dose. Plasma concentrations of vildagliptin and metformin were determined with LC-MS/MS methods. Analysis of variance (ANOVA) was performed on the log-transformed data for AUC_{0-t} and C_{max}. The study was conducted between 2020.07.30 and 2020.09.17.

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for vildagliptin, n=20.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**1083.90 ± 177.83**	**221.53 ± 62.97**	**2.22 (1.00-4.50)**
Reference	**1094.34 ± 212.38**	**235.48 ± 72.32**	**1.85 (1.33-4.52)**
***Ratio (90% CI)**	**99.09 (95.59-102.71)**	**93.77 (85.39-102.97)**	**-**

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 plasma concentration

**calculated based on ln-transformed data*

Table 4. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for metformin, n=20.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**11 026.67 ± 2222.64**	**1371.86 ± 296.38**	**4.33 (2.00-5.50)**
Reference	**11 445.48 ± 2468.08**	**1497.66 ± 358.86**	**4.00 (1.50-4.67)**
***Ratio (90% CI)**	**97.34 (91.87-103.15)**	**92.50 (85.50-100.06)**	**-**

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 plasma concentration

**calculated based on ln-transformed data*

For vildagliptin and metformin AUC_{0-t} and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

Discussion and overall conclusion

The bioequivalence studies and their statistical evaluation were in accordance with accepted standards for bioequivalence testing, as stated in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr **). The bioanalytical methods were adequately validated.

As the SmPC of the reference product recommends administration with or just after food a study in the fed state is appropriate. There is no pharmacokinetic reason why the product should be taken with food. Taking Vildagliptin/Metformin with or just after food may reduce gastrointestinal symptoms associated with metformin.

Based on the submitted bioequivalence studies, Vildagliptin/Metformin is considered bioequivalent with Eucreas.

Pharmacodynamics/Clinical efficacy/Clinical safety

No new studies on pharmacodynamics, clinical efficacy or clinical safety have been submitted. Provided that bioequivalence with the originator product is demonstrated, additional data is not necessary.

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 Vilbaco.

Safety specification
The MAH has submitted the version 1.1 RMP dated 2020-06-10 and proposed the following summary safety concerns:

Summary of safety concerns	
Important identified risks	• Transaminase elevation and drug-induced liver injury (DILI) • Angioedema • Acute pancreatitis • Lactic acidosis • Skin lesions • Hypoglycaemia
Important potential risks	• Serious infections • Cardiac events in congestive heart failure (*NYHA functional class III*) patients • Muscle events/myopathy/rhabdomyolysis, in particular with current statin use • Neuropsychiatric events • Breast cancer • Pancreatic cancer
Missing information	• Gender incidence/frequency differences • Patients with severe hepatic impairment • Patients with compromised cardiac function (*NYHA functional class IV*) • Pregnancy

Pharmacovigilance Plan
Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

With RMP version 1.1 Specific adverse reaction follow-up questionnaire i,e Targeted Follow-up Questionnaires have, in line with the reference product, been added for the following safety concerns:

- Transaminase elevations and Drug-induced liver injury (DILI) – Liver Injury
- Angioedema
- Acute pancreatitis - Pancreatitis and Amylase & Lipase Elevations
- Skin lesions - Severe Skin Reaction
- Hypoglycemia- Glycemia Disorders
- Muscle events/myopathy/rhabdomyolysis, in particular with current statin use –Myopathies including Rhabdomyolysis
- Pancreatic cancer- Malignancy and Neoplasm
- Lactic acidosis

This is endorsed.

Risk minimisation measures
Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of the RMP
The submitted Risk Management Plan, version 1.1 signed 2020-06-10 is considered acceptable.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

V. USER CONSULTATION

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PIL was English. The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product, Vilbaco, is found adequate. There are no objections to approval of Vilbaco from a non-clinical and clinical point of view. Bioequivalence between the test and reference product has been adequately demonstrated. The product information is acceptable. The benefit-risk is therefore considered positive, and the application is recommended for approval.

List of recommendations not falling under Article 21a/22a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a/22a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

The decentralised procedure for Vilbaco, 50 mg/850 mg, 50 mg/1000 mg, film-coated tablet was positively finalised on 2021-08-10.

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Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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