LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Vimetso
(vildagliptin, metformin hydrochloride)

SE/H/2027/01-02/DC

This module reflects the scientific discussion for the approval of Vimetso. The procedure was finalised on 2021-06-16. For information on changes after this date please refer to the module 'Update'.

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.lakemedelsverket.se E-mail: registrator@lakemedelsverket.se

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Vimetso, 50 mg/850 mg and 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 Vimetso, 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, Krka d.d. Novo Mesto, applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and BG, CY, CZ, EE, EL, ES, HR, HU, LT, LV, MT, PL, SI, SK as concerned member states (CMS) as indicated below.

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, film-coated tablet, from Germany with Novartis Europharm Limited as marketing authorisation holder.

Potential similarity with orphan medicinal products
According to the application form and a check of the Community Register of orphan medicinal products there is no medicinal product designated as an orphan medicinal product for a condition relating to the indication proposed in this application.

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 are widely used, well-known active substances, no further studies are required, and the applicant provides none. Overview based on literature review is, thus, appropriate.

Environmental Risk Assessment (ERA)
Since Vimetso 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 Vimetso 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

Eucreas (reference product):
Absorption: Food does not affect the extent and rate of absorption of vildagliptin from Eucreas. The rate and extent of absorption of metformin from Eucreas 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: The absolute bioavailability is 85%. Following oral administration in the fasting state, vildagliptin is rapidly absorbed with peak plasma concentrations observed at 1.7 hours.

Food slightly delays the time to peak plasma concentration to 2.5 hours, but does not alter the overall exposure (AUC). Administration of vildagliptin with food resulted in a decreased C_{max} (19%) compared to dosing in the fasting state. However, the magnitude of change is not clinically significant, so that vildagliptin can be given with or without food.

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.

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

Metformin:
Absorption: Absolute bioavailability of a 500 mg metformin tablet is approximately 50-60% in healthy subjects. After an oral dose of metformin, the maximum plasma concentration (C_{max}) is achieved after about 2.5 h.

Food slightly delays and decreases the extent of the absorption of metformin. Following administration of a dose of 850 mg, the plasma peak concentration was 40% lower, AUC was decreased by 25% and time to peak plasma concentration was prolonged by 35 minutes. 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 are non-linear.

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

Study 19-629 (50 mg/850 mg)

Methods

This was a single-dose, two-way crossover study conducted in 36 healthy volunteers (34 completed), comparing Vildagliptin/Metformin, 50 mg/850 mg, film-coated tablet with Eucreas, 50 mg/850 mg, film-coated tablet under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 16 hours (vildagliptin) and 36 hours (metformin) post-dose. Plasma concentrations of vildagliptin and metformin were determined with separate LC-MS/MS methods. Analysis of variance (ANOVA) was performed on the log-transformed data for AUC_{0-t} and C_{max}.

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=34.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**1202.23 ± 231.48**	**245.95 ± 71.56**	**3.50 (1.00-5.02)**
Reference	**1236.98 ± 255.12**	**252.32 ± 75.88**	**3.50 (1.33-5.05)**
***Ratio (90% CI)**	**97.50 (95.33-99.71)**	**98.00 (92.43-103.90)**	**-**
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 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%.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for metformin, n=34.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**14415.46 ± 3456.24**	**2036.50 ± 464.58**	**2.33 (0.67-4.68)**
Reference	**15584.19 ± 3492.15**	**2186.51 ± 416.50**	**2.17 (0.67-6.00)**
***Ratio (90% CI)**	**92.68 (88.40-97.16)**	**92.62 (88.24-97.21)**	**-**
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 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 17-565 (50 mg/1000 mg)

Methods

This was a single-dose, two-way crossover study conducted in 36 healthy volunteers (36 completed), comparing Vildagliptin/Metformin, 50 mg/1000 mg, film-coated tablet with Eucreas, 50 mg/1000 mg, film-coated tablet under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 16 hours (vildagliptin) and 36 hours (metformin) post-dose. Plasma concentrations of vildagliptin and metformin were determined with separate LC-MS/MS methods. Analysis of variance (ANOVA) was performed on the log-transformed data for AUC_{0-t} and C_{max}.

Results

The results from the pharmacokinetic and statistical analysis are presented in Table 3 and 4 below.

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for vildagliptin, n=36.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**1076.91 ± 297.09**	**230.72 ± 65.08**	**2.50 (1.37-5.00)**
Reference	**1077.31 ± 257.50**	**228.33 ± 51.78**	**2.67 (1.03-4.00)**
***Ratio (90% CI)**	**99.14 (95.81-102.59)**	**99.35 (93.26-105.82)**	**-**
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 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%.

Table 4. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for metformin, n=36.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**16103.88 ± 3493.52**	**2188.46 ± 497.68**	**2.67 (0.67-5.00)**
Reference	**16211.20 ± 3683.21**	**2243.50 ± 537.86**	**2.67 (0.77-4.00)**
***Ratio (90% CI)**	**99.58 (95.35-104.00)**	**97.82 (93.37-102.49)**	**-**
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 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.

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.

Pharmacovigilance system
The Applicant has submitted signed Summaries of the Applicant's/Proposed Future MAH's Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module, the RMS considers the Summary acceptable.

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 Krka.

Safety specification
The MAH has submitted the version 0.2 RMP dated 4.9.2020 and proposed the following summary safety concerns:

Important identified risks

- Transaminase elevations and drug-induced liver injury (DILI)
- Lactic acidosis

Important potential risks

- None

Missing information

- None

Pharmacovigilance Plan
Routine pharmacovigilance activities, including specific follow-Up questionnaires for lactic acidosis, has been proposed. This is endorsed. A follow-up questionnaire in line with the reference product has been provided.

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 applicant’s justification refers to Daltex Medochemie ltd. (procedure no. DK/H/2670/001-002/IB/003, RMP version 2.0, dated 15-November-2019) which is presented on CMDh website. The currently approved RMP for the reference medicinal product Eucreas is of version 14.1, dated 21-April-2017. At this time, the procedure number EMEA/H/C/WS1970 is ongoing. This procedure includes reclassification of safety concerns for the centrally authorised medicinal products containing vildagliptin and vildagliptin-metformin. In view of this, significant changes for Eucreas are being conducted. The first round of this procedure has been recently agreed by PRAC. It is therefore expected that the applicant will further reflect the final outcomes from this procedure in the RMP for Vildagliptin/Metformin Krka accordingly.

The MAH has satisfactorily responded to the questions raised and will observe the outcome of this procedure and amend the RMP, once the procedure has been concluded. An according commitment statement is presented as an Annex to the (unchanged) RMP in Module 1.8.2. The submitted Risk Management Plan, version 0.2 RMP dated 4.9.2020 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

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Pragiola 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg, and 300 mg hard capsules. The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product, Vimetso is found adequate. There are no objections to approval of Vimetso 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 application is therefore 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 Vimetso, 50 mg/850 mg and 50 mg/1000 mg, film-coated tablet was positively finalised on 2021-06-16.

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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)

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.lakemedelsverket.se E-mail: registrator@lakemedelsverket.se