LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Sitagliptin/Metformin Grindeks (sitagliptin hydrochloride monohydrate, metformin hydrochloride)

SE/H/2115/01-02/DC

This module reflects the scientific discussion for the approval of Sitagliptin/Metformin Grindeks. The procedure was finalised on 2022-01-24. 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 Sitagliptin/Metformin Grindeks, 50 mg/850 mg, 50 mg/1000 mg, Film-coated tablet.

The active substance is sitagliptin hydrochloride monohydrate, 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 Sitagliptin/Metformin Grindeks, 50 mg/850 mg, 50 mg/1000 mg, film-coated tablet, is a generic application made according to Article 10(1) of Directive 2001/83/EC. The applicant, AS GRINDEKS, applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and AT, BE, BG, CZ, DE, DK, EE, EL, ES, FI, FR, HR, HU, IE, IT, LT, LU, LV, NL, NO, PL, PT, RO, SI, SK, UK as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Janumet, 50 mg/850 mg, 50 mg/1000 mg, film-coated tablet authorised in the EU since 2008, with Merck Sharp & Dohme B.V. as marketing authorisation holder.

The reference product used in the bioequivalence studies is Janumet, 50 mg/850 mg, film-coated tablet and Janumet, 50 mg/1000 mg, film-coated tablet from Latvia with Merck Sharp & Dohme B.V. 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 sitagliptin and metformin are well known. As sitagliptin and metformin 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 Sitagliptin/Metformin Grindeks 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 Sitagliptin/Metformin Grindeks 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 Sitagliptin/Metformin Grindeks with the reference product Janumet.

Pharmacokinetic properties of the active substances
The following statements reflect the pharmacokinetic properties of the individual active substances:

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

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 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).

Elimination: The apparent terminal $t_{½}$ following a 100-mg oral dose of sitagliptin was approximately 12.4 hours.

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

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 (C_{max}) 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.

Study (50 mg/850 mg)

Methods

This was a single-dose, two-way crossover study conducted in 28 healthy volunteers, comparing Sitagliptin 50 mg/Metformin 850 mg, film-coated tablet with Janumet, 50 mg/850 mg, film-coated tablet under fed conditions. Blood samples for concentration analysis were collected pre-dose and up to 72 hours post-dose. Plasma concentrations of sitagliptin 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 31 May 2021 and 11 June 2021.

Results

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

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for sitagliptin, n=28.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**1305.17 ± 179.465**	**109.06 ± 29.133**	**3.00 (1.00-5.50)**
Reference	**1321.15 ± 212.056**	**116.44 ± 25.223**	**2.88 (1.00-5.50)**
***Ratio (90% CI)**	**99.07 (97.00-101.19)**	**92.70 (85.67-100.30)**	**-**

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=28.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**8776.13 ± 1985.240**	**1025.90 ± 286.475**	**4.50 (1.00-7.00)**
Reference	**8697.97 ± 2486.255**	**1023.77 ± 295.554**	**3.50 (1.00-5.50)**
***Ratio (90% CI)**	**102.38 (98.22-106.71)**	**100.53 (95.11-106.26)**	**-**

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 sitagliptin 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 (50 mg/1000 mg)

Methods

This was a single-dose, two-way crossover study conducted in 28 healthy volunteers, comparing Sitagliptin 50 mg/Metformin 1000 mg, film-coated tablet with Janumet, 50 mg/1000 mg, film-coated tablet under fed conditions. Blood samples for concentration analysis were collected pre-dose and up to 72 hours post-dose. Plasma concentrations of sitagliptin 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 23 October 2020 and 02 November 2020.

Results

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

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for sitagliptin, n=28.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**1179.3 ± 206.50**	**101.056 ± 26.36**	**2.25 (0.67-6.00)**
Reference	**1209.4 ± 218.68**	**106.267 ± 29.80**	**2.75 (1.00-6.00)**
***Ratio (90% CI)**	**97.62 (95.21-100.09)**	**95.60 (89.44-102.20)**	**-**
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=28.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**11549.3 ± 2451.49**	**1212.505 ± 252.60**	**5.00 (2.00-8.00)**
Reference	**12534.3 ± 2756.08**	**1320.892 ± 277.42**	**4.00 (2.00-8.00)**
***Ratio (90% CI)**	**92.20 (87.44-97.22)**	**91.63 (86.40-97.17)**	**-**
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 sitagliptin 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.

Based on the submitted bioequivalence studies, Sitagliptin/Metformin Grindeks is considered bioequivalent with Janumet.

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 Sitagliptin/Metformin Grindeks.

Safety specification
The MAH has submitted the version 0.2 RMP dated 09.08.2021 and proposed the following summary safety concerns:

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	*Lactic acidosis*
Important potential risks	*Pancreatic cancer*
Missing information	*Exposure during pregnancy and lactation*

The proposed RMP for Sitagliptin/Metformin Grindeks is acceptable. The safety concerns has been aligned with the most recent version of the originator's RMP (Janumet)

Pharmacovigilance Plan
Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which 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 0.2 RMP dated 09.08.2021 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 Latvian.
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, Sitagliptin/Metformin Grindeks, is found adequate. There are no objections to approval of Sitagliptin/Metformin Grindeks, 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 considered positive, and 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 Sitagliptin/Metformin Grindeks, 50 mg/850 mg, 50 mg/1000 mg, Film-coated tablet was positively finalised on 2022-01-24.

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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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