LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Mifomet
(sitagliptin hydrochloride monohydrate, metformin hydrochloride)

SE/H/2130/01-02/DC

This module reflects the scientific discussion for the approval of Mifomet. The procedure was finalised on 2022-05-18. 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 Mifomet, 50 mg/850 mg, 50 mg/1000 mg, Film-coated tablet.

The active substance is metformin, sitagliptin hydrochloride monohydrate, sitagliptin, 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 Mifomet, 50 mg/850 mg and 50 mg/1000 mg, film-coated tablets, is a generic application made according to Article 10(1) of Directive 2001/83/EC. The applicant, Bausch Health Ireland Ltd, applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and BG, CZ, DE, HU, PL and SK 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 and 50 mg/1000 mg, film-coated tablets authorised in the union since 2008, with Merck Sharp & Dohme BV as marketing authorisation holder.

The reference product used in the bioequivalence studies is Janumet, 50 mg/850 mg and 50 mg/1000 mg, film-coated tablets from Greece with Merck Sharp & Dohme BV 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/metformin are well known. As sitagliptin/metformin 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.

Environmental Risk Assessment (ERA)
Since Mifomet 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 Mifomet 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 Mifomet (Sitagliptin/metformin) with the reference product Janumet.

Pharmacokinetic properties of the active substances

Sitagliptin:
Absorption: 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. The absolute bioavailability of sitagliptin is approximately 87%. 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: 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. 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.

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

Study PMZ-P9-535

Methods

This was a single-dose, two-way crossover study conducted in 24 healthy volunteers, comparing Sitagliptin/metformin, 50 mg/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 48 hours post-dose. Plasma concentrations of sitagliptin and metformin were determined with a LC-MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for AUC_{0-t} and C_{max}. The study was conducted between 2020/03/25 and 2020/04/30.

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=24.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**1789.12 ± 262.55**	**170.04 ± 37.88**	**2.67 (1.00-10.00)**
Reference	**1743.71 ± 273.50**	**168.32 ± 33.35**	**2.67 (1.00-5.00)**
***Ratio (90% CI)**	**102.81 (100.90-104.75)**	**100.29 (94.32-106.64)**	**-**
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=24.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**12159.10 ± 2939.83**	**1402.58 ± 343.90**	**4.00 (1.50-10.00)**
Reference	**11697.42 ± 3114.57**	**1386.45 ± 351.23**	**4.00 (1.00-5.00)**
***Ratio (90% CI)**	**104.71 (100.18-109.44)**	**101.51 (97.93-105.22)**	**-**
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 PMZ-P9-060

Methods

This was a single-dose, two-way crossover study conducted in 24 healthy volunteers, comparing

Sitagliptin/metformin, 50 mg/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 48 hours post-dose. Plasma concentrations of sitagliptin and metformin were determined with a LC-MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for AUC_{0-t} and C_{max}. The study was conducted between 2020/03/13 and 2020/04/16.

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=24.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**1650.35 ± 219.65**	**151.71 ± 38.72**	**2.88 (1.20-6.00)**
Reference	**1644.82 ± 234.08**	**144.89 ± 33.30**	**3.00 (1.00-8.00)**
***Ratio (90% CI)**	**100.50 (98.03-103.04)**	**104.39 (97.12-112.21)**	**-**
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*

Table 4. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for metformin, n=24.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**13505.03 ± 3033.29**	**1548.43 ± 344.08**	**4.00 (2.00-5.02)**
Reference	**13445.39 ± 3277.79**	**1506.61 ± 346.23**	**3.79 (1.50-5.00)**
***Ratio (90% CI)**	**100.78 (95.71-106.11)**	**103.02 (98.43-107.82)**	**-**
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 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, Mifomet 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 Mifomet.

Safety specification

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

**based on the list of safety concerns of originator product, Janumet, MAH Merck Sharp & Dohme B.V., updated on 12/10/2021*

Pharmacovigilance Plan

Routine pharmacovigilance is suggested. Furthermore, in line with the reference product, additional pharmacovigilance activity; use of a lactic acidosis questionnaire, is proposed by the applicant, which is endorsed.

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance is the primary/minimum set of activities required to fulfil the legal requirements for pharmacovigilance contained in Directive 2001/83/EC and Regulation (EC) No 726/2004. The Pharmacovigilance System Master File describing these activities is not required to be repeated in the RMP.

Specific adverse reaction follow-up questionnaires

Bausch Health propose the below mentioned specific adverse reaction follow-up questionnaire:

Follow-up Questionnaire		
Objectives	Description	Safety concern
Capture and evaluate relevant information related to sitagliptin/metformin and the occurrence of adverse event with fatal outcome	Information on the details of the lactic acidosis developed by the patient including the following details: dose administered, laboratory investigations for blood levels of metformin, metabolic acidosis, renal function test as well as all risk factors for lactic acidosis are collected.	Lactic acidosis

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 MAH has satisfactorily responded to the questions raised and updated the RMP accordingly. Issue is resolved.

The submitted Risk Management Plan, version 2.1 signed 2022-03-21 is considered acceptable. The RMP including questionnaire regarding the risk for lactic acidosis; to capture and evaluate relevant information related to sitagliptin/metformin and the occurrence of adverse event with fatal outcome. The RMP is in line with the originator Janumet.

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, Mifomet, is found adequate. There are no objections to approval of Mifomet, 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 Mifomet, 50 mg/850 mg, 50 mg/1000 mg, Film-coated tablet was positively finalised on 2022-05-18.

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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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