LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Jivolar
(sitagliptin phosphate monohydrate, metformin hydrochloride)

SE/H/2205/01-02/DC

This module reflects the scientific discussion for the approval of Jivolar. The procedure was finalised on 2023-01-23. 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 Jivolar, film-coated tablet, 50 mg/850 mg and 50 mg/1000 mg, respectively.

The active substance is sitagliptin phosphate monohydrate, metformin hydrochloride, sitagliptin. 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 Jivolar, film-coated tablet, 50 mg/850 mg and 50 mg/1000 mg, respectively, is a generic application submitted according to Article 10(1) of Directive 2001/83/EC. The applicant, Medochemie Ltd, applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and BG, CY, CZ, EE, EL, ES, HR, LT, LV, MT, PT, RO, SI, 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, film-coated tablet, 50 mg/850 mg and 50 mg/1000 mg, respectively, authorised in the EU since 2008, with Merck Sharp & Dohme B.V. as marketing authorisation holder.

To support this generic application, the applicant has submitted two bioequivalence studies. The reference products used in the bioequivalence studies are Janumet, film-coated tablet, 50 mg/850 mg and 50 mg/1000 mg, respectively, from Cyprus 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

Pharmacology/Pharmacokinetics/Toxicology
Pharmacodynamic, pharmacokinetic and toxicological properties of sitagliptin/metformin are well known. As sitagliptin/metformin is a 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 Jivolar 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 Jivolar 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 hydrochloride film-coated tablets with the reference product Janumet; one with the 50 mg/850 mg strength and one with the 50 mg/1000 mg strength.

Pharmacokinetic properties of the active substances
Sitagliptin
Sitagliptin has an oral bioavailability of approximately 87 %. Following an oral dose of 100 mg, sitagliptin was rapidly absorbed, with median T_{max} occurring 1 to 4 hours post-dose. Since co-administration of a high-fat meal with sitagliptin had no effect on the pharmacokinetics, sitagliptin may be administered with or without food.
Plasma AUC of sitagliptin increased in a dose-proportional manner, whereas dose-proportionality was not established for C_{max} and C_{24hr}. The apparent terminal $t_{½}$ following a 100-mg oral dose of sitagliptin was approximately 12.4 hours.

Metformin
Absolute bioavailability of a 500 mg or 850 mg metformin tablet is approximately 50-60 % in healthy subjects. After an oral dose of metformin, Tmax is reached in 2.5 hours. 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.
After oral administration, metformin absorption is saturable and incomplete. It is assumed that the pharmacokinetics of metformin absorption is non-linear. Following an oral dose, the apparent terminal elimination half-life is approximately 6.5 hours.

Study “BC-MESI-21/842” (50 mg/850 mg) and study “BC-MESI-21/839” (50 mg/1000 mg)
Methods
Both bioequivalence studies were single-dose, two-way crossover studies conducted in 34 healthy volunteers under fed conditions. The test products Sitagliptin/Metformin hydrochloride film-coated tablets, 50 mg/850 mg and 50 mg/1000 mg were compared with the originator products Janumet film-coated tablets, 50 mg/850 mg and 50 mg/1000 mg, respectively. Study BC-MESI-21/842 was

conducted between 10th June and 10th September 2021, and study BC-MESI-21/839 was conducted between 22nd June and 16th August 2021. Blood samples were collected pre-dose and up to 72 hours post-dose. Plasma concentrations of sitagliptin and metformin were determined with an LC/MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for AUC_{0-t} and C_{max}.

Results

The pharmacokinetic and statistical analysis results from study BC-MESI-21/842 are presented in Table 1-2 below.

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

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	1347 ± 214	116 ± 40	3.93 ± 2.06
Reference	1374 ± 210	112 ± 33	4.21 ± 2.07
***Ratio (90% CI)**	99.43 (97.28-101.63)	104.07 (93.98-115.25)	-

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	11047 ± 1940	1008 ± 238	5.18 ± 2.02
Reference	11043 ± 2210	994 ± 180	4.97 ± 1.94
***Ratio (90% CI)**	100.94 (97.99-103.97)	100.93 (96.01-106.11)	-

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*

The pharmacokinetic and statistical analysis results from study BC-MESI-21/839 are presented in Table 3-4 below.

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for sitagliptin, n=31.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	1203 ± 202	90.9 ± 22.4	4.58 ± 1.83
Reference	1205 ± 179	96.6 ± 31.6	4.36 ± 2.08
***Ratio (90% CI)**	99.10 (95.38-102.97)	95.39 (87.70-103.76)	-

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=30.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	11737 ± 2622	1007 ± 217	4.55 ± 2.10
Reference	11713 ± 2557	986 ± 226	4.36 ± 2.09
***Ratio (90% CI)**	98.87 (94.01-103.98)	100.46 (94.26-107.06)	-
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 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% for both sitagliptin and metformin in both studies.

Discussion and overall conclusion

The bioequivalence studies and the 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). Moreover, the bioanalytical methods were adequately validated.

Based on the submitted bioequivalence studies, Sitagliptin/Metformin hydrochloride 50 mg/850 mg and 50 mg/1000 mg, film-coated tablets, are considered bioequivalent with the originator products Janumet 50 mg/850 mg and 50 mg/1000 mg, film-coated tablets.

Pharmacodynamics/Clinical efficacy/Clinical safety

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

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 Jivolar.

Safety specification

The MAH has submitted the RMP version 0.1 dated 17.11.2021 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 safety concerns for Jivolar is in line 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 0.1 signed 17.11.2021 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

A user consultation with target patient groups on the package information leaflet has been performed on the basis of a bridging report making reference to Janumet, film-coated tablet, 50 mg/850 mg and 50 mg/1000 mg, respectively, EU/1/08/455, and Amisulprid Medochemie Romania, tablet, 50 mg, 100 mg, 200 mg and 400 mg, DK/H/2877/01-04/DC.
The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic products, Jivolar, is found adequate. There are no objections to approval of Jivolar, 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 Jivolar, film-coated tablet, 50 mg/850 mg and 50 mg/1000 mg, respectively, are 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 Jivolar, film-coated tablet, 50 mg/850 mg and 50 mg/1000 mg, respectively, was positively finalised on 2023-01-23.

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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