COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Janecluc 50 mg/850 mg and 50 mg/1000 mg film-coated tablets

(sitagliptin hydrochloride monohydrate / metformin hydrochloride)

NL/H/5259/001-002/DC

Date: 28 January 2022

This module reflects the scientific discussion for the approval of Janecluc 50 mg/850 mg and 50 mg/1000 mg film-coated tablets. The procedure was finalised at 3 November 2021. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Janecluc 50 mg/850 mg and 50 mg/1000 mg film-coated tablets, from Demo S.A.

The product is indicated for adult patients with type 2 diabetes mellitus:

- Janecluc is indicated as an adjunct to diet and exercise to improve glycaemic control in patients inadequately controlled on their maximal tolerated dose of metformin alone or those already being treated with the combination of sitagliptin and metformin.
- Janecluc is indicated in combination with a sulphonylurea (i.e., triple combination therapy) as an adjunct to diet and exercise in patients inadequately controlled on their maximal tolerated dose of metformin and a sulphonylurea.
- Janecluc is indicated as triple combination therapy with a peroxisome proliferator-activated receptor gamma (PPARγ) agonist (i.e., a thiazolidinedione) as an adjunct to diet and exercise in patients inadequately controlled on their maximal tolerated dose of metformin and a PPARγ agonist.
- Janecluc is also indicated as add-on to insulin (i.e., triple combination therapy) as an adjunct to diet and exercise to improve glycaemic control in patients when stable dose of insulin and metformin alone do not provide adequate glycaemic control.

A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Janumet 50 mg/850 mg and 50 mg/1000 mg film-coated tablets (EU/1/08/455) marketed by Merck Sharp & Dohme B.V, which has been authorised in the European Union via the centralised procedure since 16 July 2008.

The concerned member state (CMS) involved in this procedure was Greece.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Janecluc 50 mg/850 mg is a capsule-shaped, white to off- white film-coated tablets debossed with "S18" and break line on one side and "H" on the other side. Each tablet contains

sitagliptin hydrochloride monohydrate equivalent to 50 mg of sitagliptin and 850 mg of metformin hydrochloride.

Janecluc 50 mg/1000 mg is a capsule-shaped, yellow film-coated tablets debossed with "S19" and break line on one side and "H" on the other side. Each tablet contains sitagliptin hydrochloride monohydrate equivalent to 50 mg of sitagliptin and 1000 mg of metformin hydrochloride.

The film-coated tablets are packed in PVC/Aluminium/OPA- Aluminium blister.

The excipients are:
Tablet core - microcrystalline povidone cellulose, sodium laurilsulfate, sodium stearyl fumarate
Film coating - polyvinyl alcohol part hydrolysed (E1203), titanium dioxide (E171), macrogol (E1521), talc (E553b), iron oxide yellow (E172) (only for 50mg/1000mg strength)

II.2 Drug Substances

Sitagliptin hydrochloride monohydrate
The active substance sitagliptin hydrochloride monohydrate is an established active substance not described in the European Pharmacopoeia (Ph.Eur.), but a monograph is available for sitagliptin phosphate monohydrate. Sitagliptin hydrochloride is a white to off-white powder. It is freely soluble in water. It has one chiral centre. The substance is not hygroscopic. The manufacturer consistently produces polymorph crystalline form III.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

<u>Manufacturing process</u>
The manufacturing process has been adequately described. It is based on the condensation of two larger blocks. One of these blocks is an intermediate. There are two manufacturers and two manufacturing routes for this intermediate. Three (manufacturer-I) or two (manufacturer-II) additional chemical steps are used to produce the intermediate. Full descriptions of the steps are adequately provided as well as process flow charts.

In the manufacture of a specified starting material, five genotoxic reagents are used or genotoxic intermediates are applicable. Impurities having a structural alert for genotoxicity are adequately dealt with. The reagents are all used or arising in the manufacturing process of the starting material, and all are below acceptable limits.

Quality control of drug substance
The active substance specification is considered adequate to control the quality. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance
The results of a six months accelerated and a 24 months long-term stability study are provided for three batches. There are no clear trends to be observed in the results of the test parameters. Based on the data submitted, a retest period could be granted of 36 months. This drug substance product does not require any special storage temperature conditions.

Metformin hydrochloride
The active substance metformin hydrochloride is an established active substance described in the Ph.Eur. It appears as white or almost white crystals. Crystalline form III is used. It is freely soluble in water. Polymorphic form II is used.

The CEP procedure is used for metformin hydrochloride. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The drug substance specification comprises the tests and limits of the Ph.Eur. monograph, the CEP, and additional in-house for particle size distribution and microbial quality. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance
The active substance is stable for 5 years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions are explained. The choice of the manufacturing process, wet granulation, is adequately justified also in relation to the innovator product. Optimisation of the manufacturing process has been performed. The tablets bear a break line, only intended for ease of swallowing. The products used in the bioequivalence study are acceptable.

Manufacturing process

The product is manufactured using conventional wet-granulation manufacturing process comprised of blending, wet granulation, blending and lubrication, and compression- and coating of the tablets. Batch formulae are provided for full scale batches of 140,000 tablets for each strength. Manufacturing overages are applied for the granulate and the coating solution. However, the finished drug product does not contain any overages. In view of the validation results, these overages are acceptable. The manufacturing process is adequately described and in line with the results of the optimisation studies. A hold time for the bulk tablets has been validated.
Results of process validation have been provided of three full scale batches of both strength, manufactured at the proposed site of manufacture and according the proposed process. The results indicate that the process is consistent.

Control of excipients

For the Opadry mixtures and in-house specifications are defined. These specifications are acceptable. The other excipients comply with the Ph. Eur. requirements.

Quality control of drug product

The product specification includes tests for appearance, identification and assay of both active substance, water content, average mass, dissolution, uniformity of dosage units (content uniformity for sitagliptin and mass variation for metformin), related substances, identification of the colourants, and microbiological quality. Adequate descriptions and validations of the analytical methods have been provided. In general, the analytical methods have been adequately described and validated. Batch analytical data from the proposed production sites have been provided for three full scale batches of each strength, demonstrating compliance with the current release specification.

In view of the presence of metformin, limits for N-nitrosodimethylamine (NDMA) are included in the finished product specification.

Stability of drug product

Stability data on the products have been provided for full-scale scale batches, three batches for each strength, stored for 36 months at 25°C/60% RH (blister, HDPE container, bulk tablets) and 6 months at 40°C/75% RH (blister, HDPE container). The conditions used in the stability studies are according to the ICH stability guideline. All stability results were within specifications. The only trend observed is a slight increase in impurities of sitagliptin at

40°C/75%. Results of one month in-use stability of the product in tablet container at 25°C/60% RH show no changes. The MAH has confirmed that start of shelf-life of the drug product starts from the date of dispensing of the active pharmaceutical ingredient, in compliance with the criteria of the *Note for Guidance on Start of Shelf life of the finished dosage forms* (CPMP/QWP/072/96). Results of photostability of the tablets shows the product is not photosensitive.

Based on the stability data provided, a shelf life of 36 months with no special storage condition has been granted.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Janecluc has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Janecluc is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Janumet which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Sitagliptin hydrochloride monohydrate and metformin hydrochloride are well-known active substances with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted two bioequivalence studies, one with the 50 mg/1000 mg sitagliptin/metformin strength and one with the 50 mg/850 mg sitagliptin/metformin strength. The two studies are discussed below.

IV.2 Pharmacokinetics

The MAH conducted two bioequivalence studies in which the pharmacokinetic profile of the test product Janecluc 50 mg/850 mg and 50 mg/1000 mg film-coated tablets (Demo S.A., Greece) is compared with the pharmacokinetic profile of the reference product Janumet 50 mg/850 mg and 50 mg/1000 mg film-coated tablets (Merck Sharp & Dohme B.V, the Netherlands).

The choice of the reference product in the bioequivalence study has been justified, as it has been registered through a centralised procedure. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Analytical/statistical methods
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Bioequivalence studies
Bioequivalence study I - 50 mg/1000 mg
Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fed conditions in 44 healthy male subjects, aged 8-45 years. Each subject received a single dose (50 mg/1000 mg) of one of the 2 sitagliptin/metformin formulations. After an overnight fast of at least 10 hours, the tablet was administered exactly 30 minutes after the start of high-fat high-calorie breakfast (consisting of bread with cheese, whole milk, cutlet, walnuts, green chutney and tomato chutney) with 240 mL of 20% glucose solution in water at ambient temperature. To manage the hypoglycemic episodes, 60ml of the 20% glucose solution in water was administered every 15 minutes for up to 4 hours after dosing. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.33, 0.67, 1,1.33, 1.67, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 4.33, 4.67, 5, 5.5, 6, 8, 10, 12, 16, 24, 36, 48 and 72 hours after administration of the products.

The design is acceptable, the wash-out long enough, the sampling period (72 hours) long enough, and sampling scheme adequate to estimate PK parameters. Sufficient samples are planned around the expected t_{max} (sitagliptin 1-4 hours; metformin 2.5 hours). Fed conditions are acceptable as sitagliptin/metformin tablets should be given twice daily with meals to reduce the gastrointestinal adverse reactions associated with metformin. The meal composition is acceptable.

Analytical/statistical methods
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
In the first period 44 subjects were dosed, in the second period 36 subjects were dosed. A total of 33 subjects completed both periods of the study. Pharmacokinetic and statistical analyses were performed over 33 subjects.
Eleven subjects were withdrawn:
- Three subjects withdrawn due to AE after dosing of period 1.
- Three subjects withdrawn due to AE after dosing of period 2.
- One subject withdrew consent after dosing of period 1.
- Two subjects did not report to facility during period 2 admission.
- One subject was found positive in alcohol breath test during period 2 admission.
- One subject did not complete the high fat, high calorie breakfast on the day of period 2 dosing.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of sitagliptin under fed conditions.

Treatment N=33	**AUC_{0-t} (ng.h/ml)**	**$AUC_{0-\infty}$ (ng.h/ml)**	**C_{max} (ng/ml)**	**t_{max} (h)**	**$t_{1/2}$ (h)**
Test	2276 ± 400	2329 ± 401	164 ± 44	5.5 (0.7 - 10.0)	--
Reference	2294 ± 396	2357 ± 394	160 ± 39	5.0 (3.3 - 10.0)	--
***Ratio (90% CI)**	0.99 (0.96-1.02)	--	1.03 (0.95-1.11)	--	--
CV (%)	6.96	-	18.9	--	--

$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity
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 concentration
$t_{1/2}$	half-life
CV	coefficient of variation

**ln-transformed values*

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of metformin under fed conditions.

Treatment N=33	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)	$t_{1/2}$ (h)
Test	16227 ± 3675	16364 ± 3630	1542 ± 353	5.5 (1.3 - 10.0)	--
Reference	16415 ± 4023	16563 ± 4004	1569 ± 416	5.5 (1.0 - 8.0)	--
***Ratio (90% CI)**	0.99 (0.95-1.03)	--	1.00 (0.95-1.05)	--	--
CV (%)	9.66	-	11.97	--	--

$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity
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 concentration
$t_{1/2}$	half-life
CV	coefficient of variation

**ln-transformed values*

Bioequivalence study II - 50 mg/850 mg strength

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fed conditions in 44 healthy male subjects, aged 18-40 years. Each subject received a single dose (50 mg/1000 mg) of one of the 2 sitagliptin/metformin formulations. After an overnight fast of at least 10 hours, the tablet was administered exactly 30 minutes after the start of high-fat high-calorie breakfast (consisting of toast, omlet, milk, fried chicken and French fries) with 240 mL of 20% glucose solution in water at ambient temperature. To manage the hypoglycemic episodes, 60 ml of the 20% glucose solution in water was administered every 15 minutes for up to 4 hours after dosing. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.33, 0.67, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 4.33, 4.67, 5, 5.5, 6, 6.5, 7, 8, 10, 12, 16, 24, 36, 48 and 72 hours after administration of the products.

The design is acceptable, the wash-out long enough, the sampling period (72 hours) long enough, and sampling scheme adequate to estimate PK parameters. Sufficient samples are

planned around the expected t_{max} (sitagliptin 1-4 hours; metformin 2.5 hours). Fed conditions are acceptable as sitagliptin/metformin tablets should be given twice daily with meals to reduce the gastrointestinal adverse reactions associated with metformin. The meal composition is acceptable.

Analytical/statistical methods
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
In the first period 44 subjects were dosed, in the second period 36 subjects were dosed. A total of 36 subjects completed both periods of the study. Pharmacokinetic and statistical analyses were performed over 36 subjects.
Eight subjects were withdrawn from the study:
- Seven subjects were withdrawn from the study due to vomiting in period 1.
- One subject number did not turn up for period 2 check-in.

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of sitagliptin under fed conditions.

Treatment N=36	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)	$t_{1/2}$ (h)
Test	2160 ± 365	2198 ± 370	139 ± 35	4.5 (1.7-8.0)	--
Reference	2106 ± 375	2147 ± 382	131 ± 29	4.3 (1.3 – 12.0)	--
***Ratio (90% CI)**	1.03 (1.00-1.05)	1.03 (1.00-1.05)	1.05 (1.00-1.05)	--	--
CV (%)	6.2	6.0	18.8	--	--

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
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 concentration
$t_{1/2}$ half-life
CV coefficient of variation

**ln-transformed values*

Table 4. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of metformin under fed conditions.

Treatment N=36	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)	$t_{1/2}$ (h)
Test	15213 ± 4499	15368 ± 4489	1421 ± 389	4.5 (1.7-8.0)	--
Reference	15498 ± 5070	15655 ± 5046	1433 ± 400	4.3 (0.7-8.0)	--

***Ratio (90% CI)**	0.99 (0.95-1.02)	0.99 (0.95-1.02)	0.99 (0.94-1.05)	--	--
CV (%)	8.3	8.3	13.8	--	--

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
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 concentration
$t_{1/2}$ half-life
CV coefficient of variation

**ln-transformed values*

Conclusion on bioequivalence studies

The 90% confidence intervals calculated for AUC and Cmax are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence studies Janecluc 50 mg/850 mg and 50 mg/1000 mg are considered bioequivalent with Janumet 50 mg/850 mg and 50 mg/1000 mg film-coated tablets.

The MEB has been assured that the bioequivalence studies have been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

IV.3 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 Janecluc.

Table 5. Summary table of safety concerns as approved in RMP

Important identified risks	• Lactic acidosis
Important potential risks	• Pancreatic cancer
Missing information	• Exposure during pregnancy and lactation

The member states agreed that routine risk minimisation measures are sufficient for the risks and areas of missing information. In line with the reference product and in accordance with the decision by CHMP following the article 31 referral on metformin containing medicines (EMEA/H/A-31/1432), an event follow up questionnaire for the risk of lactic acidosis (RSI) will be implemented in order to request and obtain from the reporter all relevant follow-up information including medical data available regarding the condition lactic acidosis for each individual case safety report.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Janumet. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to the PL for Janumet (EMEA/H/C/000861) regarding key safety message. The layout is bridged to Levetiracetam Hetero (PT/H/515/001-004/DC). The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Janecluc 50 mg/850 mg and 50 mg/1000 mg film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Janumet 50 mg/850 mg and 50 mg/1000 mg film-coated tablets. Janumet is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Janecluc with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 3 November 2021.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse