COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Janeo 50 mg and 100 mg, film-coated tablets (sitagliptin hydrochloride monohydrate)

NL/H/5102/001-002/DC

Date: 31 January 2022

This module reflects the scientific discussion for the approval of Janeo 50 mg and 100 mg, film-coated tablets. The procedure was finalised on 9 August 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
PPARγ	Peroxisome proliferator-activated receptor gamma
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 Janeo 50 mg and 100 mg, film-coated tablets, from Demo S.A. Pharmaceutical Industry.

The products are indicated for adult patients with type 2 diabetes mellitus to improve glycaemic control:

as monotherapy

- in patients inadequately controlled by diet and exercise alone and for whom metformin is inappropriate due to contraindications or intolerance.

as dual oral therapy in combination with

- metformin when diet and exercise plus metformin alone do not provide adequate glycaemic control.
- a sulphonylurea when diet and exercise plus maximal tolerated dose of a sulphonylurea alone do not provide adequate glycaemic control and when metformin is inappropriate due to contraindications or intolerance.
- a peroxisome proliferator-activated receptor gamma (PPARγ) agonist (i.e. thiazolidinedione) when use of a PPARγ agonist is appropriate and when diet and exercise plus the PPARγ agonist alone do not provide adequate glycaemic control.

as triple oral therapy in combination with

- a sulphonylurea and metformin when diet and exercise plus dual therapy with these medicinal products do not provide adequate glycaemic control.
- a PPARγ agonist and metformin when use of a PPARγ agonist is appropriate and when diet and exercise plus dual therapy with these medicinal products do not provide adequate glycaemic control.

The products are also indicated as add-on to insulin (with or without metformin) when diet and exercise plus stable dose of insulin 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 products Januvia 50 and 100 mg, film-coated tablets which have been registered in the EEA by Merck Sharp & Dohme Ltd. since March 2007 by the procedure EU/1/07/383.

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

Janeo 50 mg film-coated tablets are round, pink film-coated tablets, debossed with "S16" on one side and "H" on the other side and contains as active substance 50 mg sitagliptin (as hydrochloride).

Janeo 100 mg film-coated tablets are round, pink film-coated tablets debossed with "S15" on one side and "H" on the other side and contains as active substance 100 mg sitagliptin (as hydrochloride).

The film-coated tablets are packed in a transparent PVC/PE/PVdC-Al blister or in a HDPE container with a polypropylene cap.

The excipients are:
Tablet core – cellulose, microcrystalline (E460), anhydrous calcium hydrogen phosphate (E341), croscarmellose sodium (E468), magnesium stearate (E470b) and sodium stearyl fumarate.

Film-coating – Opadry II Pink 85F540099 (100 mg product) and Opadry II Pink 85F540265 (50 mg product) contain polyvinyl alcohol-part hydrolysed (E1203), titanium dioxide (E171), macrogol 4000 (E1521), talc (E553b), iron oxide red (E172) and iron oxide yellow (E172).

II.2 Drug Substance

The active substance is sitagliptin hydrochloride monohydrate, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The drug substance is a white to off-white powder. It is freely soluble in water. The active substance has one chiral centre: the amino-group is in the R-configuration: (3R)-3-amino. The substance is not hygroscopic. The polymorph crystalline form III is consistently produced.

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 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.

Manufacturing process

The manufacturing process is based on a condensation reaction. Adequate specifications have been adopted for starting materials, solvents and reagents. The active substance has been adequately characterised.

Quality control of drug substance

Drug substance specifications are applied for description, identification, water content, sulphated ash, chloride content, related substances, enantiomeric purity, assay, and residual solvents. All analytical methods have been adequately described, the quantitative methods have been fully validated. Potential elemental impurities have been evaluated according to ICH Q3D and additional control limits on elemental impurities are not necessary. Batch analytical data demonstrating compliance with this specification have been provided three batches.

Stability of drug substance

Stability data on the active substance have been provided for three batches stored at 25°C/60% RH (36 months) and 40°C/75% RH (six months) in accordance with applicable European guidelines. There were no clear trends observed in the results of the tested parameters. Based on the data submitted, a retest period could be granted of 48 months when stored in the original package to protect from light.

II.3 Medicinal Products

Pharmaceutical development

The development of the products has been described, the choice of excipients is justified and their functions explained. The choices of the packaging and manufacturing process are justified in relation to the innovator product.

The MAH performed a bioequivalence study to compare the *in vivo* bioavailability of the test and innovator products, which will be discussed in section IV. To support this study, comparative dissolution data were provided, which showed similar dissolution profiles in media of three different pH's. The dissolution method used for routine dissolution was shown to be discriminatory.

Manufacturing process

The products are manufactured using conventional manufacturing techniques. For each strength, the needed quantity of the common blend is listed. In addition the involved excipient quantities needed for common blend are listed, and for the compression stage at both scale sizes the needed quantities of the two Opadry II mixtures and purified water are listed. The manufacturing process has been validated according to relevant European

guidelines. Process validation data on the products have been presented for three pilot-scale batches per strength, in accordance with the relevant European guidelines.

Control of excipients

The excipients comply with the Ph. Eur. requirements. For the Opadry mixtures in-house specifications are defined. The specifications are acceptable. The MAH included [(EU) No 231/2012] as quality reference for the four iron oxides in the two composition tables for the film-coat mixtures. These specifications are acceptable.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance (including diameter and thickness for the three strengths), identification and assay of the active substance, water content, average mass, uniformity of dosage units, related substances, dissolution, identification of the colourants, and microbiological quality.

An adequate nitrosamines risk evaluation has been performed. The analytical methods have been adequately described and validated. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Batch analytical data from three full scale batches of each strength from the proposed production sites have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for three pilot-scale batches stored at 25°C/60% RH (18 months) and 40°C/75% RH (six months) in accordance with applicable European guidelines. The conditions used in the stability studies are according to the ICH stability guideline. All stability results were within specifications. No significant changes were observed in the accelerated stability studies. On basis of the data submitted, a shelf life was granted of two years. No specific storage conditions need to be included in the SmPC or on the label.

All bulk pack stability results were within specifications. No significant changes were observed. Herewith a hold-time of 12 months is considered accepted. The MAH chooses for a storage condition below 25°C, which is acceptable. It is additionally stated by the MAH that the Start of Shelf-life of the drug product starts from the date of dispensing of the active substance, in compliance with the criteria of the Note for Guidance on Start of Shelf life of the finished dosage forms (CPMP/QWP/072/96).

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 Janeo have 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 Janeo are 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

These products are generic formulations of Januvia which are available on the European market. Reference is made to the preclinical data obtained with the innovator products. 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 is a well-known active substance 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 one bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Janeo 100 mg, film-coated tablets (Demo S.A. Pharmaceutical Industry, Greece) is

compared with the pharmacokinetic profile of the reference product Januvia 100 mg, film-coated tablets (Merck Sharp & Dohme Ltd., the Netherlands).

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of test and reference products. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver

A bioequivalence study on the highest strength (100 mg strength) has been carried out. Pharmacokinetics are linear in the therapeutic dose range for AUC, and C_{max} increased more than dose-proportional. A biowaiver is granted for the 50 mg strength as all the following criteria are fulfilled:

a) the pharmaceutical products are manufactured by the same manufacturing process
b) the qualitative composition of the different strengths is the same
c) the composition of the strengths are quantitatively proportional, i.e. the ratio between the amount of each excipient to the amount of active substance(s) is the same for all strengths
d) *in vitro* dissolution data between the 50 and 100 mg biobatch at three pH's showing comparable dissolution have been submitted.

Bioequivalence studies

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 32 healthy male subjects, aged 18-43 years. Each subject received a single dose (100 mg) of one of the two sitagliptin hydrochloride monohydrate formulations. The tablet was orally administered with 240 ml water after an overnight fast. There were two dosing periods, separated by a washout period of ten 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, 4.5, 5, 6, 8, 10, 12, 16, 24, 36, 48 and 72 hours after administration of the products.

The design of the study is acceptable.

Sitagliptin hydrochloride monohydrate may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of sitagliptin hydrochloride monohydrate. Therefore, a food interaction study is not deemed necessary.

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

Three subjects were withdrawn from the study. One subject was withdrawn from the study due to an adverse event after dosing in Period I. One subject was found positive in alcohol breath test during admission of Period II. Another subject had taken one cup of tea in the morning on the day before dosing in Period II, hence withdrawn from the study during admission of Period II. 29 subjects were eligible for pharmacokinetic analysis.

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

Treatment N=29	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)	$t_{1/2}$ (h)
Test	4553 ± 1010	4656 ± 996	493 ± 113	2.67 (0.67 – 5.0)	9.2 ± 3.0
Reference	4483 ± 814	4581 ± 810	510 ± 159	2.33 (0.67 – 5.0)	9.3 ± 3.0
***Ratio (90% CI)**	1.01 (0.98 – 1.04)	-	0.98 (0.92 – 1.04)	-	-
CV (%)	6.7	-	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 study:

The 90% confidence intervals calculated for AUC_{0-t} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Janeo 100 mg is considered bioequivalent with Januvia 100 mg.

The MEB has been assured that the bioequivalence study has 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 Janeo.

Table 2. Summary table of safety concerns as approved in RMP

Important identified risks	• None
Important potential risks	• Pancreatic cancer
Missing information	• Exposure during pregnancy and lactation

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator products Januvia. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the 100 mg product is similar to the pharmacokinetic profile of the respective reference product. A biowaiver has been granted for the 50 mg product strength. Risk management is adequately addressed. These generic medicinal products can be used instead of the reference products.

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 Januvia, EMEA/H/C/000722. 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

Janeo 50 mg and 100 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Januvia 50 mg and 100 mg, film-coated tablets. Januvia are well-known medicinal products with established favourable efficacy and safety profiles. 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 Janeo with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 9 August 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