COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Sitagliptin/Metformin Hydrochloride Macleods 50 mg/850 mg and 50 mg/1000 mg film-coated tablets (sitagliptin tartrate hemihydrate and metformin hydrochloride)

NL/H/5453/001-002/DC

Date: 31 January 2024

This module reflects the scientific discussion for the approval of Sitagliptin/Metformin Hydrochloride Macleods 50 mg/850 mg and 50 mg/1000 mg film-coated tablets. The procedure was finalised on 5 July 2023. 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
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
HDPE	High density polyethylene
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
LDPE	Low density polyethylene
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
RMS	Reference Member State
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 Sitagliptin/Metformin Hydrochloride Macleods 50 mg/850 mg and 50 mg/1000 mg film-coated tablets, from Macleods Pharma Espana S.L.U.

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

Sitagliptin/Metformin Hydrochloride Macleods 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.

Sitagliptin/Metformin Hydrochloride Macleods 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.

Sitagliptin/Metformin Hydrochloride Macleods 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.

Sitagliptin/Metformin Hydrochloride Macleods 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 up-to-date indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC, which concerns a generic application.

In this decentralised procedure, essential similarity is proven between the new product and the innovator product Janumet 50/850 mg and 50/1000 mg film-coated tablets, which has been registered in the Netherlands via centralised procedure (EMEA/H/C/000861) since July 18, 2008 (Merck Sharp & Dohme Ltd., Germany).

The reference product contains Sitagliptin phosphate monohydrate as the active substance while in Sitagliptin/Metformin Hydrochloride Macleods the tartrate hemihydrate salt is used. However, their contents of active substance correspond to the same amount of the active moiety sitagliptin. Although the Sitagliptin/Metformin Hydrochloride Macleods generic product is different in the salt form and is not described in any Pharmacopoeia, Sitagliptin tartrate (hemihydrate) is classified as an identical therapeutically entity according to Article 10(2) of Directive 2001/83/EC (as amended): *"The different salts, esters, isomers, mixtures of isomers, complexes or derivatives of an active substance shall be considered to be the same active substance, unless they differ significantly in properties with regard to safety and /or efficacy."*

The concerned member states (CMS) involved in this procedure were Germany, Italy, and Spain.

II. QUALITY ASPECTS

II.1 Introduction

Sitagliptin/Metformin Hydrochloride Macleods 50 mg/850 mg and 50 mg/1000 mg are film-coated tablets. Each Sitagliptin/Metformin Hydrochloride Macleods 50 mg/850 mg film-coated tablet contains 50 mg of sitagliptin and 850 mg of metformin hydrochloride. Each Sitagliptin/Metformin Hydrochloride Macleods 50 mg/1000 mg film-coated tablet contains 50 mg of sitagliptin and 1000 mg of metformin hydrochloride. The two strengths can be distinguished by the different size, shape, colour, and debossing of the tablets.

The Sitagliptin/Metformin Hydrochloride Macleods 50 mg/850 mg film-coated tablets are pink in colour, capsule shaped, biconvex film-coated tablets, debossed with “K 21” on one side and plain on the other side. Dimensions are a length of 20.1 mm ± 0.2 mm and width of 9.8 mm ± 0.2 mm.

The Sitagliptin/Metformin Hydrochloride Macleods 50 mg/1000 mg film-coated tablets are red in colour, capsule shaped, biconvex film-coated tablets, debossed with “K 22” on one side and plain on the other side. Dimensions are a length of 21.4 mm ± 0.2 mm and width of 10.5 mm ± 0.2 mm.

The excipients are:
Tablet core - microcrystalline cellulose (E460), povidone K-30 (E1201), croscarmellose sodium (E468), sodium lauryl sulphate and sodium stearyl fumarate.
Film coating - polyvinyl alcohol (E1203), macrogol 3350 (E1521), talc (E553b), titanium dioxide (E171), red iron oxide (E172) and black iron oxide (E172).

The tablets are not dose proportional.

The film-coated tablets are packed in orientated polyamide aluminium polyvinyl chloride (OPA/ALU/PVC) blisters, laminated with aluminium foil.

II.2 Drug Substance

The active substances are sitagliptin tartrate hemihydrate and metformin hydrochloride.

Sitagliptin tartrate hemihydrate
Sitagliptin tartrate hemihydrate is a powder and is slightly soluble in water. Sitagliptin has one chiral centre and is synthesized as the R isomer. The control of the final isomer is described in sufficient detail. Sitagliptin tartrate hemihydrate is a known active substance not described in

any Pharmacopoeia. However, for sitagliptin phosphate monohydrate, another salt form, Ph.Eur. and BP monographs are available.

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.

Manufacturing process

Sitagliptin tartrate hemihydrate is manufactured using various starting materials, followed by coupling of the synthesized intermediates products and formation of the tartrate hemihydrate. No class 1 solvents are used during the synthesis of sitagliptin tartrate hemihydrate. A catalyst is used during the synthesis of an intermediate product. Three commercial batches of the active substance have been tested for the presence of the catalyst. In all batches, the catalyst was found to be well below the Threshold of Toxicological Concern (TTC) safety level. Adequate specifications have been adopted for starting materials, solvents and reagents. The active substance has been adequately characterised, and the manufacturing process is described in sufficient detail.

Quality control of drug substance

The active substance specification is considered adequate to control the quality and meets the in-house requirements set by the drug product manufacturer. The drug product manufacturer adopted for the drug substance the same specifications applied by the ASMF holder with the exception of the bulk density which are based on the historical trend of commercial batches. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with this specification have been provided for three drug substance batches.

Stability of drug substance

Stability data on the active substance have been provided for three production scaled batches in accordance with applicable European guidelines. The batches were stored at 25°C/ 60% RH (24 months) and 40°C/ 75% RH (6 months). Based on the data provided, a retest period could be granted of 24 months when stored under the stated conditions.

Metformin hydrochloride

Metformin hydrochloride an established active substance described in the Ph.Eur. Metformin hydrochloride is a crystalline powder, freely soluble in water. Metformin hydrochloride does not contain any chiral centre, so it does not exhibit isomerism.

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 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 consists of one chemical transformation step from the starting materials, followed by repeated washing and drying steps. No class 1 organic solvents or heavy metal catalysts are used. Adequate specifications have been adopted for starting materials, solvents and reagents. The active substance has been adequately characterised, and the manufacturing process is described in sufficient detail.

Quality control of drug substance

The active substance specification has been established in-house by the active substance manufacturer and is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with this specification have been provided for three drug substance batches.

Stability of drug substance

Stability data on the active substance have been provided for three production scaled batches stored at 25°C/ 60% RH (24 months) and 40°C/ 75% RH (6 months). Based on the data provided, a retest period could be granted of 24 months when stored under the stated conditions in accordance with applicable European guidelines.

II.3 Medicinal Product

Pharmaceutical development

The product is an established pharmaceutical form, and its development is adequately described in accordance with the relevant European guidelines.

The development of the product has been described, the choice of excipients is justified, and their functions explained. The selection of film coating material is also justified. Formulation development and formulation optimization have been sufficiently described. The discriminatory power of the QC dissolution method has been demonstrated. The data presented on polymorphism confirm that the polymorphic form of both drug substances in the drug product remains intact during manufacturing and stable over the storage period.

Manufacturing process

The drug product is manufactured by a wet granulation process, which consists of mixing, granulation, wet milling, drying, sifting and milling, followed by blending, lubrication, compression and film-coating. The manufacturing process has been validated according to relevant European guidelines. Process validation data on the product has been presented for two batches of each strength manufactured at the minimum commercial batch size. One additional batch of each strength manufactured at the minimum batch size will be validated post authorization and a commitment to conduct validation on three batches of each blend batch size (other than submission batch size) as and when they are manufactured based on

commercial demand has been provided. The product is manufactured using conventional manufacturing techniques.

Control of excipients

The excipients comply with Ph.Eur. and in-house requirements. 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 description, dimensions, identification of drug substances, identification of colourants, water content, dissolution, uniformity of dosage units, related substances, assay and microbiological quality. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. The release and shelf-life specifications are acceptable. Appropriate tests for nitrosamine presence are performed on the final product.

Satisfactory validation data for the analytical methods have been provided. Batch analytical data on four batches (two of each strength) manufactured at the minimum commercial batch size from the production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for two batches of each strength manufactured at the minimum commercial batch size and stored at 25°C/ 60% RH (24 months) and 40°C/75% RH (6 months). The batches were stored in the blisters intended for commercial use. The stability was tested in accordance with applicable European guidelines demonstrating the stability of the product for 24 months. A slight increase in an unknown impurity was observed during storage under accelerated and long-term storage conditions. All other parameters remain stable and within the specification limits and no significant changes were observed during stability studies at accelerated storage conditions. Photostability studies were performed in accordance with ICH recommendations and showed that the product is photostable if unpacked as well as in the packaging.

On basis of the data provided, a shelf life was granted of 24 months. The storage condition “Do not store above 30°C” is acceptable as precautionary measure as the confirmatory testing for nitrosamines was carried out in batches stored at 25°C/60% RH and 30°C/75% RH, but not at 40°C/75% RH.

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 Sitagliptin/Metformin Hydrochloride Macleods 50 mg/850 mg and 50 mg/1000 mg has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

The following post-approval commitments were made:

- Continue on-going long-term stability study of production batches (submission batch) of Sitagliptin/Metformin Hydrochloride Macleods 50 mg/850 mg and 50 mg/1000 mg film-coated tablets in blister packs as per the study design.
- Carry out accelerated stability study (at 40°C ± 2°C and 75% ± 5% RH) and long term stability study (at 25°C ± 2°C and 60% ± 5% RH) on one more production batch in the market pack as per the stability programme given overleaf, as and when they are manufactured based on the commercial requirement.
- Conduct long-term stability studies (at 25°C ± 2°C and 60% ± 5% RH) of Sitagliptin/Metformin Hydrochloride Macleods 50 mg/850 mg and 50 mg/1000 mg film-coated tablets, at least one production batch per year in the market pack if manufactured and packed.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Sitagliptin/Metformin Hydrochloride Macleods 50 mg/850 mg and 50 mg/1000 mg is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment was 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 was made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which was 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 tartrate hemihydrate 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 member states agreed that no further clinical studies are required, besides the two bioequivalence studies, which are discussed below.

IV.2 Pharmacokinetics

The MAH conducted two bioequivalence studies in which the pharmacokinetic profile of the test product Sitagliptin/Metformin Hydrochloride Macleods 50 mg/850 mg film-coated tablets and Sitagliptin/Metformin Hydrochloride Macleods 50 mg/1000 mg film-coated tablets (Macleods Pharma Espana S.L.U., Spain) were compared with the pharmacokinetic profile of the reference product Janumet 50/850 mg film-coated tablets and Janumet 50/1000 mg film-coated tablets (Merck Sharp & Dohme Ltd, Netherlands).

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution study results and composition. The dissolution was performed in 0.1N hydrochloric acid, acetate buffer pH 4.5 and phosphate buffer pH 6.8. The formula and preparation of the bioequivalence batch was identical to the formula for marketing.

The dissolution was investigated according to the EMA Bioequivalence guideline. The comparative dissolution profiles complementary to the bioequivalence study conducted at the rotation speed of 50 rpm have not been demonstrated to be statistically similar for both drug substances in each condition. Although possible reasons for the discrepancy have not been adequately addressed and justified by the MAH, as *in vivo* results prevail, no further objection on this point is made. Additionally, similarity of the dissolution profiles of test and reference product was confirmed at 75 rpm for both drug substances in each condition.

Bioequivalence studies

Study 1 – single dose, 50/850 mg, under fed conditions

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover, open label bioequivalence study was carried out under fed conditions in 36 healthy male subjects, aged 21-42 years. Each subject received a single dose (Sitagliptin/Metformin Hydrochloride Macleods 50 mg/850 mg) of either the test product or the reference product after an overnight fast of at least 10 hours. The tablet was orally administered with 240 mL of 20% w/v glucose solution in water at room temperature exactly 30 minutes after the start of high-fat high-calorie breakfast. The meal provided 258.14 kcal carbohydrates, 173.9 kcal protein and 560.88 kcal fat, with a total of 993 kcal energy. There were two dosing periods, separated by a washout period of 7 days. To manage the hypoglycaemic episodes, 60 mL of the 20% w/v glucose solution in water was administered every 15 minutes for up to 4 hours after dosing.

Blood samples were collected pre-dose and at 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 10, 12, 18, 24, 30, 36, 48 and 72 hours after administration of the products.

The design of the study 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
36 subjects were enrolled for the study. In the first period, 36 subjects were dosed, and in the second period 35 subjects were dosed. A total of 35 subjects completed both periods of the study. One subject was withdrawn from the study in period 1 (post-dose) due to adverse event (fever with chills). 35 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of sitagliptin, 50 mg under fed conditions.

Treatment N=35	**AUC_{0-t} (ng.h/mL)**	**$AUC_{0-\infty}$ (ng.h/mL)**	**C_{max} (ng/mL)**	**t_{max} (h)**
Test	1884 ± 237	1947 ± 244	144 ± 24	4.0 (1.5 – 8.0)
Reference	1871 ± 251	1938 ± 266	139 ± 24	4.0 (2.0 - 10.0)
***Ratio (90% CI)**	1.01 (0.98 – 1.03)	-	1.04 (0.99 – 1.09)	-

$AUC_{0-\infty}$	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 = 72 hours
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**ln-transformed values*

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of metformin, 850 mg under fed conditions.

Treatment N=35	**AUC_{0-t} (ng.h/mL)**	**$AUC_{0-\infty}$ (ng.h/mL)**	**C_{max} (ng/mL)**	**t_{max} (h)**
Test	14450 ± 2842	14544 ± 2849	1404 ± 245	5.0 (1.0 – 8.5)
Reference	14109 ± 2770	14206 ± 2774	1357 ± 266	5.0 (1.0 – 8.5)
***Ratio (90% CI)**	1.03 (0.99 – 1.06)	-	1.04 (0.98 – 1.11)	-

$AUC_{0-\infty}$	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 = 72 hours
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**ln-transformed values*

Study 2 – single dose, 50/1000 mg under fed conditions

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover, open label bioequivalence study was carried out under fed conditions in 36 healthy male subjects, aged 21-43 years. Each subject received a single dose (50/1000 mg) of either the test product or the reference product after an overnight fast of at least 10 hours. The tablet was orally administered with 240 mL of 20% w/v glucose solution in water at room temperature exactly 30 minutes after the start of high-fat high-calorie breakfast. The meal provided 258.14 kcal carbohydrates, 173.9 kcal protein and 560.88 kcal fat, with a total of 993 kcal energy. There were two dosing periods, separated by a washout period of 7 days. To manage the hypoglycaemic episodes, 60 mL of the 20% w/v glucose solution in water was administered every 15 minutes for up to 4 hours after dosing.

Blood samples were collected pre-dose and at 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5 8, 8.5, 10, 12, 18, 24, 30, 36, 48 and 72 hours after administration of the products.

The design of the study is acceptable.

Results

A total of 36 subjects were enrolled at the start of the study. One subject dropped out from the study in period 1 (pre-dose) for personal reasons. In the first and second period 35 subjects were dosed. A total of 35 subjects completed both periods of the study. 35 subjects were eligible for pharmacokinetic analysis.

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of sitagliptin, 50 mg under fed conditions.

Treatment N=35	**AUC_{0-t}** (ng.h/mL)	**$AUC_{0-\infty}$** (ng.h/mL)	**C_{max}** (ng/mL)	**t_{max}** (h)
Test	1851 ± 296	1922 ± 309	133 ± 23	4.5 (2.0-8.5)
Reference	1884 ± 295	1950 ± 305	135 ± 26	4.5 (1.5 – 10.0)
***Ratio (90% CI)**	0.98 (0.97 – 1.00)	-	0.99 (0.94 – 1.03)	-

$AUC_{0-\infty}$	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 = 72 hours
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**ln-transformed values*

Table 4. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of metformin, 1000 mg under fed conditions.

Treatment N=35	AUC_{0-t} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	C_{max} (ng/mL)	t_{max} (h)
Test	15678 ± 3100	15839 ± 3133	1539 ± 333	5.0 (1.0-8.5)
Reference	15611 ± 3025	15718 ± 3045	1543 ± 363	5.0 (1.5-8.0)
***Ratio (90% CI)**	1.00 (0.97 – 1.03)	-	1.00 (0.97 – 1.03)	-

$AUC_{0-\infty}$	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 = 72 hours
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**ln-transformed values*

Conclusion on bioequivalence studies:
Fed conditions are acceptable as according the SmPC of the test's product, Sitagliptin/Metformin Hydrochloride Macleods tablets should be given twice daily with meals to reduce the gastrointestinal adverse reactions associated with metformin. From the literature it is known that food does not interact with the pharmacokinetics of sitagliptin. Food does decrease the extent and slightly delays the absorption of metformin. Gastrointestinal symptoms are reported very commonly in clinical studies and post-marketing use of metformin.

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 studies, Sitagliptin/Metformin Hydrochloride Macleods 50 mg/850 mg and 50 mg/1000 mg is considered bioequivalent with Janumet 50/850 mg and 50/1000 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 Sitagliptin/Metformin Hydrochloride Macleods 50 mg/850 mg and 50 mg/1000 mg.

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 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 product Janumet. No new clinical studies were conducted. The MAH demonstrated through two bioequivalence studies 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

The package leaflet (PL) 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 applicant submitted a report of the readability test for the patient leaflet for Sitagliptin/Metformin Hydrochloride Macleods 50 mg/1000 mg film-coated tablets and a bridging statement for the patient leaflet for Sitagliptin/Metformin Hydrochloride Macleods 50 mg/850 mg film-coated tablets. The bridging statement is acceptable as the patient leaflet text of the two strengths are identical with the only difference being the strength and look of the medicine.

The readability test consisted of a pilot test with 4 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility, and applicability. The results show that the PL 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

Sitagliptin/Metformin Hydrochloride Macleods 50 mg/850 mg and 50 mg/1000 mg film-coated tablets have a proven chemical-pharmaceutical quality and are generic form of Janumet 50/850 mg and Janumet 50/1000 mg 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 Sitagliptin/Metformin Hydrochloride Macleods 50 mg/850 mg and 50 mg/1000 mg with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 5 July 2023.

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
-	-	-	-	-	-