COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Fordiab 50 mg/850 mg & 50 mg/1000 mg film-coated tablets (sitagliptin hydrochloride, metformin hydrochloride)

NL/H/5005/001-002/DC

Date: 17 January 2022

This module reflects the scientific discussion for the approval of Fordiab. The procedure was finalised at 15 September 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 Fordiab 50 mg/850 mg & 50 mg/1000 mg film-coated tablets, from Stada Arzneimittel AG.

The product is indicated for adult patients with type 2 diabetes mellitus 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. Furthermore, the product is indicated for:

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.

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.

Finally, the product 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 which has been registered in the European Union via the centralised procedure (EU/1/08/455) since 16 July 2008 by Merck Sharp & Dohme.

The concerned member states (CMS) involved in this procedure were Greece and Poland.

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

II. QUALITY ASPECTS

II.1 Introduction

Fordiab 50 mg/850 mg:
Oval-shaped, biconvex, pink film-coated tablet with “S476” debossed on one side.

Fordiab 50 mg/1000 mg:
Oval-shaped, biconvex, brown film-coated tablet with "S477" debossed on one side.

Fordiab 50 mg/850 mg and 50 mg/1000 mg film-coated tablets contain 50 mg of sitagliptin and 850 mg/1000 mg of metformin hydrochloride respectively.

The film-coated tablets are packed in high density polyethylene (HDPE) containers and polypropylene (PP) screw caps with tamper-evident ring and silica gel desiccant contained in the PP cap and hard aluminium/PVC/PVDC opaque blisters.

The excipients are:

For all strengths
Tablet core - cellulose microcrystalline, povidone, sodium laurilsulfate and sodium stearyl fumarate.

50 mg/850 mg strength
Film coating - lactose monohydrate, hypromellose (E464), titanium dioxide (E171), triacetin and iron oxide red (E172).

50 mg/1000 mg strength
Film coating - polyvinyl alcohol (E1203), macrogol (E1521), talc (E5553b), titanium dioxide (E171), iron oxide red (E172) and black iron oxide (E172).

II.2 Drug Substance

Sitagliptin hydrochloride monohydrate
The active substance is sitagliptin hydrochloride monohydrate, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The drug substance is a white or almost white powder. It is freely soluble in water. The drug substance has one chiral centre: the amino-group is in the R-configuration: (3R)-3-amino. The substance is not hygroscopic. It was confirmed that manufacturers I and II consistently produce the monohydrate or polymorphic form III of sitagliptin hydrochloride respectively. No routine testing for polymorphic form was deemed necessary as changes in the polymorphic form did not influence stability or dissolution of the active substance.

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

Manufacturer I
The manufacturing process of the active substance is carried out in three stages which involve the manufacturing of two intermediates followed by the synthesis of sitagliptin hydrochloride. The choice of the regulatory starting materials is justified. The active substance has been adequately characterized and acceptable specifications have been adopted for the starting material, solvents and reagents.

Manufacturer II
The manufacturing process of the active substance is carried out in three stages which involve the manufacturing of two intermediates followed by the synthesis of sitagliptin hydrochloride with isolated and non-isolated intermediates. The choice of the regulatory starting materials is justified. The active substance has been adequately characterized and acceptable specifications have been adopted for the starting material, solvents and reagents.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. or is done using in-house methods. The specification contains tests for description, identification, hydrochloric acid content, water content, residue on ignition, enantiomeric impurity, related substances, assay, residual solvents and particle size. All analytical methods have been adequately described and the quantitative methods have been fully validated. Batch analytical data demonstrating compliance with this specification have been provided for four and two batches from manufacturers I and II respectively.

Stability of drug substance
Manufacturer I
Stability data on the active substance has been provided for three production scaled batches under long term (25ºC/60% RH) and accelerated (40ºC/75% RH) for 24 and six months respectively in accordance with applicable European guidelines demonstrating the stability of the active substance for three years. There are no clear trends to be observed in the results of the test parameters. Forced degradation and photostability studies have been adequately performed. The active substance was stored in two LDPE bags, and then in HDPE containers. Based on the data submitted, a retest period could be granted of three years with no special storage conditions.

Manufacturer II
Stability data on the active substance has been provided for three pilot scaled batches under long term (25ºC/60% RH) and accelerated (40ºC/75% RH) for six months. Furthermore, the MAH submitted data on three production scaled batches under long term and accelerated conditions for 24 and six months respectively in accordance with applicable European guidelines demonstrating the stability of the active substance for two years. There are no clear trends to be observed in the results of the test parameters. Forced degradation and photostability studies have been adequately performed. The active substance was stored in

LDPE and triple laminated aluminium bags, and then in HDPE drums. Based on the data submitted, a retest period could be granted of two years when stored in an air tight container under nitrogen at a temperature up to 25°C.

Metformin hydrochloride
The active substance is metformin hydrochloride, an established active substance described in the Ph.Eur. The active substance are white to almost white crystals freely soluble in water, slightly soluble in alcohol, practically insoluble in acetone and methylene chloride. Metformin hydrochloride does not exhibit isomerism or chirality and conforms to polymorphic form I for both manufacturers.

The CEP procedure is used for the active substance. 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 active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. or is done using in-house methods. The specification contains tests for description, identification, appearance of solution, related substances, loss on drying, assay and residual solvents. Batch analytical data demonstrating compliance with this specification have been provided for four batches from manufacturer I. As the polymorphic form that is manufactured at both manufacturing sites is the same, no batch analytical data from manufacturer II has been provided. This is considered acceptable.

Stability of drug substance
Manufacturer I
The active substance is stable for five years when stored in double polyethylene bag placed in a polyethylene drum. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

Manufacturer II
The active substance is stable for 60 months when stored in polyethylene bags placed in fibreboard or polyethylene drums. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

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 choice of excipients is justified and their functions 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 using quality by design aspects. The products used in the bioequivalence studies 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 according to relevant European/ICH guidelines. Manufacturing overages are applied for the coating solution. In view of the validation results, these overages are acceptable. 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 coating mixtures are in-house specifications defined. These specifications are acceptable. The other excipients comply with the Ph. Eur. requirements.

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, identification and assay of both active substance, water content, uniformity of dosage units, dissolution, related substances, NDMA impurity and microbiological quality. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Adequate descriptions and validations of the analytical methods have been provided. The risk evaluation on presence of nitrosamine impurities is acceptable. 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.

Stability of drug product

Stability data on the product have been provided for full-scale scale batches, three batches for each strength, stored for 18 - 24 months at 25°C/60% RH (blister, tablet container, bulk tablets), 12 months at 30°C/60%RH and 6 months at 40°C/75% RH (blister, tablet container) in accordance with applicable European guidelines demonstrating the stability of the product for 24 months. Results of photostability of the tablets have been provide and demonstrate photostability of the drug product. The applicant has confirmed that 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). On basis of the data submitted, a shelf life was granted of 24 months when stored below 30°C.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Scientific data and/or certificates of suitability issued by the EDQM have been provided for lactose monohydrate and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Fordiab 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 Fordiab 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 and metformin hydrochloride are well-known active substances with an 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, which are discussed below.

IV.2 Pharmacokinetics

The MAH conducted two bioequivalence studies in which the pharmacokinetic profile of the test product Fordiab 50 mg/850 mg & 50 mg/1000 mg film-coated tablets (Laboratories Liconsa, S.A) is compared with the pharmacokinetic profile of the reference product Janumet 50 mg/850 mg & 50 mg/1000 mg film-coated tablets (Merck Sharp & Dohme). Both studies are performed under fed conditions, which is acceptable as the tablets should be given twice daily with meals to reduce the gastrointestinal adverse reactions associated with metformin.

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

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.

Bioequivalence studies

Study I with 50 mg/850 mg strength
Design
An open label, balanced, randomized, two-treatment, two-period, two-sequence, single oral dose, crossover bioequivalence study was carried out under fed conditions in 37 healthy, male adult non-smoker subjects, aged 28-39 years. Each subject received a single dose (50 mg / 850 mg) of one of the two active substance formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least ten hours, and served a high fat and high calorie vegetarian breakfast (toast, chana chat, vegetable cutlets and milk). There were two dosing periods, separated by a washout period of seven days.

Blood samples were collected prior to drug administration and 0.17, 0.33, 0.67, 1, 1.3, 1.67, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 4.5, 5, 6, 7, 8, 10, 12, 16, 24, 36, 48, and 72 hours after administration of the products.

Results

Out of 37 subjects, 35 were eligible for pharmacokinetic analysis. One subject was withdrawn because of an adverse event (vomiting) and one subject withdrew on his own accord.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of metformin hydrochloride (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	15719 ± 4639	15786 ± 4643	1736 ± 455	5.0 (3.3-6.0)
Reference	15526 ± 3987	15594 ± 3990	1695 ± 327	5.0 (3.3-6.0)
***Ratio (90% CI)**	1.003 (0.9707-1.0373)	--	1.009 (0.9497-1.0527)	--
CV (%)	8.2	--	10.4	--

$AUC_{0-\infty}$ 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
CV coefficient of variation
CI confidence interval

**ln-transformed values*

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of sitagliptin hydrochloride (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	2276 ± 438	2312 ± 444	164 ± 32	4.0 (1.7-7.0)
Reference	2305 ± 384	2342 ± 388	158 ± 30	5.0 (2.3-8.0)
***Ratio (90% CI)**	0.983 (0.9657-1.0007)	--	1.032 (0.9920-1.0735)	--
CV (%)	4.4	--	9.8	--

$AUC_{0-\infty}$ 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
CV coefficient of variation
CI confidence interval

**ln-transformed values*

Study II with 50 mg/1000 mg strength

Design

An open label, balanced, randomized, two-treatment, two-period, two-sequence, single oral dose, crossover bioequivalence study was carried out under fed conditions in 37 healthy, male adult non-smoker subjects, aged 26-39 years. Each subject received a single dose (50 mg/1000 mg) of one of the two active substance formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least ten hours, and served a high fat and high calorie vegetarian breakfast (toast, chana chat, vegetable cutlets and milk). There were two dosing periods, separated by a washout period of seven days.

Blood samples were collected prior to drug administration and 0.17, 0.33, 0.67, 1, 1.3, 1.67, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 4.5, 5, 6, 7, 8, 10, 12, 16, 24, 36, 48, and 72 hours after administration of the products.

Results

Out of 40 subjects, 38 were eligible for pharmacokinetic analysis. One subject was withdrawn from the study on medical grounds (thrombophlebitis superficial) in period two. Another subject discontinued from the study on his own accord in period two.

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of metformin hydrochloride (1000 mg) under fed conditions.

Treatment N=38	**AUC_{0-t}** (ng.h/ml)	**$AUC_{0-\infty}$** (ng.h/ml)	**C_{max}** (ng/ml)	**t_{max}** (h)
Test	16156 ± 2775	16230 ± 2774	1736 ± 455	4.5 (1.3-7.0)
Reference	15602 ± 2756	15698 ± 2749	1695 ± 327	5.3 (3.0-7.0)
***Ratio (90% CI)**	1.036 (1.0080-1.0652)	--	1.035 (0.9980-1.0744)	--
CV (%)	9.5	--	9.5	--

$AUC_{0-\infty}$ 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
CV coefficient of variation
CI confidence interval

**ln-transformed values*

Table 4. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of sitagliptin hydrochloride (50 mg) under fed conditions.

Treatment N=38	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)
Test	2032 ± 316	2068 ± 312	156 ± 33	4.0 (2.3-8.0)
Reference	1979 ± 299	2021 ± 297	155 ± 35	4.5 (1.3-8.0)
***Ratio (90% CI)**	1.026 (1.0069-1.0462)	--	1.013 (0.9694-1.0583)	--
CV (%)	11.4	--	11.4	--

$AUC_{0-\infty}$ 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
CV coefficient of variation
CI confidence interval

**ln-transformed values*

Conclusion on bioequivalence studies:
The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence studies Fordiab is considered bioequivalent with Janumet.

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 Fordiab.

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 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

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 language used for the purpose of user testing the PL was English. The test consisted of a pilot test with two participants, followed by two rounds with ten 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

Fordiab 50 mg/850 mg & 50 mg/1000 mg film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Janumet. 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 concerned member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Fordiab with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 15 September 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