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Public Assessment Report

Name of the Product:

Juzina
100 mg
film-coated tablets

(sitagliptin hydrochloride monohydrate)

Procedure number: HU/H/0683/001/DC

Marketing authorisation holder: Gedeon Richter Plc.

Date: 17. 05. 2021.

CONTENT

LAY SUMMARY

After careful assessment of its quality and therapeutic benefit/risk ratio, the member states have granted the marketing authorisation of the Juzina 100 mg film-coated tablets. The holder of the marketing authorisation is Gedeon Richter Plc.

The active substance is sitagliptin hydrochloride monohydrate.

- Juzina 100 mg film-coated tablets: each film-coated tablet contains sitagliptin hydrochloride monohydrate, equivalent to 100 mg sitagliptin.

The other ingredients are:

– tablet core: microcrystalline cellulose, calcium hydrogen phosphate, croscarmellose sodium, sodium stearyl fumarate, magnesium stearate

– film-coating: polyvinyl alcohol (E1203), titanium dioxide (E171), macrogol 4000 / PEG (E1521), talc (E553b), iron oxide yellow (E172)

The appearance of the tablets is:

– The 100 mg film-coated tablets are round, biconvex, yellow film-coated tablet engraved with “AD3” on one side, breaking line on the other side (diameter approximately: 10.5 mm). The tablet can be divided into equal doses.

The film-coated tablets are available in packs in blisters.

Juzina contains the active substance sitagliptin which is a member of a class of medicines called DPP-4 inhibitors (dipeptidyl peptidase-4 inhibitors) that lowers blood sugar levels in adult patients with type 2 diabetes mellitus.

This medicine helps to increase the levels of insulin produced after a meal and decreases the amount of sugar made by the body.

The doctor has prescribed this medicine to help lower the blood sugar, which is too high because of type 2 diabetes. This medicine can be used alone or in combination with certain other medicines (insulin, metformin, sulphonylureas, or glitazones) that lower blood sugar, which patients may already be taking for their diabetes together with a food and exercise plan.

What is type 2 diabetes?
Type 2 diabetes is a condition in which the body does not make enough insulin, and the insulin that the body produces does not work as well as it should. The body can also make too much sugar. When this happens, sugar (glucose) builds up in the blood. This can lead to serious medical problems like heart disease, kidney disease, blindness, and amputation.

What patients need to know before using Juzina

Patients must not take Juzina if they

- are allergic to sitagliptin or any of the other ingredients of this medicine.

Warnings and precautions

Cases of inflammation of the pancreas (pancreatitis) have been reported in patients receiving Juzina.

In case of encountering blistering of the skin it may be a sign for a condition called bullous pemphigoid. The doctor may ask patients to stop Juzina.

Patients must talk to their doctor if they have or have had:
- a disease of the pancreas (such as pancreatitis);
- gallstones, alcohol dependence or very high levels of triglycerides (a form of fat) in the blood. These medical conditions can increase the chance of getting pancreatitis;
- type 1 diabetes;
- diabetic ketoacidosis (a complication of diabetes with high blood sugar, rapid weight loss, nausea or vomiting);
- any past or present kidney problems;
- an allergic reaction to Juzina.

This medicine is unlikely to cause low blood sugar because it does not work when the blood sugar is low. However, when this medicine is used in combination with a sulphonylurea medicine or with insulin, low blood sugar (hypoglycaemia) can occur. The doctor may reduce the dose of sulphonylurea or insulin medicine.

Children and adolescents

Children and adolescents below 18 years should not use this medicine. It is not effective in children and adolescents between the ages of 10 and 17 years. It is not known if this medicine is safe and effective when used in children younger than 10 years.

Other medicines and Juzina

Those who are taking, have recently taken or might take any other medicines must consult their doctor.
In particular, the doctor must be contacted if patients are taking digoxin (a medicine used to treat irregular heart beat and other heart problems). The level of digoxin in the blood may need to be checked if taking with Juzina.

Pregnancy and breast-feeding

If patients are pregnant or breast-feeding, think they may be pregnant or are planning to have a baby, doctor or pharmacist should be asked for advice before taking this medicine.
This medicine should not be taken during pregnancy.

It is not known if this medicine passes into breast milk. Patients should not take this medicine if they are breast-feeding or plan to breast-feed.

Driving and using machines

This medicine has no or negligible influence on the ability to drive and use machines. However, dizziness and drowsiness have been reported, which may affect the ability to drive or use machines.

Taking this medicine in combination with medicines called sulphonylureas or with insulin can cause hypoglycaemia, which may affect the ability to drive and use machines or work without safe foothold.

Juzina contains sodium

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

How to use Juzina

This medicine must always be taken exactly as the doctor or pharmacist has told patients. If patients are not sure the doctor or pharmacist should be checked with.

The usual recommended dose is:
- one 100 mg film-coated tablet;
- once a day;
- by mouth.

In case of having kidney problems, the doctor may prescribe lower doses (such as 25 mg or 50 mg). The 50 mg dose can be obtained by breaking the 100 mg Juzina tablet into two halves. Dose of 25 mg Juzina is not available, therefore it is not suitable for patients with severe kidney problems. For these patients, other medicinal products containing sitagliptin 25 mg should be used.

This medicine can be taken with or without food and drink.

The doctor may prescribe this medicine alone or with certain other medicines that lower blood sugar.

Diet and exercise can help the body use its blood sugar better. It is important to stay on the diet and exercise recommended by the doctor while taking Juzina.

What to do if more Juzina was taken that it should have been?

In the event of taking more Juzina than it is allowed, it is necessary to contact the doctor immediately.

What to do if taking Juzina was forgotten?

In the event of missing a dose, it sould be taken as soon as patients remember. If they do not remember until it is time for their next dose, they need to skip the missed dose and go back to their regular schedule. No double dose to make up for a forgotten dose can be taken.

May patients stop taking Juzina?

This medicine should be taken as long as the doctor prescribes it so it is necessary to continue to take it which helps control the blood sugar. Without talking to the doctor taking this medicine cannot be stopped.

If there are any further questions on the use of this medicine, the doctor or pharmacist should be asked.

Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

In case of noticing any of the following serious side effects, taking Juzina should be stopped and the doctor sould be contacted immediately:
- Severe and persistent pain in the abdomen (stomach area) which might reach through to the back with or without nausea and vomiting, as these could be signs of an inflamed pancreas (pancreatitis).

In the event of having a serious allergic reaction (frequency not known), including rash, hives, blisters on the skin/peeling skin and swelling of the face, lips, tongue, and throat that may cause difficulty in breathing or swallowing, taking this medicine should be stopped and doctor should be called right away. The doctor may prescribe a medicine to treat the allergic reaction and a different medicine for diabetes.

Some patients have experienced the following side effects after adding sitagliptin to metformin:

Common (may affect up to 1 in 10 people): low blood sugar, nausea, flatulence, vomiting.

Uncommon (may affect up to 1 in 100 people): stomach ache, diarrhoea, constipation, drowsiness.

Some patients have experienced different types of stomach discomfort when starting the combination of sitagliptin and metformin together (frequency is common).

Some patients have experienced the following side effects while taking sitagliptin in combination with a sulphonylurea and metformin:

Very common (may affect more than 1 in 10 people): low blood sugar.

Common: constipation.

Some patients have experienced the following side effects while taking sitagliptin and pioglitazone:

Common: flatulence, swelling of the hands or legs.

Some patients have experienced the following side effects while taking sitagliptin in combination with pioglitazone and metformin:

Common: swelling of the hands or legs.

Some patients have experienced the following side effects while taking sitagliptin in combination with insulin (with or without metformin):

Common: flu.

Uncommon: dry mouth.

Some patients have experienced the following side effects while taking sitagliptin alone in clinical studies, or during post-approval use alone and/or with other diabetes medicines:

Common: low blood sugar, headache, upper respiratory infection, stuffy or runny nose and sore throat, osteoarthritis, arm or leg pain.

Uncommon: dizziness, constipation, itching.

Rare: reduced number of platelets.

Frequency not known: kidney problems (sometimes requiring dialysis), vomiting, joint pain, muscle pain, back pain, interstitial lung disease, bullous pemphigoid (a type of skin blister).

Children and adolescents
In children and adolescents with type 2 diabetes mellitus aged 10 to17 years, the profile of adverse reactions was comparable to that observed in adults.

How to store Juzina

This medicine does not require any special storage conditions. It should be kept out of the sight and reach of children.

SCIENTIFIC DISCUSSION

This module reflects the scientific discussion for the approval of Juzina 100 mg film-coated tablets. The procedure was finalised at 10 March 2021. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

In accordance to the Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use, an application has been submitted to the reference and competent authorities of the Member State concerned.

This Decentralised Procedure application (Reference member state, RMS: Hungary, concerned member state, CMS: Bulgaria, Czechia, Estonia, Latvia, Poland, Romania, Slovakia) concerned the generic version of sitagliptin hydrochloride monohydrate equivalent to 100 mg sitagliptin.

The application has been filed pursuant to Article 10(1) of Directive 2001/83/EC (generic application) and therefore contained no new clinical or preclinical data, other than supporting literature where necessary. The Applicant has adequately demonstrated bioequivalence between the product and reference product.

The reference product is Januvia 100 mg film-coated tablets by Merck Sharp and Dohme B.V. approved in 20 March 2007 within the European Economic Area.

Based on the review of the quality, safety and efficacy data, the Member States have granted marketing authorisations for Juzina 100 mg film-coated tablets from Gedeon Richter Plc.

For adult patients with type 2 diabetes mellitus, Juzina is indicated 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. a 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.

Juzina is 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 Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

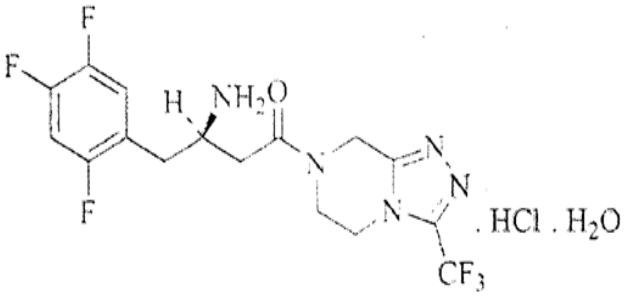
The chemical-pharmaceutical assessment report concerns the application of Juzina 100 mg film-coated tablets via a decentralized procedure according to Article 10(1) of Directive 2001/83/EC (i.e. a generic application).

Reference products are Januvia 100 mg film-coated tablets (containing 100 mg of sitagliptine as active ingredient, in the form of sitagliptin hydrochloride monohydrate) which were the original products of Merck Sharp and Dohme B.V.

II.2 Drug substance – sitagliptin hydrochloride monohydrate

Data on the quality and manufacture of the active substance were provided in the applicant's submission using the Active Substance Master File (ASMF) procedure.

INN name: sitagliptin
Chemical name: 7-[(3R)-3-amino-1-oxo-4-(2,4,5-trifluorophenyl) butyl] -5 ,6, 7 ,8-tetrahydro-3-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyrazine hydrochloride monohydrate
Structure:



The active substance is white to off-white powder, freely soluble in water, slightly soluble in ethanol. It shows polymorphism, the manufacturer consistently produces the correct isomer and the same polymorphic form.

The ASMF holder presented complete details of the manufacturing process. Description of the manufacturing process of the active pharmaceutical ingredient (API) is adequate.

Evidence of the structure has been confirmed by IR, UV, NMR (^{1}H, ^{13}C and DEPT-135), mass spectrometry and elemental analysis. The impurity profile of the API contains detailed information about genotoxic impurities, residual solvents, organic impurities in-organic impurities and elemental impurities.

Sitagliptin hydrochloride monohydrate is not official in the Ph. Eur., only its phosphate salt is described in the Ph. Eur. Therefore, an in-house specification has been set for the active substance, which includes the following tests: appearance, solubility, identification by IR, by enantiomeric HPLC and by chlorides, polymorphic form, water content, sulphated ash, chloride content by potentiometry, related substances by HPLC, enantiomeric purity by HPLC, assay by HPLC, residual solvents by GC and particle size.

The presented specification is in accordance with the Ph. Eur. general monograph on *Substances for Pharmaceutical Use* and the ICH Q6A guideline. The specifications reflect all relevant quality attributes of the active substance and were found to be adequate to control the quality of the drug substance. The limits set are properly justified.

Testing methods not described in detail in the Pharmacopoeia are adequately drawn up and sufficiently validated. Reference materials used for the control of the substance are adequately characterised.
The substance complies with the requirements of the EMA guideline on genotoxic impurities.

Batch analysis data justify the limits, indicate the good performance of testing methods and demonstrate the batch to batch consistency of the production.

Stability studies have been performed with the drug substance. According to the presented stability data, the proposed re-test period is acceptable.

Good Manufacturing Practice (GMP) compliance of the API manufacture is demonstrated by the applicant.

II.3 Medicinal product

The aim was to develop film-coated tablets containing sitagliptin (in the form of sitagliptin hydrochloride monohydrate) as drug substance in 100 mg dose, bioequivalent and pharmaceutically equivalent to the reference medicinal product Januvia 100 mg film-coated tablets, the branded original products of MSD.
A satisfactory package of data on development pharmaceutics has been presented. Brief discussion on reasons for inclusion and quantity of excipients has been provided.
As regards dissolution and impurity profile the product is shown to be similar to the reference product.

The compositions and the pharmaceutical tests evaluated during development of the final formulation are included in the documentation. As a result of development studies a product with the following appearance, composition and packaging was obtained.

Appearance: round-shaped, biconvex yellow film-coated tablets, engraved with “AD3” on one side and a breaking line on the other side. The tablets can be divided into equal doses.
The excipients used in the core are microcrystalline cellulose, calcium hydrogen phosphate, croscarmellose sodium, sodium stearyl fumarate and magnesium stearate. Excipients of the

coating are partially hydrolysed polyvinyl alcohol, titanium dioxide, macrogol 4000, talc, and yellow iron oxide. All excipients used comply with their respective European Pharmacopoeia monograph or EU regulation. Compliance of the product with the general monograph of the European Pharmacopoeia on the Products with the risk of TSE has been demonstrated by the applicant.

A description and flow chart of the manufacturing method has been provided. Appropriate in-process controls are included in the manufacturing process. Satisfactory batch formulae were also presented. GMP compliance of the manufacturing site has been demonstrated.

The finished product specification is satisfactory. Acceptance criteria have been justified with respect to conventional pharmaceutical requirements as prescribed in the relevant dosage form monograph of the Ph. Eur. and the ICH Q6A guideline. Appropriate control strategy was selected. The test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and complied with the specification. Certificates of analysis for the batches involved in the bioequivalence study are presented.

The container closure system of the product is white, opaque PVC/PE/PVDC//Al blisters. Specifications and quality certificates for all packaging components are enclosed.

Finished product stability studies have been conducted in accordance with the current guidelines. Based on the results, a shelf-life of 2 years with no special storage conditions is approved. The Summary of Product Characteristics, patient Information Leaflet and label texts are pharmaceutically acceptable.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The product has been shown to meet the current regulatory requirements with regards to its quality and content of the active substance as well as dosage-form characteristics until the end of the approved shelf-life consistently. The manufacture and the quality standards applied adequately support the safe use and efficacy of the product.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Pharmacodynamic, pharmacokinetic and toxicological properties of sitagliptin are well known. As sitagliptin is a widely used, well-known active substance, no further studies are required and the Applicant provides none. The non-clinical overview is therefore based on a review of data available in several scientific databases or published in relation to the active ingredient.

III.2 Pharmacology

Sitagliptin is an orally administered dipeptidyl peptidase-4 (DPP-4) inhibitor for the treatment of type 2 diabetes mellitus in monotherapy or in combination with other oral antidiabetics and insulin.

The active substance is a well-known compound. No further information was provided regarding the pharmacology of sitagliptin

III.3 Pharmacokinetics

No new non-clinical pharmacokinetic studies were conducted by the Applicant.

III.4 Toxicology

No new toxicity studies were submitted by the Applicant for the product, which is acceptable for this type of application.

III.5 Ecotoxicology/environmnetal risk assessment (ERA)

Juzina 100 mg film-coated tablets 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.6 Discussion onthe non-clinical aspects

Pharmacodynamics, pharmacokinetics and toxicology of sitagliptin are well-known. As Juzina 100 mg film-coated tablets is a generic product there is no need for further excessive non-clinical studies. The non-clinical part of the application is acceptable.

IV. CLINICAL ASPECTS

IV.1 Introduction

The clinical pharmacology of sitagliptin is well known.

Except for showing bioequivalence, no specific clinical studies have been performed, as the application is submitted in accordance with Article 10(1) of Directive 2001/83/EC as amended.

The application contains an adequate review of published clinical data.

IV.2 Pharmacokinetics

Absorption
Following oral administration of a 100 mg dose to healthy subjects, sitagliptin was rapidly absorbed, with peak plasma concentrations (median T_{max}) occurring 1 to 4 hours post-dose, mean plasma AUC of sitagliptin was 8.52 μM•hr, C_{max} was 950 nM. The absolute bioavailability of sitagliptin is approximately 87%. Since co-administration of a high-fat meal with sitagliptin had no effect on the pharmacokinetics, Juzina may be administered with or without food.

Plasma AUC of sitagliptin increased in a dose-proportional manner. Dose-proportionality was not established for C_{max} and C24hr (C_{max} increased in a greater than dose-proportional manner and C24hr increased in a less than dose-proportional manner).

Distribution
The mean volume of distribution at steady state following a single 100 mg intravenous dose of sitagliptin to healthy subjects is approximately 198 litres. The fraction of sitagliptin reversibly bound to plasma proteins is low (38%).

Biotransformation
Sitagliptin is primarily eliminated unchanged in urine, and metabolism is a minor pathway. Approximately 79% of sitagliptin is excreted unchanged in the urine. Following a [14C]sitagliptin oral dose, approximately 16% of the radioactivity was excreted as metabolites of sitagliptin. Six metabolites were detected at trace levels and are not expected to contribute to the plasma DPP-4 inhibitory activity of sitagliptin. *In vitro* studies indicated that the primary enzyme responsible for the limited metabolism of sitagliptin was CYP3A4, with contribution from CYP2C8.

In vitro data showed that sitagliptin is not an inhibitor of CYP isozymes CYP3A4, 2C8, 2C9, 2D6, 1A2, 2C19 or 2B6, and is not an inducer of CYP3A4 and CYP1A2.

Elimination
Following administration of an oral [^{14}C]sitagliptin dose to healthy subjects, approximately 100% of the administered radioactivity was eliminated in faeces (13%) or urine (87%) within one week of dosing. The apparent terminal t1/2 following a 100 mg oral dose of sitagliptin was

approximately 12.4 hours. Sitagliptin accumulates only minimally with multiple doses. The renal clearance was approximately 350 ml/min.

Elimination of sitagliptin occurs primarily via renal excretion and involves active tubular secretion. Sitagliptin is a substrate for human organic anion transporter-3 (hOAT-3), which may be involved in the renal elimination of sitagliptin. The clinical relevance of hOAT-3 in sitagliptin transport has not been established. Sitagliptin is also a substrate of p-glycoprotein, which may also be involved in mediating the renal elimination of sitagliptin. However, ciclosporin, a p-glycoprotein inhibitor, did not reduce the renal clearance of sitagliptin. Sitagliptin is not a substrate for OCT2 or OAT1 or PEPT1/2 transporters. *In vitro*, sitagliptin did not inhibit OAT3 (IC50=160 μM) or p-glycoprotein (up to 250 μM) mediated transport at therapeutically relevant plasma concentrations. In a clinical study sitagliptin had a small effect on plasma digoxin concentrations indicating that sitagliptin may be a mild inhibitor of p-glycoprotein.

IV.2.1 Bioequivalence studies

To support the application, the Applicant has submitteda bioequivalence study under fasting conditions. The study has been performed with the highest strength of Sitagliptin 100 mg film-coated tablets in accordance with the Guideline on the investigation of bioequivalence (*CPMP/EWP/QWP/1401/98 Rev.1/ Corr. London, 20 January 2010*).
The study was an open-label, randomised, two-treatment, two-period, two-sequence single-dose crossover study conducted in 26 healthy male and female volunteers under fasting conditions, with at least 7-days wash out period used between treatment periods.
The number of subjects included in the bioequivalence study was sufficient. No subject has been withdrawn from the study. Overall, data from twenty-six subjects who completed both study periods were included in the pharmacokinetic and statistical analyses.
The analytical method was validated and is considered to be acceptable. Statistical methods used in statistical evaluation of pharmacokinetic parameters and bioequivalence criteria were well described and in accordance with the Bioequivalence Guideline.

The 90% confidence intervals of the ratios of LSM derived from analyses on the ln-transformed PK parameters of AUC_{0-t} and C_{max} for sitagliptin in plasma were within the predefined protocol limits (80% to 125%) indicating bioequivalence with the reference product.

Based on the presented bioequivalence study the **Sitagliptin 100 mg Film-Coated Tablets** is considered to be bioequivalent with **Januvia® 100 mg film-coated tablets** (by Merck Sharp & Dohme Ltd., UK) in healthy adult volunteers under fasting conditions.

Summary of bioequivalence evaluation:

Pharmacokinetic parameter	Geometric Mean Ratio Test / Reference	Confidence Intervals	CV%
AUC_t	96.91	94.70 - 99.17	4.86
AUC_{inf}	97.50	95.29- 99.76	4.83
C_{max}	89.86	83.33 - 96.91	16.01

Safety results:

No serious adverse events were reported during the conduct of this study. There were 5 adverse events occurred involving 4 subjects. There were 3 AEs associated with 2 two subjects who received Sitagliptin 100 mg Film-Coated Tablets, which consisted of somnolence, rhinorrhoea and erythema. Two AEs from 2 subjects who received Januvia® 100 mg film-coated tablets were: abdominal distension, and headache.

IV.3 Pharmacodynamics

Clinical pharmacology studies to evaluate the pharmacodynamics of Juzina 100 mg film-coated tablets were not performed.

IV.4 Clinical efficacy

No new efficacy data have been submitted and none are required. The Applicant has provided an adequate literature review to describe the efficacy profile of sitagliptin.

IV.5 Clinical safety

With the exception of the data generated during the bioequivalence study, no new safety data were submitted and none were required for this application. No new or unexpected safety issues were raised by the bioequivalence data.

The Applicant has provided an adequate literature review to describe the safety profile of sitagliptin.

IV.6 Pharmacovigilance

IV.6.1 Summary of the Pharmacovigilance System

The Applicant has submitted signed Summary Summaries of two Proposed MAHs' Pharmacovigilance System for Gedeon Richter Plc. (dated on 12 September 2019), which is the proposed MAH in BG, CZ, EE, LV, SK and HU and for Gedeon Richter Romania S.A. (dated on 01 January 2018), which is the proposed MAH in Romania.

Gedeon Richter Polska Sp. z o.o. is the proposed MAH in Poland and a summary for this Company is provided as well (dated on 15 March 2018).

Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module, the Assessor considers the Summaries acceptable.

IV.6.2 Risk Management Plan

The applicant Gedeon Richter Plc. has submitted an updated risk management plan (version 0.2 dated on 26.10.2020), in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterize, prevent or minimize risks relating to Juzina 100 mg film-coated tablets.

Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	#1. Pancreatic cancer
Missing information	#2. Exposure during pregnancy and lactation.

The assessor considers that the safety concerns listed by Gedeon Richter Plc. in the HU/H/0683/001/DC procedure appropriate. The safety concerns are in accordance with the most recent version of the RMP of the reference product Januvia (version 10.0 with DLP of 05/09/2018).

Pharmacovigilance Plan

No special important risks have been identified for sitagliptin, which require additional PhV activities, other than routine PhV, beyond adverse drug reactions reporting and signal detection.

Risk Minimisation Measures

Routine risk minimisation measures (i.e. wording in SmPC, PL and classification as a prescription only medicine) are considered sufficient to manage all of the safety concerns connected to GEDEON RICHTER's product containing sitagliptin.

No additional activities are proposed. For any further information on risk minimisation, please refer to the product information.

IV.6.3 Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for these medicinal products are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

IV.7 Discussion on the clinical aspects

The application concerns a generic product.

The products is indicated for treatment of type 2 diabetes mellitus in adults.

To support the application the Applicant has adequately demonstrated bioequivalence between Sitagliptin 100 mg Film-Coated Tablets and the reference product Januvia® 100 mg film-coated tablets (by Merck Sharp & Dohme Ltd., UK) film-coated tablets.

There is no objection against granting the marketing authorization from a clinical point of view.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

V.1 Summary

The present application concerns Juzina 100 mg film-coated tablets. The applicant and the future holder of authorisation is Gedeon Richter Plc.

The application was submitted according to Article 10(1) of Directive 2001/83/EC (generic application). The originator product was Januvia 100 mg film-coated tablets by Merck Sharp and Dohme B.V. authorised for marketing since 20 March 2007 in the European Union.

For adult patients with type 2 diabetes mellitus, Juzina is indicated 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. a 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.

Juzina is 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.

The submitted documentation is administratively adequate and scientifically sound. The quality of the product is satisfactory. There were no non-clinical or clinical concerns raised. The therapeutic benefit/risk assessment is therefore positive.

Based on the review of the quality, safety and efficacy data, the Member States have granted marketing authorisation for Juzina 100 mg film-coated tablets from Gedeon Richter Plc.

V.2 Classification

Prescription-only medicine.

V.3 Package Leaflet and user consultation

A user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Januvia 25 mg film-coated tablets (MAH: Merck Sharp and Dohme B.V., EMEA/H/C/000722) in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC.

The bridging report submitted by the applicant has been found acceptable.

VI. UPGRADE: STEPS TAKEN AFTER THE INITIAL PROCEDURE WITH AN INFLUENCE ON THE PUBLIC ASSESSMENT REPORT

This module reflects the procedural steps and scientific information after the finalisation of the initial procedure.

Scope	Procedure number	Product information affected	Date of start of the procedure	Date of end of procedure	Approval or non approval	Assessment report attached