CMDh/223/2005
February 2014

Public Assessment Report

Scientific discussion

Maysiglu 25 mg film-coated tablets
Maysiglu 50 mg film-coated tablets
Maysiglu 100 mg film-coated tablets

Sitagliptin Krka 25 mg film-coated tablets
Sitagliptin Krka 50 mg film-coated tablets
Sitagliptin Krka 100 mg film-coated tablets

Sitagavia 25 mg film-coated tablets
Sitagavia 50 mg film-coated tablets
Sitagavia 100 mg film-coated tablets

Sitagliptin TAD 25 mg film-coated tablets
Sitagliptin TAD 50 mg film-coated tablets
Sitagliptin TAD 100 mg film-coated tablets

sitagliptin

SK/H/0207/001-003/DC
SK/H/0211/001-003/DC
SK/H/0212/001-003/DC
SK/H/0213/001-003/DC

Date: 06/2020

This module reflects the scientific discussion for the approval of above stated medical products. The procedures were finalised at 23.12.2019. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisations for:
Maysiglu 25 mg, 50 mg and 100 mg film coated tablets,
Sitagliptin Krka 25 mg, 50 mg and 100 mg film coated tablets,
Sitagavia 25 mg, 50 mg and 100 mg film coated tablets
from **Krka, d.d., Novo mesto, SI**
and
Sitagliptin TAD 25 mg, 50 mg and 100 mg film coated tablets from **TAD Pharma GmbH, DE.**

The product is indicated for:

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. 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.

*Sitagliptin Krka** 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 SmPC.

The marketing authorisations has been granted pursuant to Article10 (1) generic application of Directive 2001/83/EC."

(Name **Sitagliptin Krka is used throughout this report and refers to all above mentioned authorized medical products.)*

II. QUALITY ASPECTS

II.1 Introduction

25 mg film-coated tablets
Pink, round, slightly biconvex, film coated tablets with engraved mark K25 on one side of the tablet (diameter approx. 7 mm, thickness 2.0 – 3.2 mm).

50 mg film-coated tablets
Light orange, round, biconvex, film coated tablets with score line on one side of the tablet. Tablet is engraved with mark K on one side of the score line and with mark 50 on the other side of the score line (diameter approx. 9 mm, thickness 2.8 – 3.8 mm).
The tablet can be divided into equal doses.

100 mg film-coated tablets
Brown orange, round, biconvex, film coated tablets with score line on one side of the tablet. Tablet is engraved with mark K on one side of the score line and with mark 100 on the other side of the score line (diameter approx. 11 mm, thickness 3.3 – 4.5 mm).
The tablet can be divided into equal doses.

II.2 Drug Substance

INN: sitagliptin, Sitagliptin is a synthetic substance. There is no Ph.Eur. monograph for sitagliptin base though there is one for its salt: sitagliptin phosphate monohydrate.

Molecular Formula: $C_{16}H_{15}F_6N_5O$

Appearance: white or almost white powder

Solubility: soluble in anhydrous ethanol (33.3-100 mg/mL), slightly soluble in water and in heptane(1-10 mg/mL), freely soluble in methanol, acetone, *N*,*N*-dimethylformamide, methylene chloride (100-1000 mg/mL) soluble in 0.1 M aq. HCl (33.3-100 mg/mL), very slightly soluble in 0.1 M aq. NaOH (0.1-1 mg/mL), freely soluble in acetate buffer solution pH 4.5 and in phosphate buffer solution (100-1000 mg/mL)

Melting point: 110-120 °C

Isomerism: there is one chiral atom in the molecule (*R*-isomer), enantiomer (*S*-isomer, impurity A) is routinely controlled by the active substance manufacturer (ASM)

Manufacturing: The **ASMF procedure** was used for the active substance sitagliptin

II.3 Medicinal Product

The development of the product is described in sufficient detail.

The finished product is manufactured by granulation and a detailed description of the process has been provided in the dossier. In brief, it involves manufacturing of blend, manufacturing of granulate, manufacturing of compression mixture, tabletting and film coating. Process validation was performed on a batch size of 100,000 tablets of each. Process validation scheme to be applied in the commercial manufacture and at every scale-up has been provided in the dossier.

The proposed specification for the finished product is in line with ICH Q6A, where relevant, and is generally acceptable.

Stability data were provided for three batches of each strength under long-term and accelerated conditions which were packed in OPA/Al/PVC-Al blister as proposed for marketing.

The proposed shelf life of 2 years (24 months) is accepted as well as storage conditions:
Store in the original package in order to protect from moisture.
This medicinal product does not require any special temperature storage conditions.

III. NON-CLINICAL ASPECTS

Pharmacodynamic, pharmacokinetic and toxicological properties of sitagliptin are well known. As sitagliptin is widely used, well-known active substances, the applicant has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate.

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since *Sitagliptin Krka* 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.
Although the Applicant has submitted document to justify the absence of complete ERA for sitagliptin. Justification for the absence of a complete ERA for sitagliptin, based on the generic approach was accepted.

IV. CLINICAL ASPECTS

IV.1 Introduction

Sitagliptin is a member of a class of oral anti-hyperglycaemic agents called dipeptidyl peptidase 4 (DPP-4) inhibitors. The improvement in glycaemic control observed with this medicinal product may be mediated by enhancing the levels of active incretin hormones. Incretin hormones, including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), are released by the intestine throughout the day, and levels are increased in response to a meal. The incretins are part of an endogenous system involved in the physiologic regulation of glucose homeostasis. When blood glucose concentrations are

normal or elevated, GLP-1 and GIP increase insulin synthesis and release from pancreatic beta cells by intracellular signalling pathways involving cyclic AMP.

Pharmacotherapeutic group: Drugs used in diabetes, Blood glucose lowering drugs, excl. insulins, ATC code: A10BH01.

IV.2 Pharmacokinetics

Bioequivalence study

To support the application, the applicant has submitted as report 1 bioequivalence study:
- 17-562 – *A single-dose, comparative bioavailability study of two formulations of sitagliptin 100 mg film-coated tablets under fasting conditions* and requested biowaiver for additional 25 mg and 50 mg strengths.

Considering that the proposed medicinal product is a film-coated tablet with immediate release, and food has no effect on the pharmacokinetics of sitagliptin, one single dose bioequivalence study under fasting conditions is acceptable. As all the criteria for additional strengths biowaiver according to the Guideline on investigation of bioequivalence are met, the results of the bioequivalence study with 100 mg strengths can be extrapolated to the strengths 25 mg and 50 mg.

Biowaiver

Applicant submitted bioequivalence study with *Sitagliptin Krka* 100 mg film-coated tablets and requested biowaiver for additional 25 mg and 50 mg strengths.

In order to fulfil criteria for biowaiver for 25 mg and 50 mg strengths, following criteria have been met:
a) active substance sitagliptin express linear pharmacokinetics over the dose 25 mg – 400 mg,
b) all strengths of sitagliptin are manufactured by the same manufacturing process,
c) the qualitative composition of the different strengths is the same,
d) the composition of the strengths is quantitatively proportional (the core of the tablet is quantitatively proportional, not the coating),
e) the dissolution profiles of all three strengths are comparable

Conclusion on bioequivalence studies:
Based on the submitted bioequivalence study, *Sitagliptin Krka* 100 mg film-coated tablets could be considered bioequivalent with Januvia 100 mg film-coated tablets.

The results of study 17-562 with 100 mg formulation CAN be extrapolated to other strengths 25 mg and 50 mg, according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6.

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 Krka*.

Pharmacovigilance Plan

Routine pharmacovigilance is suggested, and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures

The safety information in the proposed product information is aligned to the reference medicinal product. Routine risk minimisation was suggested, and no additional risk minimisation activities are proposed by the applicant, which was endorsed.

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

V. USER CONSULTATION

The package leaflet 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 PIL was English.

The results show that the package leaflet 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

The benefit risk of this medical product was considered positive. Therefore the RMS and CMSs recommended approval of *Sitagliptin Krka* film coated tablets.