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Public Assessment Report

Scientific discussion

Mapoli 25 mg/ml oral solution

sitagliptin hydrochloride monohydrate

SK/H/0261/001/DC

Date: 05/2022

This module reflects the scientific discussion for the approval of Mapoli 25 mg/ml oral solution. The procedure was finalised at 08.12.2021. 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 authorisation for Mapoli 25 mg/ml, oral solution, from Glenmark Pharmaceuticals s.r.o..

The product is indicated for*:*

For adult patients with type 2 diabetes mellitus, Mapoli 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.

Mapoli 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 authorisation has been granted pursuant to Article 10(1) generic application of Directive 2001/83/EC."

II. QUALITY ASPECTS

II.1 Introduction

Mapoli 25 mg/ml is a slightly opalescent off-white oral solution with forest fruits odour.
Each 1 ml of oral solution contains sitagliptin hydrochloride monohydrate, equivalent to 25 mg sitagliptin.
It is packed in amber (Type III) glass bottle, sealed with child proof and tamper evident cap with plug, with one CE marked (CE 0459) 5-ml oral medication syringe (plastic dosing) with 0.5ml graduation

II.2 2.2 Drug Substance

INN: sitagliptin hydrochloride

Molecular Formula: $C_{16}H_{15}F_6N_5O$ HCl H_2O

Appearance: White to off-white powder

Solubility: Soluble in water, very slightly soluble in anhydrous ethanol and practically insoluble in n-Heptane.

Isomerism: Sitagliptin HCl exhibits isomerism. Two isomers (R and S) are possible. 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 main aim of the development was to develop a new oral pharmaceutical form for sitagliptin as a generic to Januvia film-coated tablets. A single strength of the product was developed whereby the required dose can be adjusted by the administered volume.

The development of the product is described in sufficient detail.

The finished product is manufactured by mixing of all components. A detailed description of the process has been provided in the dossier. In brief, it involves mixing of all components in the mixing vessel, pH adjustment, filtration and filling in the proposed container closure. Process validation was performed on two batches of 150 L and a batch of 25 L of the bulk solution. Process validation scheme to be applied in the commercial manufacture has been provided.

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

Stability data up to 12 months of storage at the long-term conditions (2-8°C) were presented for the product. Accelerated stability data on the product allow extrapolation of shelf life up to 18 months. Therefore, the proposed shelf life of 18 months and storage conditions in the refrigerator (2-8°C) are acceptable

Presented photostability study is acceptable. In-use stability data was described in detail and supports the shelf life of 90 days (3 months) after first opening.

Medical device, i.e. oral syringe (applicator) is supplied in the pack with the product. One 5 ml oral medication syringe with 0.5 ml graduation able to fit with the plug of the cap is concerned. It is a class I medical device with measuring function according to EU Directive 93/42/CEE.

III. NON-CLINICAL ASPECTS

Pharmacodynamic, pharmacokinetic and toxicological properties of sitagliptin are well known. As sitagliptin is widely used, well-known active substance, the applicant has not provided additional studies. The overview based on literature review is appropriate.

III.1 Ecotoxicity/environmental risk assessment (ERA)

The applicant provided calculation of the predicted environmental concentration (PEC) based

on the published literature.
According to the data the overall consumption data of the active ingredient sitagliptin is rather stable or even decreasing.
The $PEC_{surface\ water}$ as calculated by the Applicant is above the requirements as stated in the CHMP Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00). However, the overall consumption of sitagliptin and data from the Phase I (Log Kow) did not show any significant risks. Log Kow was determined experimentally.

IV. CLINICAL ASPECTS

IV.1 Introduction

Mode of action
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 sitagliptin 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 signaling pathways involving cyclic AMP.

Pharmacological classification
Pharmacotherapeutic group: drugs used in diabetes, dipeptidyl peptidase 4 (DPP-4) inhibitors; ATC code: A10BH01.

IV.2 Pharmacokinetics

Bioequivalence study
To support the application, the applicant has submitted one bioequivalence study; with the 25 mg/ ml strength (**study no. ARL/19/191)** with reference product Januvia 100 mg film coated tablets**.** The study was performed under fasting conditions.

Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range)

Pharmacokinetic parameter	Arithmetic Means (±SD)	
	Test Product T	Reference Product R
$AUC_{(0\text{-}inf)}$ (ng*hr/mL)	5640.715±778.029	5492.439±784.342
$AUC_{(0\text{-}t)}$ (ng*hr/mL)	5589.723±777.034	5443.247±785.003
C_{max} (ng /mL)	525.262±91.570	545.828±122.784
t_{max} [1] (hrs)	2.000(1.330-5.000)	2.000(1.000-5.000)

[1] Median (Min, Max)

Pharmacokinetic parameter	Geometric Mean Ratio Test T/Ref R	Confidence Intervals	CV%[1]
$AUC_{(0\text{-}inf)}$	102.8464	100.2343-105.5266	5.0685
$AUC_{(0\text{-}t)}$	102.8441	100.2204-105.5365	5.0914
C_{max}	97.1958	90.2419-104.6857	14.6944

[1] Estimated from the Residual Mean Squares.

The 90% confidence interval of geometric mean ratio of log transformed pharmacokinetic parameters C_{max} and $AUC_{0\text{-}t}$ between test and reference products falls within the range of 80.00 % to 125.00 % for Sitagliptin

Conclusion on bioequivalence studies:
Based on the submitted bioequivalence study Mapoli 25 mg/ml oral solution is considered bioequivalent with Januvia 100 mg film coated tablets.

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 Mapoli 25 mg/ml oral solution.

Pharmacovigilance Plan
Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant.

Risk minimisation measures
Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant.

Summary table of safety concerns as approved in RMP

Summary of safety concerns	
Important identified risks	• None
Important potential risks	• Pancreatic cancer • Overdose due to dosing errors
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 *Mapoli 25 mg/ml oral solution.*