COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Vildagliptine Macleods 50 mg tablets (vildagliptin)

NL/H/5277/001/DC

Date: 14 March 2022

This module reflects the scientific discussion for the approval of Vildagliptine Macleods 50 mg tablets. The procedure was finalised on 27 January 2022. 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
BCS	Biopharmaceutics Classification System
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 Vildagliptine Macleods 50 mg tablets, from Macleods Pharma España, S.L.U.

Vildagliptin is indicated as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus:

- as monotherapy in patients in whom metformin is inappropriate due to contraindications or intolerance.
- in combination with other medicinal products for the treatment of diabetes, including insulin, when these do not provide adequate glycaemic control (see sections 4.4, 4.5 and 5.1 of the SmPC for available data on different combinations).

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 Galvus 50 mg, tablets (NL RVG 73399) which has been registered in the European Economic Area (EEA) by Novartis Europharm limited since 26 September 2007 via the centralised procedure EU/1/07/414.

The concerned member state (CMS) involved in this procedure was Spain.

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

II. QUALITY ASPECTS

II.1 Introduction

Vildagliptine Macleods is a white to off white, round, flat faced bevelled edge, uncoated tablet debossed with 'L 45' on one side and plain on other side.

Each tablet contains 50 mg of vildagliptin

The tablets are packed in Aluminium/Aluminium (PA/Al/PVC/Al) blisters.

The excipients are: lactose, microcrystalline cellulose, sodium starch glycolate (type A) and magnesium stearate

II.2 Drug Substance

The active substance is vildagliptin, an established active substance not described in the European Pharmacopoeia (Ph.Eur.). The active substance is a crystalline powder highly soluble in water. The polymorphic form is consistently manufactured as the stable form A, which is the enantiopure S-isomer.

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

The manufacturing process consists of several chemical reaction steps with isolated and non-isolated intermediates to form eventually the final active substance. No class 1 solvents or heavy metal catalysts are used. The non-micronised form of the drug substance is used. Adequate specifications have been adopted for starting materials, solvents and reagents. The active substance has been adequately characterised.

Quality control of drug substance

The active substance specification by the finished product manufacturer has been established in-house and is identical to that of the drug substance manufacturer, with additional requirements for particle size distribution and bulk density. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for two batches by the finished product manufacturer and three batches by the drug substance supplier.

Stability of drug substance

Stability data on the active substance have been provided for three production scale batches stored at 25°C/60% RH (6 months) and 40°C/75% RH (6 months), in accordance with applicable European guidelines. The batches were stored in double LDPE bags, with silica gel in triple laminated bag in HDPE container. At accelerated conditions, an increase was seen in impurities but the levels remained within the specification limits. No clear changes or trends were seen at long-term conditions.

Based on the results of the stability studies, a retest period could be granted of 12 months when stored in a well closed air tight container at room temperature, and protected from light.

II.3 Medicinal Product

Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately performed in accordance with the relevant European guidelines. The choice of excipients is justified and their functions are explained. The main development studies performed were the characterisation of the reference product, dissolution method development, formulation optimisation studies and performance of comparative *in vitro* dissolution studies.

The choices of the packaging and manufacturing process are justified. No bioequivalence study was performed to support the application, but a Biopharmaceutics Classification System (BCS)-based biowaiver was requested, which will be discussed in section IV on clinical aspects. Comparative *in vitro* dissolution testing at three pHs has been successfully studied in support of the BCS-based biowaiver. The batches used in the comparison are representative batches that were manufactured according to the finalised formulation and manufacturing process at a representative scale.

Manufacturing process

The main steps of the manufacturing process are dry mixing and lubrication, dry granulation, second lubrication, tablet compression and packaging. The manufacturing process has been adequately validated according to relevant European guidelines. The product is manufactured using conventional manufacturing techniques. Process validation for full scaled batches will be performed post-authorisation.

Control of excipients

The excipients comply and are tested in accordance with their Ph.Eur. monographs with control of additional functionality related characteristics. 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, identification, hardness, friability, water content, disintegration time, uniformity of dosage units, dissolution, related substances, assay and microbial quality. Except for water content and related substances, the release and shelf-life requirements are identical. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for the analytical methods have been provided.

Batch analytical data three pilot scaled from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product has been provided on three production scaled batches stored at 25°C/60% RH (18 months) and 40°C/75% RH (six months). The conditions used in the stability studies are according to the ICH stability guideline. The stability data showed an

increase in impurities at both storage conditions, most pronounced at the accelerated storage conditions. No clear trends or changes were observed in any of the other parameters tested at both storage conditions. All parameters remained within the specification limits. Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light.

On basis of the data submitted, a shelf life was granted of two years, without any special storage requirements.

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 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 Vildagliptine Macleods 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 Vildagliptine Macleods 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 Galvus 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

Vildagliptin is a well-known active substance with 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. The MAH requested a BCS-based biowaiver, which is discussed below.

IV.2 Pharmacokinetics

Biowaiver

As per the *Guideline on the Investigation of Bioequivalence* (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**), *in vivo* bioequivalence studies may be exempted if an assumption of equivalence in *in vivo* performance can be justified by satisfactory *in vitro* data. Applying for a BCS-based biowaiver is restricted to highly soluble drug substances with known human absorption and considered not to have a narrow therapeutic index. The concept is applicable to immediate release, solid pharmaceutical products for oral administration and systemic action having the same pharmaceutical form.

The following requirements for a BCS-based biowaiver have been met:

- The proposed drug product contains the same active drug substance and similar inactive ingredients in line with the reference product Galvus.
- The drug substance vildagliptin can be classified as BCS class I (high soluble, high permeable), based on available data of saturation solubility study and absorption.
- *In vitro* dissolution similarity of the test and reference product has been demonstrated.
- None of the excipients present in the formulation of the test product is suspected for impact on bioavailability.
- Vildagliptin is not considered as narrow therapeutic index drug.

Based on the above mentioned information, a BCS-based biowaiver for the current marketing authorisation application of Vildagliptine Macleods has been granted.

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 Vildagliptine Macleods.

Table 1. Summary table of safety concerns as approved in RMP

Important identified risks	• Drug-induced liver injury • Acute pancreatitis
Important potential risks	• Muscle events/ myopathy/rhabdomyolysis, in particular with current statin use (events of myalgia excluded)
Missing information	• None

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 Galvus. No new clinical studies were conducted. Equivalence between the proposed product and innovator product in *in vivo* performance could be justified by satisfactory *in vitro* data, therefore, a BCS-based biowaiver has been granted. 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 four 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

Vildagliptine Macleods 50 mg tablets has a proven chemical-pharmaceutical quality and is a generic form of Galvus 50 mg, tablets. Galvus 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 Vildagliptine Macleods with the reference product, and have therefore granted a marketing authorisation. The decentralized procedure was finalised with a positive outcome on 27 January 2022.

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