COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Vildagliptine Intas 50 mg tablets

(vildagliptin)

NL/H/4860/001/DC

Date: 11 August 2020

This module reflects the scientific discussion for the approval of Vildagliptine Intas 50 mg tablets. The procedure was finalised at 4 June 2020. 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 Vildagliptine Intas 50 mg tablets, from Intas Third Party Sales 2005, S.L.

The product is indicated in the treatment of type 2 diabetes mellitus in adults:

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, in patients with insufficient glycaemic control despite maximal tolerated dose of monotherapy with metformin,
- a sulphonylurea, in patients with insufficient glycaemic control despite maximal tolerated dose of a sulphonylurea and for whom metformin is inappropriate due to contraindications or intolerance,
- a thiazolidinedione, in patients with insufficient glycaemic control and for whom the use of a thiazolidinedione is appropriate.

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.

This product is also indicated for use in combination with insulin (with or without metformin) when diet and exercise plus a stable dose of insulin 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 Galvus 50 mg, tablets, which has been registered in the EEA by Novartis Europharm Limited since 26 September 2007 through a centralised procedure (EU/1/07/414).

The concerned member states (CMS) involved in this procedure were France, Greece, Italy and Spain.

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

II. QUALITY ASPECTS

II.1 Introduction

Vildagliptine Intas is a white to off-white, round, flat, bevelled edge, uncoated tablet, debossed with "GF1" on one side and plain on the other side. Each tablet contains 50 mg vildagliptin.

The tablets are packed in Aluminium/Aluminium blisters.

The excipients are: lactose (anhydrous), microcrystalline cellulose (E460), sodium starch glycolate (type A) and magnesium stearate (E 470b).

II.2 Drug Substance

The active substance is vildagliptin, an established active substance however not described in the European Pharmacopoeia (Ph.Eur.). The substance is a white to off-white powder and freely soluble in water, methanol, methylene dichloride and practically insoluble in ethyl acetate. Vildagliptin has one asymmetric carbon atom in the structure and it exhibits isomerism. Polymorphic form A is produced.

The Active Substance Master File (ASMF) procedure is used for the active substance from two ASMF holders. 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 is described in sufficient detail. The active substance has been adequately characterised and acceptable specifications have been adopted for the starting materials, solvents and reagents.

Quality control of drug substance

The active substance specification is considered adequate to control the quality. The substance is not described in the Ph. Eur. The in-house specification is set in line with the specifications of the ASMF holder. Batch analytical data demonstrating compliance with this specification have been provided for six batches.

Stability of drug substance

Stability studies have been performed with the drug substance by the active substance manufacturer. No significant changes in any parameters were observed. The proposed retest period of 3 years is justified.

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 drug product Vildagliptin Intas 50 mg is a generic medicinal product with an immediate release solid dosage form for oral administration which has been developed to be similar to the reference product Galvus. The request and justification for BCS class I biowaiver are acceptable from chemical pharmaceutical perspective.

Manufacturing process

The manufacturing process has been validated according to relevant European guidelines. Process validation data on the product have been presented for three batches in accordance with the relevant European guidelines.

Control of excipients

The excipients used are commonly used for this type of drug product and comply with Ph. Eur. Functionality related characteristics of excipients indicated in the respective Ph.Eur. monographs are defined in the excipient specifications and tested. 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, average weight of tablets, identification, resistance to crushing, water content, dissolution, uniformity of dosage units, related substances, assay and microbial examination. 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 from three batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for three batches stored at 25°C/65% RH (24 months) and 40°C/75% RH (6 months). All results comply with and remain within the proposed specifications. The batches were stored in accordance with applicable European guidelines. The results of a photostability study showed that the product is not sensitive to light. On basis of the data submitted, a shelf life was granted of 24 months. This medicinal product does not require any special storage conditions.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

Lactose is the only material of animal or human origin included in the drug product. An acceptable BSE statement from the manufacturer has been provided.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Vildagliptine Intas 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 Intas 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

Vildagliptine 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.

IV.2 Pharmacokinetics

Biowaiver

No clinical trials (bioequivalence study) have been carried on the product as a BCS based bio-waiver is requested for Vildagliptin 50 mg tablets as per Appendix III of guideline on the investigation of bioequivalence (Doc.Ref.:CPMP/EWP/QWP/1401/98 Rev.1/Corr **).

The BCS-based bio-waiver has been granted based on the following criteria:

- the drug substance (vildagliptin) has been proven to exhibit high solubility and complete absorption (BCS class I);
- similarly rapid (85 % within 30 min) in vitro dissolution characteristics of the test and reference product have been demonstrated considering specific requirements;
- excipients that might affect bioavailability are qualitatively the same in both test and reference product.

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 Intas.

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

Important identified risks	- Transaminase elevation and Drug-induced liver injury (DILI) - Angioedema - Acute pancreatitis - Skin lesions - Hypoglycaemia
Important potential risks	- Serious Infections - Cardiac Events in CHF (NYHA Functional Class III) patients - Muscle events/ myopathy/ rhabdomyolysis, particular with current statin use - Neuropsychiatric events - Breast cancer - Pancreatic cancer
Missing information	- Gender incidence / frequency differences - Patients with severe hepatic impairment - Patients with compromised cardiac function (NYHA Functional Class IV) - Pregnancy

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. 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

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Galvus 50 mg, tablets (for content) and Zoledronic Acid 4 mg/5 ml (for design and layout). The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Vildagliptine Intas 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 Intas with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 4 June 2020.

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