COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Vildagliptine Denk 50 mg tablets

(vildagliptin)

NL/H/4062/001/DC

Date: 6 December 2018

This module reflects the scientific discussion for the approval of Vildagliptine Denk 50 mg tablets. The procedure was finalised at 26 July 2018. 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 Denk 50 mg tablets, from DENK PHARMA GmbH & Co. KG.

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 Germany and Malta.

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

II. QUALITY ASPECTS

II.1 Introduction

Vildagliptine Denk is a white to off white round flat tablet and contains 50 mg vildagliptin.

The tablets are packed in Aluminium/Aluminium blisters.

The excipients are: lactose (anhydrous), cellulose microcrystalline (E460), (maize) starch (partially) pregelatinised 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 crystalline powder and is highly soluble. Vildagliptin does not show polymorphism and both manufacturers have demonstrated consisted manufacture of this form.

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 described manufacturing process from both manufacturers involves three stages. The active substance has been adequately characterised and acceptable specifications have been adopted for the starting materials, solvents and reagents. No class 1 solvents or heavy metal catalysts are used in the synthesis.

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 holders. Batch analytical data demonstrating compliance with this specification have been provided for three batches from each supplier.

Stability of drug substance

Manufacturer one - Stability data on the active substance have been provided for three batches stored at 30°C/65% RH (36 months) and 40°C/75% RH (6 months). No clear up- or downward trends are observed during the stability studies, up to 6 months accelerated

conditions and up to 36 months long term conditions, therefore, the proposed retest period of 48 months is acceptable, based on the provided stability data.

Manufacturer two - Stability data on the active substance have been provided for six full scale batches stored at 25°C/65% RH (3 batches 36 months and 3 batches 24 months) and 40°C/75% RH (6 months). No clear up- or downward trends are observed during the stability studies, up to 6 months accelerated conditions and up to 36 months long term conditions, therefore, the proposed retest period of 48 months is acceptable, based on the provided stability data.

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 development is based on the reference product Galvus, however different excipients are used.
One bioequivalence study has been carried out between the test product Vildagliptine Denk 50 mg tablets and the reference product Galvus 50 mg, tablets. The biobatch used is acceptable in view of batch size and potency. The data show that more than 85% is dissolved in 15 minutes, indicating comparable dissolution profile with the reference product.

Manufacturing process

The drug product is prepared by a standard manufacturing process and comprises dry granulation (consisting of premixing, dry granulation, sizing and second mixing), final mixing, lubrication, and compression. The manufacturing process is described in sufficient detail. A summary of the in-process information during manufacture is provided to confirm that the proposed vildagliptin 50 mg tablets can be manufactured according to the proposals in the dossier. All parameters and attributes were found to be within acceptable ranges and according to acceptance criteria. 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 appearance, diameter, thickness, identification, water content, average weight, dissolution, uniformity of dosage units by mass variation, assay, related substances, and microbiological quality. 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 36 months. This medicinal product does not require any special storage conditions.

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

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

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Vildagliptine Denk 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 Denk 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.

For this generic application, the MAH has submitted a bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Vildagliptine Denk 50 mg tablets (DENK PHARMA GmbH & Co. KG, Germany) is compared with the pharmacokinetic profile of the reference product Galvus 50 mg, tablets (Novartis Europharm Ltd, United Kingdom).

The choice of the reference product in the bioequivalence study has been justified. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Bioequivalence study

Design

An open-label, balanced, single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 28 healthy male subjects, aged 18-45 years. Each subject received a single dose (50 mg) of one of the 2 vildagliptin formulations. The tablet was orally administered with approximately 240 ml of 20% glucose solution after fasting. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected at pre-dose and at 0.25, 0.50, 0.75, 1.00, 1.25, 1.50, 1.75, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16 and 24 after administration of the products.

The design of the study is acceptable.

Vildagliptin may be taken without reference to food intake. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

Analytical/statistical methods

The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
A total of 28 subjects completed the study and were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of vildagliptin under fasted conditions.

Treatment N=28	**AUC_{0-t}** (ng.h/ml)	**$AUC_{0-\infty}$** (ng.h/ml)	**C_{max}** (ng/ml)	**t_{max}** (h)
Test	1285.6 ± 206.2	1310.3 ± 207.9	313.5 ± 75.6	1.75 (1.0 – 5.0)
Reference	1301.2 ± 216.7	1326.2 ± 217.5	337.2 ± 123.9	1.75 (0.75 – 4.0)
***Ratio (90% CI)**	0.98 (0.97 – 1.00)	--	0.96 (0.89 – 1.03)	--

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration

**ln-transformed values*

Conclusion on bioequivalence study
The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Vildagliptine Denk 50 mg tablets is considered bioequivalent with Galvus 50 mg, tablets.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

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 Denk.

Table 2. 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

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 test consisted of: a pilot test with 2 participants, followed by two rounds with 10 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 Denk 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 Denk with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 26 July 2018.

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