Summary Public Assessment Report

Generics

Vildagliptin Galenicum 50mg tablets

(Vildagliptin)

MT/H/0286/001/DC

Date: 26/06/2019

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Vilgagliptin, tablets, 50mg

This is a summary of the public assessment report (PAR) for Vildagliptin Galenicum. It explains how Vildagliptin Galenicum was assessed and its authorisation recommended as well as its conditions of use. It is not intended to provide practical advice on how to use Vildagliptin Galenicum.

For practical information about using Vildagliptin Galenicum, patients should read the package leaflet or contact their doctor or pharmacist.

What is Vildagliptin Galenicum and what is it used for?

Vildagliptin Galenicum is a 'generic medicine'. This means that Vildagliptin Galenicum is similar to a 'reference medicine' already authorised in the European Union (EU) called Galvus 50mg tablets by Novartis Europharm.

Vildagliptin is used to treat adult patients with type 2 diabetes. It is used when diabetes cannot be controlled by diet and exercise alone. It helps to control the level of sugar in the blood. Vildagliptin Galenicum is prescribed either alone or together with certain other antidiabetic medicines, if these alone have not proved sufficiently effective to control diabetes.

Type 2 diabetes develops if the body does not make enough insulin or if the insulin that the body makes does not work as well as it should. It can also develop if the body produces too much glucagon.

Insulin is a substance which helps to lower the level of sugar in the blood, especially after meals. Glucagon is a substance with triggers the production of sugar by the liver, causing the blood sugar level to rise. The pancreas makes both of these substances.

How does Vildagliptin Galenicum work?

The active substance of Vildagliptin Galenicum, vildagliptin, belongs to a group of medicines called "oral antidiabetics". Vildagliptin Galenicum works by making the pancreas produce more insulin and less glucagon. This helps to control the blood sugar level. This medicine has been shown to reduce blood sugar, which may help to prevent complications from diabetes.

How is Vildagliptin Galenicum used?

The pharmaceutical form of Vildagliptin Galenicum is a tablet and the route of administration is by mouth.

Please read section 3 of the PL for detailed information on dosing recommendations, the route of administration, and the duration of treatment.

The amount of Vildagliptin Galenicum people have to take varies depending on their condition. A doctor will tell a patiene exactly how many tablets of Vildagliptin Galenicum are required. The maximum daily dose is 100 mg.

The usual dose of Vildagliptin Galenicum is either:

- 50mg daily taken as one dose in the morning if patients are taking Vildagliptin Galenicum with another medicine called sulphonylurea.

- 100mg daily taken as 50mg in the morning and 50mg in the evening if patients are taking Vildagliptin Galenicum alone, with another medicine called metformin or glitazone, with a combination of metformin and sulphonylurea, or with insulin.

- 50mg daily in the morning if patients have moderate or severe kidney disease or if you are on dialysis.

Vildagliptin Galenicum must be taken every day for as long as it is prescribed. The patient may have to take this treatment over a long period of time.

The doctor will regularly monitor the condition to check that the treatment is having the desired effect.

The medicine can only be obtained with a prescription.

What benefits of Vildagliptin Galenicum have been shown in studies?

Because Vildagliptin Galenicum is a generic medicine, studies in patients have been limited to tests to determine that it is bioequivalent to the reference medicine, Galvus 50mg tablets. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the possible side effects of Vildagliptin Galenicum?

Because Vildagliptin Galenicum is a generic medicine and is bioequivalent to the reference medicine, its benefits and possible side effects are taken as being the same as the reference medicine.

Why is Vildagliptin Galenicum approved?

It was concluded that, in accordance with EU requirements, Vildagliptin Galenicum has been shown to have comparable quality and to be bioequivalent to Galvus 50mg tablets. Therefore, the Malta Medicines Authority decided that, as for reference medicine called Galvus 50mg tablets, the benefits are greater than its risk and recommended that it can be approved for use.

What measures are being taken to ensure the safe and effective use of Vildagliptin Galenicum?

A risk management plan has been developed to ensure that Vildagliptin Galenicum is used as safely as possible. Based on this plan, safety information has been included in the summary of product characteristics and the package leaflet for Vildagliptin Galenicum, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously as well.

Other information about Vildagliptin Galenicum

The marketing authorisation for Vildagliptin Galenicum was granted on the 23 April 2019.

The full PAR for Vildagliptin Galenicum can be found on the website http://medicinesauthority.gov.mt For more information about treatment with Vildagliptin Galenicum, read the package leaflet http://medicinesauthority.gov.mt/medicine-details?id=99808 or contact your doctor or pharmacist.

This summary was last updated in 06-2019.

Public Assessment Report

Scientific discussion

Vildagliptin Galenicum 50mg tablets

(Vildagliptin)

MT/H/0286/001/DC

Date: 26/06/2019

This module reflects the scientific discussion for the approval of Vildagliptin Galenicum 50mg tablets. The procedure was finalised at Day 210. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Malta Medicines Authority granted a Marketing Authorisation for Vildagliptin Galenicum 50mg tablets on the 23rd April 2019. 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 thiazolidinendione 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 adequately glycaemic control.

Vildagliptin 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 application was submitted under Article 10.1 of Directive 2001/83/EC as a so called "generic application". The reference product used for Malta is that registered in the European Community.

The originator product is Galvus 50mg tablets by Novartis Europharm registered in the European Community since September 2007. (EU/1/07/414/001-10,118).

II. QUALITY ASPECTS

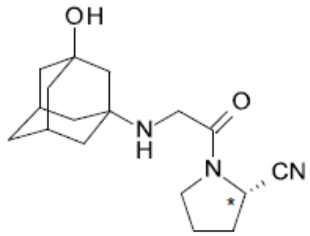
II.1 Introduction

The product is presented as tablets containing 50mg vildagliptin as active substance. The excipients present are lactose anhydrous, sodium stearyl fumarate, microcrystalline cellulose (E460), croscarmellose sodium (E468).

The finished product is packaged in Aluminium/Aluminium blisters and are available in packs containing 7, 14, 28, 30, 56, 60, 90, 112, 180 or 336 tablets and in multipacks containing 336 (3 packs of 112) tablets.

Packaging material specifications and analytical methods applied on all packaging material, have been provided together with typical CoAs along with declarations of compliance from the respective supplier with relevant EU legislation and Ph Eur chapters, as applicable, for all the packaging materials.

II.2 Drug Substance



* Chiral atom

International non-proprietary name (INN):	Vildagliptin
United States Adopted Name (USAN):	Vildagliptin
Chemical names:	(S)-1-[2-(3-Hydroxyadamantan-1-ylamino)acetyl]-pyrrolidine-2-carbonitrile
CAS registry number:	[274901-16-5]
Laboratory code:	N/A
Molecular formula:	$C_{17}H_{25}N_3O_2$
Relative molecular mass:	303.39
Description:	White to slightly yellowish crystalline powder
Polymorphism:	The obtained polymorphic form is the same crystalline phase (form A) as the commercially available product (Galvus). Complete details are provided in section "3.2.S.3.1 Elucidation of Structure and other Characteristics".

The chemical-pharmaceutical documentation and Quality Overall Summary in relation to the Vildagliptin 50mg tablets are of sufficient quality in view of the present European regulatory requirements.

The manufacturing process has been adequately described. The proposed starting materials are acceptable. The control tests and specifications for drug substance product are adequately drawn up. Stability studies have been performed with the drug substance. No significant changes in any parameters were observed. Stability studies submitted support the proposed retest period of 60 months.

II.3 Medicinal Product

The development of the product has been described, the choice of excipients is justified, and their functions explained; excipients used in the formulation are common excipients used in pharmaceutical preparations. The applicant has conducted dissolution testing on pilot scale batches. The specifications for the in vitro dissolution to be used for quality control of the product have been derived from the dissolution profile of the test product batch that was found to be bioequivalent to the reference product. Adequate dissolution data has been provided. The size of the bio-batch is 100,000 tablets. Dissolution conditions employed are in accordance to Ph. Eur. monograph on dissolution as well as in

accordance with the BE guideline. The manufacturing process and process controls are in adequately drawn up. Adequate process validation data has been presented.

The product specifications cover appropriate parameters for this dosage form; the control tests and specifications for drug product have been adequately drawn up. Analytical methods are adequately described together with validations of the analytical methods. Batch analytical data presented on three pilot scale batches (including the bio-batch) from each of the proposed finished product manufacturing sites, complies with the proposed finished product specifications.

The conditions used in the stability studies are according to the ICH stability guideline. The control tests and specifications for drug product are adequately drawn up. The proposed shelf-life of 36 months at no special storage conditions can be granted.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The grant of this Marketing Authorisation is recommended.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Pharmacodynamic, pharmacokinetic and toxicological properties of Vildagliptin are well known.

As Vildagliptin is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate. The non-clinical overview refers to 39 publications up to year 2015.

The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate.

The quantity of impurities in the final Vildagliptin product has been adequately and comprehensively discussed by the Applicant in accordance with ICH Q3C (R5) guideline.

III.2 Ecotoxicity/environmental risk assessment (ERA)

Since Vildagliptin Galenicum 50mg tablets 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.3 Discussion on the non-clinical aspects

The application is made under reference to article 10(1) of Directive 2001/83/EC as amended. Abridged applications avoid the need for repetitive tests on animals and humans.

IV. CLINICAL ASPECTS

IV.1 Introduction

This application for marketing authorisation is based on the Art 10(1) of the 2001/83/EC which allows the generic applicant to reference the clinical and non-clinical data from the originator.

To support the application, the applicant has submitted one bioequivalence study.

IV.2 Pharmacokinetics

Bioequivalence studies

The study was a single centre, randomised, single dose, laboratory-blinded, two-period, two sequence, crossover comparative oral bioavailability study to establish comparative bioequivalence of Vildagliptin 50mg tablets and Galvus 50mg tablets (MAH: Novartis Pharma GmbH Germany) in healthy, adult, male and female subjects under fasting conditions. The objective of the study was to compare the rate and extent of absorption of both products and to monitor the adverse events to ensure the safety and tolerability of a single dose of Vildagliptin 50mg tablets.

Product Characteristics	**Test Product**	**Reference Product**
Name	Vildagliptin	Galvus®
Strength	50 mg	50 mg
Dosage form	Tablet	Tablet
Manufacturer	SAG Manufacturing S.L.U, Spain	Novartis Pharma GmbH (Germany)
Batch number	VLD1502	B5276
Batch size (Biobatch)	100,000 tablets	N/A
Measured content(s) (% of label claim)	99.7% of label claim	100.7% of label claim
Commercial Batch Size	N/A	N/A
Expiry date (Retest date)	05/2016 (Retest date)	06/2018

Table 1. Summary of Pharmacokinetic Parameters for Vildagliptin 50mg under fasting conditions (n=24)

Pharmacokinetic parameter	**Arithmetic Means (±SD)**	
	Test Product	**Reference Product**
$AUC_{(0-T)}$ (ng·h/mL)	1295.67 (±250.35)	1330.53 (±266.47)
$AUC_{(0-\infty)}$ (ng·h/mL)	1302.04 (±250.34)	1336.57 (±265.65)
C_{max} (ng/mL)	273.35 (±68.07)	266.28 (±60.77)
T_{max}[1] (hours)	1.25 (0.50, 5.00)	1.88 (0.50, 5.00)

[1] *Median (Min, Max)*

Table 2. ANOVA 90% CI (Log transformed) and CV% for primary parameters of Vildagliptin 50mg (test vs. reference) (Fasting, n=24).

Pharmacokinetic parameter	**Geometric Mean Ratio Test/Ref**	**Confidence Intervals (%)**	**CV%[1]**
$AUC_{(0-T)}$	97.42	94.11 - 100.85	7.0
C_{max}	102.16	91.77 - 113.72	21.9

[1] *Estimated from the Residual Mean Squares.*

Conclusion on bioequivalence studies:
Based on the submitted bioequivalence study Vildagliptin Galenicum 50mg tablets is considered bioequivalent with Galvus 50mg 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 Vildagliptin Galenicum 50mg tablets.

Safety specification

Below is a summary of the safety concerns and planned risk minimisation measures, as approved in the RMS:

Summary of safety concerns	
Important identified risks	• Transaminase elevations 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 with and without concurrent 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 / Breast feeding

Pharmacovigilance Plan

Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are required.

Risk minimisation measures

Routine risk minimisation is suggested and no additional risk minimisation activities are required.

Summary of the RMP

The submitted Risk Management Plan, is considered acceptable.

Periodic Safety Update Report (PSUR)

For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.

IV.4 Discussion on the clinical aspects

The application is made under reference to article 10(1) of Directive 2001/83/EC as amended. Abridged applications avoid the need for repetitive tests on animals and humans.

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 the user testing the PIL was English.

The test was carried out by Altiex Life s.r.o. including participants with English as their first language. The targeted demographic group were potential users of the medication. The protocol and questionnaire used in the study are provided in the documentation. A pilot study with 4 subjects and then testing over 2 rounds with 10 different subjects in each round was carried out. After the second round, the package leaflet was amended slightly due to typo errors identified during the test and also to improve the presentation of the leaflet. These errors were so minimal that they had no impact on the location and understanding of the safety messages during the three rounds of the interviews.

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 application contains adequate data with respect to quality of the drug substance and the drug product. In conclusion, from a quality point of view, the benefit/risk ratio for the product is positive and the application is approvable. The application contained adequate review of published clinical data and the bioequivalence has been shown. From a non-clinical point of view this application was also acceptable. Based on the review of the data on quality, safety and efficacy, the RMS considers that the application for Vildagliptin Galenicum 50mg tablets is approvable.