LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Vandetva
(vildagliptin)

SE/H/2067/01/DC
Asp no: 2020-0320

This module reflects the scientific discussion for the approval of Vandetva. The procedure was finalised on 2021-04-22. For information on changes after this date please refer to the module 'Update'.

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.lakemedelsverket.se E-mail: registrator@lakemedelsverket.se

I. INTRODUCTION

The application for Vandetva, 50 mg, tablet, is a generic application made according to Article 10(1) of Directive 2001/83/EC. The applicant, Stada Arzneimittel AG, applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and the following concerned member states (CMS): DE

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Galvus, 50 mg, tablet, authorised in the Union since 2007, with Novartis Europharm Limited as marketing authorisation holder.

The reference product used in the bioequivalence study is Galvus, 50 mg, tablet, from DE with Novartis Europharm Limited as marketing authorisation holder.

For approved indications, see the Summary of Product Characteristics.

For recommendations to the marketing authorisation not falling under Article 21a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a or 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

III.1 Discussion on the non-clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to preclinical data, no further such data have been submitted or are considered necessary.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

To support the marketing authorisation application the applicant has conducted one bioequivalence study comparing Vandetva with the reference product Galvus.

Pharmacokinetic properties of the active substance
Absorption: The absolute bioavailability is 85%. Following oral administration in the fasting state, vildagliptin is rapidly absorbed, with peak plasma concentrations observed at 1.7 hours. Food slightly delays the time to peak plasma concentration to 2.5 hours, but does not alter the overall exposure (AUC). Administration of vildagliptin with food resulted in a decreased C_{max} (19%). However, the magnitude of change is not clinically significant, so that vildagliptin can be given with or without food.

Linearity/non-linearity: The C_{max} for vildagliptin and the area under the plasma concentrations versus time curves (AUC) increased in an approximately dose proportional manner over the therapeutic dose range.

Elimination: The elimination half-life after oral administration is approximately 3 hours.

Study 011B18
Methods
This was a single-dose, two-way crossover study conducted in 30 healthy volunteers, comparing Vildagliptin, 50 mg, tablet with Galvus, 50 mg, tablet under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 16 hours post-dose. Plasma concentrations of vildagliptin were determined with an LC-MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for AUC_{0-t} and C_{max}. The study was conducted between 25.06.2018 and 09.07.2018.

Results
The results from the pharmacokinetic and statistical analysis are presented in Table 1 below.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for vildagliptin, n=30.

Treatment	**AUC_{0-t}** ng*h/ml	**C_{max}** ng/ml	**t_{max}** h
Test	**1112.443 ± 227.6**	**263.778 ± 68.0**	**1.17 (0.67-5.00)**
Reference	**1064.400 ± 249.2**	**242.266 ± 75.5**	**1.67 (0.67-5.00)**
***Ratio (90% CI)**	**105.17 (101.73-108.72)**	**110.52 (101.03-120.89)**	**-**
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 plasma concentration			

**calculated based on ln-transformed data*

For AUC_{0-t} and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

Discussion and overall conclusion
The bioequivalence study and its statistical evaluation were in accordance with accepted standards for bioequivalence testing, as stated in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr). The bioanalytical methods were adequately validated.

Based on the submitted bioequivalence study, Vandetva is considered bioequivalent with Galvus.

IV.2 Discussion on the clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to clinical efficacy/safety data, no further such data have been submitted or are considered necessary.

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 Vandetva.

The MAH has submitted the updated version 1.2 RMP dated 2021-01-27 and proposed the following summary of safety concerns:

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
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, in 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

---

Summary of the RMP
The submitted Risk Management Plan, version 1.2 RMP signed 2021-01-27 is considered acceptable. RMS agrees with the CMS CZ and HU assessors. The questionnaire on “lactic acidosis” is only required for Eucreas and not for Galvus and not for STADA product containing only vildagliptin. Referral EMEA/H/A-31/143 concerns metformin and metformin-containing medicines.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

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 quality of the generic product, Vandetva, is found adequate. There are no objections to approval of Vandetva from a non-clinical and clinical point of view. Bioequivalence between the test and reference product has been adequately demonstrated. The product information is acceptable. The benefit/risk ratio is considered positive and the application is therefore recommended for approval.

List of recommendations not falling under Article 21a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

The decentralised procedure for Vandetva, 50 mg, tablet was positively finalised on 2021-04-22.

LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.lakemedelsverket.se E-mail: registrator@lakemedelsverket.se