VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Vildagliptin belongs to a group of medicines called “oral antidiabetics”.

Vildagliptin is used in a certain form of diabetes (type 2 diabetes mellitus) in adults, when diet and exercise alone do not have an adequate effect on keeping blood sugar at the correct level. Vildagliptin is prescribed either alone or together with certain other antidiabetic medicines which you will already be taking, if these have not proved sufficiently effective to control diabetes.

Type-2 diabetes is a disease in which the pancreas does not make enough insulin to control the level of glucose (sugar) in the blood or when the body is unable to use insulin effectively. Patients with high blood sugar will typically experience polyuria (frequent urination), they will become increasingly thirsty (polydipsia) and hungry (polyphagia).

It was estimated that 2.8% people in 2000 and 4.4% in 2030 will have diabetes. The total number of people with diabetes is projected to rise from 171 million in 2000 to 366 million in 2030.[1]

VI.2.2 Summary of treatment benefits

Vildagliptin 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. Even though a patient is now starting a medicine for diabetes, it is important to continue following the recommended diet and/or exercise.

Vildagliptin has been extensively evaluated in several well-designed double-blind, placebo-controlled or active-controlled, randomized clinical studies in T2DM patients of up to 52 weeks duration both in monotherapy and add-on combination therapy in comparison with several other oral antidiabetics. Significant and clinically meaningful improvement of glycemic control accompanied with good tolerability was consistenly demonstrated in long- term clinical studies proving vildagliptin is an effective and safe therapeutic option for approved therapeutic indications.

VI.2.3 Unknowns relating to treatment benefits

Use of vildagliptin is not recommended in pediatric population, pregnant and lactating women, patients with hepatic impairment and patients with heart failure due to a lack of efficacy/safety data.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Liver disease (drug-induced liver injury)	Rare cases of hepatic dysfunction (including hepatitis) have been reported. In these cases, the patients were generally asymptomatic without clinical sequelae and liver function test results returned to normal after discontinuation of treatment. Symptoms of liver disease include yellow skin and eyes, nausea, loss of appetite or dark-coloured urine.	A test to determine patient's liver function will be performed before the start of vildagliptin treatment, at three-month intervals for the first year and periodically thereafter. This is so that signs of increased liver enzymes can be detected as early as possible. A patient who develops signs suggestive of liver disease should discontinue vildagliptine. If the patient has previously taken vildagliptin but had to stop taking it because of liver disease, he should not take this medicine.
Serious allergic reaction which causes swelling of the face or throat (Angioedema)	Rare cases of angioedema have been reported on vildagliptin at a similar rate to controls. A greater proportion of cases were reported when vildagliptin was administered in combination with an angiotensin converting enzyme inhibitor (ACE-inhibitor). The majority of events were mild in severity and resolved with ongoing vildagliptin treatment. Symptoms of angioedema include swollen face, tongue or throat, difficulty swallowing, difficulties breathing, sudden onset rash or hives.	Yes, by monitoring for early symptoms. The doctor or pharmacist should be informed if the patient is allergic to vildagliptin or any of the other ingredients of this medicine – in this case the patient should not take this medicine. The doctor or pharmacist should be informed if the patient is also taking angiotensin converting enzyme inhibitor.
Inflammation of the pancreas (Acute pancreatitis)	Use of vildagliptin has been associated with a risk of developing inflammation of the pancreas. Symptoms include severe and persistent pain in the abdomen (stomach area), which might reach through to the back, as well as nausea and vomiting.	Yes, by monitoring for early symptoms. The doctor or pharmacist should be informed if the patient has or has had a disease of the pancreas. Patient should know the signs and symptoms of disease of the pancreas. If disease of the pancreas is suspected, vildagliptin should be withdrawn; if the disease of the pancreas is confirmed, vildagliptin should not be restarted.

Localised peeling of skin or blisters (**Exfoliative and bullous skin lesions, including bullous pemphigoid**)	Diabetic skin lesions are a common complication of diabetes.	It is advised to follow the recommendations for skin and foot care that are given by the doctor or nurse. It is also advised to pay particular attention to new onset of blisters or ulcers while taking vildagliptin. Should these occur, prompt consultation with the doctor is needed.
Low blood glucose (Hypoglycaemia)	Sulphonylureas are known to cause low blood glucose. Patients receiving vildagliptin in combination with a sulphonylurea may be at risk for low blood glucose. Therefore, a lower dose of sulphonylurea may be considered to reduce the risk of low blood glucose.	Yes, by monitoring for early symptoms. The doctor or pharmacist should be informed if the patient is also taking an anti-diabetic medicine known as a sulphonylurea – the doctor may want to reduce the dose of the sulphonylurea when taken together with vildagliptin in order to avoid low blood glucose.

Important potential risks:

Risk	What is known
Heart problems which can cause shortness of breath or ankle swelling (Cardiac events in CHF (NYHA Functional Class III) patients)	A clinical trial of vildagliptin in patients with New York Heart Association (NYHA) functional class I-III showed that treatment with vildagliptin was not associated with a change in left-ventricular function or worsening of pre-existing congestive heart failure (CHF) versus placebo. Clinical experience in patients with NYHA functional class III treated with vildagliptin is still limited and results are inconclusive.
Muscle aches with our without concomitant cholesterol-lowering drugs (Muscle events/myopathy/rhabdomyolysis with current statin use)	Based on preclinical findings, clinical trials and EudraVigilance data the Pharmacovigilance Risk Assessment Committee has agreed that there is insufficient evidence for an association between vildagliptin and rhabdomyolysis at the moment, in particular with current statin use.

Missing information

Risk	What is known
Use in patients with impaired liver function (Use in patients with severe hepatic impairment)	The effect of impaired hepatic function on the pharmacokinetics of vildagliptin was studied in patients with mild, moderate and severe hepatic impairment based on the Child-Pugh scores (ranging from 6 for mild to 12 for severe) in comparison with healthy subjects. The exposure to vildagliptin after a single dose in patients with mild and moderate hepatic impairment was decreased (20% and 8%, respectively), while the exposure to vildagliptin for patients with severe impairment was increased by 22%. The maximum change (increase or decrease) in the exposure to vildagliptin is ~30%, which is not considered to be clinically relevant. There was no correlation between the severity of the hepatic disease and changes in the exposure to vildagliptin.

Use in patients with heart problems which can cause shortness of breath or ankle swelling (Use in patients with compromised cardiac function (NYHA functional class IV))	There is no experience of vildagliptin use in clinical trials in patients with NYHA functional class IV.
Use in pregnant and breast-feeding women (Use in pregnancy and lactation)	There are no sufficient data from the use of vildagliptin in pregnant women. The potential risk for humans is unknown. It is not known if vildagliptin passes into breast milk.
Use in children and adolescents (Use in paediatric population)	There is no data on use of vildagliptin in children and adolescents.

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

The Summary of Product Characteristics and the Package leaflet for this product can be found at the agency's EPAR page.

VI.2.6 Planned post authorisation development plan

Not applicable. No postauthorisation studies are planned.

VI.2.7 Summary of changes to the Risk Management Plan over time

Version	*Date*	*Safety concerns*	*Comment*

1.1	13.06.2017	• Transaminase elevation and Drug-induced liver injury (DILI) replaced with Drug-induced liver injury (DILI) as an identified risk • Skin lesions replaced with Exfoliative and bullous skin lesions, including bullous pemphigoid as an identified risk • Serious infections removed as a potential risk • Compromised cardiac function replaced with Cardiac events in CHF (NYHA Functional Class III) patients as a potential risk • Muscle events/myopathy with and without concurrent statin use replaced with Muscle events/myopathy/rhabdomyolysis, in particular with current statin use as a potential risk • Neuropsychiatric events removed as a potential risk • Breast cancer removed as a potential risk - Gender incidence/frequency differences removed as missing information • Patients with compromised cardiac function (NYHA functional class III-IV) replaced with Use in patients with compromised cardiac function (NYHA functional class IV) as missing information • Pregnancy replaced with Use in pregnancy and lactation as missing information • Use in paediatric population added as missing information	6 risks have been renamed/replaced, 4 risks have been removed and one risk has been added from/to the list of safety concerns.

Part VII- Annexes

Annex 1 – EudraVigilance Interface

Not applicable.

Annex 2 - SmPC & Package Leaflet

Please see attached document.