2. Elements for a public summary

2.1 Overview of disease epidemiology

Type 2 diabetes mellitus (T2DM) is a disorder that causes increased blood sugar concentrations. The disease comes from a dysfunction of insulin which is important in regulating sugars and fat in the body. It is estimated that in 2011, about 366 million people had diabetes worldwide; by 2030 this will rise to 552 million. Most people with T2DM are between 40-59 years old. Being overweight is one of the biggest causes of T2DM. T2DM is linked to many disorders which may occur as a result of T2DM, such as some heart or kidney diseases, eye disorders, nerve damage causing pain and numbness in fingers and toes, or problems with the digestive system, blood vessels or heart.

2.2 Summary of treatment benefits

The active substance vildagliptin belongs to a group of medicines called "oral antidiabetics." They are used to treat adult patients with type 2 diabetes when diabetes cannot be controlled by diet and exercise alone. They help to control the level of sugar in the blood and the level of glycosylated hemoglobin (HbAlc), which is a measure of how well the sugar has been controlled over a period of about 3 months.

Medicines containing active substances vildagliptin and metformin have been studied in many clinical trials conducted all over the world in patients with type 2 diabetes. In all studies, vildagliptin improved the level of HbAlc and fasting sugar in the blood and did not cause significant weight gain or produce episodes of low blood sugar (hypoglycemia) when compared to an inactive pill or other antidiabetic medications. Vildagliptin was also shown to be safe to use with about the same frequency of side effects as an inactive pill or other antidiabetic medication.

2.3 Unknowns relating to treatment benefits

Studies medicines containing vildagliptin have been performed in a large number of patients and long-term efficacy has been demonstrated. Therefore, there is no evidence to suggest that further efficacy studies are needed.

2.4 Summary of Safety Concerns

Important identified risks

Risk	**What is known**	**Preventability**
High level of liver function test and liver damage due to drug intake (Transaminase elevation and Drug-induced liver injury (DILI)	Abnormal liver function including a special type of liver abnormality called hepatitis is rare in Vildagliptin treated patients and may affect between 1 in 10,000 up to 1 in 1,000 people. These patients do not show any symtoms (asymptomatic) or clinical effects (sequelae) and liver function returned to normal once the drug was stopped. Vildagliptin should not be used in patients with abnormal liver function.	Yes. Liver function tests (LFTs) should be performed prior to the initiation of treatment with Vildagliptin and during treatment at three-month intervals during the first year and periodically thereafter.
Swelling mainly in the face and throat due to allergic reaction (Angioedema)	Angioedema is a rare condition (affecting up to 1 in 1,000 people) and symptoms include swollen face, tongue or throat, difficulty swallowing, difficulty breathing and sudden onset of rash or hives. Clinical trials showed angioedema occurred about the same number of times with patient who took vildagliptin as with patients who took something else. More cases were reported when vildagliptin was taken with a class of drugs called ACE inhibitors. Most events were not severe and resolved with ongoing vildagliptin treatment.	Possibly, with monitoring of patient's other medications and symptoms of angioedema.
Sudden inflammation of the pancreas (Acute pancreatitis)	Cases of inflammation of the pancreas (pancreatitis) have been reported in patients receiving Vildagliptin. Pancreatitis can be a serious, potentially life-threatening medical condition.	No. Patients should be monitored for symptoms of pancreatitis, like episodes of pain in the stomach region with or without vomiting.
Wound in skin (Skin lesions)	Diabetic skin lesions are a common complication of diabetes. Skin lesions, including swelling of skin (blistering and ulceration)	Yes. Regular monitoring for skin disorders, such as blistering or ulceration, is recommended. Patients should be advised to

Risk	**What is known**	**Preventability**
	have been reported with vildagliptin in animal studies.	follow recommendations for skin and foot care. Patients should also be advised to pay particular attention to new onset of blisters or ulcers while taking Vildagliptin.
Low blood glucose (Hypoglycaemia)	Sulphonylureas can cause hypoglycaemia. Patients receiving vildagliptin with a class of drugs called sulphonylureas may be at risk for hypoglycaemia. Therefore, a lower dose may be considered to reduce the risk of hypoglycaemia.	Yes. Patients should be monitored if taking an anti- diabetic medicine known as a sulphonylurea and the dose of the sulphonylurea may be changed.

Important potential risks

Risk	**What is known**
Serious infection (Serious infection)	Serious infection is considered to be a possible risk because of the class of drugs (DPP-4 inhibitor class) of Vildagliptin. Patients with diabetes already have a high chance for infections and related problems. Clinical trials showed that treatment with Vildagliptin does not carry an increased risk of infections and infestation compared to other drugs used for comparison during trials.
Heart is unable to provide sufficient pump action to maintain blood flow to meet the needs of the body (Cardiac events in CHF [NYHA Functional Class III] patients)	One clinical study in patients with abnormal heart function showed that vildagliptin did not change function of the heart when compared to an inactive pill. However, a definite conclusion could not be drawn. Vildagliptin is permitted in patients with abnormal heart function, as long as it is not severe. Section 4.4 of the SmPC: 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 (see section 5.1 of the SmPC). There is no experience of vildagliptin use in clinical

Risk	**What is known**
	trials in patients with NYHA functional class IV and therefore use is not recommended in these patients.
Muscle disorder with and without use of class of drug called statins (Muscle events / myopathy with and without concurrent statin use)	Animal studies showed muscle disorder symptoms and an increase in a muscle enzyme called CPK. Patients in one study had muscle pain after taking a dose higher than that recommended for treatment.
Mental illness due to nervous disorder (Neuropsychiatric events)	Animal studies in dogs treated with vildagliptin showed neurological findings like tremors, loss of muscle coordination, and dilated pupils. No clinical trial data is available. It is not clear if there is a link between vildagliptin and an increased risk of neurological problems in diabetic patients
Tumor in breast (Breast cancer)	Animal studies showed incidence of breast tumors when vildagliptin was given at a much higher dose than recommended for humans. Breast cancer was seen in clinical trials as well. Vildagliptin has been evaluated in many tests and these did not show a risk of cancer in humans.
Tumor in pancreas (Pancreatic cancer)	Cases of inflammation of the pancreas (pancreatitis) have been reported in patients receiving Vildagliptin. Current evidence, however, does not suggest role of vildagliptin in the occurrence of pancreatic cancer, or that patients are at an increased risk of development of pancreatic cancer. In clinical trials, very low and about the same number of reports of pancreatic cancer have been received compared to the population of diabetic patient's not receiving vildagliptin.

Missing information

Risk	**What is known**
Variation of adverse events in different genders (Gender incidences / frequency differences)	Limited information is available about the variation of incidence of adverse events in men compared to women.
Patients with severe hepatic impairment	Vildagliptin are not recommended in patients with liver disorder. Hence, there is limited information available for patients with severe liver disorder.
Patients with severe heart disorder (Patients with compromised cardiac function [NYHA Functional Class IV])	Vildagliptin is not recommended in patients with heart disorder. Hence, there is limited information available for patients with severe heart disorder.
Pregnancy / Breast feeding	*Pregnancy* There are limited data available for the use of vildagliptin in pregnant women. Studies in animals

Risk	**What is known**
	have shown toxic effect to offspring and adverse effects on sexual function and fertility in adult males and females (reproductive toxicity) at high doses. Studies in animals performed with vildagliptin and metformin have not shown evidence of developmental abnormality in offspring, but do effect the fetus. The potential risk for humans is unknown. Vildagliptin should not be used during pregnancy. *Breast-feeding* Studies in animals have shown excretion of vildagliptin in milk. It is unknown whether vildagliptin is excreted in human milk. Due to lack of human data with vildagliptin, Vildagliptin should not be used during breast-feeding (see section 4.6 of the SmPC).

2.5 Summary of additional 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.

This medicine has no additional risk minimisation measures.

2.6 Planned post-authorisation development plan

Not applicable

2.7 Summary of changes to the risk management plan over time

Not applicable