Part VI.2 Elements for a Public Summary

Part VI.2.1 Overview of disease epidemiology

Type 2 diabetes (lifelong condition that causes high blood sugar level) results from the body's ineffective use of insulin. 90% of people with diabetes around the world suffer from Type 2 diabetes which largely is the result of excess body weight and physical inactivity. In 2012 diabetes was the direct cause of 1.5 million deaths [WHO, 2015]. Worldwide, there is an estimated increase in the existence of diabetes from 382 million (8.3%) in 2013 to 592 million (10.1%) in 2035. The increase in the occurrence of obesity in childhood has led to the appearance of Type 2 diabetes in children and young adults. There is only a small gender difference in numbers of people with diabetes globally, with about 14 million more men than women estimated to have diabetes in 2013. The occurrence increases sharply with age in both sexes [Forouhi, 2014].

Part VI.2.2 Summary of treatment benefits

It has been shown that vildagliptin/metformin is efficacious, safe and well-tolerated in Japanese patients with Type 2 Diabetes Mellitus (T2DM). Clinically relevant drop was observed in level of glycosylated hemoglobin (HbA1c), which is a measure of how well the sugar has been controlled over a period of 3 months, thus, highlighting the benefit of switching patients who are inadequately controlled with vildagliptin monotherapy to vildagliptin/metformin single pill combination. The reduction in fasting blood sugar levels was also significantly higher for the vildagliptin/metformin group compared with the placebo (dummy medicine containing no active ingredient)+vildagliptin group [Odawara M, 2015].

The addition of vildagliptin to a stable dose of metformin monotherapy has been shown to be effective in sustaining controlled blood sugar levels for at least 1 year, and in improving function of β-cell (cells producing insulin i.e. the hormone which regulates the amount of glucose in the blood) and reducing insulin resistance and inflammatory markers. A recent study of vildagliptin/low-dose metformin combination therapy in patients who have never undergone treatment for T2DM, showed superior blood sugar level control and was favorably tolerated by stomach and gut compared with high-dose metformin therapy. This suggests the potential of vildagliptin/metformin combination therapy in the management of T2DM [Ji L-N, 2013].

Part VI.2.3 Unknowns relating to treatment benefits

The efficacy of vildagliptin+metformin in children and adolescents (< 18 years) has not been established. The efficacy of vildagliptin and metformin as triple oral therapy in combination with a thiazolidinedione has not been established. There are no adequate data from the use of vildagliptin+metformin in pregnant women.

Part VI.2.4 Summary of safety concerns

Table 6-5 Important identified risks

Risk	What is known	Preventability
Elevation in laboratory parameter that determine the degree of liver disease and drug-induced liver damage (Transaminase elevation and drug induced liver injury)	Rare cases of hepatic dysfunction (including hepatitis) have been reported. In these cases, the patients generally didn't show any symptoms without clinical outcomes and liver function test results returned to normal after discontinuation of treatment. Signs and symptoms include yellow skin and eyes, nausea, loss of appetite or dark-coloured urine, which may indicate liver disease (hepatitis).	Patients should not take vildagliptin+metformin if they have liver problems. Patient is advised not to take vildagliptin if the patient had taken it previously and had to stop taking it because of liver disease. Physician should perform a test to determine the liver function of the patient before the start of treatment with vildagliptin+metformin, 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. Physician should withdraw the therapy with vildagliptin+metformin if there is an increase in laboratory parameters (Liver enzymes like AST or ALT of 3 times upper limit of normal range or greater) suggesting liver disease.
Swelling of the deeper layers of the skin, caused by a build-up of fluid (Angioedema)	Rare cases of angioedema have been reported while using vildagliptin+metformin. Signs and symptoms include swollen face, tongue or throat, difficulty swallowing, difficulty breathing, sudden onset rash or hives. There may be an increased risk of angioedema in patients taking ACE-inhibitors (medicines used to treat high blood pressure and heart failure) concurrently with vildagliptin+metformin.	If patients notice any of these symptoms, they should stop taking vildagliptin+metformin and immediately consult the doctor as these symptoms need immediate medical attention. Patients should inform their doctor or pharmacist if they are taking, have recently taken or might take any other medicines. This is particularly important if they are already taking any medicine to treat a heart condition or problems with their blood pressure such as medicines containing ACE-inhibitors.

Risk	What is known	Preventability
Sudden inflammation of a glandular organ located in the abdomen.(Acute pancreatitis)	Inflammation of the pancreas (pancreatitis) may occur by use of vildagliptin+metformin. Frequency of the risk is not known. Signs and symptoms include severe and persistent pain in the abdomen (stomach area), which might reach through to back, as well as nausea and vomiting.	Patients should talk to their doctor, pharmacist or diabetes nurse before taking vildagliptin+metformin if they have or have had a disease of the pancreas. Patients should be informed of the characteristic symptom of acute pancreatitis and if they notice any of these symptoms, they should stop taking vildagliptin+metformin and immediately consult the doctor as these symptoms need immediate medical attention. If pancreatitis is suspected, vildagliptin should be discontinued; if acute pancreatitis is confirmed, vildagliptin should not be restarted. Caution should be exercised in patients with a history of acute pancreatitis.
Superficial growth or patch of the skin that does not resemble the area surrounding it (Skin lesions)	Diabetic skin lesions are a common complication of diabetes. There have been reports of exfoliative and bullous skin lesions, including bullous pemphigoid (scaling and shedding of the skin including inflammatory and blistering disease) skin lesions. Frequency of these reactions is not known. Signs and symptoms include: itchy rash, localized peeling of skin or blisters.	Patient is advised to follow the recommendations given by doctor or nurse for skin and foot care. Patients especially diabetics are advised to pay particular attention to new onset of blisters or ulcers while taking vildagliptin+metformin. Doctor should be consulted as early as possible if any such symptoms occur.
Low blood glucose levels (Hypoglycemia)	Sulphonylureas are known to cause decrease in blood glucose levels. Patients receiving vildagliptin in combination with a sulphonylurea may be at risk for decreased blood glucose levels. Low blood glucose is one of the common side effects of vildagliptin+metformin.	Before taking vildagliptin, doctor or pharmacist or diabetes nurse should be informed if the patient is taking an anti-diabetic medicine known as a sulphonylurea so that the doctor may reduce the dose of sulphonylurea when taking it together with vildagliptin+metformin in order to avoid low blood glucose levels.

Risk	What is known	Preventability
A condition caused by a build-up of lactate in the body (Lactic acidosis)	Vildagliptin+metformin.may cause a very rare, but very serious side effect called lactic acidosis (lactic acid in the blood), particularly if your kidneys are not working properly. The risk of developing lactic acidosis is also increased with uncontrolled diabetes, serious infections, prolonged fasting or alcohol intake, dehydration (see further information below), liver problems and any medical conditions in which a part of the body has a reduced supply of oxygen (such as acute severe heart disease). Signs include drowsiness or dizziness, severe nausea (feeling sick) or vomiting, abdominal pain (pain in or around stomach), irregular heart beat or deep, rapid breathing, muscle pain and feeling cold or uncomfortable.	Patients should stop taking vildagliptin+metformin and talk to their doctor if they experience one or more of the symptoms of lactic acidosis: Patients should avoid alcohol while taking vildagliptin+metformin since alcohol may increase the risk of lactic acidosis

Table 6-6 Important potential risks

Risk	What is known
Serious infections	Patients should not take vildagliptin+metformin if they have a severe infection.
Heart related events in heart failure patients who have breathlessness on excursion (Cardiac events in congestive heart failure (NYHA functional class III) patients)	Patients should not take vildagliptin+metformin if they have recently had a heart attack or if they have heart failure or serious problems with their blood circulation or difficulties in breathing which could be a sign of heart problems.
Muscle pain or muscle diseases with or without the use of drugs that reduces the levels of fat in the blood (Muscle events/myopathy, in particular with current statin use)	Muscle pain is one of the side effects of vildagliptin+metformin and its frequency is not known.
Mental disorders due to diseases of the nervous system (Neuropsychiatric events)	Currently no adequate data are available about the association of neuropsychiatric events and the use of vildagliptin+metformin.
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.

Risk	What is known
Cancer of pancreas (Pancreatic cancer)	Currently no adequate data are available about the association of pancreatic cancer and the use of vildagliptin+metformin.

Table 6-7 Missing information

Risk	What is known
Variation of adverse events in different genders (Gender incidence/frequency differences	No clinically relevant differences in the pharmacokinetics (study of the movement of drugs in the body) of vildagliptin were observed between male and female healthy patients within a wide range of age and body mass index (body mass divided by the square of the body height). Effect of vildagliptin is not affected by gender.
Patients with severe liver problems (Patients with severe hepatic impairment)	Vildagliptin should not be used in patients with hepatic impairment, including patients with abnormal laboratory parameters (ALT or AST > 3 x the upper limit of normal range). Before taking vildagliptin, doctor or pharmacist or diabetes nurse should be informed if the patient has a history of liver disease. Patient is advised not to take vildagliptin if the patient had taken vildagliptin previously and had to stop taking it because of liver disease. Physician should perform a test to determine the liver function of the patient before the start of treatment with vildagliptin, at three month intervals for the first year and periodically thereafter. If the patient develops increased transaminase levels.
Patients with severe heart problems who have breathlessness even at rest (Patients with compromised cardiac function [NYHA functional class IV) (NYHA functional class IV])	Patients should not take vildagliptin+metformin if they have recently had a heart attack or if they have heart failure or serious problems with their blood circulation or difficulties in breathing which could be a sign of heart problems.
Pregnancy	There are no adequate data from the use of vildagliptin+metformin in pregnant women. Doctor should be asked for advice if a woman is pregnant; think may be pregnant or planning to have a baby, before taking vildagliptin+metformin. Patient is advised not to use vildagliptin+metformin during pregnancy.

Part VI.2.5 Summary of additional risk minimization measures by safety concern

All medicines have a SmPC which provides physicians, pharmacists and other HCPs with details on how to use the medicine, the risks and recommendations for minimizing them. An abbreviated version of this in lay language is provided in the form of the package leaflet. The measures in these documents are known as routine risk minimization measures.

This medicine has no additional risk minimization measures.

Part VI.2.6 Planned post authorization development plan

None

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

Not applicable (first submission)