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Summary of the risk management plan (RMP) for Trulicity (dulaglutide)

This is a summary of the risk management plan (RMP) for Trulicity, which details the measures to be taken in order to ensure that Trulicity is used as safely as possible. For more information on RMP summaries, see here.

This RMP summary should be read in conjunction with the EPAR summary and the product information for Trulicity, which can be found on Trulicity's EPAR page.

Overview of disease epidemiology

Trulicity is a medicine used to treat type 2 diabetes in adults. Type 2 diabetes is a condition 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. In 2010, about 1 out of every 15 adults in Europe had this condition. Type 2 diabetes is more likely to develop in people who have family members with the condition, people with an ethnic background known to be associated with a higher risk (for example Asian or African), people aged over 40 years old, or who are overweight or obese, do not exercise, have high blood pressure, or smoke.

People with type 2 diabetes tend to have other diseases at the time of diagnosis and they are at greater risk of developing conditions such as cardiovascular disorders, diabetic eye disease and kidney disease.

Summary of treatment benefits

Trulicity contains the active substance dulaglutide. It is given by injection under the skin, alone or together with other diabetes medicines, including insulin, in patients whose blood glucose cannot be controlled with diet and other medicines alone.

The benefits of Trulicity have been studied in 5 main studies involving over 4,500 patients with type 2 diabetes. In these studies Trulicity was compared with placebo (a dummy treatment) or with other diabetes medicines when used alone or as an add-on to various combination treatments. Information from a sixth study that was submitted during the procedure was also considered.

The main measure of effectiveness was the change in the level of glycosylated haemoglobin (HbA1c), which is the percentage of haemoglobin in the blood that has glucose attached. HbA1c gives an indication of how well the blood glucose is controlled. The patients' average HbA1c at baseline ranged from 7.6 to 8.5% and patients were treated for at least 52 weeks.

Trulicity was more effective than metformin at reducing HbA1c levels when used alone, and was more effective than the diabetes medicines exenatide (given twice daily) or sitagliptin, and at least as good as insulin glargine, when used as add-on to other treatments.

After 26 weeks of treatment, Trulicity reduced HbA1c by between 0.71 and 1.59 percentage points at the lower dose, and by between 0.78 and 1.64 percentage points at the higher dose. This was

considered to be clinically meaningful and there was evidence that the benefits were maintained during long-term treatment. About 51% of those given the lower dose and 60% of patients given the higher dose of Trulicity achieved a target HbA1c below 7.0% and this was generally more than the proportion achieving this target with alternative treatments.

Unknowns relating to treatment benefits

Dulaglutide has not been studied as an add-on to treatment with a sulphonylurea (another diabetes medicine) alone, although it is expected that these patients will also benefit from the addition of dulaglutide if needed for improved glucose control. There were only a small number of patients with kidney disease in the dulaglutide studies, and dulaglutide has not been studied in a large group of patients with severe kidney disease. Trulicity has not been studied in children and adolescents under the age of 18 years, nor in pregnant and breastfeeding women; studies have also included only a limited number of patients over the age of 75 years as well as only small numbers of those with heart failure or reduced liver function. It is not known if the benefits and risks of Trulicity are the same in these groups.

Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Low blood sugar (Hypoglycaemia)	Low blood sugar is seen in between 1 and 10 patients in 100 when dulaglutide is used alone, and may become dangerous if patients experience dizziness or become unconscious. If Trulicity is combined with some other diabetes medicines (such as sulphonylureas or insulin) the risk of low blood sugar is greater (seen in more than 1 patient in 10).	Patients should be made aware of the signs of low blood sugar and how to manage them. Patients should monitor their blood sugar levels regularly and should take glucose tablets or a high-sugar snack if they notice signs of low blood sugar. Doctors should consider decreasing the prescribed dose of insulin or sulphonylureas where these are used together with Trulicity.
Inflammation of the pancreas (acute pancreatitis)	Pancreatitis is a serious and potentially life-threatening condition that has occurred rarely (in less than 1 in 1,000 patients) during treatment with dulaglutide. Medicines such as dulaglutide might increase the risk of pancreatitis in patients with diabetes.	Patients should be informed of the signs and symptoms of pancreatitis, such as persistent, severe pain in the stomach (abdomen) and should contact their doctor if these occur; treatment with dulaglutide should be stopped if pancreatitis is suspected, and should not be started again if the condition is confirmed.
Effects on the digestive system (gastrointestinal events)	Gastrointestinal events such as nausea (feeling sick), diarrhoea and vomiting are the most common side effects reported with dulaglutide, and are seen in more than 1 patient in 10.	These side effects are usually mild to moderate in severity and most will lessen over time with continued use of the medicine.

Important potential risks

Risk	What is known
Cancer of the thyroid gland or pancreas (thyroid C-cell tumours or pancreatic malignancy)	When rats were treated with dulaglutide an increased number of certain rare thyroid cancers (known as C-cell tumours) were seen. It is unknown whether dulaglutide could cause these rare types of thyroid cancer in humans. The risk of certain cancers, including cancer of the pancreas, is increased in patients with diabetes, regardless of their treatment. However, there have also been concerns that medicines that work in the same way as dulaglutide might increase the risk. Clinical studies with Trulicity have not so far shown an increased risk of cancer, including cancers of the thyroid and pancreas, but the number of events is too small to draw final conclusions; until better evidence is obtained cancer is considered a potential risk.
Allergy (hypersensitivity)	Dulaglutide is made from proteins, so it could potentially cause an allergic reaction. Symptoms of a serious allergic reaction may include swelling of the face, lips, tongue, or throat; fainting or feeling dizzy; very rapid heartbeat; problems breathing or swallowing; or severe rash or itching.
Cardiovascular effects	Dulaglutide, like similar medicines, causes small increases in heart rate and a change in the movement of electrical signals in the heart (first-degree heart block). Patients may not notice any symptoms although changes may be seen in tests when the heart is monitored by an electrocardiogram (ECG). A potential risk of more serious heart problems is therefore considered to exist.
Medication error	Medication errors can occur if the patient takes dulaglutide wrongly or it is confused with another injectable diabetes medicine. Dulaglutide is used in patients with diabetes who are often using several different medicines. Adding a new medicine that is taken once a week may be confusing for some patients as they may be used to taking their diabetes medicines once a day. This may result in patients injecting dulaglutide more frequently than needed. This occurred in a few patients who were taking part in the clinical trials for dulaglutide and some of these patients developed mild or moderate side effects like feeling sick or vomiting. Once they received further instructions on how to use the medicine properly, it did not happen again. The label must always be checked before each injection to ensure the right medicine is injected, and patients should consult the package leaflet and labelling to help use the medicine correctly.

Missing information

Risk	What is known
Use in children and adolescents less than 18 years of age	Dulaglutide has not been studied in children and adolescents under 18 years of age, so it is not known if it would be safe and effective in this age group.
Use in pregnant	Dulaglutide has not been studied in pregnant or breastfeeding women.

Risk	What is known
and/or breastfeeding women	Therefore the medicine should not be used by women who are pregnant or are breastfeeding, think they are pregnant or are planning to have a baby.
Use in patients aged over 75 years	Dulaglutide has only been tested in a few patients aged over 75 years; therefore it is not known whether the benefits and risks are the same as in younger patients.
Use in patients with severe kidney failure	Dulaglutide has been studied in some patients with moderate kidney disease, but not in those with more severe kidney problems. It is not known at the moment whether the benefits and risks of dulaglutide are the same for patients with severe kidney disease as they are for patients without kidney disease. A further study in patients with moderate or severe kidney disease is currently under way.
Use in patients with reduced liver function (hepatic impairment)	Dulaglutide has been studied in very few patients with liver impairment. Currently, it is not known whether the benefits and risks of dulaglutide are the same in patients with reduced liver function as in those without problems with their liver.
Use in patients with heart failure	Dulaglutide has been studied in very few patients with heart failure. Currently it is not known whether the benefits and risks of dulaglutide are the same for patients with heart failure as they are for patients without heart failure.
Effects on memory seen in rats	When pregnant rats were given very high doses of dulaglutide, resulting in about 16 times the highest blood level that would occur in human patients given the medicine, memory problems were seen in their female offspring. These effects were not seen in the male offspring. Currently there is not enough information to explain this finding, so a further study is taking place.

Summary of risk minimisation measures by safety concern

All medicines have a summary of product characteristics (SmPC) which provides physicians, pharmacists and other healthcare professionals with details on how to use the medicine, and also describes the risks and recommendations for minimising them. Information for patients is available in lay language in the package leaflet. The measures listed in these documents are known as ‘routine risk minimisation measures’.

The SmPC and the package leaflet are part of the medicine’s product information. The product information for Trulicity can be found on Trulicity’s EPAR page.

This medicine has no additional risk minimisation measures.

Planned post-authorisation development plan

List of studies in post-authorisation development plan

Study / activity (including study number)	**Objectives**	**Safety concerns / efficacy issue addressed**	**Status**	**Planned date for submission of (interim and) final results**
H9X-MC-GBDX: A study comparing the effect of once-weekly dulaglutide with insulin glargine on glycaemic control in patients with type 2 diabetes and moderate or severe CKD	The aim of this efficacy study is to demonstrate that the effect of 26 weeks' treatment with dulaglutide on blood glucose in patients with type 2 diabetes and moderate or severe kidney disease is at least similar to insulin glargine.	Benefits of dulaglutide in patients with moderate or severe kidney disease.	Started	May 2017
H9X-MC-GBDE: A study comparing the effect of once-weekly dulaglutide with once-daily liraglutide in patients with type 2 diabetes (AWARD-6: Assessment of Weekly AdministRation of LY2189265 in Diabetes-6).	The aim of this study is to demonstrate that once-weekly dulaglutide 1.5 mg is similar to once-daily liraglutide 1.8 mg as measured by blood sugar at 26 weeks in patients with type 2 diabetes who are also taking metformin.	Efficacy of dulaglutide compared with daily liraglutide.	Started	10 April 2014
H9X-MC-GBDG: A study comparing the effect of once-weekly dulaglutide with placebo in patients with type 2 diabetes mellitus on	The aim of this study is to demonstrate that once-weekly dulaglutide 1.5 mg is better	Efficacy of dulaglutide when added to sulphonylurea.	Started	13 May 2015

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
sulfonylurea therapy (AWARD-8: Assessment of Weekly AdministRation of LY2189265 in Diabetes-8)	than placebo as measured by blood sugar at 24 weeks in patients with type 2 diabetes also taking sulphonylurea therapy.			
H9X-CR-GBDK: The efficacy and safety of once-weekly, subcutaneous dulaglutide compared to once-daily insulin glargine in patients with type 2 diabetes mellitus on metformin and/or a sulfonylurea.	The aim of this study is to determine that the change in blood sugar with once-weekly dulaglutide is similar to once-daily insulin glargine after 26 weeks of treatment in Asian patients with type 2 diabetes mellitus taking metformin and/or a sulphonylurea.	Efficacy of add-on dulaglutide compared with insulin glargine in an Asian (China) type 2 diabetes patient population.	Started	31 Mar 2015
H9X-JE-GBCG: The efficacy and safety of once-weekly, subcutaneous dulaglutide compared to glimepiride in patients with type 2 diabetes mellitus.	The aim of this study is to determine that blood sugar control achieved with once-weekly dulaglutide (1.5 mg) is similar to that achieved with glimepiride (1 to 3 mg/day) after 26 weeks of treatment in Asian patients	Efficacy of dulaglutide alone compared with a sulphonylurea in Chinese type 2 diabetes patient population.	Started	18 Dec 2014

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
	with type 2 diabetes mellitus who have stopped or have not taken other diabetes medicines by mouth.			
H9X-JE-GBDP: A study of dulaglutide compared to placebo and liraglutide in patients with type 2 diabetes mellitus.	The aim of this study is to demonstrate the superiority of once-weekly dulaglutide versus placebo in controlling blood glucose at 26 weeks in Japanese patients with type 2 diabetes mellitus who have not taken diabetes medicines by mouth.	Efficacy of dulaglutide alone in a Japanese type 2 diabetes patient population.	Started	14 Nov 2014
H9X-JE-GBDQ: A 52-week safety study of dulaglutide in combination with oral antihyperglycaemic medications in Japanese patients with type 2 diabetes mellitus.	The aim of this study is to assess adverse events, serious adverse events, low and high blood-glucose, and patients having to stop therapy during 1-year treatment with dulaglutide as an add-on to sulphonylurea, biguanides, thiazolidinedione, or glinides in	Safety of dulaglutide when taken with other diabetes medicines given by mouth in a Japanese type 2 diabetes patient population.	Started	23 May 2014

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
	the treatment of type 2 diabetes.			
H9X-JE-GBDY: A study of dulaglutide compared to insulin glargine in patients with type 2 diabetes mellitus on a sulfonylurea and/or biguanide.	The aim of this study is to demonstrate the similarity of once-weekly dulaglutide versus insulin glargine on blood sugar at 26 weeks in Japanese patients with type 2 diabetes taking a sulphonylurea and/or biguanide.	Efficacy of dulaglutide compared with insulin glargine, added on to sulphonylurea and/or metformin, in a Japanese type 2 diabetes patient population.	Started	30 May 2014
H9X-MC-GBDJ: Cardiovascular outcomes study	The aim is to test if once-weekly dulaglutide reduces the occurrence of death from heart or circulatory (cardiovascular) causes, nonfatal heart attack, or nonfatal stroke when added to the glucose-lowering regimen of patients with type 2 diabetes, compared with once-weekly placebo. Additionally to monitor adverse events including	Cardiovascular effects. Potential risk of acute pancreatitis.	Started	March 2020

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
	pancreatitis.			
H9X-MC-GBDL: The amount of drug in the blood after a single dulaglutide dose in healthy Chinese subjects and of multiple dulaglutide doses in Chinese patients with type 2 diabetes mellitus	To evaluate the amount of medicine in the blood after a single dose of dulaglutide in healthy Chinese subjects and the distribution of the medicine in the body after multiple doses in Chinese patients with type 2 diabetes.	Safety in Chinese patients.	Started	28 Nov 2014
An active surveillance program for cases of medullary thyroid carcinoma (MTC)	To determine the annual incidence of this type of thyroid cancer in the US and to identify any possible increase related to the introduction of liraglutide and related medicines such as dulaglutide into the US market.	Potential risk of medullary thyroid carcinoma.	Planned	March 2032

Studies which are a condition of the marketing authorisation

None of the above studies are a condition of the marketing authorisation.

Summary of changes to the risk management plan over time

Not applicable.

This summary was last updated in 10-2014.