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Summary of the risk management plan (RMP) for Xultophy (insulin degludec / liraglutide)

This is a summary of the risk management plan (RMP) for Xultophy, which details the measures to be taken in order to ensure that Xultophy 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 Xultophy, which can be found on Xultophy's EPAR page.

Overview of disease epidemiology

Xultophy 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

Xultophy contains the active substances insulin degludec and liraglutide. It is given by injection under the skin, together with diabetes medicines given by mouth, in patients whose blood glucose (blood sugar) cannot be controlled with medicines by mouth alone.

Once-daily injection of Xultophy has been shown to be of benefit in controlling blood glucose in two main studies in patients with type 2 diabetes. In both studies, the main measure of effectiveness was the change after 6 months of treatment in the level in the blood of a substance called glycosylated haemoglobin (HbA1c), which gives an indication of how well blood glucose is controlled.

- The first study involved 1,663 patients whose diabetes was not adequately controlled with the diabetes medicines metformin or metformin and pioglitazone taken by mouth; adding Xultophy to their treatment was compared with adding either of its active substances, insulin degludec or liraglutide. The average HbA1c level was 8.3% at the start. After 6 months of treatment with Xultophy it fell to 6.4%, compared with 6.9% with insulin degludec and 7.0% with liraglutide. Comparable results were seen in a group of patients who continued treatment up to 1 year.
- The second study involved 413 patients whose blood glucose was not adequately controlled by a combination of insulin and metformin with or without other diabetes medicines taken by mouth. Treatment with Xultophy and metformin was compared with treatment using insulin degludec and

metformin. Average HbA1c at the start was 8.7% in the Xultophy group, which fell after 6 months of treatment to 6.9%. In the comparator group it fell from 8.8% to 8.0%.

The majority of patients treated with Xultophy achieved control of their blood glucose (target levels of HbA1c below 7.0%) and many achieved HbA1c below 6.5%. The studies also looked at other effects of treatment, including on bodyweight; this was generally stable or fell slightly in patients treated with Xultophy, but tended to increase in those given insulin degludec and to decrease with liraglutide.

Unknowns relating to treatment benefits

Xultophy has not been studied in patients with liver problems or moderate and severe kidney problems. Studies used to license Xultophy did not include patients who had been treated with liraglutide or other medicines of the same class before transferring to Xultophy, or patients who were injecting more than 40 units of basal insulin before transferring to Xultophy, and it is not known if the effects of the medicine would be equivalent in such patients.

Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Diarrhoea or feeling or being sick (Gastrointestinal disorders: diarrhoea, nausea and vomiting)	Up to 1 out of every 10 patients will get diarrhoea, feel sick or be sick. This is usually mild and happens at the start of treatment or when increasing the dose. It usually goes away after a few days or weeks. However, if it is severe, it can cause dehydration due to loss of fluids from the body.	Patients should be advised by their healthcare professional about the need to drink sufficient fluids to avoid dehydration if diarrhoea or vomiting occur.
Low blood sugar (Hypoglycaemia)	Low blood sugar is the most common side effect of Xultophy, seen in more than 1 patient in 10. In rare cases (4 out of every 1,000 patients) this can be severe and may be life threatening. When Xultophy is combined with a type of diabetes medicine called a sulphonylurea, hypoglycaemia may occur more frequently.	The product information for Xultophy contains warnings about the risk of low blood sugar and how to manage it.If patients notice signs of low blood sugar they should eat glucose tablets or a high-sugar snack. Patients should monitor their blood-sugar levels regularly. The risk of low blood sugar when Xultophy is used with a sulphonylurea can be lowered by a reduction in the dose of sulphonylurea.
Allergic reactions	Allergic reactions to Xultophy are uncommon, with skin reactions such as itchy rash (urticaria) seen in less than 1 patient in 100. More severe allergic reactions, including swelling of the tissues around the neck, face, mouth and/or throat, are rare.	The product information for Xultophy contains warnings for doctors and patients on the possibility of allergic reactions. Patients must not use this medicine if they are allergic to any of its ingredients.

Risk	What is known	Preventability
Inflamed pancreas (Pancreatitis)	In very rare cases medicines that work like liraglutide may be linked to pancreatitis.	The product information for Xultophy contains warnings for doctors and patients about the risk of pancreatitis. Patients should tell their doctor if they develop a severe stomach ache which does not go away, as this could be a sign of pancreatitis. If pancreatitis is suspected, treatment with Xultophy should be stopped, and if it is confirmed, Xultophy should not be restarted. Caution should be exercised in patients with a history of pancreatitis.

Important potential risks

Risk	What is known
Kidney problems (Altered renal function)	If patients get dehydrated due to diarrhoea and vomiting, it can reduce how well the kidneys work. Patients should be advised by their healthcare professional about the need to drink sufficient fluids to avoid dehydration if diarrhoea or vomiting occur.
Heart disease and stroke (Cardiovascular disorders)	Patients with type 2 diabetes have a higher risk of heart disease and stroke, which might lead to death, and this risk may be increased further in patients taking some diabetes medicines. The company that markets Xultophy is carrying out a study with liraglutide to evaluate whether it affects the risk of these conditions.
Antibody development	Taking insulin or liraglutide may cause the immune system (the body's natural defences) to produce antibodies against the medicine. In rare cases, these antibodies can neutralise the effects of the medicine so that the doctor has to change the dose or the medicine. However, this has not been seen in any studies of Xultophy.
Medication errors	Medication errors can occur if the patient takes the wrong dose, or if Xultophy is confused with another injectable diabetes medicine such as fast-acting (bolus) insulin. The label must always be checked before each injection to ensure the right medicine is injected. The company that markets Xultophy has prepared educational material for doctors in the EU to help explain the use of the medicine and reduce the risk of medication errors.
Cancer and tumours, including cancers of the thyroid and	There have been studies which raised concerns that insulins like the insulin degludec in Xultophy might be associated with a small increased risk of cancer. However, no conclusive data exist to date that link these insulins with

Risk	What is known
pancreas (Neoplasms including medullary thyroid cancer and pancreatic cancer)	such an increase in risk of cancer. When liraglutide, the other active substance in Xultophy, was given to rats and mice for most of their lifetime, more thyroid cancers were seen. It is unknown whether liraglutide causes these rare types of thyroid cancer (thyroid C-cell tumours, including medullary thyroid carcinoma), in humans. In addition, there have been concerns that medicines that work in the same way as liraglutide may increase the risk of cancer of the pancreas. Evidence to date from studies with liraglutide and results following its marketing does not indicate that treatment with liraglutide causes cancer. To date, studies with Xultophy itself have not raised concern about an association with 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 it is therefore considered as a potential risk.

Missing information

Risk	What is known
Use in children and adolescents	Xultophy has not been studied in people under 18 years of age so it is not known if Xultophy is safe and effective in this age group.
Patients whose hearts cannot pump blood around the body properly (severe congestive heart failure, NYHA III-IV)	Xultophy has not been studied in patients with severe congestive heart failure. These patients also did not take part in studies with insulin degludec. However, they are included in a study with liraglutide, which is ongoing at the moment.
Using warfarin and Xultophy at the same time (Drug–drug interactions with warfarin)	Many medicines are known to affect the action of warfarin (a medicine used to thin the blood and stop it clotting). Up to now, there have been no reports of problems of effectiveness or safety in patients taking warfarin who also used liraglutide or insulin degludec, and Xultophy has been safely used in some patients also taking warfarin. However, the number of patients using both Xultophy and warfarin in studies is too low to draw any conclusions. Patients who start Xultophy while taking warfarin or similar medicines should therefore check their blood clotting more often (called 'INR monitoring').
Use of Xultophy by type 1 diabetes patients (Off-label use by T1DM patients)	Xultophy has not been tested in patients with type 1 diabetes, and is therefore not approved for this indication. It is not known if Xultophy is effective and safe in type 1 diabetes patients.

Risk	What is known
Patients with liver problems (Use in patients with hepatic impairment)	Xultophy has not been properly tested in patients with liver problems and there is not much information about Xultophy use in this group of patients. This means Xultophy cannot currently be recommended for use in these patients.
Patients with moderate and severe kidney problems (Use in patients with moderate and severe renal failure)	Xultophy has not been properly tested in patients with moderate and severe kidney problems. There is little information about Xultophy use by patients with moderate kidney problems. There is no information about Xultophy use by patients with severe kidney problems. This means that Xultophy cannot currently be recommended for use in these patients. This includes patients with 'end-stage' kidney problems.
Women who want to become pregnant, are pregnant or are breastfeeding	Xultophy has not been properly studied in pregnant or breastfeeding women. 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.
Transfer from injected diabetes medicines	Xultophy has not been studied in patients who have previously been treated with liraglutide or other medicines of the same class, nor in patients being treated with more than 40 units of long-acting (basal) insulin daily. Patients who have been treated with these medicines may need more blood sugar checks when transferring to treatment with Xultophy. This should be discussed with a doctor.
Use of Xultophy in patients older than 75 years	Xultophy was tested in very few patients older than 75 years. It is not known if Xultophy can be used safely by patients older than 75 years.

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 Xultophy can be found on Xultophy's EPAR page.

This medicine has special conditions and restrictions for its safe and effective use (additional risk minimisation measures). Full details on these conditions and the key elements of any educational material can be found in Annex II of the product information which is published on Xultophy's EPAR page; how they are implemented in each country however will depend upon agreement between the marketing authorisation holder and the national authorities.

These additional risk minimisation measures are for the following risks:

Medication errors

Risk minimisation measure: Educational material for healthcare professionals
Objective and rationale: Xultophy is a new kind of treatment option for people with type 2 diabetes. The dose of Xultophy is measured in 'dose steps'. The phrase 'dose steps' has been introduced to combine units of insulin degludec and milligrams of liraglutide as a single term that describes the dose of Xultophy. Since Xultophy is a new treatment option and 'dose step' a new way of describing doses, there could be a risk of medication errors (mistakes in the dosage). Selecting an incorrect starting dose or adjusting the dose incorrectly could result in too much or too little medicine being given, which in turn could lead to too high or low blood sugar or reactions like nausea, vomiting and diarrhoea. It is therefore important that healthcare professionals advise patients correctly, and report all medication errors.
Description: The company that markets the medicine is providing educational material to healthcare professionals in the EU, explaining: • that Xultophy is a new kind of treatment option for people with type 2 diabetes; • how to administer Xultophy in dose steps and set the dose; • how to select the recommended Xultophy starting dose; • how to adjust the dose of Xultophy; • that there is a need to report all medication errors. The content, format and distribution of these materials will be agreed with the health authorities of the individual EU countries.

Planned post-authorisation development plan

There are no studies of safety or efficacy planned after authorisation.

Studies which are a condition of the marketing authorisation

Not applicable.

Summary of changes to the risk management plan over time

Not applicable.

This summary was last updated in 08-2014.