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Summary of the risk management plan (RMP) for Jardiance (empagliflozin)

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

Overview of disease epidemiology

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

Jardiance (empagliflozin) is used for the treatment of adults with type 2 diabetes in patients whose blood glucose levels are not satisfactorily controlled on diet and exercise alone and who cannot be treated with another diabetes medicine, metformin. Jardiance can also be used as 'add-on' to other diabetes medicines, including insulin, when these medicines together with exercise and diet are not providing adequate control of the diabetes. The active substance in Jardiance, empagliflozin, works in the kidneys, where it increases the amount of glucose being released into the urine, thereby lowering and helping to control blood sugar levels.

In clinical studies, treatment with empagliflozin 10 mg or 25 mg once daily had a consistent and relevant effect in reducing glycosylated haemoglobin (HbA1c), a substance in the blood that measures how well blood glucose is controlled. In each of the 4 main studies (in which patients were taking different combinations of diabetes medicines), both doses of empagliflozin were more effective than placebo (a dummy treatment), with the average improvement in HbA1c over placebo varying between 0.48% and 0.74% for empagliflozin 10 mg and between 0.59% and 0.85% for empagliflozin 25 mg after 24 weeks of treatment. In addition decreases in blood pressure and body weight were seen in patients treated with empagliflozin, which could represent possible additional benefits.

Unknowns relating to treatment benefits

It is not known if the effects of Jardiance on blood pressure and body weight reduction will, if sustained, provide a significant additional reduction in the risk of conditions such as heart attacks and strokes.

It is not known if children (aged between 10 and less than 18 years) with type 2 diabetes will have a similar treatment benefit profile as adult patients. Empagliflozin has also not been studied in patients taking a class of injectable diabetes medicines called glucagon-like peptide 1 (GLP-1) analogues.

Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Urinary tract infection	Because empagliflozin increases the amount of sugar in the urine, it may encourage the growth of bacteria. Up to 1 patient in 10 treated with empagliflozin may experience a urinary tract infection, although in studies this also occurred in patients taking placebo. The risk is increased in patients with a history of urinary tract infections and infection may be more likely in women than in men.	Patients should drink plenty of water and other liquids, urinate often, and wipe themselves carefully after a bowel movement, particularly if they have previously had urinary tract infections. Serious infections may be caused by abnormalities in the urinary system, which could lead to permanent kidney damage. If patients have recurring infections, they should talk with their doctor who may consider additional tests. In addition, temporary interruption of empagliflozin may be considered in patients with complicated urinary tract infections.
Genital infection	Mild or moderate genital infection such as vulvovaginitis (inflammation of the vulva and vagina due to infection), moniliasis (a type of yeast infection), and balanitis (infection causing inflammation of the head of the penis) has occurred in up to about 1 patient in 20 given empaglifozin. Genital infection may be more likely in women than in men.	Preventive measures for genital infection are similar to those described above for urinary tract infections.
Fluid loss (volume depletion)	Because of the way empagliflozin works, which encourages urination, less than about 1 patient in 100 may experience symptoms related to fluid loss or dehydration (including low blood pressure and	Doctors should take extra care when prescribing Jardiance to patients in whom a drop in blood pressure due to fluid loss could pose a risk, such as patients with known cardiovascular disease, patients who have had low

Risk	What is known	Preventability
	dizziness). Symptoms may be more common in patients 75 years and older (occurring in up to 1 in 20 at the higher dose of 25 mg).	blood pressure while taking blood pressure medicines, or patients 75 years of age or older. Where patients have another condition that may cause fluid loss (e.g. diarrhoea) careful monitoring of fluid status is needed. Temporarily stopping treatment with Jardiance should be considered until any fluid loss is corrected.
Low blood sugar levels (hypoglycaemia with insulin and/or sulfonylureas)	A few patients may experience low blood sugar levels due to treatment with empagliflozin. The risk of low blood sugar is increased when a patient is also taking other medicines known to cause low blood sugar levels (insulin or sulfonylureas), occurring in more than 1 patient in 10.	A lower dose of insulin or a sulfonylurea may be required to reduce the risk of low blood sugar when used in combination with empagliflozin.

Important potential risks

Risk	What is known
Cancer of the kidney and bladder (urinary tract)	An increased risk of renal cancer (cancer of the kidney) with empagliflozin was seen in one study in male mice, though not in other animals. In patients given empagliflozin, the overall number who developed cancer of the kidney or bladder was low and comparable to placebo. There is no obvious way that empagliflozin could increase the risk of renal tumours.
Kidney injury (renal impairment)	Because of the way empagliflozin works there is a risk of effects on the kidneys that could reduce their function (renal impairment). The overall number of patients with renal impairment was low. Renal impairment was slightly more common in patients receiving empagliflozin than in patients receiving placebo, and increased with increasing age and use of diuretics (water tablets).
Liver injury	Liver injury was considered an important potential risk due to small changes observed in laboratory tests looking at liver function. The overall number of empagliflozin patients with liver injury has been low and any relationship to empagliflozin treatment has not been established.
Off-label use (e.g. for weight	Because empagliflozin produces weight loss (due to the increase in sugar lost in the urine), there is the potential for inappropriate use to

Risk	What is known
loss in non-diabetic patients)	encourage weight loss in non-diabetic patients. Empagliflozin will be available as a prescription medicine only, which would restrict access to people who have diabetes and are under close medical surveillance by their doctor.
Bone fracture	Bone fracture was considered an important potential risk because it has been seen with other medicines of the same class. The overall number of patients with bone fractures was low and bone fracture was no more common with empagliflozin than with placebo. No loss in bone mineral density (a measure of bone strength) was observed after 1 and 2 years of treatment.

Missing information

Risk	What is known
Children (paediatric patients)	Empagliflozin has not been studied in patients younger than 18 years. A paediatric investigational plan (PIP) is in place to study the use of empagliflozin in paediatric patients aged 10 to less than 18 years.
Elderly patients	Since elderly patients are at increased risk of adverse events from medicines, post-marketing safety information will be collected regarding treatment of the elderly.
Pregnancy/breastfeeding	Empagliflozin has not been investigated in pregnant and/or breastfeeding women. Empagliflozin has not been shown to produce abnormalities during development in the womb. Experimental studies in animals have detected empagliflozin in breast milk. Due to lack of information regarding human use, women should not be treated with empagliflozin during pregnancy and breastfeeding.
Clinical impact of altered blood fats (dyslipidaemia)	Small increases in laboratory values for blood fats (lipids) were seen in all treatment groups in the clinical studies. No increased cardiovascular risk (risk of effects on the heart and circulation) is expected during empagliflozin treatment.
Long-term safety (particularly cardiovascular)	Experience with long-term safety is currently limited, the maximum exposure being up to 2 years. Long-term studies are ongoing. Clinical data did not reveal an increase in the risk of cardiovascular events upon the use of empagliflozin.
Concomitant use with GLP-1 analogues	Empagliflozin has not been studied in combination with certain diabetes medicines known as GLP-1 analogues.
Use in patients with severe reduction of liver function (hepatic impairment)	Empagliflozin has not been studied in patients with severe hepatic impairment.
Long-term safety (melanoma)	A small numerical difference in melanoma (a type of skin cancer)

Risk	What is known
	was observed between empagliflozin and placebo in clinical trials. The overall number of patients with malignancy was low (less than 0.1%). There is no obvious way that empagliflozin could increase the risk of cancer, including melanoma.

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 Jardiance can be found on Jardiance'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
Long-term CV safety study 1245.25	To evaluate long-term cardiovascular safety of empagliflozin in patients with type 2 diabetes and increased cardiovascular risk.	Long-term safety (particularly cardiovascular), dyslipidaemia, use with GLP-1 analogues, urinary tract cancer, bone fracture, missing long-term safety information on melanoma	Started	Event driven, final results 4th quarter of 2015
PASS (1245.96) to assess the risk of renal and liver injury, urinary tract and genital infection	To evaluate the risk of urinary tract and genital infection, acute renal (kidney) and hepatic (liver) injury, resulting in hospitalisations, in empagliflozin-treated patients, compared with users of other diabetes treatment.	Urinary tract infection, genital infection, renal impairment, liver injury	Planned	Will depend on patient uptake; estimated submission date to be determined in the final study protocol

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
PASS (1245.97) to assess the risk of urinary tract malignancies, preceded by feasibility assessment	To evaluate the risk of renal (kidney) and bladder cancer in empagliflozin-treated patients, compared with users of other diabetes treatment.	Urinary tract cancer	Planned	Will be determined in the final study protocol

Studies which are a condition of the marketing authorisation

None of the above studies are conditions of the marketing authorisation.

Summary of changes to the risk management plan over time

Not applicable.

This summary was last updated in 04-2014.