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Summary of the risk management plan (RMP) for Synjardy (empagliflozin / metformin)

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

Overview of disease epidemiology

Synjardy is a medicine used to treat adults with type 2 diabetes. 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

Synjardy contains the active substances empagliflozin and metformin. It is used as an addition to diet and exercise in adults with type 2 diabetes whose blood glucose levels are not satisfactorily controlled by adding metformin alone or with another diabetes medicine (including insulin). It can also be used to replace empagliflozin and metformin as separate tablets in patients who are already taking both.

The benefits of empagliflozin in combination with metformin have been shown in 3 main studies involving 1,679 patients with type 2 diabetes whose blood sugar was not adequately controlled by metformin, alone or combined with other diabetes medicines (pioglitazone or a type of diabetes medicine called a sulphonylurea). The studies compared the effect of emplagliflozin plus metformin versus placebo (dummy treatment) with metformin. The main measure of effectiveness was the change in the level of a substance in the blood called glycosylated haemoglobin (HbA1c), which gives an indication of how well the blood glucose is controlled, after 24 weeks of treatment.

The studies showed a clinically relevant reduction in HbA1c when the Synjardy combination of empagliflozin plus metformin was given, compared with placebo plus metformin. Overall, the additional reduction was 0.58 percentage points with the combination providing 5 mg of empagliflozin twice daily and 0.62 percentage points with the 12.5 mg dose. Similar benefits were seen in the studies regardless of the other diabetes medicines being taken. In addition, the results indicated that Synjardy treatment was associated with a decrease in body weight and blood pressure.

Supportive evidence was provided from several further studies. Some of these were continuations of the main studies that suggested the benefits of the medicine continued with longer therapy. Studies also indicated Synjardy was as effective as empagliflozin and metformin taken separately, and that the combination helped reduce HbA1c when added to treatment including insulin.

Unknowns relating to treatment benefits

It is not known if the effects of Synjardy 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 (younger than 18 years) with type 2 diabetes would have a similar treatment benefit profile to adult patients. Synjardy 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. In studies to license Synjardy, the percentage of patients who had urinary tract infection was comparable between those given Synjardy (11.9%) and those given placebo and metformin (12.3%).	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 Synjardy may be considered in patients with complicated urinary tract infections.
Genital infection	In studies to license Synjardy, the percentage of patients who had genital infection was higher among those given Synjardy (6.7%) than those given placebo and metformin (1.5%). 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 the empagliflozin component in Synjardy 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 dizziness). Symptoms may be more	Doctors should take extra care when prescribing Synjardy 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 blood pressure while taking blood pressure medicines, or

Risk	What is known	Preventability
	common in patients aged 75 years and older.	patients aged 75 years of age or older. Where patients have another condition that may cause fluid loss (e.g. gastrointestinal illness) careful monitoring of fluid status is needed. Temporarily stopping treatment with Synjardy should be considered until any fluid loss is corrected.
Build-up of acids and lactate in body tissues and blood (lactic acidosis)	Lactic acidosis is a very rare but serious condition due to a build-up of lactic acid in the blood that can occur in patients taking metformin-containing medicines. This occurs primarily in patients whose kidneys are not working properly, who have a severe infection or are dehydrated, who have diabetic ketoacidosis (a complication of diabetes with high blood sugar, rapid weight loss, nausea or vomiting), who have severe circulatory problems such as 'shock', who have liver problems or who drink alcohol to excess. In studies to license Synjardy, 2 patients given the medicine experienced lactic acidosis.	Synjardy should not be used by patients at high risk of lactic acidosis. If lactic acidosis is suspected during treatment with Synjardy, treatment should be immediately discontinued and the patient should be admitted to the hospital.
Low blood sugar levels (hypoglycaemia with insulin and/or sulphonylureas)	A few patients may experience low blood sugar levels due to treatment with Synjardy. 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 sulphonylureas). In studies to license Synjardy, low blood sugar in patients also taking insulin and/or sulphonylureas occurred in 30.6% of those given Synjardy and 27.9% of those not given this medicine.	A lower dose of insulin or a sulphonylurea may be required to reduce the risk of low blood sugar when used in combination with Synjardy.

Important potential risks

Risk	What is known
Cancer of the kidney and bladder (urinary tract carcinogenicity)	An increased risk of kidney cancer with empagliflozin was seen in one study in male mice, though not in other animals.

Risk	What is known
	In patients given Synjardy, the number of patients who developed cancer of the kidney (2 patients) or bladder (2 patients) was low and comparable to placebo. There is no obvious way that Synjardy could increase the risk of kidney 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). Decreased kidney function might be more common in elderly patients (75 years and older). In studies to license Synjardy, the percentage of patients with kidney impairment was low (0.7% of those given Synjardy and 0.3% of those given placebo and metformin).
Liver injury	Liver injury is considered an important potential risk of empagliflozin alone, due to small changes observed in laboratory tests looking at liver function. The percentage of Synjardy patients with liver injury has been low (1.6%) and any relationship to treatment with the medicine has not been established.
Bone fracture	Bone fracture is considered an important potential risk because it has been seen with other medicines of the same class as empagliflozin. The percentage of Synjardy patients with bone fractures was low (1.5%) and bone fracture was no more common with Synjardy than with placebo. No loss in bone mineral density (a measure of bone strength) was observed after 1 and 2 years of treatment with empagliflozin alone.

Missing information

Risk	What is known
Children (paediatric patients)	Synjardy has not been studied in patients younger than 18 years. Children should not take Synjardy.
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	Synjardy has not been investigated in pregnant and/or breastfeeding women. Empagliflozin and metformin have not been shown to produce abnormalities during development in the womb. Due to a lack of information regarding human use, women should not be treated with Synjardy 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 with empagliflozin alone. No increased cardiovascular risk (risk of effects on the heart and circulation) is expected during Synjardy treatment.
Long-term safety (particularly cardiovascular)	Experience with long-term safety is currently limited, the maximum exposure in completed studies being up to 2 years. Long-term studies are ongoing. Clinical data did not reveal an increase in the risk of cardiovascular events following the use of Synjardy.
Concomitant use with GLP-1 analogues	Synjardy has not been studied in combination with certain diabetes medicines known as GLP-1 analogues.
Long-term safety	A small numerical difference in melanoma (a type of skin cancer) was

Risk	What is known
(melanoma)	observed between Synjardy and placebo in clinical trials. The percentage of patients with malignancy was low (less than 0.11%). There is no obvious way that Synjardy 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 Synjardy can be found on Synjardy'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; patients treated with Synjardy will be included.	Long-term safety (particularly cardiovascular), dyslipidaemia, concomitant use of 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 (trial 1245.96) to assess the risk of renal and liver injury, and urinary tract and genital infection	To evaluate the risk of urinary tract and genital infection, and acute kidney and liver injury resulting in hospitalisations, in patients treated	Urinary tract infection, genital infection, acute kidney failure, liver injury.	Planned	Will depend on patient uptake; submission date to be determined in the final trial protocol.

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

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 04-2015.