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EPAR summary for the public

Synjardy

empagliflozin / metformin

This is a summary of the European public assessment report (EPAR) for Synjardy. It explains how the Agency assessed the medicine to recommend its authorisation in the EU and its conditions of use. It is not intended to provide practical advice on how to use Synjardy.

For practical information about using Synjardy, patients should read the package leaflet or contact their doctor or pharmacist.

What is Synjardy and what is it used for?

Synjardy is a diabetes medicine used with diet and exercise to treat adults with type 2 diabetes. It contains the active substances empagliflozin and metformin. Synjardy is used:

- in patients whose diabetes is not sufficiently controlled by metformin alone;
- in combination with other diabetes medicines in patients whose diabetes is not sufficiently controlled on these medicines plus metformin;
- in patients who are already taking metformin and empagliflozin as separate tablets.

How is Synjardy used?

Synjardy is available as tablets containing 5 or 12.5 mg of empagliflozin with 850 or 1,000 mg of metformin, and can only be obtained with a prescription.

The recommended dose of Synjardy is one tablet twice a day with meals, and treatment is normally started with a tablet that supplies the dose of metformin the patient is already taking, together with the lowest dose (5 mg) of empagliflozin. Doses are adjusted as necessary.

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If Synjardy is used in combination with insulin or a sulphonylurea (a medicine that increases the body's production of insulin), the doses of these medicines may need to be lowered to avoid hypoglycaemia (low blood sugar levels).

For further information, see the package leaflet.

How does Synjardy work?

In type 2 diabetes the body does not make enough insulin to control the level of glucose (sugar) in the blood or the body is unable to use insulin effectively. This leads to a high level of glucose in the blood. The two active substances in Synjardy, empagliflozin and metformin, work in different ways to lower blood glucose, and thus to control symptoms of the disease.

Empagliflozin works by blocking a protein in the kidneys (called sodium-glucose co-transporter 2 or SGLT2). As blood is filtered by the kidneys, SGLT2 stops glucose in the bloodstream from being passed out into the urine. By blocking the action of SGLT2, empagliflozin causes more glucose to be removed in the urine, thereby reducing the levels of glucose in the blood. Empagliflozin has been authorised in the EU under the trade name Jardiance since 2014.

Metformin works mainly by reducing the production of glucose in the body and reducing its absorption from the gut. Metformin has been available in the EU since the 1950s.

What benefits of Synjardy have been shown in studies?

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 (such as pioglitazone or a type of diabetes medicine called a sulphonylurea). The studies compared the effect of empagliflozin plus metformin versus placebo (a dummy treatment) with metformin. The main measure of effectiveness was the reduction in the level of a substance in the blood called glycosylated haemoglobin (HbA1c) after 24 weeks of treatment. HbA1c gives an indication of how well the blood glucose is controlled.

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

Another main study showed that adding empagliflozin (one of the active substances of Synjardy) to usual treatment reduced adverse cardiovascular (heart and blood vessels) effects. The study involved patients with type 2 diabetes who already had cardiovascular disease (such as angina, heart attack and stroke). The main measure of effectiveness was the occurrence of one of three major cardiovascular events: stroke, heart attack or death caused by cardiovascular disease. On average, patients in the study were followed up for 3.1 years. In those receiving empagliflozin, cardiovascular events occurred in 10.5% (490 out of 4,687) of patients compared with 12.1% (282 out of 2,333) of patients receiving placebo. Among these, in patients who were also taking metformin (the other active

substance in Synjardy), the three major cardiovascular events occurred in 9.9% (344 out of 3,459) of patients receiving empagliflozin and in 10.9% (189 out of 1,734) of patients receiving placebo.

What are the risks associated with Synjardy?

The most common side effects with Synjardy are hypoglycaemia (low blood sugar levels) when the medicine is taken with a sulphonylurea or insulin, infections of the urinary tract and genitals, and increased urination. For the full list of all side effects reported with Synjardy, see the package leaflet.

Synjardy must not be used in patients with:

- metabolic acidosis (when the body produces more acid than it gets rid of) or diabetic pre-coma (dangerous complications of diabetes);
- severely reduced kidney function or conditions that could affect the kidneys such as dehydration, severe infection or a steep fall in blood pressure;
- a condition that could reduce the supply of oxygen to body tissues (such as in patients with worsening heart failure, recent heart attack, breathing difficulty or a steep fall in blood pressure);
- liver impairment, or problems with alcoholism or alcohol intoxication.

For the full list of restrictions, see the package leaflet.

Why is Synjardy approved?

The Agency's Committee for Medicinal Products for Human Use (CHMP) decided that Synjardy's benefits are greater than its risks and recommended that it be approved for use in the EU. The CHMP concluded that the medicine could help produce a clinically meaningful reduction in blood glucose in patients with type 2 diabetes, and the benefits and risks were in line with those of the individual active substances. Synjardy was also shown to reduce cardiovascular events in patients with type 2 diabetes who already had cardiovascular disease. Because of concerns about the balance of benefit and risk in patients with reduced kidney function taking the fixed-dose combination, the CHMP recommended restricting its use in these patients.

What measures are being taken to ensure the safe and effective use of Synjardy?

Recommendations and precautions to be followed by healthcare professionals and patients for the safe and effective use of Synjardy have been included in the summary of product characteristics and the package leaflet.

Other information about Synjardy

The European Commission granted a marketing authorisation valid throughout the European Union for Synjardy on 27 May 2015.

The full EPAR and risk management plan summary for Synjardy can be found on the Agency's website: ema.europa.eu/Find medicine/Human medicines/European public assessment reports. For more information about treatment with Synjardy, read the package leaflet (also part of the EPAR) or contact your doctor or pharmacist.

This summary was last updated in 02-2017.