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EPAR summary for the public

Jentadueto

linagliptin / metformin hydrochloride

This is a summary of the European public assessment report (EPAR) for Jentadueto. It explains how the Committee for Medicinal Products for Human Use (CHMP) assessed the medicine to reach its opinion in favour of granting a marketing authorisation and its recommendations on the conditions of use for Jentadueto.

What is Jentadueto?

Jentadueto is a medicine that contains the active substances linagliptin and metformin hydrochloride. It is available as tablets (2.5 mg/850 mg and 2.5 mg/1,000 mg).

What is Jentadueto used for?

Jentadueto is used in adults with type 2 diabetes to improve the control of blood glucose (sugar) levels. It is used in addition to diet and exercise in the following ways:

- in patients who are not satisfactorily controlled on metformin (a diabetes medicine) used on its own;
- in patients who are already taking a combination of linagliptin and metformin as separate tablets;
- in combination with a sulphonylurea or insulin (other types of diabetes medicines) in patients who are not satisfactorily controlled on this medicine and metformin.

The medicine can only be obtained with a prescription.

How is Jentadueto used?

Jentadueto is taken twice a day. The strength of tablet to use depends on the dose of the other diabetes medicines that the patient was taking before. If Jentadueto is taken with a sulphonylurea or insulin, the dose of these medicines may need to be lowered, to avoid hypoglycaemia (low blood sugar levels).

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The maximum dose is 5 mg of linagliptin and 2,000 mg of metformin per day. Jentadueto should be taken with food to reduce stomach problems caused by metformin.

How does Jentadueto work?

Type 2 diabetes is a disease in which the pancreas does not make enough insulin to control the level of glucose in the blood or when the body is unable to use insulin effectively. The active substances in Jentadueto, linagliptin and metformin hydrochloride, each working in a different way.

Linagliptin is a dipeptidyl-peptidase-4 (DPP 4) inhibitor. It works by blocking the breakdown of 'incretin' hormones in the body. These hormones are released after a meal and stimulate the pancreas to produce insulin. By prolonging the action of incretin hormones in the blood, linagliptin stimulates the pancreas to produce more insulin when blood glucose levels are high. Linagliptin does not work when the blood glucose is low. Linagliptin also reduces the amount of glucose made by the liver, by increasing insulin levels and decreasing the levels of the hormone glucagon. Together, these processes reduce blood glucose levels and help to control type 2 diabetes. Linagliptin has been authorised in the European Union (EU) as Trajenta since 2011.

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

As a result of the action of both active substances, blood glucose levels are reduced and this helps to control type 2 diabetes.

How has Jentadueto been studied?

The company presented the results of four studies with linagliptin in patients with type 2 diabetes, which were used to support the approval of Trajenta in the EU, comparing linagliptin given at 5 mg once per day with placebo (a dummy treatment). The studies looked at the effectiveness of linagliptin used on its own (503 patients), in combination with metformin (701 patients), with metformin plus a sulphonylurea (1,058 patients) or with another diabetes medicine pioglitazone (389 patients).

Another study was carried out involving 791 patients with type 2 diabetes, where the combination of linagliptin plus metformin given twice per day was compared with giving metformin alone, linagliptin alone or placebo. Linagliptin was given at 2.5 mg twice per day in the combination treatment and at 5 mg once per day in the single treatment. Metformin was given at either 500 mg or 1,000 mg twice per day, for both the combination and the single treatment.

A further study was carried out involving 491 patients with type 2 diabetes taking metformin twice per day, where placebo or linagliptin at either 2.5 mg twice per day or at 5 mg once per day was added to their treatment. The study compared the effects of adding linagliptin to metformin in these ways, since metformin needs to be taken at least twice per day.

Another study carried out in 1040 patients with type 2 diabetes compared patients taking 5 mg linagliptin and insulin given with metformin, with patients taking placebo given with insulin and metformin.

In all studies, the main measure of effectiveness was the change in blood levels of a substance called glycosylated haemoglobin (HbA1c) after 24 weeks of treatment. This gives an indication of how well blood glucose is controlled.

What benefit has Jentadueto shown during the studies?

The studies with linagliptin showed that it was more effective than placebo at reducing HbA1c levels. When used on its own, linagliptin gave a reduction of 0.46 points compared with a rise of 0.22 points. When given in combination, linagliptin with metformin gave a reduction of 0.56 points compared with a rise of 0.10 points; linagliptin with metformin plus a sulphonylurea gave a reduction of 0.72 points compared with 0.10 points.

The study with the combination of linagliptin and metformin showed that it was more effective than linagliptin or metformin alone, as well as placebo, at reducing HbA1c levels. The combination gave a reduction of 1.22 points when metformin was given at 500 mg and a reduction of 1.59 points when metformin was given at 1,000 mg. This compared with a reduction of 0.45 with linagliptin alone, 0.64 with 500 mg metformin alone, 1.07 with 1,000 mg metformin alone, and 0.13 with placebo.

The study looking at adding linagliptin 2.5 mg twice per day or 5 mg once per day to metformin showed a similar reduction in HbA1c levels compared with placebo (0.74 and 0.80 points more than placebo respectively).

The study looking at linagliptin in combination with metformin and insulin showed that this combination was more effective than the combination of insulin and metformin at reducing HbA1c levels (reduction of 0.77 percentage points was seen with linagliptin compared with a reduction of 0.10 percentage points with placebo).

What is the risk associated with Jentadueto?

The most frequent side effect with the combination of linagliptin plus metformin was diarrhoea (seen in around 2% of patients, with a similar rate seen in patients taking metformin plus placebo). When linagliptin and metformin were given with a sulphonylurea or insulin, hypoglycaemia was the most frequent side effect (seen in more than 1 patient in 10). For the full list of all side effects reported with Jentadueto, see the package leaflet.

Jentadueto must not be used in patients with:

- diabetic ketoacidosis or diabetic pre-coma (dangerous complications of diabetes);
- moderately to severely reduced kidney function or with acute (sudden) conditions which can affect kidney function such as dehydration, severe infection or shock;
- a condition that could lead to reduced supply of oxygen to body tissues (such as in patients who are being treated for worsening heart failure, have recently had a heart attack, have difficulty breathing 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 has Jentadueto been approved?

The CHMP concluded that the combination of linagliptin and metformin has been shown to be effective at lowering HbA1c levels, and that linagliptin 2.5 mg twice per day was as effective as 5 mg once per day, which is approved in the EU for use on its own and in combination with metformin and with metformin plus a sulphonylurea or insulin. The CHMP noted that fixed dose combinations may increase the likelihood of patients taking their medicine correctly. With regard to side effects, the Committee considered that in general the risks seen were only slightly greater than those seen with placebo.

Therefore the CHMP decided that Jentadueto's benefits are greater than its risks and recommended that it be given marketing authorisation.

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

A risk management plan has been developed to ensure that Jentadueto is used as safely and effectively as possible. Based on this plan, safety information has been included in the summary of product characteristics and the package leaflet for Jentadueto, including the appropriate precautions to be followed by healthcare professionals and patients.

Other information about Jentadueto

The European Commission granted a marketing authorisation valid throughout the European Union for Jentadueto on 20 July 2012.

The full EPAR for Jentadueto 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 Jentadueto, read the package leaflet (also part of the EPAR) or contact your doctor or pharmacist.

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