EMA/790709/2014
EMEA/H/C/001235

EPAR summary for the public

Ristfor

sitagliptin / metformin hydrochloride

This document is a summary of the European Public Assessment Report (EPAR) for Ristfor. 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 Ristfor.

What is Ristfor?

Ristfor is a diabetes medicine that contains two active substances, sitagliptin and metformin hydrochloride. It is available as tablets (50 mg sitagliptin and 850 mg metformin hydrochloride; 50 mg sitagliptin and 1,000 mg metformin hydrochloride).

What is Ristfor used for?

Ristfor is used in patients 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 sitagliptin and metformin as separate tablets;
- in combination with a sulphonylurea, a PPAR-gamma agonist such as a thiazolidinedione, or insulin (other types of diabetes medicine) in patients who are not satisfactorily controlled on this medicine and metformin.

The medicine can only be obtained with a prescription.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

How is Ristfor used?

Ristfor 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 Ristfor is taken with a sulphonylurea or insulin, the dose of the sulphonylurea or insulin may need to be lowered, to avoid hypoglycaemia (low blood sugar levels).

The maximum dose of sitagliptin is 100 mg a day. Ristfor should be taken with food to avoid any stomach problems caused by metformin.

How does Ristfor 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 Ristfor, sitagliptin and metformin hydrochloride, each have a different mode of action.

Sitagliptin 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 increasing the levels of incretin hormones in the blood, sitagliptin stimulates the pancreas to produce more insulin when blood glucose levels are high. Sitagliptin does not work when the blood glucose is low. Sitagliptin also reduces the amount of glucose made by the liver, by increasing insulin levels and decreasing the levels of the hormone glucagon. Sitagliptin has been authorised in the European Union (EU) as Januvia and Xelevia since 2007 and as Tesavel since 2008.

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 Ristfor been studied?

Sitagliptin on its own as Januvia/Xelevia/Tesavel can be used with metformin, and with both metformin and a sulphonylurea, in type 2 diabetes patients. The company presented the results of three studies of Januvia/Xelevia to support the use of Ristfor in patients who were not satisfactorily controlled on their existing metformin treatment. Two of the studies looked at sitagliptin as an add-on to metformin: the first compared it with placebo (a dummy treatment) in 701 patients, and the second compared it with glipizide (a sulphonylurea) in 1,172 patients. The third study compared sitagliptin with placebo, when used as an add-on to glimepiride (another sulphonylurea), with or without metformin, in 441 patients.

The results of three further studies were used to support the use of Ristfor. The first included 1,091 patients who were not satisfactorily controlled on diet and exercise alone and compared the effect of Ristfor with that of metformin or sitagliptin alone. The second included 278 patients who were not satisfactorily controlled on the combination of metformin and rosiglitazone (a PPAR-gamma agonist) and compared the effects of adding sitagliptin or placebo. The third included 641 patients who were not satisfactorily controlled on a stable dose of insulin, three-quarters of whom were also taking metformin. This study also compared the effects of adding sitagliptin or placebo.

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

The company carried out additional studies to show that the active substances in Ristfor are absorbed by the body in the same way as the two medicines given separately.

What benefit has Ristfor shown during the studies?

Ristfor was more effective than metformin alone. Adding 100 mg sitagliptin to metformin reduced HbA1c levels by 0.67% (from around 8.0%) after 24 weeks, compared with a fall of 0.02% in the patients adding placebo. The effectiveness of adding sitagliptin to metformin was similar to that of adding glipizide. In the study in which sitagliptin was added to glimepiride and metformin, the levels of HbA1c were reduced by 0.59% after 24 weeks, compared with an increase of 0.30% in the patients adding placebo.

In the first of the three further studies, Ristfor was more effective than metformin or sitagliptin alone. In the second, HbA1c levels were reduced by 1.03% after 18 weeks in patients adding sitagliptin to metformin and rosiglitazone, compared with a fall of 0.31% in those adding placebo. Finally, they were reduced by 0.59% after 24 weeks in patients adding sitagliptin to insulin, compared with a fall of 0.03% in those adding placebo. There was no difference in this effect between the patients also taking metformin and those not taking it.

What is the risk associated with Ristfor?

Serious side effects reported with Ristfor include pancreatitis (inflammation of the pancreas) and hypersensitivity (allergic reactions). Hypoglycaemia has been reported in combination with a sulphonylurea in 13.8% of patients and with insulin in 10.9% of patients. For the full list of all side effects reported with Ristfor, see the package leaflet.

Ristfor must not be used in patients who have diabetic ketoacidosis or pre coma (dangerous conditions that can occur in diabetes), problems with the kidneys or liver, conditions that may affect the kidneys, or a disease that causes a reduced supply of oxygen to the tissues such as failure of the heart or lungs or a recent heart attack. It must also not be used in patients who consume excessive amounts of alcohol or are alcoholic, or in women who are breast-feeding. For the full list of restrictions, see the package leaflet.

Why has Ristfor been approved?

The CHMP decided that Ristfor's benefits are greater than its risks and recommended that it be given marketing authorisation.

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

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

Other information about Ristfor:

The European Commission granted a marketing authorisation valid throughout the EU for Ristfor on 15 March 2010. This authorisation was based on the authorisation granted to Janumet in 2008 ('informed consent').

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

This summary was last updated in 01-2015.