European Medicines Agency
Pre-Authorisation Evaluation of Medicines for Human Use

London, 17 December 2009
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COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE
SUMMARY OF POSITIVE OPINION*
for
RISTFOR

International Nonproprietary Name (INN): ***sitagliptin / metformin hydrochloride***

On 17 December 2009 the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion,** recommending to grant a marketing authorisation for the medicinal product Ristfor, 50 mg / 850 mg, 50 mg / 1000 mg, film-coated tablet intended for patients with type 2 diabetes mellitus.

The applicant for this medicinal product is Merck Sharp & Dohme Ltd.

The active substances of Ristfor (A10BD07), a combination product of oral blood glucose-lowering drugs, are sitagliptin and metformin hydrochloride. Sitagliptin is a dipeptidyl peptidase-4 (DPP-4) inhibitor. DPP-4 inhibition reduces the cleavage and inactivation of the active (intact) form of the incretin hormones, including GLP-1 (glucagon-like peptide 1) and GIP (glucose-dependent insulinotropic polypeptide). This way active incretin concentrations are elevated and that leads to enhancement of glucose-dependent insulin secretion and a reduction in glucagon release, thus contributing to the maintenance of glucose homeostasis. Metformin is a biguanide and has an antihyperglycaemic effect, lowering both basal and postprandial plasma glucose concentrations via various mechanisms, including decreasing hepatic glucose production, decreasing intestinal absorption of glucose, and improving insulin sensitivity by increasing peripheral glucose uptake and utilisation. Ristfor combines these two antidiabetic agents with complementary mechanisms of action.

The benefits with Ristfor are its clinically relevant and significant reduction of blood glucose levels in patients inadequately controlled by metformin alone, although non-inferior efficacy versus the addition of glipizide was not proven, a clinically relevant improvement of glycaemic control when added to a SU agent, and a presumed improvement of compliance by use of two antidiabetic agents in one tablet to improve glycaemic control in patients with type 2 diabetes. The effect on body weight is similar to that of metformin alone. The most common side effect when taking Ristfor is nausea. When sitagliptin is taken as monotherapy side effects in excess (0.2% of patients and >1 patient) of that in patients receiving placebo are headache, hypoglycaemia, constipation, and dizziness. Furthermore, the following adverse reactions for the metformin component are known: gastrointestinal symptoms such as nausea, vomiting, diarrhoea, abdominal pain, loss of appetite, and metallic taste. When Ristfor is taken in combination with a sulphonylurea, common side effects are low blood sugar and constipation. When taking Ristfor with PPARγ agonists the most common side effects are headache, diarrhoea, vomiting, low blood sugar and foot swelling. When taking Ristfor with insulin the most common side effect is low blood sugar.

A pharmacovigilance plan for Ristfor, as for all medicinal products, will be implemented as part of the marketing authorisation.

The approved indication is: "For patients with type 2 diabetes mellitus:

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* Summaries of positive opinion are published without prejudice to the Commission Decision, which will normally be issued within 67 days from adoption of the Opinion.

** Applicants may request a re-examination of any CHMP opinion, provided they notify the European Medicines Agency in writing of their intention to request a re-examination within 15 days of receipt of the opinion.

7 Westferry Circus, Canary Wharf, London E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 86 13
E-mail: mail@ema.europa.eu http://www.ema.europa.eu

Ristfor is indicated as an adjunct to diet and exercise to improve glycaemic control in patients inadequately controlled on their maximal tolerated dose of metformin alone or those already being treated with the combination of sitagliptin and metformin.

Ristfor is indicated in combination with a sulphonylurea (i.e., triple combination therapy) as an adjunct to diet and exercise in patients inadequately controlled on their maximal tolerated dose of metformin and a sulphonylurea.

Ristfor is indicated as triple combination therapy with a PPARγ agonist (i.e., a thiazolidinedione) as an adjunct to diet and exercise in patients inadequately controlled on their maximal tolerated dose of metformin and a PPARγ agonist.

Ristfor is also indicated as add-on to insulin (i.e., triple combination therapy) as an adjunct to diet and exercise to improve glycaemic control in patients when stable dosage of insulin and metformin alone do not provide adequate glycaemic control.

Detailed recommendations for the use of this product will be described in the Summary of Product Characteristics (SPC) which will be published in the European Public Assessment Report (EPAR) and will be available in all official European Union languages after the marketing authorisation has been granted by the European Commission.

The CHMP, on the basis of quality, safety and efficacy data of the reference product Janumet, considers that there is favourable benefits to risk balance for Ristfor and therefore recommends the granting of the marketing authorisation.