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
RISTABEN

International Nonproprietary Name (INN): ***sitagliptin***

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 Ristaben, 25 mg, 50 mg and 100 mg, film-coated tablet intended for treatment of type 2 diabetes mellitus.

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

The active substance of Ristaben is sitagliptin, an Dipeptidyl peptidase-4 (DPP-4) inhibitor, ATC code : A10BH01. DPP-4 inhibition reduces the cleavage and inactivation of the active (intact) form of the incretin hormones, including glucagon-like peptide 1 (GLP-1) and glucose dependent inhibitory peptide (GIP), producing an elevation of incretin concentrations that lead to enhancement of glucose-dependent insulin secretion and a reduction in glucagon release.

The benefit of Ristaben is a demonstrated reduction in baseline HbA1c at 24 weeks in combination with metformin, or a PPARγ agonist, or a sulphonylurea, or a sulphonylurea and metformin, or a metformin and PPARγ agonist (54 weeks study), or a insulin with or without metformin. It has also shown a reduction in fasting plasma glucose (FPG). The most common side effect when taking Ristaben with metformin is nausea. When taking Ristaben with pioglitazone, they are low blood sugar, flatulence and foot swelling. The most common side effect when taking Ristaben with a sulfonylurea is low blood sugar. When taking Ristaben with metformin and a sulfonylurea the most common side effects are low blood sugar and constipation. When taking Ristaben with metformin and PPARγ agonist the most common side effects are headache, vomiting, low blood sugar, foot swelling and diarrhoea. When taking Ristaben alone, the most common side effects are low blood sugar, headache, stuffy or runny nose and sore throat. When taking Ristaben with insulin with or without metformin the most common side effects are headache, low blood sugar and infuenza. Additional adverse experiences reported regardless of causal relationship to medication that occurred more frequently in patients treated with Ristaben included osteoarthritis and pain in extremity. During post-marketing experience of the reference product the following additional side effects have been reported (frequency not known): hypersensitivity reactions including anaphylaxis, angioedema, rash, urticaria, cutaneous vasculitis, and exfoliative skin conditions including Stevens-Johnson syndrome, pancreatitis.

* 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.

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A pharmacovigilance plan for Ristaben, 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, Ristaben is indicated to improve glycaemic control:

as monotherapy
• in patients inadequately controlled by diet and exercise alone and for whom metformin is inappropriate due to contraindications or intolerance.

as dual oral therapy in combination with
• metformin when diet and exercise plus metformin alone do not provide adequate glycaemic control.
• a sulphonylurea when diet and exercise plus maximal tolerated dose of a sulphonylurea alone do not provide adequate glycaemic control and when metformin is inappropriate due to contraindications or intolerance.
• a PPARγ agonist (i.e. a thiazolidinedione) when use of a PPARγ agonist is appropriate and when diet and exercise plus the PPARγ agonist alone do not provide adequate glycaemic control.

as triple oral therapy in combination with
• a sulphonylurea and metformin when diet and exercise plus dual therapy with these agents do not provide adequate glycaemic control.
• a PPARγ agonist and metformin when use of a PPARγ agonist is appropriate and when diet and exercise plus dual therapy with these agents do not provide adequate glycaemic control.

Ristaben is also indicated as add-on to insulin (with or without metformin) when diet and exercise plus stable dosage of insulin 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 Januvia, considers that there is a favourable benefit to risk balance for Ristaben and therefore recommends the granting of the marketing authorisation.