European Medicines Agency
Evaluation of Medicines for Human Use

London, 17 December 2009
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CHMP ASSESSMENT REPORT

FOR

Ristaben

International Nonproprietary Name: sitagliptin

Procedure No. EMEA/H/C/001234

Assessment Report as adopted by the CHMP with
all information of a commercially confidential nature deleted.

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1. BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission of the dossier

The applicant Merck Sharp & Dohme Ltd. submitted on 2 October 2009 an application for Marketing Authorisation to the European Medicines Agency for Ristaben, through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the CHMP on 23 July 2009.

The legal basis for this application refers to Article 10(c) of Directive 2001/83/EC, as amended – relating to informed consent from a marketing authorisation holder Merck Sharp & Dohme Limited for an authorised medicinal product Januvia (EU/1/07/383/001-018). The applicant Merck Sharp & Dohme Ltd. previously obtained a Marketing Authorization for the multiple application Xelevia (EU/1/07/382/001-018) on 21 March 2007 and Tesavel (EU/1/07/435/001-018) on 11 January 2008.

The application submitted is a dossier composed of administrative information, quality, non-clinical and clinical data with a letter from a MAH Merck Sharp & Dohme Ltd. allowing the cross reference to relevant quality, non-clinical and/or clinical data.

The applicant applied for the following indication:

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.

Information on Paediatric requirements

The European Medicines Agency agreed on a PIP granting a deferral and a waiver for Januvia (EMEA-000470-PIP01-08). The waiver applies to children of less than 10 years on the grounds that type 2 diabetes mellitus hardly occurs in the specified paediatric subset. A clinical trial in children/adolescents 10 to 18 years was agreed upon and should be completed by October 2017.

Scientific Advice
The applicant did not seek scientific advice at the CHMP.

Licensing status:
The initial product, Januvia, has been given a Community Marketing Authorisation on 21 March 2007.

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: **Pieter de Graeff** Co-Rapporteur: **Harald Enzmann**

1.2 Steps taken for the assessment of the product

- The application was received by the European Medicines Agency on 2 October 2009.
- The procedure started on 18 October 2009.
- The Rapporteur's preliminary Assessment Report was circulated to all CHMP members on 13 November 2009. The Co-Rapporteur's preliminary Assessment Report was circulated to all CHMP members on 18 November 2009.
- During the meeting on 14-17 December 2009, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Ristaben on 17 December 2009. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 11 December 2009.

2 SCIENTIFIC DISCUSSION

3.1 Introduction

This application has been submitted as an informed consent application in accordance with Article 10c of Directive 2001/83/EC as amended.

The MAH for Januvia provided consent to make use of the pharmaceutical, preclinical and clinical documentation contained in the file of Januvia, assessed and approved.
As a consequence, quality, safety and efficacy of Ristaben are identical to the up to date quality, safety and efficacy profile of Januvia. The application for Ristaben concerns the strengths of 25mg, 50 mg and 100 mg of film-coated tablets with pack sizes identical to those approved for Januvia and consists only of Module 1 information.

As a consequence, quality, safety and efficacy of Ristaben medicinal product are identical to the up-to-date quality, safety and efficacy profile of Januvia.
Information on the scientific discussions can be found in the Januvia CHMP assessment reports and in the European Public Assessment Report (EPAR).

The Ristaben informed consent application concerns only the 25mg, 50 mg and 100 mg strengths of Januvia. The Summary of Product Characteristics for Ristaben appropriately reflects this.

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.

The active substance of Ristaben is sitagliptin phosphate monohydrate, 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 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.

Ristaben should not be used in individuals below 18 years of age.

3.2 Quality aspects

Since this application is an informed consent of the Januvia application, the quality data in support of the Ristaben application are identical to the up-to-date quality data of the Januvia dossier , which have been assessed and approved (including all post-marketing procedures).

3.3 Non-clinical aspects

Since Ristaben application is an informed consent of the Januvia application, the non-clinical data in support of the Januvia application are identical to the up-to-date non-clinical data of the Januvia dossier, which have been assessed and approved (including all post-marketing procedures).

3.4 Clinical aspects

Since this application is an informed consent of the Januvia application, the clinical data in support of the Ristaben application are identical to the up-to-date clinical data of the Januvia dossier, which have been assessed and approved (including all post-marketing procedures). No additional clinical studies are provided.

3.5 Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system (version 6.0) as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The MAA submitted a risk management plan (version 2.0) identical with that for Januvia.

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

PSURs

As requested by the MAH and agreed by the CHMP, the PSUR cycle of informed consent application will correspond to the one attributed to the product, [anuvia, unless otherwise specified.

3.6 Overall conclusions, risk/benefit assessment and recommendation

Since this application is an informed consent of the Januvia application, the CHMP considered that the risk-benefit balance of Ristaben was favourable and therefore recommended the granting of the marketing authorisation by consensus for the following indication:

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.

- User consultation

A justification for not conducting a user testing for this application was provided, in view of the fact that a readability test had been performed at the time of the original MAA for Januvia. Since the

content of the package leaflet is identical to the latest approved leaflet of Januvia and therefore no further testing is warranted.