European Medicines Agency
Evaluation of Medicines for Human Use

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CHMP ASSESSMENT REPORT

FOR

Ristfor

International Nonproprietary Name: sitagliptin / metformin hydrochloride

Procedure No. EMEA/H/C/001235

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 Ristfor, 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 27 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 Ltd. for an authorised medicinal product Janumet (EU/1/08/455/001-016). The applicant Merck Sharp & Dohme Ltd. previously obtained a Marketing Authorization for multiple applications Velmetia (EU/1/08/456/001-016) and Efficib (EU/1/08/457/001-016) on 16 July 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:

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.

Information on Paediatric requirements

The Agency refused the proposed PIP for Janumet and granted a waiver for all subsets of the paediatric population on the grounds that the specific medicinal product does not present a significant therapeutic benefit over existing treatments for paediatric patients (EMEA-000165-PIP01-07).

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

Licensing status:
The initial product, Janumet, has been given a Community Marketing Authorisation on 16 July 2008.

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 Ristfor 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 Janumet provided consent to make use of the pharmaceutical, non-clinical and clinical documentation contained in the file of Janumet, assessed and approved.
As a consequence, quality, safety and efficacy of Ristfor are identical to the up to date quality, safety and efficacy profile of Janumet. The application for Ristfor concerns the strengths of 50 mg/850 mg and 50 mg/1000 mg of film-coated tablets with pack sizes identical to those approved for Janumet and consists only of Module 1 information.

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

The Ristfor informed consent application concerns only the 50 mg/850 mg and 50 mg/1000 mg, strengths of Janumet. The Summary of Product Characteristics for Ristfor appropriately reflects this.

The approved indication is:

For patients with type 2 diabetes mellitus:

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.

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. It is thought to act 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.

3.2 Quality aspects

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

3.3 Non-clinical aspects

Since Ristfor application is an informed consent of the Janumet application, the non-clinical data in support of the Janumet application are identical to the up-to-date non-clinical data of the Janumet 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 Janumet application, the clinical data in support of the Ristfor application are identical to the up-to-date clinical data of the Janumet 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) 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 Janumet.

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, Janumet, unless otherwise specified.

3.6 Overall conclusions, risk/benefit assessment and recommendation

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

For patients with type 2 diabetes mellitus:

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.

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- 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 Janumet and the content of the package leaflet is identical to the latest approved leaflet of Janumet, no further testing is warranted.