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

London, 29 April 2008
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COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE
SUMMARY OF POSITIVE OPINION*
for
JANUMET

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

On 24 April 2008 the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion,** recommending to grant a marketing authorisation for the medicinal product Janumet, 50 mg/850 mg and 50mg/1000 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 substances of Janumet (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. Janumet combines these two antidiabetic agents with complementary mechanisms of action.

The benefits with Janumet 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 Janumet 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 Janumet is taken in combination with a sulphonylurea, common side effects are hypoglycaemia and constipation.

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

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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 EMEA in writing of their intention to request a re-examination within 15 days of receipt of the opinion.

*corr.: The International Nonproprietary Name has been corrected.

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

Janumet is indicated as an adjunct to diet and exercise to improve glycaemic control in patients inadequately controlled on metformin alone or those already being treated with the combination of sitagliptin and metformin.
Janumet is also 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.”

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 submitted, considers that there is a favourable benefit to risk balance for Janumet and therefore recommends the granting of the marketing authorisation.