



FOR UK MEDICAL MEDIA ONLY

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Committee for Medicinal Products for Human Use (CHMP) Recommends Janumet™ (sitagliptin/metformin) for EU Approval for Type 2 Diabetes

24 April 2008 – Merck Sharp & Dohme (MSD) today received a positive opinion from the Committee for Medicinal Products for Human Use (CHMP) recommending European approval for Janumet™ (sitagliptin/metformin), a new option for the treatment of type 2 diabetes. Sitagliptin/metformin delivers substantial glucose lowering through a combination of sitagliptin, an incretin enhancer (DPP-4 inhibitor), and metformin, with a low risk of hypoglycaemia and weight gain.^{1,2} Sitagliptin/metformin targets three key defects of diabetes: insulin deficiency from pancreatic beta cells, insulin resistance, and overproduction of glucose by the liver.^{3,4,5}

The CHMP, which reviews medicines for the European Commission (EC), has recommended sitagliptin/metformin be approved to improve glycaemic control in type 2 diabetes patients inadequately controlled on diet and exercise plus their maximally tolerated dose of metformin alone or those already being treated with the combination of sitagliptin and metformin. Sitagliptin/metformin is also recommended for approval in combination with a sulphonylurea (SU) as an adjunct to diet and exercise in patients inadequately controlled on their maximal tolerated dose of metformin and an SU. The decision will be applicable to the 27 countries that are members of the EU, as well as Norway and Iceland. Marketing authorisation is expected in mid June assuming the EMEA adopts the opinion of the CHMP.

Kamlesh Khunti, Professor of Primary Care Diabetes and Vascular Medicine, University of Leicester said, “Many patients remain poorly controlled on their existing oral combination therapy. In order to improve quality of life for our patients, we need simple and effective treatments that address glucose control and common tolerability issues such as hypoglycaemia and weight gain. The complementary mechanisms of action of sitagliptin and metformin provide us with a further option to substantially improve glucose control and are generally well tolerated.”

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The CHMP positive opinion was based on phase III data showing significant reductions in blood sugar. In a 30-week, placebo-controlled clinical study to evaluate at 18 and 30 weeks the safety and efficacy of the addition of sitagliptin 100 mg once-daily to patients inadequately controlled on ongoing metformin (n=190; mean baseline HbA1c 9.2%), sitagliptin provided significant improvements in HbA1c levels compared with placebo ($p<0.001$). In this study, the mean placebo-adjusted HbA1c reduction was -1.0 percent after prior metformin therapy at 18 and 30 weeks. In a subgroup of patients with baseline HbA1c $\geq 10\%$, the mean placebo-adjusted reduction was -1.8% beyond metformin alone at week 18 and, due to improved response from the placebo group, was 1.4% at 30 weeks.¹

In this 30-week study, the overall incidence of adverse reactions considered as drug-related was similar in the two treatment groups. There were no statistically significant differences between the two treatment groups in the incidence of hypoglycaemia or in the incidence of pre-specified gastrointestinal adverse events (abdominal pain, diarrhoea, nausea, vomiting). A small decrease in mean body weight of 0.5kg was seen in both groups.¹

In a separate, 24-week, randomized, double-blind, placebo-controlled study with 701 patients with mildly to moderately elevated HbA1c levels (mean baseline 8.0 percent) inadequately controlled on metformin, patients taking sitagliptin/metformin (n=453) experienced significant additional mean placebo-subtracted reductions in HbA1c of 0.7 percent beyond that achieved by patients who continued on metformin alone (n=224) ($p<0.001$).²

The CHMP also reviewed phase III clinical trial results supporting the tolerability and efficacy of sitagliptin 100 mg once-daily in combination with glimepiride (a sulphonylurea) alone or with glimepiride plus metformin.⁶ Overall, the trial data showed that the addition of sitagliptin significantly reduced HbA1c levels and fasting plasma glucose levels, and was generally well tolerated.⁶

In the clinical trial⁶ in combination with a sulphonylurea (glimepiride) with metformin, sitagliptin demonstrated an overall incidence of adverse reactions higher than that seen with placebo, in part related to a higher incidence of hypoglycaemia with the treatment compared to placebo (16.4 percent vs. 0.9 percent, respectively). A higher rate of hypoglycaemia is commonly seen when antihyperglycaemic agents are used in combination with sulphonylurea agents. When sitagliptin is used in combination with a sulphonylurea, a lower dose of the sulphonylurea may be considered to reduce the risk of hypoglycaemia.

Sitagliptin/metformin is not to be used in patients with moderate or severe renal impairment or in patients with hepatic insufficiency. It is contraindicated in patients with: hypersensitivity to the active substances or to any of the excipients; diabetic ketoacidosis, diabetic pre-coma; acute conditions with the potential to alter renal function; acute or chronic disease which may cause tissue hypoxia; acute alcohol intoxication, alcoholism; or who are lactating.

Sitagliptin was licensed in the UK in April 2007 and currently offers the broadest range of indications of all licensed DPP-4 inhibitors in the UK.⁷ There have been over four million prescriptions for sitagliptin and more than 600,000 prescriptions for sitagliptin/metformin worldwide.⁸ Sitagliptin/metformin has received approval in 17 countries and sitagliptin is approved in more than 70 countries and is available in every region around the world, having achieved global sales of \$1 billion. It is estimated that over 53 million people in Europe have diabetes⁹, including over 2.3 million people diagnosed in the UK.¹⁰

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JANUMET™ is a registered trademark of Merck & Co., Inc., of Whitehouse St, NJ, USA known in many countries as Merck Sharp & Dohme

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Notes to editor

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 - ⁷ 'Januvia' (sitagliptin). Summary of Product Characteristics. MSD UK 2007
 - ⁸ IMS Health, NPA™ Weekly, TRxs, week-ending October 20, 2006 through week-ending March 21, 2008.
 - ⁹ International Diabetes Federation: Diabetes Atlas, 3rd ed. 2006 Chapter 1, p.28.
 - ¹⁰ Diabetes UK web site. What is Diabetes? <http://www.diabetes.org.uk> (Accessed February 2007)