CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-044

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

MEMORANDUM **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: February 20, 2007

TO: Mary Parks, M.D., Director
Division of Metabolic and Endocrine Products

THROUGH: Ellis Unger, M.D., Acting Deputy Director
Office of Surveillance and Epidemiology

FROM: Office of Surveillance and Epidemiology (OSE) Risk Management Team

DRUG: Janumet (sitagliptin phosphate / metformin hydrochloride) Tablets

NDA#: 22-044

SPONSOR: Merck & Co.

SUBJECT: Review of Proposed Risk Management Plan (RMP) submitted May 22, 2006

RCM #: 2006-668

INTRODUCTION/BACKGROUND

This consult follows a request by the Division of Metabolic and Endocrine Products (DMEP), for the Office of Surveillance and Epidemiology (OSE) to review and comment on the Sponsor's proposed Risk Management Plan (RMP) for Janumet (sitagliptin phosphate / metformin hydrochloride fixed-dose combination) Tablets.

Janumet is a fixed-dose combination of sitagliptin, a dipeptidyl peptidase IV (DPP4) inhibitor approved October 16, 2006 as a single-ingredient product (Januvia) and meformin, a biguanide approved March 3, 1995 as a single-ingredient product (Glucophage). Sitagliptin exerts glycemic control in patients with type 2 diabetes by preventing the rapid degradation of incretin hormones. Incretin hormones, including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP), are released by the intestine throughout the day, and levels are increased in response to a meal. Metformin acts by decreasing hepatic glucose output and improving insulin sensitivity in liver and muscle. The proposed indication for Janumet is as an adjunct to

diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus who fail to achieve adequate control with diet and exercise and either ingredient alone, or in patients who are already being treated with both single-ingredient products. The proposed dosage is sitagliptin 50mg and metformin 500mg orally twice daily or sitagliptin 50mg and metformin 1000mg orally twice daily.

The safety information for Janumet consists of data from four studies in which patients were co-administered sitagliptin and metformin. In the four studies combined, 1569 subjects received metformin at daily doses ≥ 1500mg and sitagliptin at daily doses of 100mg. In these studies, the subjects received combination therapy with sitagliptin and metformin for a mean period of 36.4 weeks. The Sponsor did not identify any safety signals or potential risks in any of the studies that would warrant risk management measures beyond routine labeling and pharmacovigilance. They noted that there is one important potential risk, necrotic skin lesions in the monkey, which has been identified with another DPP4 inhibitor. To date, this event has not been seen with sitagliptin. Additionally, there are no safety data in the following patient populations: children, pregnant women, patients with congestive heart failure, and patients with renal function impairment (metformin is contraindicated for patients with congestive heart failure or renal function impairment).

The Ilan Irony, M.D., the medical officer assigned to the clinical review of this NDA, indicated in a draft review[1] that there are no new concerns regarding the safety of the co-administration of sitagliptin and metformin than those already noted in the review of the sitagliptin NDA and the known safety profile of metformin. Neither of these products has a Risk Minimization Action Plan (RiskMAP). Dr. Irony agrees with the routine risk management activity proposed by the Sponsor.

REVIEW OF SPONSOR'S RMP

The Sponsor does not believe that a RiskMAP is warranted for this product. They are proposing the following pharmacovigilance/ surveillance and post-marketing safety activities:

- Labeling – professional labeling and the patient package insert will be utilized to convey to prescribers, other healthcare professionals, and patients about the risks associated with Janumet.
- Routine Pharmacovigilance Practices – reporting of adverse event information will be accomplished in accordance with the relevant legal requirements.
- Necrotic skin lesions in monkeys – based on the Agency's concern regarding animal data indicating that the administration of DPP-IV inhibitors to monkeys results in dose-dependent and duration-dependent increases in necrotic skin lesions, the Sponsor is undertaking an oral toxicity study in monkeys over a range of doses for up to 3 months duration, the design of which has been reviewed and agreed upon by the U.S. FDA.

[1] Ilan Irony, MD, Medical Officer. Clinical Review of Janumet (sitagliptin phosphate and metformin hydrochloride fixed-dose combination), NDA 22-044; draft clinical review forwarded 2/7/07.

- Pregnancy Registry – In order to develop a better assessment of the safety profile of sitagliptin in pregnant women and for exposed fetuses, the Sponsor is establishing a pregnancy registry for follow-up of sitagliptin pregnancy exposures. The pregnancy registry will be an enhanced surveillance program of women exposed to sitagliptin, including women exposed to sitagliptin and metformin tablets, at any time from the date of the last menstrual period through the duration of the pregnancy.

CONCLUSION

The Sponsor's proposed RMP does not differ substantially from routine risk management measures, such as FDA-approved professional labeling and routine post-marketing surveillance. The Sponsor has proposed other risk assessment measures for sitagliptin, including a plan to undertake an oral toxicity study in monkeys to assess the risk of necrotic skin lesions over a range of doses and a pregnancy registry to determine if there is any risk to the pregnant woman or developing fetuses.

OSE concludes that the Sponsor's proposal for routine risk management measures and planned pharmacovigilance activities is sufficient at this time. If the Sponsor or the reviewing division identifies a safety concern in the future that might warrant a RiskMAP, or if the reviewing division wants OSE to review any proposed Phase IV protocols or epidemiological post-marketing studies, please provide a consult request.

OSE Risk Management Team
Mary Dempsey, Risk Management Program Coordinator
Claudia Karwoski, PharmD, Team Leader, Risk Management Team
Joyce Weaver, PharmD, Senior Risk Management Analyst
Mary Willy, PhD, Senior Risk Management Epidemiologist

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Mary Dempsey
2/20/2007 04:30:50 PM
DRUG SAFETY OFFICE REVIEWER

Ellis Unger
2/20/2007 04:42:10 PM
MEDICAL OFFICER