# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 202343Orig1s000

# RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

**Risk Evaluation and Mitigation Strategy (REMS) Memorandum**
**REMS Retraction**

**U.S. FOOD AND DRUG ADMINISTRATION**
**CENTER FOR DRUG EVALUATION AND RESEARCH**
**OFFICE of Drug Evaluation II**
**DIVISION of Metabolism and Endocrinology Products**

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**NDA/BLA #s:** 202343
**Products:** (b) (4) (sitagliptin/simvastatin) Tablets
**APPLICANT:** Merck Sharp & Dohme Corporation
**FROM:** Mary H. Parks, M.D.
**DATE:** August 2, 2011

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The purpose of this memorandum is to document the rationale for retracting the requirement for a risk evaluation and mitigation strategy (REMS) for (b) (4) (sitagliptin/simvastatin) Tablets. On February 16, 2011, we notified the applicant for the pending NDA for (b) (4) (sitagliptin/simvastatin) that a REMS was necessary to ensure the benefits of the drug outweigh the risk of acute pancreatitis, including necrotizing pancreatitis. The REMS was to consist of a Medication Guide, and a timetable for submission of assessments of the REMS. The same REMS requirement had been issued for other products containing sitagliptin.

On March 25, 2011, the applicant submitted a proposed REMS which included a Medication Guide and a timetable for submission of assessments of the REMS.

The February 2011 Draft Guidance for Industry, *Medication Guides — Distribution Requirements and Inclusion in Risk Evaluation and Mitigation Strategies (REMS)*, states that the FDA may approve a Medication Guide under 21 CFR 208 without requiring the Medication Guide to be a part of a REMS when the Medication Guide is adequate to address the serious and significant public health concern and meets the standard set forth under that regulation.

On April 14, 2011 we issued Release REMS Requirement letters for NDA 021995/S-017 JANUVIA (sitagliptin) and NDA 022044/S-016 JANUMET (sitagliptin/metformin hydrochloride) and on July 22, 2011 we issued a REMS Retraction letter for NDA 202270 JANUMET XR (sitagliptin and extended-release metformin hydrochloride fixed-dose combination) after a determination was made that a REMS for these products was no longer necessary to ensure the benefits of the drug outweigh the risk described above. The applicant also amended their NDA application to request that they be released from the REMS requirement for (b) (4) (sitagliptin/simvastatin).

After consultations between the Division of Metabolism and Endocrinology Products (DMEP) in the Office of New Drugs (OND) and the Division of Risk Management (DRISK) in the Office of Surveillance and Epidemiology (OSE), we have determined that a REMS for (b) (4) (sitagliptin/simvastatin) will not be necessary to ensure the benefits of the drug outweigh the risks described above. If (b) (4) (sitagliptin/simvastatin) is approved, the Medication Guide would be approved as part of the labeling and would be adequate to describe the serious risks. The

Medication Guide would be part of the approved labeling and be subject to the requirements under 21 CFR 208. Like other labeling, Medication Guides are subject to the safety labeling change provisions of section 505(o)(4) of the FDCA.

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/s/

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AMY G EGAN
08/18/2011
Amy Egan for Mary Parks

# Risk Evaluation and Mitigation Strategy (REMS) Memorandum

**U.S. FOOD AND DRUG ADMINISTRATION**
**CENTER FOR DRUG EVALUATION AND RESEARCH**
**OFFICE OF DRUG EVALUATION II**
**DIVISION OF METABOLISM AND ENDOCRINOLOGY PRODUCTS**

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**NDA/BLA #s:** 202343
**Products:** (b) (4) (sitagliptin/simvastatin) Tablets
**APPLICANT:** Merck Sharp & Dohme Corporation
**FROM:** Mary H. Parks, M.D.
**DATE:** February 4, 2011

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Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)]. Section 505-1(a)(1) provides the following factors:

(A) The estimated size of the population likely to use the drug involved;
(B) The seriousness of the disease or condition that is to be treated with the drug;
(C) The expected benefit of the drug with respect to such disease or condition;
(D) The expected or actual duration of treatment with the drug;
(E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
(F) Whether the drug is a new molecular entity (NME).

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS is necessary for (b) (4) (sitagliptin/ simvastatin) to ensure that the benefits of the drug outweigh the risks of acute pancreatitis, including necrotizing pancreatitis. In reaching this determination, we considered the following:

A. Approximately 24 million people in the U.S. have type 2 diabetes, of whom more than one-third will require more than one anti-diabetic agent to maintain adequate glycemic control within several years of initiation of drug therapy. From marketing (October 2006) through December 2008, an estimated (b) (4) prescriptions of JANUVIA (sitagliptin), one of the components of (b) (4) (sitagliptin/simvastatin), have been dispensed. Adults with diabetes have heart disease death rates about 2 to 4 times higher than adults without diabetes. Improved control of LDL cholesterol can reduce cardiovascular complications by 20-50%. (b) (4) (sitagliptin/simvastatin) is a therapeutic option for patients to achieve both glycemic control and lipid lowering.

B. Patients with type 2 diabetes who require anti-diabetic medication for glycemic control are at risk for a variety of complications including heart disease, stroke, blindness, kidney failure, nervous system damage, amputations, and death if untreated. (b) (4) (sitagliptin/

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