CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-044

PHARMACOLOGY REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	**22-044**
SERIAL NUMBER:	**000**
DATE RECEIVED BY CENTER:	**31 May 2006**
PRODUCT:	**Janumet (Sitagliptin/Metformin Fixed-Dose Combination)**
INTENDED CLINICAL POPULATION:	**Type 2 Diabetics**
SPONSOR:	**Merck**
DOCUMENTS REVIEWED:	**eCTD**
REVIEW DIVISION:	**Division of Metabolic and Endocrine Products**
PHARM/TOX SUPERVISOR:	**Todd Bourcier, Ph.D.**
DIVISION DIRECTOR:	**Mary Parks, M.D.**
PROJECT MANAGER:	**Lina Aljuburi, Pharm. D., M.S.**

Date of review submission to Division File System (DFS):

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EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability
AP (Approval)
Pharmacology/Toxicology recommends approval of NDA 22-044 (Janumet)

B. Recommendation for nonclinical studies
No additional nonclinical studies are required.

C. Recommendations on labeling
The proposed labeling language relevant to pharmacology/toxicology has been accurately reproduced from the approved labels for Januvia and Glucophage. No further changes are recommended.

II. Summary of non-clinical findings

A. Brief overview of non-clinical findings

Non-clinical studies with the fixed-dose combination product were not performed. Potential toxicity unique to the combination of sitagliptin phosphate (MK-0431) and metformin was evaluated in dogs co-administered each drug separately. The combination of MK-0431 and high-dose metformin (50 mg/kg) in dogs may have resulted in more numerous and earlier deaths than observed with metformin alone. The combination of MK-0431 and a lower dose of metformin (20 mg/kg) that better approximates human exposure of 2,500mg/day resulted in no deaths and yielded no evidence of exacerbated toxicity. Convincing evidence is provided that the deaths at 50 mg/kg are due to metformin toxicity and not to the combination. Nevertheless, there is a slight possibility of exacerbated toxicity in the setting of high metformin exposure ($\geq$ 400μM*h AUC) and clinical exposure to MK-0431 (~10μM*h AUC).

The following summary is taken from the pharmacology/toxicology review for Januvia, NDA 21-995.

Pharmacology

MK-0431 (sitagliptin phosphate) is a competitive inhibitor of dipeptidyl peptidase 4 (DPP4), an enzyme principally responsible for degrading incretin peptides glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP). MK-0431 prolongs incretin half-life and biological activity and thus potentiates glucose-dependent insulin release and delays gastric emptying. In non-clinical models of diabetes, MK-0431 moderates glucose excursion and improves insulin release and islet cell function/mass without provoking hypoglycemia. MK-0431 is body weight-neutral, unlike marketed glitazones (weight gain) and GLP-1 analogues (weight loss).

Immunomodulatory effects of DPP4 (aka CD26) are reportedly not altered by MK-0431, based on normal responses of murine T- and B-cells to antigens and mitogens. However, rodent DPP4/CD26 differs in some aspects from human DPP4/CD26 (e.g., binding of adenosine deaminase) and Merck's experiments did not directly test the T-helper memory function ascribed to CD26. Therefore, the non-clinical data do not adequately predict potential effects of MK-0431 on DPP4/CD26's role in human immunity.

Safety pharmacology assessment of neurological, renal, pulmonary, and gastrointestinal effects of MK-0431 did not identify any significant liabilities.

Absorption, Distribution, Metabolism, and Excretion

An oral dose of MK-0431 is rapidly absorbed and is 60-90% bioavailable in rats and dogs. MK-0431 distributes to most rat tissues with low amounts distributing to the brain, eyes, and bone. Plasma protein binding is moderate (30%). Metabolism of MK-0431 is minimal with 80% of unchanged parent compound being eliminated in the urine of rats,

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