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):

Appears This Way
On Original

TABLE OF CONTENTS

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 (≥ 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,

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.