CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-044

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

NDA Number	**22-044**	**Brand Name**	**Janumet ™**
OCP Division (I, II, III,IV, V)	**DCP II**	**Generic Name**	**Sitagliptin phosphate/Metformin hydrochloride fixed-dose combination**
Medical Division	**HFD-510**	**Drug Class**	**Anti-diabetic**
OCPB Reviewer	**Xiaoxiong (Jim) Wei**	**Indication(s)**	**Type 2 Diabetes**
OCPB Team Leader	**Hae-Young Ahn**	**Dosage Form**	**tablets**
		Dosing Regimen	**100 mg /1500-2000mg/day**
Date of Submission	**05-31-2006**	**Route of Administration**	**oral**
Estimated Due Date of OCPB Review	**March 2, 2007**	**Sponsor**	**Merck**
Division Due Date	**March 2, 2007**	**Priority Classification**	**S1**
PDUFA Due Date	**March 30, 2007**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				

hepatic impairment:				
PD:	[redacted]	[redacted]		
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
Thorough QT Study				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	X	2		
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		3		

Filability and QBR comments

	"X" if yes	Comments
Application filable ?	**YES**	
Comments sent to firm?	**No**	
Primary reviewer Signature and Date	Appears This Way On Original	
Secondary reviewer Signature and Date		

Briefing In Content:

Merck submitted this NDA for seeking approval of fixed dose combination drug products of Sitagliptin and Metformin. Sitagliptin phosphate (MK-0431) is a potent and selective dipeptidyl peptidase-4 (DPP-4) inhibitor developed by Merck & Co., Inc. for the treatment of type 2 diabetes mellitus, which is currently with the Agency for review under NDA21-995. Metformin hydrochloride is an approved anti-hyperglycemic agent widely used for the treatment of type 2 diabetes mellitus. The sponsor has developed an immediate release product containing a fixed dose of sitagliptin phosphate and multiple dose levels of metformin hydrochloride for the treatment of patients with type 2 diabetes who are not adequately controlled with either agent alone or patients already being treated with the combination of sitagliptin and metformin. Two dose strengths of a film-coated fixed-dose combination (FDC) tablet have been developed for the U.S. market: sitagliptin/metformin 50/500 mg/mg and 50/1000 mg/mg.

To support this combo drug product, the sponsor submitted three new PK studies, two of which are BE studies, and one of which is PD study. All three studies were conducted in healthy subjects:

1) Study P38 (BE with test formulations)

A 2-Part, Open-Label, Randomized, 3-Period Crossover Study to Evaluate the Pharmacokinetic Profiles of MK-0431 and Metformin After Oral Administration of Single Doses of MK-0431/Metformin Fixed-Dose Combination Tablet Probe Formulations or Coadministration of MK-0431 With Metformin as Individual Tablets to Healthy Adult Subjects

2) Study P48 (BE with commercial formulations)

An Open-Label, Randomized, Two-Part, Two-Period Crossover Study to Demonstrate the Definitive Bioequivalence After Administration of the Final Market Image (FMI) of the MK-0431/Metformin 50/500 mg and 50/1000 mg Fixed-Dose Combination (FDC) Tablet and Concomitant Administration of 50-mg Doses of MK-0431 and 500- or 1000-mg Doses of Metformin as Individual Tablets to Healthy Adult Subjects

3) Study P50 (PD study)

This is a randomized, placebo-controlled, double-blind, double-dummy, four-period crossover study to assess the effects of concomitant administration of sitagliptin and metformin alone and in combination on post-meal incretin hormone concentrations in healthy adult subjects. The objectives are to determine the effect of concomitant administration of sitagliptin and metformin on post-meal plasma incretin hormone concentrations (e.g., active and inactive and/or total glucagon-like peptide-1 [GLP-1] and gastric inhibitory peptide [GIP] concentrations, the ratio of active to total GLP-1 and GIP concentrations) in healthy adult subjects. This study is to assess the effects of sitagliptin and metformin on post-meal incretin hormone (active and total GLP-1 and GIP) concentrations after concomitant administration of sitagliptin and metformin and after administration of sitagliptin alone, metformin alone and placebo in healthy adult subjects. In each 2-day treatment period, subjects were randomized to receive either sitagliptin alone (active sitagliptin and placebo to metformin), metformin alone (placebo to sitagliptin and active metformin), concomitant administration of sitagliptin, and metformin or placebo (concomitant administration of placebo to sitagliptin and placebo to metformin) according to a computer-generated allocation schedule (see treatment schedule below). Each subject received all treatments and there was a minimum of a 7-day washout interval between the last dose of study drug in one treatment period and the first dose of study drug in subsequent treatment periods.

The Sponsor cited many supportive studies in NDA21-995 including drug interaction studies between sitagliptin and metformin.

The sponsor has developed dissolution specification for this combo drug product: no less than — dissolved in 20 min.

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