CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-995

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 21-995 (000)	Submission Date: 12/16/2005
Brand Name	Januvia™
Generic Name	Sitagliptin
Reviewer	Xiaoxiong (Jim) Wei, M.D., Ph.D.
Team Leader	Hae-Young Ahn, Ph.D.
Pharmacometrics Reviewer	Atul Bhattaram, Ph.D.
PM Team Leader	Jogarao Gobburu, Ph.D.
OCP Division	Division of Clinical Pharmacology II
OND division	Division of Metabolic and Endocrine Products (HFD-510)
Sponsor	Merck
Relevant IND(s)	65,495
Submission Type; Code	Original
Formulation; Strength(s)	Tablets; 100 mg, 50mg, 25 mg
Dosing regimen	Once a day
Indication	Type 2 diabetes mellitus

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1 Executive Summary

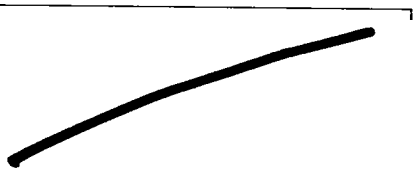
Merck submitted a 505 (b) (1) NDA for marketing of Januvia™ (Sitagliptin). A total of 33 human Phase 1 and Phase 2 pharmacokinetic and pharmacodynamic studies, bioavailability/bioequivalence studies, in vitro drug metabolism studies and a thorough QT study were submitted to support the section of Clinical Pharmacology and Biopharmaceutics.

Sitagliptin is the first drug of a new class of oral anti-hyperglycemic agents called dipeptidyl peptidase 4 (DPP-4) inhibitors. 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. The activity of GLP-1 and GIP is limited by the DPP-4 enzyme, which rapidly hydrolyzes the incretin hormones to produce inactive products. Sitagliptin prevents the hydrolysis of incretin hormones by DPP-4, thereby increasing plasma concentrations of the active forms of GLP-1 and GIP. By enhancing active incretin levels, sitagliptin increases insulin release and decreases glucagon levels in a glucose-dependent manner.

Sitagliptin is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus. Sitagliptin is also indicated in patients with type 2 diabetes mellitus to improve glycemic control in combination with metformin or a PPARγ agonist (e.g., thiazolidinedione) when diet and exercise, plus the single agent do not provide adequate glycemic control. The recommended dose of sitagliptin is 100 mg once daily as monotherapy or as combination therapy.

1.1 Recommendation

The Office of Clinical Pharmacology/Division of Clinical Pharmacology II (OCP/DCP-2) has reviewed the information provided in the original NDA 21-995 for Januvia™ in the section of human pharmacokinetics and biopharmaceutics. OCP has found the application acceptable. This recommendation and dissolution method and acceptance criterion below should be conveyed to the sponsor as appropriate.

Apparatus	
In vitro dissolution medium	
Volume of dissolution medium	
Medium temperature	
Stirring speed	
Acceptance criterion	

OCP Briefing Notes:
A Required OCP Office Level CPB Briefing was held on August 29, 2006. The following staff were attended: from OCP: Larry Lesko, Shiew-Mei Huang, Chandra Sahajwalla, Mehul Mehta, John Lazor, Atik Rahman, Dennis Bashaw, Hae-Young Ahn, Kelly Reynolds, Jaya Vaidyanathan, Albert Chen, David Lee, Srikanth Nallani, Sandhya Apparaju, Lei Zhang, Partha Roy, Atul Bhattaram; From DMEP: Mary Parks, Ilan Irony, Hylton Joffe, Lina Aljuburi; From ONDQA: Stephen Moore.

During Briefing, the OCP management reached a consensus to recommend a dissolution method as a post approval test method, not disintegration. Speaking for the four OCP division directors present Dr. Bashaw (Division Director, DCP-3), explained that disintegration does not necessarily correlate with solubilization of drug substance. Dissolution testing, on the other hand, incorporates both disintegration and the solubilization of drug substance into the media in its specification. As in the case with this drug, dissolution testing did not discriminate between hardness values as once the tablet disintegrated, the high solubility of the drug substance allowed it to enter the media readily. However, as a general release test, disintegration is not generally considered adequate as there could be formulation changes in the future that would result in decreased solubility (for example, a change in drug substance particle size) that would not be picked up by disintegration testing but would be detected by dissolution testing. Given that the burden of dissolution testing is minimal and is usually automated today, compared to the manual observation required for disintegration testing, it is recommended that a dissolution test be used.

1.2 Phase IV Commitment

None

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

• Single and multiple dose pharmacokinetics:

After oral administration of a 100-mg dose to healthy subjects, sitagliptin was rapidly absorbed, with peak plasma concentrations (median T_{max}) occurring 1 to 4 hours post-dose. Following a single oral 100-mg dose to healthy volunteers, mean plasma AUC of sitagliptin was 8.52 μM•hr, C_{max} was 950 nM, and apparent terminal half-life ($t_{1/2}$) was 12.4 hours. Plasma AUC of sitagliptin increased approximately 14% following 100-mg doses at steady-state compared to the first dose. The pharmacokinetics of sitagliptin was generally similar in healthy subjects and in patients with type 2 diabetes.

• Absolute bioavailability and food effect:

The absolute bioavailability of sitagliptin is approximately 87%. The co-administration of a high-fat meal with sitagliptin had no effect on the pharmacokinetics; sitagliptin may be administered with or without food.

• Dose proportionality:

The power law model of geometric mean $AUC_{0-\infty}$ values versus dose administered along with the fitted regression line indicated that the slope (90% CI) was 1.00 (0.98, 1.01). The sitagliptin dose adjusted (to 100 mg) $AUC_{0-\infty}$ geometric least-squares mean ratio (GMR, 400 mg/100 mg) was 1.02 with corresponding 90% CI of (0.99, 1.06). Therefore, sitagliptin $AUC_{0-\infty}$ increases dose proportionally with increasing dose across the tested dose range. Sitagliptin Cmax increases in a modestly greater than dose proportional manner with dose.

• Distribution:

The mean volume of distribution at steady state following a single 100-mg intravenous dose of sitagliptin to healthy subjects is approximately 198 liters. The fraction of sitagliptin reversibly bound to plasma proteins is about 38%.

• Metabolism:

Sitagliptin is primarily eliminated unchanged in urine, and metabolism is a minor pathway. Approximately 79% of sitagliptin is excreted unchanged in the urine. Following a [^{14}C]sitagliptin oral dose, approximately 16% of the radioactivity was excreted as metabolites of sitagliptin. Six metabolites were detected at trace levels and are not expected to contribute to the plasma DPP-4 inhibitory activity of sitagliptin. *In vitro* studies indicated that the primary enzyme responsible for the limited metabolism of sitagliptin was CYP3A4, with contribution from CYP2C8. Sitagliptin is a substrate of P-gp.

• Excretion:

Following administration of an oral [^{14}C]sitagliptin dose to healthy subjects, approximately 100% of the administered radioactivity was eliminated in feces (13%) or urine (87%) within one week of dosing. The renal clearance was approximately 350 mL/min. Elimination of sitagliptin occurs primarily via renal excretion and involves active tubular secretion. Sitagliptin is a substrate for human organic anion transporter-3 (hOAT-3).

• Renal impairment:

Mild renal insufficiency increased sitagliptin AUC by 1.6 fold. An approximately 2-fold or greater increase in the plasma AUC of sitagliptin was observed in patients with moderate renal insufficiency, and an approximately 4-fold or greater increase was observed in patients with severe renal insufficiency and in patients with ESRD on hemodialysis, as compared to normal healthy control subjects. Sitagliptin was

modestly removed by hemodialysis (13.5% over a 3- to 4-hour hemodialysis session starting 4 hours postdose). To achieve plasma concentrations of sitagliptin similar to those in patients with normal renal function, 50-mg and 25-mg once a day are recommended for moderately renally impaired and severely renally impaired or ESRD patients, respectively.

- Drug interactions:

In clinical pharmacokinetic studies, sitagliptin did not meaningfully alter the pharmacokinetics of metformin, glyburide, simvastatin, rosiglitazone, warfarin, or oral contraceptives. Multiple doses of sitagliptin slightly increased digoxin concentrations.

A single 600-mg oral dose of cyclosporine increased the AUC and C_{max} of sitagliptin by approximately 29% and 68%, respectively.

- Pharmacodynamics:

In patients with type 2 diabetes, administration of single oral doses of sitagliptin leads to inhibition of DPP-4 enzyme activity for a 24-hour period, resulting in a 2- to 3-fold increase in circulating levels of active GLP-1 and GIP, increased plasma levels of insulin and C-peptide, decreased glucagon concentrations, reduced fasting glucose, and reduced glucose excursion following an oral glucose load or a meal.

- Exposure-response:

The relationship between plasma sitagliptin concentrations and inhibition of plasma DPP-IV activity was explored. No significant hysteresis was observed. Using an Emax model the plasma EC50 was 25.7 nM and the EC80 was approximately 100 nM. In a study of multiple doses of 25 mg to 600 mg sitagliptin in healthy subjects, there was a dose- and concentration-related increase in the percent inhibition of plasma DPP-IV enzyme activity for multiple doses from 25 to 600 mg. Multiple doses of 100 mg once daily or higher were associated with geometric mean values for inhibition of DPP-IV activity at steady-state trough of approximately 80% or higher. These pharmacodynamic data support a once daily dosing regimen for sitagliptin in the treatment of type 2 diabetes.

- Analytical assay:

High turbulence liquid chromatography (HTLC) extraction and liquid chromatography/tandem mass spectrometry (LC-MS/MS) methods were used to analyze sitagliptin concentrations in human biological fluids (plasma, urine and dialysate). The lower limit of quantitation (LLOQ) for the plasma assay is 0.500 ng/mL (1.23 nM) and the linear calibration range is 0.500 to 1000 ng/mL (1.23 to 2455 nM). The assays are selective and specific for sitagliptin in human biological fluids. The accuracy of the intra-day analysis (n=5) of quality control (QC) samples did not deviate by more than 10% of the nominal concentrations. The precision (coefficient of variation, CV%) of the intra-day analysis (n=5) of QC samples was less than 10% at each concentration.

2. QUESTION BASED REVIEW (QBR)

2.1 GENERAL ATTRIBUTES OF THE DRUG

2.1.1 What are the highlights of the chemistry and physico-chemical properties of the drug substance, and the formulations of the drug product?

Sitagliptin phosphate is described chemically as 7-[(3*R*)-3-amino-1-oxo-4-(2,4,5-trifluorophenyl) butyl]-5,6,7,8-tetrahydro-3-(trifluoromethyl)-1,2,4-triazolo[4,3-*a*] pyrazine phosphate (1:1) monohydrate. The empirical formula is C16H15F6N5O•H3PO4•H2O and the molecular weight is 523.32. The structural formula is as follows:

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