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APPLICATION NUMBER:

202270Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA:202270	**Submission Date: August 02, 2011**
Brand Name	**Janumet XR**
Generic Name	**Sitagliptin/metformin HCl extended fixed dose combination (FDC) tablets**
Reviewer	**Jee Eun Lee, Ph.D.**
Team Leader (Acting)	**Jayabharathi Vaidyanathan, Ph.D.**
OCP Division	**Clinical Pharmacology II**
OND Division	**Metabolism and Endocrinology Products**
Sponsor	**Merck Sharp Dohme**
Relevant IND, NDA	**IND 101,964; NDA 22-044 (Janumet®), NDA 21-748 (Glumetza®), NDA 21-995 (Januvia®)**
Submission Type	**Resubmission NDA 505(b)(1)**
Formulation; Strength(s)	**FDC products of sitagliptin/metformin XR at dose strengths 50 mg/500 mg, 50 mg/1000 mg, 100 mg/1000 mg**
Indication	**Treatment of Type 2 Diabetes Mellitus**

1 Executive Summary

This 505(b)(1) application by Merck Sharp Dohme is in pursuit of approval for the fixed dose combination (FDC) 50 mg/500 mg, 50 mg/1000 mg, and 100 mg/1000 mg of sitagliptin/metformin extended release (MK-0431A XR, Janumet XR) tablets. For complete review of clinical pharmacology information from the original NDA, readers can refer to the original clinical pharmacology review of NDA 20-2770 in DAARTS dated 6/17/2011

Prior to this resubmission, Merck received a complete response letter for the original NDA, 20-2270. Janumet XR contains sitagliptin and metformin XR and the registration of this product is based on demonstration of bioequivalence (BE) between Janumet XR (MK-0431A XR) and co-administration of sitagliptin and an approved metformin XR formulation (Glumetza®, NDA 21-748). In the complete response letter issued on July 22, 2011, the sponsor was asked to submit the updated completed study report (CSR) for the pivotal BE study 147. This comment was based on the recommendation of office of

scientific investigation (OSI). Division of Bioequivalence and GLP Compliance (DBGC) of OSI issued FDA-483 at the bioanalytical laboratory, (b) (4) which analyzed blood samples obtained from the pivotal BE study. (b) (4) response to the Form FDA-483 was submitted on July 11, 2011, and reviewed by DBGC (see Dr. Gopa Biswas' review dated to July 15, 2011). Deficiencies listed in the Form FDA-483 were resolved and consequently the bioanalytical data were updated. Therefore, the sponsor repeated the bioequivalence assessment with the reintegrated data and updated the CSR accordingly. This review is focused on the updated study results of the pivotal BE study.

2 Recommendation

The Office of Clinical Pharmacology/Division of Clinical Pharmacology-II (OCP/DCP-II) has reviewed the clinical pharmacology data submitted under NDA 202270 resubmission dated 8/02/2011 and finds it acceptable to support approval.

3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

The pivotal BE study compared the administration of Janumet XR to the co-administration of sitagliptin IR and GLUMETZA®, and also the administration of two tablets of 50 mg/500 mg and the administration of one tablet of 100 mg/1000 mg in terms of pharmacokinetic characteristics. This study was conducted with the final market composition (FMC) of Janumet XR tablets, demonstrated BE between the Janumet XR tablets for both 50 mg/500 mg and 100 mg/1000 mg strengths, and between the Janumet XR tablets and co-administration of corresponding doses of sitagliptin and GLUMETZA®. The treatment arms were:

TRT A: sitagliptin 50 mg + GLUMETZA® 500 mg
TRT B: single Janumet XR 50 mg/500 mg tablet
TRT C: sitagliptin 100 mg + GLUMETZA® 1000 mg
TRT D: single Janumet XR 100 mg/1000 mg tablet
TRT E: two tablets of Janumet XR 50 mg/500 mg

The resulting data allows for the bridging of the existing safety and efficacy data from studies with JANUVIA® (sitagliptin), GLUMETZA® (metformin XR) and the combination of sitagliptin and metformin IR (from the JANUVIA® and JANUMET® programs) to Janumet XR (MK-0431A XR).

The sponsor repeated the pharmacokinetic analysis with the revised bioanalytical data and the summary statistics for metformin and sitagliptin was updated in the resubmission accordingly. The estimated values for PK parameters with revised data are very similar to the original estimates, rendering no change in the bioequivalence assessment results.
As shown in the Tables 1 and 2 that the 90% confidence intervals (CIs) of the geometric least square mean ratios for the pharmacokinetic parameters ($AUC_{0-\infty}$ and Cmax) for sitagliptin (Table 1) and metformin (Table 2) after administration of single tablet of

Janumet XR 100 mg/1000 mg tablet and those after administration of sitagliptin 100 mg + GLUMETZA® 1000 mg fell within the range of [0.80, 1.25]. The bioequivalence between FDC and co-administration of sitagliptin and Glumetza® has been established for two strength levels.

Furthermore, the BE between two tablets of FDC Janumet XR 50 mg/ 500 mg and one tablet of FDC Janumet XR 100 mg/1000 mg has been established in as seen in both tables. Likewise, the 90% CIs of the geometric least square mean ratios for $AUC_{0-\infty}$ and Cmax of sitagliptin (Table 1) and metformin (Table 2) after administration of single tablet of Janumet XR 100 mg/1000 mg tablet and those after administration of two tablets of Janumet XR 50 mg/500 mg fell within the range of [0.80, 1.25].

Table 1. Summary statistics and statistical comparisons for the potency unadjusted plasma PK parameters of sitagliptin after administration of a single Janumet XR 100 mg/1000 mg tablet, co-administration of corresponding doses of sitagliptin and metformin XR (Glumetza®) in healthy adult subjects

Treatment	A	B	C	D	E
PK Parameter	GM (95% CI)	GM (95% CI)	GM (95% CI)	GM (95% CI)	GM (95% CI)
$AUC_{0-\infty}$ (hr*ng/mL)	3994 (3883, 4161)	4010 (3849, 4178)	7773 (7461, 8098)	7837 (7521, 8166)	7835 (7520, 8164)
$AUC_{0\text{-last}}$ (hr*ng/mL)	3893 (3736, 4057)	3917 (3758, 4082)	7667 (7357, 7989)	7728 (7415, 8054)	7719 (7407, 8044)
Cmax (ng/mL)	356 (333, 381)	342 (320, 366)	778 (727, 832)	780 (728, 835)	747 (698, 800)
Between-Treatment Comparison (Geometric Mean Ratio [90% CI])					
Parameter	FDC vs. Co-ad 50/500 mg		FDC vs. Co-ad 100/1000 mg	2×FDC 50/500 mg vs. FDC 100/1000 mg	
$AUC_{0-\infty}$ (hr*ng/mL)	1.00 (0.99, 1.02)		1.01 (0.99, 1.03)	1.00 (0.98, 1.02)	
$AUC_{0\text{-last}}$ (hr*ng/mL)	1.01 (0.99, 1.02)		1.01 (0.99, 1.02)	1.00 (0.98, 1.02)	
Cmax (ng/mL)	0.96 (0.92, 1.01)		1.00 (0.96, 1.05)	0.96 (0.92, 1.00)	

GM: Geometric Mean; CI: Confidence Interval

Table 2. Summary statistics and statistical comparisons for the potency unadjusted plasma PK parameters of metformin after administration of a single Janumet XR 100 mg/1000 mg tablet, co-administration of corresponding doses of sitagliptin and metformin XR (Glumetza®) in healthy adult subjects

Treatment	A	B	C	D	E
PK Parameter	GM (95% CI)	GM (95% CI)	GM (95% CI)	GM (95% CI)	GM (95% CI)
$AUC_{0-\infty}$ (hr*ng/mL)	6614 (6090, 7184)	7045 (6492, 7645)	12458 (11493, 13504)	11963 (11017, 12990)	12286 (11339, 13312)
$AUC_{0\text{-last}}$ (hr*ng/mL)	6570 (6093, 7084)	6874 (6374, 7412)	12187 (11304, 13139)	11840 (10976, 12772)	12006 (11133, 12946)
Cmax (ng/mL)	560 (526, 596)	607 (570, 646)	866 (813, 922)	986 (925, 1051)	999 (937, 1064)
Between-Treatment Comparison (Geometric Mean Ratio [90% CI])					
Parameter	FDC vs. Co-ad 50/500 mg		FDC vs. Co-ad 100/1000 mg	2×FDC 50/500 mg vs. FDC 100/1000 mg	

$AUC_{0-\infty}$ (hr*ng/mL)	1.07 (1.01, 1.13)	0.96 (0.91, 1.01)	1.03 (0.97, 1.08)
$AUC_{0\text{-last}}$ (hr*ng/mL)	1.05 (1.00, 1.09)	0.97 (0.93, 1.02)	1.01 (0.97, 1.06)
Cmax (ng/mL)	1.08 (1.03, 1.14)	1.14 (1.09, 1.19)	1.01 (0.97, 1.06)

GM: Geometric Mean; CI: Confidence Interval

Reviewer's Comments:

The key results from the revised data indicate that co-administration of sitagliptin and GLUMETZA® and administration of Janumet XR are bioequivalent, and the Janumet XR tablets for both 50 mg/500 mg and 100 mg/1000 mg strengths are bioequivalent for both sitagliptin and metformin XR components. The results obtained from reviewer's independent analysis with raw data provided by the sponsor are in agreement with the sponsor's results. The conclusions made from the original submission regarding BE assessment have not changed by revised bioanalytical data.

Appendix: Synopsis Summary of Pivotal BE Study (Protocol 147)

Title: A Definitive Bioequivalence Study for Sitagliptin/Metformin XR FDC Tablets in Healthy Subjects

<table>
<tr><td>Objectives</td><td>Primary:
To demonstrate bioequivalence between the final market composition (FMC) sitagliptin/metformin (Janumet) extended release (XR) 50 mg/500 mg tablet and co-administration of corresponding doses of sitagliptin and Glumetza as individual tablets
To demonstrate bioequivalence between the FMC Janumet XR 100 mg/1000 mg tablet and co-administration of corresponding doses of sitagliptin and Glumetza as individual tablets
To demonstrate bioequivalence between two FMC Janumet XR 50 mg/500 mg tablets and a single FMC Janumet XR 100 mg/1000 mg tablet</td></tr>
<tr><td>Study Design</td><td>Open-label, randomized, five-period crossover</td></tr>
<tr><td>Study population</td><td>Forty-eight (male 28, female 20, age 18-45 years) enrolled and 39 subjects completed.</td></tr>
<tr><td>Investigational drug</td><td>
<table>
<tr><th>Drug</th><th>Potency</th><th>Formulation #</th><th>Dosage Form</th><th>Control #</th></tr>
<tr><td>Sitagliptin*</td><td>50 mg</td><td>WL00030296</td><td>Tablet</td><td>WL00034966</td></tr>
<tr><td>Sitagliptin*</td><td>100 mg</td><td>WL00032275</td><td>Tablet</td><td>WL00034978</td></tr>
<tr><td>Glumetza**</td><td>500 mg</td><td>WL00034364</td><td>Tablet</td><td>WL00034968</td></tr>
<tr><td>Glumetza**</td><td>1000 mg</td><td>WL00034365</td><td>Tablet</td><td>WL00034972</td></tr>
<tr><td>Janumet XR</td><td>50 mg/500 mg</td><td>WL00033696</td><td>FDC tablet</td><td>WL00034970</td></tr>
<tr><td>Janumet XR</td><td>50 mg/500 mg</td><td>WL00033696</td><td>FDC tablet</td><td>WL00034974</td></tr>
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