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APPLICATION NUMBER:

202270Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA SDN 31
Application Number(s)	202-270
Priority or Standard	Standard
Submit Date(s)	08-03-11
Received Date(s)	08-03-11
PDUFA Goal Date	02-03-12
Division / Office	DMEP/ODEII/OND
Reviewer Name(s)	Valerie S. W. Pratt, M.D.
Review Completion Date	11-10-11
Established Name	Sitagliptin/metformin XR
(Proposed) Trade Name	Janumet XR
Therapeutic Class	DPP-4 inhibitor/biguanide
Applicant	Merck
Formulation(s)	50/500, 50/1000, & 100/1000 mg tablets
Dosing Regimen	Once daily
Indication(s)	Type 2 diabetes mellitus
Intended Population(s)	Adult type 2 diabetes

Medical Officer Safety Review
Division of Metabolism and Endocrinology Products

NDA: 202-270 SDN 31 (Complete Response [CR])
Date of Submission: August 3, 2011
Name of drug: Sitagliptin/metformin fixed dose combination (FDC) tablet
Indication: For use as an adjunct to diet and exercise to improve glycemic control in patients with T2DM
Sponsor: Merck

Medical Reviewer: Valerie Pratt, M.D.
Medical Team Leader: Ilan Irony, M.D.

Background: On July 22, 2011, a CR letter was issued due to deficiencies at the Arecibo, Puerto Rico manufacturing facility. Satisfactory resolution of the Chemistry, Manufacturing, and Controls (CMC) deficiencies is required before the application may be approved. The updated complete study report (CSR) for clinical pharmacology study 147-00 (147) was also required, after review of (b) (4) July 11, 2011 response to our Form FDA 483.

Please refer to my review of NDA 202-270 which recommended approval of the FDC, pending resolution of the Office of Compliance, Division of Manufacturing and Product Quality (OC-DMPQ) issues.

CR: No additional nonclinical or clinical studies of sitagliptin/metformin XR FDC were undertaken by the applicant. Thus, there were no additional data to submit. No additions or changes to the safety profile were reported by the applicant.

As requested in the CR letter, however, the applicant submitted an updated CSR for clinical pharmacology study 147, a pivotal study that characterized the single dose pharmacokinetics (PK) of sitagliptin and metformin following administration of 50/500 mg or 100/1000 mg of the FDC in healthy subjects. (The revised CSR was requested because of (b) (4) July 11, 2011 response to the Form FDA 483 and the applicant's submission of updated study 147 datasets in SAS transport files on July 21, 2011.) As described in Jee Eun Lee's June 17, 2011 original clinical pharmacology review, the 90% CIs of the geometric mean ratios for the pharmacokinetic parameters ($AUC_{0-\infty}$ and Cmax) for sitagliptin and metformin after administration of single tablet of sitagliptin/metformin XR 100 mg/1000 mg tablet and those after administration of sitagliptin 100 mg + Glumetza (metformin XR) 1000 mg fell within the range of [0.80, 1.25]. Thus, the bioequivalence (BE) between FDC and co-administration of sitagliptin and Glumetza was established for two of the three dose strengths.

When BE was evaluated using the updated datasets as requested in the CR letter, the 90% CIs of the geometric mean ratios for the pharmacokinetic parameters ($AUC_{0-\infty}$ and Cmax) for sitagliptin and metformin after administration of single tablet of sitagliptin/metformin XR 50/500 mg or 100 mg/1000 mg tablet and those after co-administration of corresponding doses of sitagliptin + Glumetza (metformin XR) again fell within the range of [0.80, 1.25]. Thus, the bioequivalence (BE) between FDC and co-administration of sitagliptin and Glumetza was reestablished for two strength levels. Clinical pharmacology concurs. Please also refer to Dr. Jee Eun Lee's review.

Table 1. Statistical comparison of plasma PK parameters of sitagliptin and metformin after administration of a single 50/500 or 100/1000 mg FDC tablet and co-administration of corresponding doses of sitagliptin and Glumetza (metformin XR) in healthy adults

	Sita/met XR FDC Tablets vs. Co-administration of sitagliptin and Glumetza (metformin XR)	
Parameter	**Sita/met XR FDC 50/500 mg**	**Sita/met XR FDC 100/1000 mg**
Sitagliptin		
$AUC_{0-\infty}$	1.00 (0.99, 1.02)	1.01 (0.99, 1.03)
Cmax	0.96 (0.92, 1.01)	1.00 (0.96, 1.05)
Metformin		
$AUC_{0-\infty}$	1.07 (1.01, 1.13)	0.96 (0.91, 1.01)
Cmax	1.08 (1.03, 1.14)	1.14 (1.09, 1.19)

Source: CSR 147-00 Tables 11-1 and 11-2

Recommendation: I recommend approval of sitagliptin/metformin XR FDC, pending resolution of the Office of Compliance, Division of Manufacturing and Product Quality (OC-DMPQ) issues.

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/s/

VALERIE S PRATT
11/10/2011

ILAN IRONY
11/10/2011
I concur with Dr. Pratt's review and recommendation for approval, pending OC/OMPQ recommendation.

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