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RESEARCH**

APPLICATION NUMBER:
202270Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	January 27, 2012
From	Hylton V. Joffe, M.D., M.M.Sc.
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	NDA 202270
Supplement#	
Applicant	Merck
Date of Submission	August 3, 2011
PDUFA Goal Date	February 3, 2012
Proprietary Name / Established (USAN) names	Janumet XR (sitagliptin/metformin extended-release fixed-dose combination tablet)
Dosage forms / Strength	50/500 mg, 50/1000 mg, 100/1000 mg tablets
Proposed Indication(s)	As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both sitagliptin and metformin extended-release is appropriate
Recommended:	<i>Approval, pending agreement on labeling</i>

Cross Discipline Team Leader Review Template

1. Introduction

Janumet XR is a fixed-dose combination (FDC) tablet that contains two anti-diabetic medications: sitagliptin and an extended-release formulation of metformin. This is a 505(b)(1) application because Merck is the sponsor for sitagliptin (Januvia), a dipeptidyl-peptidase 4 inhibitor approved by FDA in 2006, and has a full right of reference to Glumetza, an extended-release metformin approved by FDA in 2005.

Janumet XR is dosed once daily and will be available in the following strengths (shown as sitagliptin/metformin extended-release): 50 mg/500 mg, 50 mg/1000 mg, and 100 mg/1000 mg.

2. Background

This is the second review cycle for Janumet XR. We issued a Complete Response letter on July 22, 2011. Our letter noted FDA Form 483 deficiencies identified during the pre-approval inspection of the Puerto Rico manufacturing facility that needed to be satisfactorily resolved before the application could be approved. In addition, we requested an updated study report for the pivotal bioequivalence study (see Section 5 for more details).

Please see reviews from the first cycle for further details, including Dr. Ilan Irony's Cross-Discipline Team Leader memorandum.

3. CMC

The Office of Compliance issued an overall "acceptable" recommendation on January 25, 2012, for the manufacturing facilities for Janumet XR. Therefore, the FDA Form 483 deficiencies identified in our Complete Response letter have been adequately addressed. Chemistry/Manufacturing/Controls (CMC) recommends approval.

4. Nonclinical Pharmacology/Toxicology

This resubmission does not contain new nonclinical pharmacology/toxicology data.

5. Clinical Pharmacology/Biopharmaceutics

The pivotal bioequivalence Study (147) was reviewed during the first cycle and showed bioequivalence between Janumet XR and the co-administered individual components (sitagliptin and Glumetza). However, [REDACTED] ^{(b) (4)} the site that analyzed the blood samples for

this study, had to rerun some of its analyses in response to concerns raised by the Office of Scientific Investigation. These new analyses changed some of the underlying data. Therefore, OSI requested confirmation that the FDC and individual components are still bioequivalent when these updated data are used in the pharmacokinetic analyses. This deficiency was included in the Complete Response letter and has now been adequately addressed, as shown below.

Study 147 compared the administration of Janumet XR to the co-administration of sitagliptin and Glumetza. This study also compared the administration of two 50/500 mg FDC tablets to the administration of one 100/1000 mg FDC tablet. Using the updated (b) (4) data, the 90% confidence intervals for the geometric mean ratios all still fall within the bioequivalence criteria of 80%-125%, as shown in Table 1. Therefore, the updated (b) (4) data do not change the prior conclusion regarding bioequivalence between Janumet XR and the co-administered components. Please see the review by Dr. Jee Eun Lee for additional details.

Table 1. Pharmacokinetic analyses - geometric means with 90% confidence intervals			
Revised analyses using updated data			
(adapted from Tables 1 and 2 in Dr. Lee's review)			
Parameter	FDC 50/500 mg vs. Co-administration	FDC 100/1000 mg vs. Co-administration	Two FDC 50/500 mg vs. FDC 100/1000 mg
Sitagliptin			
AUC _{0-inf}	1.00 (0.99, 1.02)	1.01 (0.99, 1.03)	1.00 (0.98, 1.02)
AUC _{0-last}	1.01 (0.99, 1.02)	1.01 (0.99, 1.02)	1.00 (0.98, 1.02)
C _{max}	0.96 (0.92, 1.01)	1.00 (0.96, 1.05)	0.96 (0.92, 1.00)
Metformin			
AUC _{0-inf}	1.07 (1.01, 1.13)	0.96 (0.91, 1.01)	1.03 (0.97, 1.08)
AUC _{0-last}	1.05 (1.00, 1.09)	0.97 (0.93, 1.02)	1.01 (0.97, 1.06)
C _{max}	1.08 (1.03, 1.14)	1.14 (1.09, 1.19)	1.01 (0.97, 1.06)
FDC=fixed dose combination			

6. Clinical Microbiology

This resubmission does not contain new clinical microbiology data.

7. Clinical/Statistical- Efficacy

This resubmission does not contain new clinical data.

8. Safety

This resubmission does not contain new clinical data.

9. Advisory Committee Meeting

This submission did not identify new efficacy or safety issues that rose to the level of needing input from an advisory panel. Therefore, this submission was not taken to advisory committee.

10. Pediatrics

This submission triggers new pediatric studies under the Pediatric Research and Equity Act (PREA). The pediatric plan had been addressed during the first review cycle. During the current review cycle, Merck provided updated timelines for the two pediatric studies, which are shown below. These timelines are acceptable.

PMR 1802-1: A pharmacokinetic study of JANUMET XR in pediatric patients 10 through 17 years of age (inclusive) with type 2 diabetes mellitus.

Final Protocol Submission:	by June 1, 2012
Trial Completion:	by December 1, 2013
Final Report Submission:	by June 1, 2014

PMR 1802-2: A 54-week, randomized, double-blind placebo-controlled trial to evaluate the efficacy and safety of JANUMET XR vs. metformin in pediatric patients who are inadequately controlled on diet and exercise. You must also evaluate whether pediatric patients can safely swallow JANUMET XR over the course of the trial.

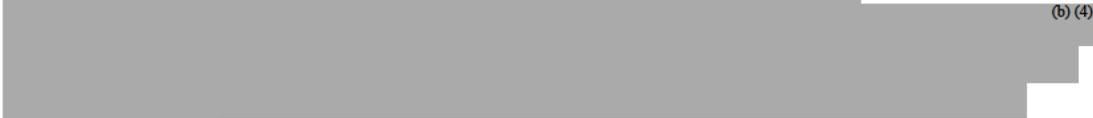
Final Protocol Submission:	by June 1, 2012
Trial Completion:	by September 1, 2016
Final Report Submission:	by March 1, 2017

11. Other Relevant Regulatory Issues

Tradename re-review: The Division of Medication Error Prevention and Analysis (DMEPA) completed its re-review of the Janumet XR tradename on November 2, 2011, and concluded that this tradename is acceptable. Please see the review by Richard Abate for details. DMEPA confirmed via an email, dated January 6, 2012, that another review of the tradename is not needed provided we approve this application by the action goal date of February 3, 2012.

12. Labeling

Most of the language in the label and Medication Guide had been finalized during the first review cycle. During this review cycle, we have requested the following additional revisions to the label:

-  (b) (4)
-  (b) (4)
- Minor formatting issues

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

APPROVAL, pending agreement on labeling.

- Risk Benefit Assessment

There are no new considerations regarding the risk-benefit assessment.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

There are no new safety findings from the submitted data that prompt the need for Risk Evaluation and Mitigation Strategies.

- Recommendation for other Postmarketing Requirements and Commitments

There are no new safety findings from the submitted data that prompt the need for new postmarketing required trials. Two pediatric studies will be required under PREA (see Section 10).

- Recommended Comments to Applicant

None.

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/s/

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01/27/2012

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