

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
202270Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA #/Product Name: 202270/JANUMET XR (sitagliptin/metformin hydrochloride extended-release)

PMR/PMC Description: Deferred randomized and controlled pediatric study under Pediatric Research Equity Act (PREA) to evaluate the pharmacokinetics of JANUMET XR (sitagliptin/metformin hydrochloride extended-release) in pediatric patients ages 10 to 17 years (inclusive).

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>06/01/2012</u>
	Study/Trial Completion:	<u>12/01/2013</u>
	Final Report Submission:	<u>06/01/2014</u>
	Other:	_____

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

JANUMET XR is ready for approval for use in adults; however, the pediatric studies have not been completed.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Deferred pediatric study required under PREA to assess the pharmacokinetics of JANUMET XR (sitagliptin/metformin hydrochloride extended-release) in pediatric patients ages 10 to 17 years (inclusive) with type 2 diabetes, (b) (4)

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
 Animal Efficacy Rule
 Pediatric Research Equity Act
 FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
 Assess signals of serious risk related to the use of the drug?
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

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

Required

- Observational pharmacoepidemiologic study
 Registry studies
 Primary safety study or clinical trial
 Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 Thorough Q-T clinical trial
 Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials
- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
Subpopulation: Pediatric patients ages 10 to 17 years (inclusive) with type 2 diabetes mellitus
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA #/Product Name: 202270/JANUMET XR (sitagliptin/metformin hydrochloride extended-release)

PMR/PMC Description:

(b) (4)

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>06/01/2012</u>
	Study/Trial Completion:	<u>09/01/2016</u>
	Final Report Submission:	<u>03/01/2017</u>
	Other:	_____

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

JANUMET XR is ready for approval for use in adults; however, the pediatric studies have not been completed.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Deferred pediatric study required under PREA in pediatric patients ages 10 to 17 years (inclusive) with type 2 diabetes. The goal of the trial is to establish the safety and efficacy of JANUMET XR in this subpopulation.

3. If the study/clinical trial is a PMR, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A (b) (4) randomized, double-blind placebo-controlled trial to evaluate the efficacy and safety of JANUMET XR vs. metformin (b) (4) in pediatric patients who are inadequately controlled on diet and exercise. As part of this study, you must evaluate whether pediatric patients can safely swallow JANUMET XR over the course of the trial. (b) (4)

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial

Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)

Pharmacokinetic studies or clinical trials

Drug interaction or bioavailability studies or clinical trials

Dosing trials

Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

Meta-analysis or pooled analysis of previous studies/clinical trials

Immunogenicity as a marker of safety

Other (provide explanation)

Subpopulation: Pediatric patients ages 10 to 17 years (inclusive) with type 2 diabetes mellitus

Agreed upon:

Quality study without a safety endpoint (e.g., manufacturing, stability)

Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)

Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E

Dose-response study or clinical trial performed for effectiveness

Nonclinical study, not safety-related (specify)

Other

5. Is the PMR/PMC clear, feasible, and appropriate?

Does the study/clinical trial meet criteria for PMRs or PMCs?

Are the objectives clear from the description of the PMR/PMC?

Has the applicant adequately justified the choice of schedule milestone dates?

Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

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/s/

AMY G EGAN
01/26/2012

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: July 15, 2011

TO: Mary Parks, Director,
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation

FROM: Gopa Biswas, Ph.D.
Bioequivalence Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

THROUGH: Martin K. Yau, Ph.D.
Acting Team Leader - Bioequivalence Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

SUBJECT: Review of [REDACTED] (b) (4) response dated July 11, 2011: Addendum to EIR review covering NDA 202-270, JANUMET XR (Sitagliptin/ Metformin Hydrochloride XR) Tablets 50/ 500 mg, 50/ 1000 mg and 100/ 1000 mg, sponsored by Merck Sharp & Dohme Corp.

At the request of the Division of Metabolism and Endocrinology Products (DMEP), the Division of Bioequivalence and GLP Compliance (DBGC) conducted inspections of clinical and analytical portions of the following bioequivalence study:

Study #: 147

Study Title: "An open-label, randomized, 5-period crossover study to demonstrate bioequivalence between the final market image (FMI) sitagliptin/ metformin XR 50 mg/ 500 mg and 100 mg/ 1000 mg fixed-dose combination (FDC) tablets and co-administration of corresponding doses of sitagliptin and GLUMETZA® as individual tablets in healthy adult, human subjects"

Page 2 - NDA 202-270 JANUMET XR (Sitagliptin/ Metformin Hydrochloride XR) Tablets 50/ 500 mg, 50/ 1000 mg and 100/ 1000 mg

DBGC's review submitted on July 1, 2011 evaluated the Form FDA-483 items issued at the analytical site, (b)(4) (b)(4)). There were no significant findings after inspection of the clinical portion at Covance, Dallas, TX (April 11-21, 2011). An electronic response to the Form FDA-483 was received from (b)(4) on July 11, 2011 (Attachment 1). This addendum provides DBGC's evaluation of (b)(4) response to the 483 items that needed to be resolved prior to accepting the bioanalytical study data for review. The evaluation is as follows:

(b)(4)

(b)(4)

Conclusion:

DBGC has evaluated and found that (b) (4) has provided adequate response to the Form FDA-483. DBGC recommends that the review division should ask the sponsor to repeat the bioequivalence determination using the new reintegrated data and re-evaluate the study outcomes.

After you have reviewed this transmittal memo, please append it to the original NDA submission.

Gopa Biswas, Ph.D.
Bioequivalence Branch, DBGC, OSI

Page 4 - NDA 202-270 JANUMET XR (Sitagliptin/ Metformin Hydrochloride XR) Tablets 50/ 500 mg, 50/ 1000 mg and 100/ 1000 mg

Final Classification:

NAI - Covance Clinical Research Unit Inc., Dallas, TX

FEI: 3007024261

VAI - [REDACTED] (b) (4)

FEI: Not Available

CC:

OSI/Ball

OSI/DBGC/Salewski/Viswanathan/Dejernet

OSI/DBGC/BB/Mada/Biswas/Yau/Haidar

OCP/DCP2/Lee/Choe

ODE2/DMEP/Parks/Chiang

HFR-SW150/Fleming/Osei

HFR-SW350/Kuchenthal

Draft: GB 07/13/2011

Edit: MKY 07/14/2011, 07/15/2011

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/s/

GOPA BISWAS
07/15/2011

MARTIN K YAU
07/15/2011

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

*****Pre-decisional Agency Information*****

Memorandum

Date: July 14, 2011

To: Raymond Chiang, Regulatory Project Manager, DMEP

From: Samuel Skariah, Regulatory Review Officer, DDMAC

CC: Lisa Hubbard, Professional Group Leader, DDMAC
Shefali Doshi, DTC Group Leader, DDMAC
Kendra Jones, Regulatory Review Officer

Subject: NDA 202270/S-023/S-024

DDMAC labeling comments for JANUMET[®] XR (sitagliptin and metformin HCl extended-release) tablets

General Comments

In response to DMEP's October 26, 2010 consult request, DDMAC has reviewed the proposed carton and container labels for JANUMET[®] XR (sitagliptin and metformin HCl extended-release) tablets.

DDMAC's comments on the proposed carton and container labels are based on the draft proposed versions of the carton and container labels submitted by Merck and Co. Inc. on July 1, and July 11, 2011, located in the EDR.

DDMAC has reviewed the proposed carton and container labels and we have no comments at this time.

Thank you for the opportunity to comment on these proposed materials.

If you have any questions on the PI, please contact Samuel Skariah at 301. 796. 2774 or Sam.Skariah@fda.hhs.gov.

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/s/

SAMUEL M SKARIAH
07/14/2011

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label and Labeling Review

Date: July 11, 2011

Reviewer: Richard A. Abate, RPh, MS, Safety Evaluator
Division of Medication Error Prevention and Analysis

Team Leader: Lubna Merchant, MS, PharmD, Team Leader
Division of Medication Error Prevention and Analysis

Associate Director: Kellie Taylor, PharmD, MPH, Associate Director
Division of Medication Error Prevention and Analysis

Drug Name and Strengths: Janumet XR (Sitagliptin and Metformin HCl Extended-release) Tablets, 50 mg/500 mg, 50 mg/1000 mg, and 100 mg/1000 mg tablets

Application Type/Number: NDA 202270

Applicant: Merck, Sharpe and Dohme

OSE RCM #: 2010-2299-1

1 INTRODUCTION

This memo summarizes DMEPA's evaluation of the revised proposed container labels and carton labeling for Janumet XR (Sitagliptin and Metformin HCL Extended-release) Tablets. The revisions were made based on comments provided by DMEPA in OSE review # 2010-2299 dated June 15, 2011 and comments from DDMAC.

2 MATERIALS REVIEWED

DMEPA reviewed the revisions to the proposed container labels and carton labeling submitted July 1, 2011 and July 11, 2011. We also evaluated our recommendations made in OSE review # 2010-2299 to determine whether the revisions address DMEPA's concerns from a medication error perspective.

3 CONCLUSIONS AND RECOMMENDATIONS

DMEPA finds the revised container labels and carton labeling for Janumet XR in NDA 202270 acceptable. We have no additional comments at this time.

If you have further questions or need clarification, please contact OSE project manager, Rita Tossa, at 301-796-4053.

4 REFERENCES

OSE review #2010-2299, Label and Labeling Review Janumet XR; Abate, R, June 15, 2011.

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/s/

RICHARD A ABATE
07/11/2011

LUBNA A MERCHANT
07/11/2011

KELLIE A TAYLOR
07/13/2011

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: June 30, 2011

TO: Mary Parks, M.D.
Director, Division of Metabolism and Endocrinology
Products
Office of Drug Evaluation

FROM: Sripal R. Mada, Ph.D.
Bioequivalence Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

THROUGH: Martin K. Yau, Ph.D.
Acting Team Leader - Bioequivalence Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

SUBJECT: Review of EIR Covering NDA 202-270, JANUMET XR
(Sitagliptin / Metformin Hydrochloride XR) Tablets
50 / 500 mg, 50 / 1000 mg, 100 / 1000 mg, from Merck
Sharp & Dohme Corp.

At the request of the Division of Metabolism and Endocrinology Products (DMEP), the Division of Bioequivalence and GLP Compliance (DBGC) conducted inspections of clinical and analytical portions of the following study:

Study: 147: "An open-label, randomized, 5-period crossover study to demonstrate bioequivalence between the final market image (FMI) sitagliptin / metformin XR 50 mg / 500 mg and 100 mg / 1000 mg fixed-dose combination (FDC) tablets and co-administration of corresponding doses of sitagliptin and GLUMETZA® as individual tablets in healthy adult, human subjects"

CLINICAL SITE INSPECTION:

The inspection of clinical portion was conducted at **Covance Clinical Research Unit Inc., Dallas, TX**. Following the inspection (April 11-21, 2011), No Form FDA-483 was issued.

ANALYTICAL SITE INSPECTION:

The inspection of analytical portion was conducted at [REDACTED] (b)(4)

[REDACTED]

[REDACTED] Following the inspection at [REDACTED] (b)(4)

[REDACTED] Form FDA-483 was issued (Attachment SRM1).

Our evaluation of the Form FDA-483 observations follows:

[REDACTED] (b)(4)

Conclusions:

Following the inspection, DBGC recommends the following:

- (b) (4) should provide (b) (4) data for MK-0431 and metformin using (b) (4) (see Form FDA-483, item 2).
- (b) (4) should provide (b) (4) data for MK-0431 (see Form FDA-483, item 4).
- (b) (4) (b) (4) see Form FDA-483, item 5).

The clinical data and other analytical data are acceptable for your review.

Please note that DBGC has not yet received the written response to the Form FDA-483 from (b) (4) DBGC will update DMEP if our review of the response upon receipt results in a change of our recommendation.

After you have reviewed this transmittal memo, please append it to the original NDA submission.

Page 4 - NDA 202-270, JANUMET XR (Sitagliptin / Metformin HCl XR)
Tablets 50 / 500 mg, 50 / 1000 mg, 100 / 1000 mg

Sripal R. Mada, Ph.D.
Bioequivalence Branch, DBGCC, OSI

Final Classification:

NAI - Covance Clinical Research Unit Inc., Dallas, TX
FEI: 3007024261

VAI - [REDACTED] (b) (4)

FEI: Not Available

CC:

OSI/Ball

OSI/DBGCC/Salewski/Dejernet

OSI/DBGCC/BB/Mada/Yau/Haidar

OCP/DCP2/Lee/Choe

ODE2/DMEP/Parks/Chiang

HFR-SW150/Fleming/Osei

HFR-SW350/Kuchenthal

Draft: SRM 06/27/2011

Edit: MKY 06/28/2011, 06/30/2011

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FACTS: 1255786

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**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications**

*****Pre-decisional Agency Information*****

Memorandum

Date: June 21, 2011

To: Raymond Chiang, Regulatory Project Manager,
Division of Metabolism and Endocrinology Products (DMEP)

From: Samuel Skariah, Regulatory Review Officer
Kendra Jones, Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

CC: Lisa Hubbard, Group Leader, DDMAC
Shefali Doshi, Group Leader, DDMAC
Mike Wade, Project Manager, DDMAC

Subject: NDA 202270 Janumet XR (sitagliptin/metformin XR FDC)

DDMAC labeling review – carton/container labeling

DDMAC has reviewed the proposed carton and container labeling for Janumet XR (sitagliptin/metformin XR) originally consulted to DDMAC on October 26, 2010. DDMAC has based its review on the carton and container labels submitted by the applicant on September 24, 2010, available in the EDR at:

<\\CDSESUB1\EVSPROD\NDA202270\202270.enx>

We offer the following comments:

General Comment

- Professional Sample Cartons (all strengths)

- [REDACTED] (b) (4)

Thank you for the opportunity to comment on these proposed materials.

If you have any questions please contact Samuel Skariah at 301.796.2774 or Sam.Skariah@fda.hhs.gov or Kendra Jones at 301.796.3917 or Kendra.Jones@fda.hhs.gov

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/s/

SAMUEL M SKARIAH
06/21/2011

KENDRA Y JONES
06/21/2011

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label and Labeling Review

Date: June 15, 2011

Reviewer: Richard A. Abate, RPh, MS, Safety Evaluator
Division of Medication Error Prevention and Analysis

Team Leader: Lubna Merchant, MS, PharmD, Acting Team Leader
Division of Medication Error Prevention and Analysis

Division Director: Carol Holquist, RPh, Director
Division of Medication Error Prevention and Analysis

Drug Name and Strength: Janumet XR (Sitagliptin and Metformin HCl Extended-release) Tablets, 50 mg/500 mg, 50 mg/1000 mg, and 100 mg/1000 mg

Application Type/Number: NDA 202270

Applicant/sponsor: Merck, Sharpe and Dohme

OSE RCM #: 2010-2299

1 INTRODUCTION

This review summarizes the Division of Medication Error Prevention and Analysis' (DMEPA's) evaluation of the proposed container labels and carton and insert labeling for Janumet XR (Sitagliptin and Metformin HCl Extended-release) Tablets for NDA 202270 for areas of vulnerability that could lead to medications errors.. The review responds to a request from the Division of Metabolism and Endocrinology Products (DMEP) to review the container labels and carton labeling for this Application.

1.1 REGULATORY HISTORY

Merck, the Applicant for this NDA, has standardized the label design for the container labels of their oral solid dosage forms. DMEPA reviewed and provided recommendations for the labels of the effected products included in a bundled supplement in OSE review # 2010-628 dated August 13, 2010 and 2010-628-1 dated April 11, 2011. Additionally, Janumet (Sitagliptin and Metformin HCl) tablets (NDA 022044) was approved March 30, 2007. Janumet is currently marketed in 50 mg/500 mg and 50 mg/1000 mg strength presentations.

1.2 PRODUCT INFORMATION

Janumet XR (Sitagliptin and Metformin HCl Extended-release) tablets are indicated as an adjunct to exercise and diet to improve glycemic control in adults with type 2 diabetes mellitus. Janumet XR is designed to release Sitagliptin immediately with Metformin HCl as an extended-release formulation is the core of the tablet. Janumet XR will be marketed as 50 mg/500 mg, 50 mg/1000 mg, and 100 mg/1000 mg tablets. Janumet XR is dosed as two tablets (50 mg/500 mg or 50 mg/1000 mg) or one tablet (100 mg/1000 mg) by mouth once daily, up to a maximum daily dose of 100 mg of Sitagliptin and 2000 mg of Metformin. (b) (4)

In addition, professional samples are proposed in a presentation of cartons containing two bottles of 14 tablets of either 50 mg/500 mg tablets or 50 mg/1000 mg Janumet XR and cartons containing two bottles of 7 tablets of 100 mg/1000 mg Janumet XR. The product is stored at room temperature.

2 METHODS AND MATERIALS REVIEWED

Using Failure Mode and Effects Analysis¹ and postmarketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted September 24, 2010 (Appendix A)
- Carton Labeling submitted September 24, 2010 (Appendix B)
- Insert Labeling submitted May 27, 2011

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

Additionally, since Janumet is currently marketed, DMEPA searched the FDA Adverse Event Reporting System (AERS) database to identify medication errors involving Janumet. DMEPA searched the Adverse Event Reporting System (AERS) database on March 29, 2011 using the following search terms: trade name “Janumet%”; verbatim terms “Janume%” and “Sitagliptin%,” selecting only those sitagliptin terms that also included metformin; and the MedDRA High Level Group Term (HLGT) “Medication Errors,” and High Level Terms (HLT) “Product Label Issues” and “Product Quality Issues NEC.” No time limit was set. The ISR numbers of the cases retrieved appear in Appendix C.

The reports were manually reviewed to determine if a medication error occurred. Duplicate reports were combined into cases. The cases that described a medication error were categorized by type of error. We reviewed the cases within each category to identify factors that contributed to the medication errors. If a root cause was associated with the label or labeling of the product, the case was considered pertinent to this review. Reports excluded from the case series include those that did not describe a medication error, those in which Janumet was a concomitant medication not involved in the medication error, the medication error related to patient compliance with using medication including intentional overdose, or the report involved a product complaint.

Following exclusions we evaluated a total of 13 cases relevant to this review. The medication errors are classified into the following medication error types:

- Wrong Drug (n=4): These cases involve the confusion between Janumet and other marketed products. The cases were discussed in the review of the proprietary name Janumet XR, OSE review # 2011-1111.
- Wrong Technique (n=4): These cases involve the patient splitting the tablets in half and taking one half tablet twice daily. However, the reasons for cutting the tablets could not be determined from the details provided in the case narrative. The patients in these cases experienced indigestion and diarrhea which was reported to have improved when the tablets were administered whole.
- Extra Dose (n=3): These cases involve the patients taking Janumet more frequently than twice daily. One case noted the patient had developed pancreatitis after taking Janumet four times a day. However, the cause could not be determined. The remaining two cases were foreign and resulted from the prescribers instructing the patient to take Janumet three times daily.
- Overdose of Sitagliptin (n=2): Both overdose cases involved patients who had been prescribed Januvia, and the therapy was then switched to Janumet. However, each patient mistakenly took both Januvia and Janumet, concurrently. One patient took both products for three weeks and developed right upper quadrant pain as well as elevated serum amylase and lipase which resolved when the medications were held. The other patient reportedly received both products for three months and developed an exfoliative rash requiring hospitalization with the diagnosis of drug hypersensitivity which resolved over several weeks after the medications were stopped.

3 DISCUSSION OF DEFICIENCIES IDENTIFIED

DMEPA identified the following deficiencies with the packaging, labels and labeling or areas that are vulnerable to confusion and lead to medication errors.

3.1 PRODUCT DESIGN

The Applicant proposes to use the same strength presentations (50 mg/500 mg and 50 mg/1000 mg) for Janumet XR as are currently marketed for Janumet. This overlap in strength presentations increases the risk of selection errors between the two formulations of this medication as both formulations will be side by side on pharmacy shelves. However, the Applicant uses a field of differentiating color in the strength presentation on the container labels to help differentiate Janumet XR from Janumet.

3.2 CONTAINER LABELS

Medication errors cases have been reported involving the splitting of Janumet tablets and resulting in adverse events. The container labels lack instruction to swallow these tablets whole. Although the product has a Medication Guide which includes this information, the warning does not appear on the immediate container label which would reach the patient because Janumet XR is packaged in unit of use quantities (e.g., 30 and 90 count bottles for 100 mg/1000 mg tablets and 60 and 180 count bottles for 50 mg/500 mg and 50 mg/1000 mg tablets). Thus, a prominent statement about swallowing the tablet whole should be included on the container labels of these quantities (b) (4)

Additionally, the container labels are standardized with demonstrated improvement of readability for oral solids manufactured by the Applicant. Therefore, DMEPA attempted to maintain this standardized presentation for the container labels.

3.3 CARTON LABELING

The Applicant proposes carton labeling for the professional samples of Janumet XR which presents all strength presentations in the same color (red). Additionally, the graphic design appearing above the proprietary name, a swoosh in maroon and gold broken by a blue dot, is very similar to the graphic on the carton labeling for the professional samples of Janumet. The products are likely to be stored near each other at a physician's office. Thus, the carton labeling requires further enhancements to differentiate these products from one another.

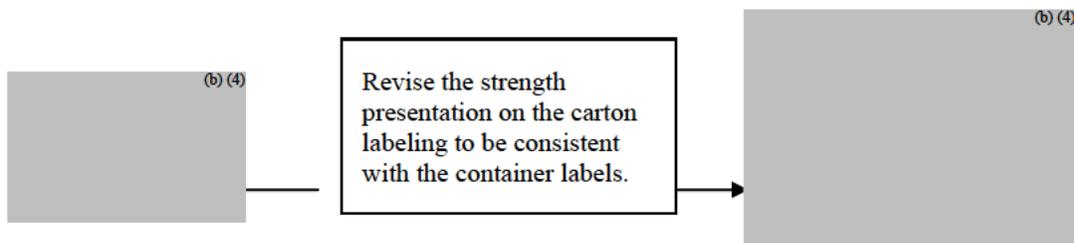
4 CONCLUSIONS AND RECOMMENDATIONS

DMEPA concludes that the proposed labels and labeling introduce vulnerability that can lead to medication errors because the strengths of Janumet XR overlap with Janumet and the carton labeling inadequately differentiates the strengths of Janumet XR. We recommend the following:

A. General Comments to the Division:

DMEPA believes the established name should be presented as "(Sitagliptin and Metformin HCL Extended-release) tablets". However, we defer to CMC for the presentation of the established name on the labels and labeling.

- B. Container Labels (all strengths - 30, 60, 90, and 180 count bottles)
1. Revise and increase the prominence of the Medication Guide statement. If additional space is needed, relocate the statement, ‘Each tablet contains...’ to the side panel.
 2. Include the statement “Swallow whole. Do not crush, split, or chew.” to the principle display panel, if space permits, or to the side panel of the label.
- C. Container Labels: (all strengths - 1000 count bottles)
Revise and increase the prominence of the Medication Guide statement.
- D. Carton Labeling (Professional Samples - all strengths)
1. Revise the presentation of the established name so that the established name is printed in letters that are at least half as large as the letters comprising the proprietary name or designation with which it is joined, and the established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features, per 21 CFR 201.10(g)(2).
 2. Revise the strength presentation, including the colors of the field and of the print font to be consistent with the strength presentation on the respective container labels.



3. Revise the strength presentation so that the unit of measure “mg” is on the same line as the numeric strengths and in the same size font to improve readability. Currently, the unit of measure appears as a superscript.
4. Revise the presentation of the proprietary name using one color font for the root name and modifier to improve readability. In addition, increase the font used for the presentation of “XR” in the proprietary name to be commensurate with the capitalized “J” in Janumet. Additionally, revise the color of the font for the proprietary name. The appearance of Janumet XR should differ from that of the carton labeling for the professional samples for Janumet. (see below.)



5. Delete or reduce the size of the graphic above the proprietary name, Janumet XR, it as it distracts from the prominence of the proprietary name. Additionally, if retained, revise the color and shape of the graphic as it appears too similar to the graphic that appears on the carton labeling for the professional samples for Janumet.
 6. Revise and increase the prominence of the Medication Guide statement.
- E. Carton Labeling (Professional Samples - 50 mg/500 mg and 50 mg/1000 mg)
Revise the net quantity statement so that it reads:

14 tablets per bottle
Carton contains 2 bottles

- F. Carton Labeling (Professional Samples – 100 mg/1000 mg)
Revise the net quantity statement so that is reads:

7 tablets per bottle
Carton contains 2 bottles

If the Division has further questions or need clarifications, please contact Margarita Tossa, project manager, at 301-796-4053.

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/s/

RICHARD A ABATE
06/17/2011

LUBNA A MERCHANT
06/17/2011

CAROL A HOLQUIST
06/17/2011

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications**

*****Pre-decisional Agency Information*****

Memorandum

Date: June 9, 2011

To: Raymond Chiang, Regulatory Project Manager,
Division of Metabolism and Endocrinology Products (DMEP)

From: Samuel Skariah, Regulatory Review Officer
Kendra Jones, Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

CC: Lisa Hubbard, Group Leader, DDMAC
Shefali Doshi, Group Leader, DDMAC
Mike Wade, Project Manager, DDMAC

Subject: NDA 202270 Janumet XR (sitagliptin/metformin XR FDC)

DDMAC labeling review

DDMAC has reviewed the proposed Prescribing Information (PI) and Medication Guide for Janumet XR (sitagliptin/metformin XR) originally consulted to DDMAC on October 26, 2010. DDMAC has based its review on the substantially complete label sent via email from DMEP (Raymond Chiang) on May 31, 2011.

General Comment

Comments regarding the PI and the Medication Guide are provided directly in the attached version below.

Thank you for the opportunity to comment on these proposed materials.

If you have any questions on the PI, please contact Samuel Skariah at 301.796.2774 or Sam.Skariah@fda.hhs.gov.

If you have any questions on the PPI, please contact Kendra Jones at 301.796.3917 or Kendra.Jones@fda.hhs.gov.

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/s/

SAMUEL M SKARIAH
06/09/2011

KENDRA Y JONES
06/09/2011

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

PATIENT LABELING REVIEW

Date: **June 06, 2011**

To: Mary Parks, MD, Director
**Division of Metabolism and Endocrinology Products
(DMEP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Acting Team Leader, Patient Labeling Reviewer
Division of Risk Management (DRISK)

Melissa Hulett, MSBA, BSN, RN
Acting Team Leader, Patient Labeling Reviewer
Division of Risk Management (DRISK)

From: Shawna Hutchins, MPH, BSN, RN
Patient Labeling Reviewer
Division of Risk Management (DRISK)

Subject: DRISK Review of Patient Labeling (Medication Guide)

Drug Name (established name): JANUMET XR (sitagliptin/metformin hydrochloride extended-release)

Dosage Form and Route: Tablets

Application Type/Number: NDA 202270

Applicant: Merck Sharp & Dohme Corporation

OSE RCM #: 2010-2296

1 INTRODUCTION

On September 24, 2010 the applicant submitted a New Drug Application (NDA) for Janumet XR, an extended-release formulation of Janumet (NDA 22-044). Janumet XR is indicated 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 is appropriate.

This review is written in response to a request by the Division of Metabolism and Endocrinology Products (DMEP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Medication Guide (MG), for Janumet XR (sitagliptin/metformin hydrochloride extended-release).

2 MATERIAL REVIEWED

- Draft JANUMET XR (sitagliptin/metformin hydrochloride extended-release) Medication Guide (MG), received on September 24, 2010, and sent to DRISK on May 31, 2011.
- Draft JANUMET XR (sitagliptin/metformin hydrochloride extended-release) Prescribing Information (PI) received September 24, 2010, revised by the Review Division throughout the current review cycle, and received by DRISK on May 31, 2011.
- Approved JANUMET (sitagliptin/metformin hydrochloride) comparator labeling dated May 13, 2011.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the MG, the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the MG, document using the Verdana font, size 11.

In our review of the MG we have:

- ensured that the MG is consistent with the prescribing information (PI)
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with the approved comparator labeling where applicable

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DRISK on the correspondence.
- Our annotated versions of the MG are appended to this memo. Consult DRISK regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

SHAWNA L HUTCHINS
06/06/2011

LASHAWN M GRIFFITHS
06/07/2011

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 202270 BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: JANUMET XR Established/Proper Name: Sitagliptin/Metformin Hydrochloride extended release Dosage Form: Tablet Strengths: 50/500, 50/1000, 100/1000 mg sita/metformin XR		
Applicant: Merck Sharp and Dohme Corp. Agent for Applicant (if applicable):		
Date of Application: September 23, 2010 Date of Receipt: September 23, 2010 Date clock started after UN:		
PDUFA Goal Date: July 23, 2010		Action Goal Date (if different): July 22, 2010
Filing Date: November 22, 2010		Date of Filing Meeting: November 3, 2010
Chemical Classification: (1,2,3 etc.) (original NDAs only) Type 4		
Proposed indication(s)/Proposed change(s): new fixed dose combination of sitagliptin and metformin hCl XR for the treatment of Type 2 Diabetes Mellitus. The combo is already approved, the change is the extended-release formulation.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html and refer to Appendix A for further information.</i>		
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
Resubmission after withdrawal? <input type="checkbox"/>		Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system <input type="checkbox"/> Pre-filled biologic delivery device/system <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	

<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product):				
List referenced IND Number(s): 101964				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>		X		
Are all classification properties [e.g., orphan drug, OTC, 505(b)(2)] entered into tracking system? <i>If no, ask the document room staff to make the appropriate entries.</i>	X			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>		X		
<i>If yes, explain in comment column.</i>			X	
<i>If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:</i>			X	
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			
<u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i>	Payment for this application: <input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			

<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>		Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
505(b)(2)		YES	NO	NA	Comment
(NDAs/NDA Efficacy Supplements only)					
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?			X		The RLD is Glumetza—See b(2) assessment form
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].			X		
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?			X		
<p><i>Note: If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).</i></p>					
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm			X		
If yes, please list below:					
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration		
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>					
Exclusivity		YES	NO	NA	Comment
Does another product have orphan exclusivity for the same indication? Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm			X		
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?				X	
<p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)</i></p>					

Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>) If yes, # years requested: <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>		X		
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?		X		
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i>			X	

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
	If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?			
Overall Format/Content	YES	NO	NA	Comment
If electronic submission, does it follow the eCTD guidance? ¹ If not, explain (e.g., waiver granted).	X			
Index: Does the submission contain an accurate comprehensive index?	X			
Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including: <input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only) If no, explain.	X			

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

BLAs only: Companion application received if a shared or divided manufacturing arrangement?			X	
If yes, BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	X			
<i>If foreign applicant, both the applicant and the U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	X			
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	X			
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				
<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature?	X			
<i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i>				
<i>Note: Debarment Certification should use wording in FD&C Act</i>				

section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”				
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>			X	

Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>			X	

Pediatrics	YES	NO	NA	Comment
<p><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)²</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	X			Scheduled for PeRC for April 27, 2011
<p>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>		X		
<p>If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?</p> <p><i>If no, request in 74-day letter</i></p>		X		

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

<p>If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3)</p> <p><i>If no, request in 74-day letter</i></p>	X			(b) (4) pediatric language will be included in the 74-day letter
<p>BPCA (NDAs/NDA efficacy supplements only):</p> <p>Is this submission a complete response to a pediatric Written Request?</p> <p><i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i></p>		X		
<p>Proprietary Name</p>	YES	NO	NA	Comment
<p>Is a proposed proprietary name submitted?</p> <p><i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i></p>		X		The sponsor plans to submit request for proprietary name review
<p>REMS</p>	YES	NO	NA	Comment
<p>Is a REMS submitted?</p> <p><i>If yes, send consult to OSE/DRISK and notify OC/ DCRMS via the DCRMSRMP mailbox</i></p>		X		Will request sponsor to submit MedGuide-only REMs in the 74-day letter
<p>Prescription Labeling</p>	<input type="checkbox"/> Not applicable			
<p>Check all types of labeling submitted.</p>	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input checked="" type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
<p>Is Electronic Content of Labeling (COL) submitted in SPL format?</p> <p><i>If no, request in 74-day letter.</i></p>		X		Will request in 74-day letter
<p>Is the PI submitted in PLR format?⁴</p>	X			
<p>If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted, what is the status of the request?</p>			X	

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

⁴ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

<i>If no waiver or deferral, request PLR format in 74-day letter.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	X			OSE will also review REMs
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted?				
<i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)?				
<i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?				
<i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)		X		
<i>If yes, specify consult(s) and date(s) sent:</i>				
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s):		X		In lieu of meeting, we provided comments to their EOP2 meeting package
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): May 10, 2010	X			
<i>If yes, distribute minutes before filing meeting</i>				

<p>Any Special Protocol Assessments (SPAs)? Date(s): <i>If yes, distribute letter and/or relevant minutes before filing meeting</i></p>		X		
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ATTACHMENT

MEMO OF FILING MEETING

DATE: 11.03.10

BLA/NDA/Supp #: 202270

PROPRIETARY NAME: Janumet XR

ESTABLISHED/PROPER NAME: sitagliptin/metformin hydrochloride extended release

DOSAGE FORM/STRENGTH: Tablet: 50/500, 50/1000, 100/1000 mg sita/metformin XR

APPLICANT:

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): new fixed dose combination of sitagliptin and metformin hCl XR for the treatment of Type 2 Diabetes Mellitus. The combo is already approved, the change is the extended-release formulation.

BACKGROUND:

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Raymond Chiang	Y
	CPMS/TL:	Lina Aljuburi	Y
Cross-Discipline Team Leader (CDTL)	Ilan Irony		Y
Clinical	Reviewer:	Valerie Pratt	Y
	TL:	Ilan Irony	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:	N/A	
	TL:		
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:	N/A	
	TL:		
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:	N/A	
	TL:		

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APPEARS THIS WAY ON ORIGINAL

Clinical Pharmacology	Reviewer:	Jee Eun Lee	Y
	TL:	Sally Choe	Y
Biostatistics	Reviewer:	Todd Sahlroot	N
	TL:		
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Patricia Brundage	Y
	TL:	Todd Bourcier	Y
Statistics (carcinogenicity)	Reviewer:	N/A	
	TL:		
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:	N/A	
	TL:		
Product Quality (CMC)	Reviewer:	Su Tran/Olen Stephens	Y
	TL:	Ali Al Hakim	N
Quality Microbiology (<i>for sterile products</i>)	Reviewer:	N/A	
	TL:		
CMC Labeling Review	Reviewer:	Olen Stephens	Y
	TL:		
Facility Review/Inspection	Reviewer:	Mahesh Ramandham	N
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Not submitted by sponsor yet	
	TL:		
OSE/DRISK (REMS)	Reviewer:	Twanda Scales (review MedGuide); Shawna Hutchins (review MedGuide-only REMS)	Shawna Hutchins present
	TL:	Melissa Hulett	
OC/DCRMS (REMS)	Reviewer:	N/A	
	TL:		

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APPEARS THIS WAY ON ORIGINAL

Bioresearch Monitoring (DSI)	Reviewer:	Jyoti Patel	DSI bioequivalence reviewer, clinical inspections not needed as per DSI and clinical reviewer
	TL:	Martin Yau	
Controlled Substance Staff (CSS)	Reviewer:	N/A	
	TL:		
Other reviewers			
Other attendees			

FILING MEETING DISCUSSION:

GENERAL	
<ul style="list-style-type: none"> 505(b)(2) filing issues? <p>If yes, list issues:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Electronic Submission comments <p>List comments:</p>	<input checked="" type="checkbox"/> Not Applicable
CLINICAL	
<p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain: The regulatory decision for this NDA is based on the BE study and its inspection studies</p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO

<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:
<ul style="list-style-type: none"> Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments: Team leader stated that no new phase 3 data, so no statistical reviewer assigned. Todd</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<p>Sahlroot will handle any statistical issues that come up during the review cycle.</p>	
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> FILE</p> <p><input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>

<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? <p>Comments: EER request was sent by ONDQA PM on October 5, 2010.</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>

<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter</p>
<p><u>CMC Labeling Review</u></p> <p>Comments: CMC reviewer will review carton and container.</p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>REGULATORY PROJECT MANAGEMENT</p>	
<p>Signatory Authority: Mary Parks, M.D.</p> <p>21st Century Review Milestones (see attached) (listing review milestones in this document is optional):</p> <p>Comments:</p>	
<p>REGULATORY CONCLUSIONS/DEFICIENCIES</p>	
<p><input type="checkbox"/></p>	<p>The application is unsuitable for filing. Explain why:</p>
<p><input checked="" type="checkbox"/></p>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):</p> <p><u>Review Classification:</u></p> <p><input checked="" type="checkbox"/> Standard Review</p> <p><input type="checkbox"/> Priority Review</p>
<p>ACTIONS ITEMS</p>	
<p><input type="checkbox"/></p>	<p>Ensure that any updates to the review and chemical classifications and other properties [e.g., orphan drug, OTC, 505(b)(2)], are entered into tracking system.</p>
<p><input type="checkbox"/></p>	<p>If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).</p>
<p><input type="checkbox"/></p>	<p>If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.</p>
<p><input type="checkbox"/></p>	<p>BLA/BLA supplements: If filed, send 60-day filing letter</p>

<input type="checkbox"/>	
<input type="checkbox"/>	<p>If priority review:</p> <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify DMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Conduct labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	<p>BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action (BLAs/BLA supplements only) [These sheets may be found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822]</p>
<input type="checkbox"/>	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RAYMOND S CHIANG
01/13/2011