# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

**202343Orig1s000**

# 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.

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NDA #/Product Name: 202-343/JUVISYNC (sitagliptin and simvastatin fixed-dose combination [FDC])

PMR/PMC Description: A randomized,,double-blind, active-controlled clinical trial to study the effect of sitagliptin and simvastatin FDC versus sitagliptin on glycemic control in type 2 diabetic patients on background metformin therapy.

PMR/PMC Schedule Milestones:

| | |
|---|---|
| Final Protocol Submission: | 04/30/2012 |
| Study/Trial Completion: | 01/29/2015 |
| Final Report Submission: | 07/29/2015 |
| 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

Meta-analyses in the published literature have shown increases in fasting plasma glucose and hemoglobin A1C in patients receiving statin therapy, including simvastatin. The applicant conducted a meta-analysis of clinical trial data with simvastatin in diabetic patients showing that there was no clinically significant worsening of glycemic control. However, this involved a limited number of subjects and was not a rigorous appraisal of this safety concern. The applicant is being required to further assess this safety signal in a dedicated clinical trial. It is understood that the individual components in this FDC are already available and are frequently being co-administered.

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."

The goal of the study is to conclusively demonstrate the effect of simvastatin on glycemic control in type 2 diabetic patients being treated with sitagliptin and simvastatin FDC on a background of metformin therapy versus type 2 diabetic patients being treated with sitagliptin.

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 randomized, double-blind, active-controlled clinical trial in ≥ 200 type 2 diabetic subjects per treatment arm on background metformin therapy randomized to sitagliptin and simvastatin FDC or sitagliptin alone for ≥ 16 weeks to assess the effect of simvastatin on glycemic control. Glycemic control should be assessed by the change in HbA1c (primary endpoint), change in fasting plasma glucose, and change in 2-hour postprandial glucose. |

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)

_____

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?

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**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/

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AMY G EGAN
10/06/2011

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