# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**202343Orig1s000**

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

**ADDENDUM**
**CLINICAL PHARMACOLOGY REVIEW**

| | |
|---|---|
| **NDA** | 202343 |
| **Submission Date(s)** | December 3, 2010 |
| **Brand Name** | Juvisync ™, MK-0431D |
| **Generic Name** | Sitagliptin phosphate+simvastatin tablet |
| **Reviewers** | Sang M. Chung, Ph.D. |
| **Team Leader** | Jayabharathi Vaidyanathan, Ph.D. (Acting) |
| **OCP Division** | Clinical Pharmacology II |
| **OND Division** | Metabolism and Endocrinology Products (DMEP) |
| **Sponsor** | Merck |
| **Submission Type** | 505(b)(1), Standard |
| **Formulation Strength(s)** | 100/10, 100/20, and 100/40 (mg sitagliptin / mg simvastatin) |
| **Indication** | Treatment with both sitagliptin and simvastatin |
| **Dosage & Administration** | Patients switching from co-administered sitagliptin (100 mg) and simvastatin (10, 20, or 40 mg) can initiate JUVISYNC at the doses of sitagliptin and simvastatin already being taken. JUVISYNC can be taken with or without food in the evening. |

This addendum is to finalize the pending recommendation in the original Clinical Pharmacology review upon the availability of the Office of Scientific Investigations (OSI) inspection review issued on September 7, 2011. Also provided is the comments on the development of fixed-dose combination with sitagliptin 50 mg from the clinical pharmacology perspective.

**Pending Recommendation in the Original Review dated September 1, 2011:**
The Office of Clinical Pharmacology / Division of Clinical Pharmacology 2 (OCP/DCP-2) has reviewed NDA 202343 for (b) (4)™ and finds it acceptable provided that 1) the Agency and the sponsor agree on the labeling and 2) there is no significant issue from the review of Office of Scientific Investigation.

**Final Recommendation:**
The Office of Clinical Pharmacology / Division of Clinical Pharmacology II (OCP/DCP-II) has reviewed NDA 202343 for Juvisync™. Data presented in the submission and the analysis of data indicates that the proposed FDC formulations meet the bioequivalence criteria and the results are acceptable. However, the findings of OSI inspection indicate that there were compliance issues at the clinical study site related to the authenticity of the test and reference formulations. The issues identified are not related to the validity of analytical methods or data presented in the NDA but may be legal or regulatory in nature and are being addressed by the OSI.

**Phase IV Commitments:**
The sponsor has agreed to develop the FDC with sitagliptin 50 mg to permit dosing of patients with moderate renal impairment. The new strengths needs to be developed and data to support its approval (e.g., *in vivo* and/or *in vitro* study) should be submitted to the Agency per the schedule specified in the approval letter.

**Reviewer's Comment:**

<u>Comments on the OSI recommendation from the clinical pharmacology perspective</u>
The main issue raised by the OSI was that drug product was not randomly chosen to be administered to the volunteers, but pre-specified by the sponsor, which raised the authenticity question (refer the OSI memo in Attachment 1). To evaluate the impact of this issue, this reviewer looked at additional information available in the NDA as follows:

1. All pivotal studies were open-label and not blinded. Further, reference drug was 2 tablets and test product was 1 tablet. Therefore, it would be obvious if authenticity was being compromised, i.e., the person administering the treatment to volunteers would have known if the treatment is test or a reference.

2. In the NDA, additional pilot BE study (Study 153, Part I, n=24) study had been submitted. The product used in this study was manufactured from the same bulk lot as the pivotal BE study (Study 153, Part II) but different packaging lot (refer the detailed information in Attachment 2). The results from pilot BE study indicated that among the 3 components, sitagliptin and simvastatin acid met the BE criteria. On the other hand, while simvastatin AUC met the BE criteria, its Cmax was marginally outside the BE limits (i.e., upper bound 1.26 instead of 1.25). Therefore both the studies, pilot and pivotal, showed similar results, i.e., the products are BE. The above conclusions are also supported by the following analysis conducted by this reviewer;
   - Means of pharmacokinetic parameters of sitagliptin, simvastatin, and simvastatin acid from Part I are not significantly different ($p>0.05$) compared to those of Part II according to the ANOVA test using SAS 9.2. In addition, variances of those pharmacokinetic parameters from Part I are not significantly different ($p>0.05$) from those of Part II according to Levene's test for homogeneity (equality) of variances using SAS 9.2.

3. All the pharmacokinetic parameters met the BE criteria with tight confidence interval (CI) even though there was significant variability in simvastatin and simvastatin exposure (Table 1 and 2). Therefore, potential difference among kits/packaging lots of the test formulation may not affect the BE conclusion
4. During the drug development, site, equipment and scale changes for the to-be-marketed product was bridged to the biobatch using dissolution comparison data. The difference among packaging lots/kits within the same bulk lot of biobatch would be smaller than the difference between biobatch and to-be-marketed.

**Table 1 Summary Statistics and Statistical Comparisons for the Plasma PK Parameters of Sitagliptin, Simvastatin and Simvastatin Acid**

**P153, Part I**

| Pharmacokinetic Parameter | MK-0431D | | | Simvastatin + Sitagliptin | | |
|---|---|---|---|---|---|---|
| | N | AM* | SD (CV%) | N | AM* | SD (CV%) |
| **Sitagliptin** | | | | | | |
| AUC0-∞ ‡ (nM*hr) | 24 | 7395 | 1295 (17) | 24 | 7625 | 1419 (18) |
| AUC0-last ‡ (nM*hr) | 24 | 7296 | 1236 (17) | 24 | 7532 | 1389 (17) |
| Cmax ‡ (nM) | 24 | 951 | 321 (31) | 24 | 913 | 261 (27) |
| **Simvastatin** | | | | | | |
| AUC0-last ‡ (ng/mL*hr) | 24 | 105.89 | 53.59 (73) | 24 | 102.45 | 44.72 (55) |
| Cmax ‡ (ng/mL) | 24 | 20.34 | 15.30 (81) | 24 | 19.84 | 15.97 (81) |
| **Simvastatin Acid** | | | | | | |
| AUC0-last ‡ (ng/mL*hr) | 24 | 52.07 | 27.11 (58) | 24 | 57.46 | 39.08 (61) |
| Cmax ‡ (ng/mL) | 24 | 4.88 | 2.81 (58) | 24 | 5.66 | 5.17 (73) |

AM = Arithmetic Mean
SD: Standard Deviation
CV% = 100 x sqrt( exp(s2) - 1), where s2 is the observed variance on the natural log-scale

**P153, Part II**

| Pharmacokinetic Parameter | MK-0431D | | | Simvastatin + Sitagliptin | | |
|---|---|---|---|---|---|---|
| | N | AM* | SD (CV%) | N | AM* | SD (CV%) |
| **Sitagliptin** | | | | | | |
| AUC0-∞ ‡ (nM*hr) | 99 | 7994 | 1469 (18) | 99 | 8128 | 1451 (17) |
| AUC0-last ‡ (nM*hr) | 99 | 7907 | 1455 (18) | 99 | 8036 | 1431 (17) |
| Cmax ‡ (nM) | 99 | 948 | 268 (28) | 99 | 975 | 287 (30) |
| **Simvastatin** | | | | | | |
| AUC0-last ‡ (ng/mL*hr) | 99 | 123.11 | 70.13 (59) | 99 | 124.7 | 68.31 (57) |
| Cmax ‡ (ng/mL) | 99 | 17.46 | 10.94 (60) | 99 | 18.41 | 12.45 (68) |
| **Simvastatin Acid** | | | | | | |
| AUC0-last ‡ (ng/mL*hr) | 99 | 60.70 | 39.59 (66) | 99 | 55.54 | 40.61 (69) |
| Cmax ‡ (ng/mL) | 99 | 4.86 | 3.14 (65) | 99 | 5.16 | 3.38 (66) |

AM = Arithmetic Mean
SD: Standard Deviation
CV% = 100 x sqrt( exp(s2) - 1), where s2 is the observed variance on the natural log-scale

**Table 2 Summary of statistical analysis on the BE.**

| PK Parameter | Strength | | | |
|---|---|---|---|---|
| | 100/80 | | 100/10 | |
| | GMR* | 90% CI | GMR | 90% CI |
| **Sitagliptin** | | | | |
| AUC0-last (nM*hr) | 0.99 | (0.98, 1.00) | 1.01 | (0.99, 1.02) |
| Cmax (nM) | 0.98 | (0.94, 1.02) | 1.03 | (0.98, 1.07) |
| **Simvastatin** | | | | |
| AUC0-last (ng/mL*hr) | 0.99 | (0.93, 1.05) | 1.07 | (0.99, 1.16) |
| Cmax (ng/mL) | 0.98 | (0.92, 1.06) | 1.13 | (1.05, 1.21) |
| **Simvastatin Acid** | | | | |
| AUC0-last (ng/mL*hr) | 0.93 | (0.87, 0.98) | 1.03 | (0.96, 1.11) |
| Cmax (ng/mL) | 0.95 | (0.88, 1.02) | 1.04 | (0.97, 1.12) |

*: geometric mean ratio (FDC / (Simvastatin + Sitagliptin))

Comments on the development program for FDC with sitagliptin 50 mg from the clinical pharmacology perspective

The development of the FDC strengths of sitagliptin/simvastatin 50/10, 50/20 and 50/40 to permit dosing in patients with moderate renal impairment was raised by the FDA in Type C meting on September 30, 2010 (refer the meeting minute in Attachment 3). The sponsor agreed to develop those strengths as Phase IV commitment. (b) (4) The above data indicate that a BE study may not be needed and possible biowaiver request may be submitted as discussed during the Type C meeting. However, if substantial changes need to be made to develop FDC with sitagliptin 50 mg, a BE may be needed.

In conclusion, the new strengths needs to be developed and data to support its approval (e.g., *in vivo* and/or *in vitro* study) should be submitted to the Agency per the schedule in the approval letter.

**Table 3 Summary of amount per tablet**

| | Strength | Amount per tablet (mg) | | |
|---|---|---|---|---|
| | | Total | Sitagliptin layer | Simvastatin layer |
| NDA data | 100/10 | 500 | 400 | 100 |
| | 100/20* | 600 | 400 | 200 |
| | 100/40* | 800 | 400 | 400 |
| | (b) (4) | | | |
| proposed development | (b) (4) | | | |
| | | | | |
| | | | | |

*: biowaiver was granted by the ONDQA-Biopharmaceutics review team.

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