



NDA 202343

**NDA APPROVAL**

Merck Sharp & Dohme Corp.  
Attention: Richard J. Swanson, Ph.D.  
Senior Director, Regulatory Affairs  
P.O. Box 1000, UG2C-50  
North Wales, PA 19454-1099

Dear Dr. Swanson:

Please refer to your New Drug Application (NDA) dated December 6, 2010, received December 7, 2010, pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for JUVISYNC (sitagliptin and simvastatin fixed-dose combination) Tablets, 100 mg/10mg, 100 mg/20 mg, and 100 mg/40 mg.

We acknowledge receipt of your amendments dated December 16, 2010; and February 16, March 25 and 28, April 5, 27 and 28, June 22 (2) and 27, July 13, August 1 and 18, September 2 (3), 7, 13, 14, 15, 20, and 30, and October 5(2), 2011.

We also acknowledge receipt of your letter submitted October 5, 2011 stating that you commit to submitting by November 30, 2011, a supplemental NDA to 202,343 to register additional doses of JUVISYNC (sitagliptin and simvastatin fixed-dose combination), appropriate for the treatment of patients with type 2 diabetes mellitus with moderate renal impairment (50/10, 50/20, and 50/40 [mg sitagliptin/mg simvastatin]).

This new drug application provides for the use of JUVISYNC (sitagliptin and simvastatin fixed-dose combination) in patients for whom treatment with both sitagliptin and simvastatin is appropriate. Sitagliptin is a dipeptidyl peptidase-4 (DPP-4) inhibitor indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Simvastatin is an HMG-CoA reductase inhibitor (statin) indicated as an adjunctive therapy to diet to:

- Reduce the risk of total mortality by reducing CHD deaths and reduce the risk of non-fatal myocardial infarction, stroke, and the need for revascularization procedures in patients at high risk of coronary events.
- Reduce elevated total-C, LDL-C, Apo B, TG and increase HDL-C in patients with primary hyperlipidemia (heterozygous familial and nonfamilial) and mixed dyslipidemia.
- Reduce elevated TG in patients with hypertriglyceridemia and reduce TG and VLDL-C in patients with primary dysbetalipoproteinemia.

- Reduce total-C and LDL-C in adult patients with homozygous familial hypercholesterolemia.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

### **CONTENT OF LABELING**

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the package insert and text for the Medication Guide). Information on submitting SPL files using eLIST may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As” at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible via publicly available labeling repositories.

### **CARTON AND IMMEDIATE CONTAINER LABELS**

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels and carton and immediate container labels submitted on September 2 (carton labeling and 7- and 1000- count container labeling) and 20 (30- and 90-count container labeling), 2011, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled “Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008).” Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission “**Final Printed Carton and Container Labels for approved NDA 202343.**” Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

### **REQUIRED PEDIATRIC ASSESSMENTS**

We are waiving the pediatric study requirement for this application because this product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients **and** is not likely to be used in a substantial number of pediatric patients.

### **POSTMARKETING REQUIREMENTS UNDER 505(o)**

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a signal of a serious risk of worsening glycemic control associated with the use of simvastatin.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a signal of the serious risk described above.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

**PMR 1826-1** A randomized, double-blind, active-controlled clinical trial to study the effect of sitagliptin and simvastatin fixed-dose combination versus sitagliptin on glycemic control in type 2 diabetic patients on background metformin therapy.

The timetable you submitted on October 5, 2011, states that you will conduct this trial according to the following schedule:

|                            |                 |
|----------------------------|-----------------|
| Final Protocol Submission: | by April 2012   |
| Trial Completion:          | by January 2015 |
| Final Report Submission:   | by July 2015    |

Submit the protocol to your IND 103183, with a cross-reference letter to this NDA. Submit the final report to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **“Required Postmarketing Protocol Under 505(o)”**, **“Required Postmarketing Final Report Under 505(o)”**, **“Required Postmarketing Correspondence Under 505(o)”**.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

### **PROMOTIONAL MATERIALS**

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Drug Marketing, Advertising, and Communications  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

### **REPORTING REQUIREMENTS**

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Raymond Chiang, Regulatory Project Manager, at (301) 796-1940.

Sincerely,

*{See appended electronic signature page}*

Mary H. Parks, M.D.  
Director  
Division of Metabolism and Endocrinology  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

ENCLOSURES:

Package Insert  
Medication Guide  
Container Label – 100 mg/10mg, 30 tablet bottle (Trade)  
Container Label – 100 mg/10mg, 90 tablet bottle (Trade)  
Container Label – 100 mg/10mg, 1000 tablet bottle (Trade)  
Container Label – 100 mg/20mg, 7 tablet bottle (Sample)  
Container Label – 100 mg/20mg, 30 tablet bottle (Complimentary)  
Container Label – 100 mg/20mg, 30 tablet bottle (Trade)  
Container Label – 100 mg/20mg, 90 tablet bottle (Trade)  
Container Label – 100 mg/20mg, 1000 tablet bottle (Trade)  
Container Label – 100 mg/40mg, 7 tablet bottle (Sample)  
Container Label – 100 mg/40mg, 30 tablet bottle (Complimentary)  
Container Label – 100 mg/40mg, 30 tablet bottle (Trade)  
Container Label – 100 mg/40mg, 90 tablet bottle (Trade)  
Container Label – 100 mg/40mg, 1000 tablet bottle (Trade)  
Carton Label – 100mg/20mg tablets (Physician Sample)  
Carton Label – 100mg/40mg tablets (Physician Sample)

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

/s/  
-----

MARY H PARKS  
10/07/2011