CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202343Orig1s000

MEDICAL REVIEW(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993-002

Division Director's Memo

NDA	202-343
Drug Product	Sitagliptin-Simvastatin Fixed-Dosed Combination Tablets
Company	Merck
Date of Submission	December 6, 2010
PDUFA Goal Date	October 7, 2011

This NDA is for the fixed-dose combination (FDC) of sitagliptin and simvastatin. Both of these drug products are approved for use as described in the clinical reviews of Drs. Pratt and Irony. The pivotal studies supporting approval were bioequivalence studies to determine if the pharmacokinetics of the individual components in the FDC differed from when they are individually co-administered. These studies have been reviewed by Drs. Chung and Vaidyanathan and the Office of Clinical Pharmacology has recommended approval. The FDC will be available in the following sitagliptin/simvastatin dosage strengths: 100 mg/10 mg, 100 mg/20 mg, and 100 mg/40 mg. I concur with the medical and clinical pharmacology reviewers that this application can be approved and my memo will only note selected issues in the NDA which need to be highlighted.

Dosage Strengths

Sitagliptin is available in 25, 50, and 100 mg strengths. The 50 mg dose is recommended for patients with moderate renal impairment and the 25 mg dose is recommended for patients with severe renal impairment or with endstage renal disease. Simvastatin is available in 5, 10, 20, 40 and 80 mg strengths. Drug utilization data for both drug products revealed minimal use of the lowest dosage strengths; therefore, the company was not required to develop a FDC containing sitagliptin 25 mg and simvastatin 5 mg. However, extensive discussions were held with the company regarding the availability of dosage strengths of sitagliptin 50 mg and simvastatin 80 mg.

For sitagliptin 50 mg, it was felt that the population of patients with T2DM and moderate renal impairment was not an insignificant number. Not making available a FDC with sitagliptin 50 mg might result in such patients taking a higher dose than recommended. Labeling against its use was not appropriate given the sizeable patient population. The company proposed to develop and manufacture a FDC containing sitagliptin 50 mg and requested submission of data to support approval of sitagliptin/simvastatin 50/10, 50/20, and 50/40 as an efficacy supplement after approval of the FDC tablets containing sitagliptin 100 mg. This was deemed acceptable as the applicant provided a letter committing to submit this supplement to FDA by November 30, 2011, which did not signify an unreasonable delay to market. In the meanwhile, the label will include a "Limitations of Use" stating that patients with moderate and severe renal impairment should not take the FDC product due to unavailability of the 50 and 25-mg dosage strengths of sitagliptin.

Prior to submission of this efficacy supplement, the Division was evaluating data from the SEARCH trial and assessing the risk of muscle toxicity associated with simvastatin 80 mg. Plans were underway to restrict the use of this dose to only those patients who were already on simvastatin 80 mg and tolerating

the drug without evidence of muscle symptoms. The Division did not feel that it would be appropriate to consider approval of a FDC that would include the simvastatin 80 mg dose strength as it might further encourage the inappropriate use of this dose, especially as a new initiation only for the purpose of convenience dosing. (b) (4) The applicant acknowledged the Division's position on the matter and did not pursue marketing of the simvastatin 80 mg dosage strength; however, bioequivalence data including the sita/simva 10/80 fixed-dose combination tablet were accepted for review with biowaiver consideration for the lower dosage strengths intended for marketing.

Statins and Diabetes

Recently, two published meta-analyses of several randomized statin trials revealed an increased risk of developing diabetes associated with statin use, notably atorvastatin, rosuvastatin, and simvastatin.[1,2] This was also observed by FDA in its review of rosuvastatin's JUPITER trial and such an association has been included in rosuvastatin's label (Warnings and Precautions and Adverse Reactions).

The significance of this finding, particularly with a FDC to be used in the diabetic population was considered. As summarized by the authors of one meta-analysis, the risk of developing diabetes in absolute terms was low in comparison to the benefits of statins in lowering a patient's risk for future cardiovascular events. Reassuring for simvastatin is that analyses of large outcomes trial did not exclude the benefits of CV risk reduction from patients with T2DM. However, labeling to describe this observation is appropriate such that healthcare providers and patients are aware of the potential for worsening glycemic control and adjust diabetic medications accordingly.

The applicant has proposed to conduct a randomized, double-blind, active-controlled trial to study the effect of the FDC versus sitagliptin on glycemic control in T2DM patients on background metformin therapy as a postmarketing trial to prospectively evaluate the effects of simvastatin on glycemic control. This is an important trial that will inform prescribers and patients on the risk and benefits of this FDC product and will therefore be a required trial under FDAAA.

Labeling

The applicant is proposing that the FDC be indicated in patients for whom treatment with both sitagliptin and simvastatin is appropriate. Although FDA reviews and the applicant's rationale for development of this product suggest a benefit with convenience dosing, the label should not include language which may be promotional to this effect. The applicant has not provided any data to support an assertion that the administration of one pill instead of two improves compliance or leads to better clinical outcomes. Although not a consideration in the approval process, one could argue from a health economics standpoint that a new FDC product might cost more than co-administration of the individual components, especially given that simvastatin is available as a generic. More importantly, the 'convenience' of the FDC should not encourage prescribing practice that runs contrary to the safe use of the individual components. To this end, the recent labeling changes recommended for simvastatin must be incorporated into the FDC label prior to approval.

(b) (4)

[1] Sattar N et al. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. *The Lancet*. 2010; 375:735-742.

[2] Rajpathak S et al. Statin therapy and risk of developing type 2 diabetes: a meta-analysis. *Diabetes Care*. 2009; 32:1924-1929.

[redacted] (b) (4) Although this labeling request was made to the [redacted] (b) (4) the changes are important to the safe use of any drug product containing simvastatin and therefore the FDC of sitagliptin and simvastatin should include these changes prior to approval.

Recommendations

Pending agreed-upon labeling, this application can be approved.

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
10/06/2011
Division Director's memo

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.