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APPLICATION NUMBER:

202343Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	8/15/2011
From	Ilan Irony, M.D.
Subject	Cross-Discipline Team Leader Review
NDA #	202343 Original submission under 505 (b)(1)
Applicant	Merck
Date of Submission	07/12/2010
PDUFA Goal Date	10/07/2011
Proprietary Name / Established (USAN) names	Juvisync / sitagliptin simvastatin fixed dose combination tablets
Dosage forms / Strength	Sitagliptin simvastatin 100 mg / 10 mg, 100 mg / 20 mg and 100 mg / 40 mg
Proposed Indication(s)	1. Improve glycemic control in adults with T2DM 2. Reduce risk of cardiovascular mortality, non-fatal MI, stroke and need for revascularization procedures 3. Reduce elevated total cholesterol, LDL-cholesterol, apo-B lipoprotein, and triglycerides in settings for which simvastatin is approved.
Recommended:	Approval

1. Introduction

This is a new drug application for a fixed dose combination tablet (FDC) of sitagliptin, an oral antidiabetic drug for the treatment of adults with type 2 diabetes (T2DM) and simvastatin (a lipid lowering drug. Both components are approved and marketed drugs in the US. While FDCs where both drug components treat the same indication are common, there is precedent within CDER and OND for approval of a FDC with each component treating a separate indication (Caduet is a FDC of amlodipine, an antihypertensive drug and atorvastatin, a lipid lowering statin drug).

From a scientific and regulatory standpoint, this is a fairly straightforward application. The two drugs that comprise the FDC are approved in the US, and each carries substantial postmarketing experience.

Recent published studies and metanalyses [1,2,3] have suggested a small interference of statins as a class (with the exception of pravastatin) on glycemic control, and among pre-diabetics, a slightly higher tendency to progress to overt diabetes among users of statins.

A large rosuvastatin outcome trial (n = 17802 subjects) conducted in patients with elevated C reactive protein and normal LDL cholesterol levels (JUPITER) also showed a small increase in investigator-reported diabetes (2.8 % vs. 2.3% for placebo, HR = 1.27) and an increase in HbA1c among diabetics (refer to Dr. Mary Roberts review of Rosuvastatin NDA 21366 supplement 16, filed on 2/5/2010).

In SPARCL (atorvastatin 80 mg vs placebo), diabetes was reported as an AE in 144 subjects (6.1%) in the atorvastatin group and 89 subjects (3.8%) in the placebo group. The reported percentage of diabetes was 8.9% in the atorvastatin and 5.3% in the placebo group in subjects with a medical history of diabetes, and 5.5% and 3.5%, respectively, in subjects without a medical history of diabetes.

In ASCOT-LLA (atorvastatin 10 mg vs placebo), a slightly larger percentage of patients in the atorvastatin group also developed diabetes during the course of the study, although the difference did not achieve statistical significance. At 12 months, there was a small statistically significant difference in mean blood sugar change, slightly favoring the placebo group. This difference (mean % increase of 0.26% for the atorvastatin group vs 0.16% for the placebo group) was small.

But the conclusion from these metanalyses, JUPITER, SPARCL and ASCOTT-LLA has been that the benefits of a statin treatment in diabetics far outweigh the risks, and such treatment continues to be recommended for patients with T2DM, due to major impact cardiovascular disease has on the morbidity, mortality and health care costs in the diabetic population. For this particular NDA, a dedicated trial to examine the magnitude of the simvastatin interference with sitagliptin-promoted glycemic control will be a postmarketing requirement, already

[1] Sattar N, Preiss D Murray HM et al. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. Lancet 2010; 375: 735–42

[2] Rajpathak SN, Kumbhani DJ, Crandall J et al. Statin Therapy and Risk of Developing Type 2 Diabetes: A Meta-Analysis. Diabetes Care 2009; 32:1924 – 1929

[3] Koh KK, Quon MJ, Han SH at al. Atorvastatin causes insulin resistance and increased ambient glycemia in hypercholesterolemic patients. Journal of the American College of Cardiology 2010; 55: 1209-1216

discussed with the applicant during a teleconference in May 2010 and repeated at the pre-NDA meeting.
So the main issue for this application is the demonstration of bioequivalence (BE) between the to-be-marketed formulation of the FDC and its components namely, sitagliptin and simvastatin.
As reported in Dr. Chung's Clinical Pharmacology review, BE was established in a study conducted in healthy volunteers. However, inspection of the clinical and analytical sites by the Division of Bioequivalence and GLP Compliance (DBGC) in the Office of Scientific Investigations (OSI) uncovered violations of the handling of reserve samples of tablets at the clinical study site, Icon Development Solutions in San Antonio TX. DBGC recommended rejecting the BE data, (b) (4) The clinical and clinical pharmacology review teams discussed these recommendations with DBGC, and learned that the lots inspected and used for the BE studies were the same as those submitted in the NDA, and passed all specifications. The applicant received a biowaiver from Bipharmacology with regard to the minor differences between these lots and the to-be-marketed lots.

2. Background

Sitagliptin, a dipeptidyl peptidase 4 (DPP-4) inhibitor, has been approved for treatment of T2DM in the US since October 2006 under NDA 21995. The recommended dose is 100 mg daily for subjects with normal renal function, 50 mg daily for subjects with moderate renal impairment, and 25 mg daily for subjects with severe and end stage renal disease (ESRD).
Simvastatin, a hydroxymethyl glutaryl coenzyme A (HMG-CoA) reductase inhibitor (statin), was approved in December 1991 under NDA 19766 and currently has five lipid lowering and cardiovascular (CV) indications (refer to Zocor label).
The filing of the sitagliptin/simvastatin FDC NDA is based on the demonstration of BE between the FDC tablets and coadministration of corresponding doses of sitagliptin and simvastatin (for the latter, 10 and 80 mg to bracket the dose range). Although no phase 3 clinical studies were conducted with the sitagliptin/simvastatin FDC or with the co-administration of sitagliptin and simvastatin, seven clinical pharmacology studies support registration of the FDC.
Although the FDC tablet can be regarded as a convenience product (i.e., taking only one tablet daily, rather than two separate tablets), many diabetics have indications for the use of a statin drug, due to their prevalent dyslipidemia and higher cardiovascular risks, and this combination makes sense for the targeted population. The FDC has the disadvantage that patients for whom sitagliptin is being considered as the antidiabetic drug will also be taking a statin (simvastatin) associated with significant interactions with other drugs, as well as the added cost, when compared to adding generic simvastatin to a regimen of brand sitagliptin.
Prior to submitting NDA, the applicant reached agreement with FDA on two issues:
• The 100/80 mg tablet is not approvable because of the recently identified safety issue (increased risk of rhabdomyolysis) associated with the 80 mg simvastatin dose.
• Submission of a NDA without the 50 mg sitagliptin dose for use in subjects with moderate renal insufficiency is both a review and safety issue. If not contained in the original NDA, the development of the 50 mg sitagliptin doses may be a post-marketing requirement (PMR).

Thus, the current NDA 202-343 proposes sitagliptin/simvastatin 100/10, 100/20, and 100/40 mg FDC tablets, as previously agreed. The applicant is now developing 50/10, 50/20, and 50/40 mg FDC dose strengths and plans to submit a supplemental NDA (sNDA) for them by (b) (4)

3. CMC/Device

The proposed formulation is a bilayer tablet comprised of:
1) A sitagliptin layer (layer weight (b) (4)), which is based on (b) (4) JANUVIA® Tablet formulation, and
2) A (b) (4) simvastatin layer (b) (4) from a common simvastatin (b) (4). This (b) (4) is the same as that used in the manufacture of ZOCOR® Tablets.

During review, CMC noted that the stability analysis of samples of sitagliptin 100 mg / simvastatin 80 mg were out of the applicant's self-defined range of 95 to 105% at release and during the 52 week stability period. In response to an information request, Merck expanded the specification range to 90 – 110% (as allowed per US regulations), and the assay data fell within the range.
Based on the provided real-time stability data, a two and a half (2 1/2) year expiry period is granted for the 100/10, 100/20 and 100/40 mg /mg sitagliptin/ simvastatin FDC tablets supplied in 30 and 90 count bottles.
Based on the provided real-time stability data, a one (1) year expiry period is granted for the 100/10, 100/20 and 100/40 mg /mg sitagliptin/ simvastatin FDC tablets supplied in the 1000 count bottle.

The CMC review team recommends approval; a final review of the facility inspection in ESS is pending at the time of this review.

4. Nonclinical Pharmacology/Toxicology

Due to the concern of possible toxicologic interactions between sitagliptin and simvastatin, especially regarding adverse effects on the skeletal muscle, the sponsor conducted a 3-month toxicology study in rats to assess the potential toxicity due to coadministration of sitagliptin and simvastatin. There was no mortality or significant adverse effects associated with the coadministration of sitagliptin and simvastatin at exposures greater than 20 times those at the maximum clinical dose of either drug in the FDC. Although there were no adverse muscle or pancreas effects associated with either drug administered alone or in combination, coadministration of sitagliptin and simvastatin did cause an increase in adverse liver effects. Administration of the simvastatin high dose (60 mg/kg; ~47-114X MHRD; based on AUC) caused an increase in liver weight, hepatocellular hypertrophy, and an increase in ALT levels (~2-3X compared to controls). Although these effects were not observed in animals administered sitagliptin alone, the coadministration of sitagliptin (180 mg/kg; ~20X MHRD; based on AUC) and simvastatin caused a slightly greater dose-related increase in liver weight (females only) and ALT levels with both the low (30 mg/kg; ~20-66X MHRD; based on AUC) and high (60 mg/kg; ~47-114X MHRD; based on AUC) simvastatin doses suggesting a

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