CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

200153Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	1 April 2013
From	Eric Colman, MD, Deputy Division Director
NDA#	200153
Applicant Name	MSP Singapore Company
Date of Submission	Original 2 September 2009; resubmission 29 April 2011; resubmission 5 November 2012
PDUFA Goal Date	5 May 5 2013
Proprietary Name / Established (USAN) Name	Liptruzet/Ezetimibe/Atorvastatin
Dosage Forms / Strength	10/10, 10/20, 10/40, and 10/80 mg FDC Tablets
Proposed Indication(s)	Treatment of primary hypercholesterolemia and homozygous familial hypercholesterolemia
Recommended Action for NME:	Approve

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	Iffat Chowdhury, MD
Statistical Review	Janice Derr, PhD
Pharmacology Toxicology Review	Indra Antonipillai, PhD
CMC Review/OBP Review	Joseph Leginus, PhD/Deepika Lakhani, PhD
Microbiology Review	NA
Clinical Pharmacology Review	Johnny Lau, PhD
OSI	Michael Skelly, PhD
OSE/DMEPA	Anne Tobenkin, PharmD

OND=Office of New Drugs
CMC=Chemistry, Manufacture, and Control
OBP=Office of Biopharmaceutics
OSI=Office of Scientific Investigations
OSE=Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis

1. Background

This is a 505b2 New Drug Application (NDA) for a fixed-dose combination (FDC) of ezetimibe and atorvastatin (hereafter eze/atorva). The NDA was originally submitted on 2 September 2009. Due to chemistry, manufacturing, and controls (CMC) deficiencies, a refuse-to-file action was taken on 20 October 2009. The applicant addressed these deficiencies and resubmitted the application on 28 April 2011. Following review of the submitted data, the Division issued a Complete Response on 29 February 2012 because the sponsor failed to demonstrate bioequivalence for the 10/20 and 10/40 doses of eze/atorva compared with coadministered ezetimibe and atorvastatin. Specifically, the C_{max} values for atorvastatin from the eze/atorva combination 10/20 mg and 10/40 mg tablets were (b) (4), respectively, compared with the respective coadministered doses of ezetimibe and atorvastatin. The sponsor was provided with two options to address these deficiencies: 1) reformulate the 10/20 mg and 10/40 mg FDC tablets, or 2) provide evidence that the 10/20 mg and 10/40 mg FDC tablets are pharmacodynamically (i.e., LDL-C lowering) equivalent to the coadministered ezetimibe and 20 mg and 40 mg atorvastatin tablets.

An end-of-review meeting was granted and written responses to the sponsor's questions were sent on 17 May 2012. In these responses, the Division agreed that, pending full review, data demonstrating pharmacodynamic equivalence in terms of LDL-C lowering between the eze/atorva 10/20 mg and 10/40 mg tablets and coadministered ezetimibe 10 mg and atorvastatin 20 mg and 40 mg tablets would satisfy the bioequivalency deficiencies. Pharmacodynamic equivalence was defined as the 95% confidence interval of the difference between the two treatments being $\pm$ 4% for the changes in LDL-C following 6 weeks of treatment.

2. CMC/Biopharmaceutics

All of the original CMC deficiencies that led to the refuse-to-file action have been satisfactorily addressed by the applicant in their resubmission. I concur with the conclusions reached by the CMC reviewer regarding the acceptability of the manufacturing of the drug product and drug substance. There are no outstanding CMC issues.

The biopharmaceutics reviewer, Dr. Lakhani, recommends approval of this application. I concur that there are no outstanding biopharmaceutics issues that would prevent approval of this application.

3. Nonclinical Pharmacology/Toxicology

According to Dr. Antonipillai, nonclinical studied conducted with ezetimibe and atorvastatin (Lipitor) under the ezetimibe NDA adequately characterize the safety of these two drugs. The applicant submitted a 3-month toxicity/toxicokinetics study of atorvastatin amorphous in dogs and 2 gene-toxicity studies. These studies adequately qualified the impurities/excipients of the atorvastatin amorphous formulation. No safety issues were identified in these studies. Dr.

Antonipillai recommends approval of this application and indicates that there are no outstanding nonclinical pharmacology or toxicology issues. I concur.

4. Clinical Pharmacology

No new clinical pharmacology data were submitted during this review cycle. The application received a Complete Response on 29 February 2012 due to failed bioequivalency between the 10/20 mg and 10/40 mg eze/atorva FDC tablets and coadministered ezetimibe 10 mg and atorvastatin 20 mg and 40 mg tablets. These deficiencies are addressed in two pharmacodynamic clinical trials, as discussed below.

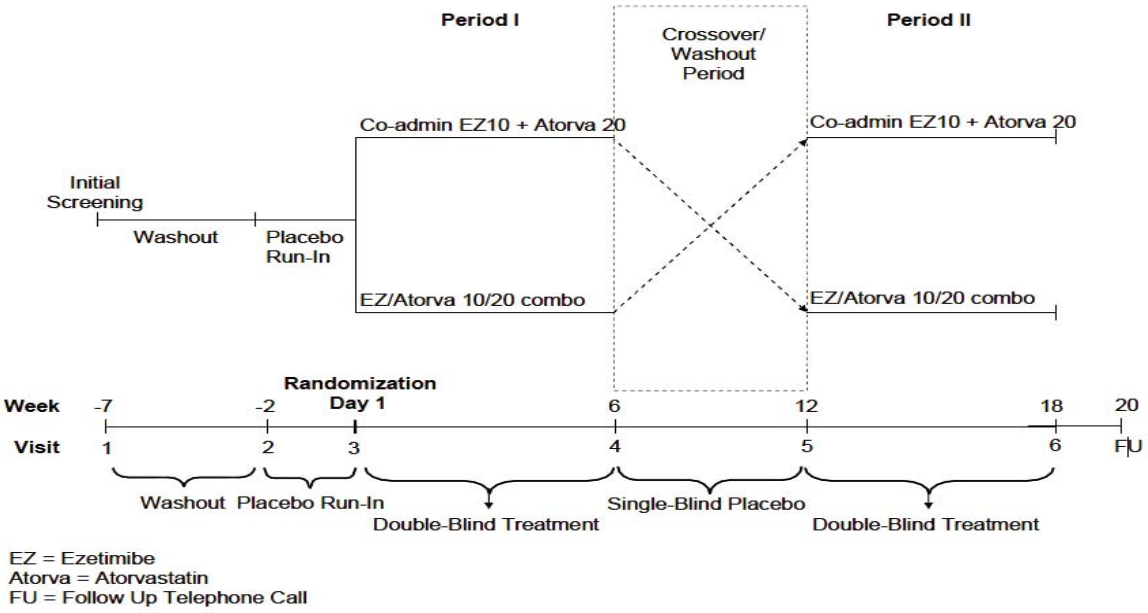
5. Clinical Microbiology

Not applicable.

6. Clinical/Statistical-Efficacy

The sponsor submitted data from two clinical trials to demonstrate that the 10/20 mg and 10/40 mg doses of eze/atorva FDC are pharmacodynamically equivalent in terms of LDL-C reduction compared to co-administered ezetimibe10 mg with atorvastatin 20 mg and 40 mg. These clinical trials, P185 and P190, were of the same design and differed only in that P185 included atorvastatin 20 mg and P190 included atorvastatin 40 mg.

The trials were randomized, double-blind, 2-period crossover investigations consisting of a 5-week washout, a 2-week single-blind placebo run-in period, and two 6-week treatment periods separated by a 6-week single-blind placebo washout period (see below figure for P185).



Eligible subjects included men or women, ages 18 to 80 years old, with primary hypercholesterolemia at low, moderate, or moderately high cardiovascular risk per the NCEP ATP III guidelines. Off-therapy LDL-C levels were between 130 mg/dl and 300 mg/dl for low risk subjects; between 100 mg/dl and 300 mg mg/dl for moderate risk subjects; and between 100 mg/dl and 275 mg/dl for moderately high risk subjects. Subjects were instructed to take the study medications with or without food at roughly the same time each day. Subjects were also instructed to maintain a NCEP therapeutic lifestyles changes or similar cholesterol-lowering diet.

The primary objective of the studies was to evaluate the LDL-C lowering efficacy of eze/atorva 10/20 mg and 10/40 mg to ezetimibe 10 mg coadministered with atorvastatin 20 mg and atorvastatin 40 mg. The treatments were to be considered equivalent if the 95% confidence interval for the differences in LDL-C following 6 weeks of therapy between the treatment groups were within $\pm$ 4% in the per protocol population. The Division has accepted a non-inferiority margin of 6% for LDL-C reduction with other products.

A total of 406 and 328 subjects were randomized into studies P185 and P190, respectively. Roughly 90% of subjects in P185 and 86% of subjects in P190 completed the studies. The subject populations were mostly Caucasian, approximately 60% female, with a mean age of about 55 years, and an average BMI of 30 kg/m^2. The mean baseline LDL-C was 162 mg/dl.

The changes in LDL-C are shown in the following table adapted from Dr. Derr's statistical review.

P185 and P190 – Primary Efficacy Analyses

	N	Baseline mean LDL-C (mg/dl)	Adjusted mean % change from baseline LDL-C after 6 weeks	FDC minus Co-admin: Difference in adjusted mean % change from baseline (95% CI)
Study P185				
FDC 20 mg	353	162	-54.0%	-0.2% (-1.7, 1.3)
Co-admin 20 mg	346	162	-53.8%	
Study P190				
FDC 40 mg	280	162	-58.9%	-0.2% (-1.9, 1.4)
Co-admin 40 mg	280	162	-58.7%	

The primary analysis model with an analysis of covariance, repeated measures with terms for treatment, baseline LDL-C, period, and sequence.

Because the 95% confidence intervals for the difference in the changes in LDL-C were within $\pm$ 4%, one can conclude that the eze/atorva FDC tablets were pharmacodynamically equivalent to the co-administered tablets.

As noted by Dr. Derr, "The statistical significance of Period in study P185 was driven by a somewhat greater LDL-C lowering effect in Period 1 compared with Period 2. However, the two treatments differ in the effect of Period: the FDC formulation had a greater LDL-C lowering effect in Period 1 and the co-administered tablets had a greater LDL-C lowering effect in Period 2."

In an exploratory analysis of this finding, Dr. Derr conducted a separate ANCOVA on the Period 1 data. In the comparison of FDC minus co-administered, the adjusted mean difference was -2.7% (-6.1, 0.7). Although the lower bound of the confidence interval fall outside of -4%, the results indicate greater LDL-C lowering with the FDC compared with the co-administered drugs. Hence, this analysis supports the LDL-C lowering efficacy of the 10/20 mg eze/atorva FDC tablet.

The effects on other lipoprotein lipid levels of the eze/atorva FDC tablets and the co-administered tablets were very similar, as shown in the following table of data from P185 modified from Dr. Derr's statistical review.

P185 – Major Lipoprotein Lipid Levels

	N	Baseline mean value (mg/dl)	Adjusted mean % change from baseline after 6 weeks	FDC minus Co-admin: Difference in adjusted mean % change from baseline (95% CI)
Total Cholesterol				
FDC 20 mg	353	247	-38%	0.3% (-0.8, 1.4)
Co-admin 20 mg	346	247	-39%	
HDL-C				
FDC 20 mg	353	54	5.4%	0.8% (-0.6, 2.2)
Co-admin 20 mg	346	54	4.6%	
Non-HDL-C				
FDC 20 mg	353	95	-50.1%	0.0% (-1.3, 1.4)
Co-admin 20 mg	346	95	-50.2%	
TG				
FDC 20 mg	353	140	-28.3%	1.6% (-3.2, 6.3)
Co-admin 20 mg	346	141	-29.9%	

In study P190, similar results for changes in the major lipoprotein lipids were observed for the FDC eze/atorva 40 mg tablet compared with the co-administered ezetimibe and atorvastatin 40 mg tablets.

7. Safety

Dr. Chowdhury's review of the safety data from studies P185 and P190 did not identify any novel toxicity. The adverse events that were reported during these two studies were consistent with the adverse event profiles noted by Dr. Chowdhury during her review of the clinical trial data during the first review cycle.

8. Advisory Committee Meeting

An advisory committee meeting was not considered necessary for this application given that both products are approved and there are no clinical or regulatory issues that require input from our advisory committee.

9. Pediatrics

The applicant was granted a full waiver for pediatric studies because the FDC product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients and it is not likely to be used in a substantial number of pediatric patients.

Pediatric studies were conducted with ezetimibe and atorvastatin, under their respective original applications.

10. Other Relevant Regulatory Issues

The Division of Medication Error Prevention and Analysis (DMEPA) reviewed the proposed tradename, Liptruzet, and found it acceptable.

Routine inspections have been completed and no significant violations were noted.

11. Labeling

Labeling negotiations with the sponsor were completed on May 2, 2013.

12. Decision/Action/Risk Benefit Assessment

With the conduct of two pharmacodynamics studies, the sponsor has adequately responded to the clinical pharmacology deficiencies noted in the Complete Response. Both atorvastatin and ezetimibe are marketed products. I recommend that this application be approved.

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/s/

ERIC C COLMAN
05/03/2013