

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
200153Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

CLINICAL PHARMACOLOGY MEMO

NDA	200-153
Submission Dates	April 29, 2011 and July 22, 2011
Brand Name	ATOZET™
Generic Names	Ezetimibe/atorvastatin calcium
Reviewers	S.W. Johnny Lau, R.Ph., Ph.D.
Team Leader (Acting)	Jayabharathi Vaidyanathan, Ph.D.
OCP Division	Clinical Pharmacology 2
OND Division	Metabolism and Endocrinology Products
Sponsor	Merck Sharp & Dohme Corp.
Formulation; Strength	Fixed dose combination immediate release oral tablets; 10/10, 10/20, 10/40, and 10/80 mg/mg
Relevant IND	101,953
Indication	Treatment of primary hyperlipidemia and homozygous familial hypercholesterolemia

This memo concerns the findings of the Office of Scientific Investigations (OSI), Division of Bioequivalence and GLP Compliance on the inspections of the clinical and bioanalytical sites for Study P145 (see Attachment for OSI's February 29, 2012 memo).

OSI Findings

OSI found that there is at least one blood sample from Subject 146, Period 1, at 72 hours, in Study P145 is misidentified. OSI recommends excluding Subject 146 of Study P145 for pharmacokinetic calculations. Upon discussion with OSI's Dr. Michael Skelly, Subject 146 did not appear at the clinical site for the 72 hours sample collection for Period 1 of Study 145. However, the clinical site's shipping record and the bioanalytical site's receiving record showed that Subject 146 did have the plasma sample for the 72 hours sample. The bioanalytical report has a measurable concentration at 72 hours for Subject 146, which the ezetimibe concentration is consistent with a 72 hours sample. OSI postulated that there might be another mishandled 72 hours plasma sample from another subject but OSI could not identify the other mishandled 72 hours sample. Thus, OSI stated in the memo that "at least one blood sample" was mishandled. OSI did not issue a Form 483 for this sample's misidentification.

Impact of OSI's Findings on the Bioequivalence's Assessment of Study P145

No significant impact. Study P145 had the following 3 treatment groups:

- 1) single doses of coadministration of 10 mg ezetimibe tablet plus 10 mg atorvastatin calcium tablet compared to a single dose of the to-be-marketed ezetimibe/atorvastatin calcium 10/10 mg fixed dose combination tablet
- 2) single doses of coadministration of 10 mg ezetimibe tablet plus 20 mg atorvastatin calcium tablet compared to a single dose of the to-be-marketed ezetimibe/atorvastatin calcium 10/20 mg fixed dose combination tablet
- 3) single doses of coadministration of 10 mg ezetimibe tablet plus 80 mg atorvastatin calcium tablet compared to a single dose of the to-be-marketed ezetimibe/atorvastatin calcium 10/80 mg fixed dose combination tablet

Subject 146 participated in the ezetimibe/atorvastatin 10 mg/20 mg versus the coadministration of 10 mg ezetimibe and 20 g atorvastatin treatment group. The misidentified sample is for the determination of the ezetimibe and ezetimibe metabolites samples since the sampling time for atorvastatin and atorvastatin metabolites ended at 48 hours and the sampling time for ezetimibe and ezetimibe metabolites ended at 96 hours (see Attachment for sampling schedule). Evidently, this misidentified sample will not affect the bioequivalence assessment of atorvastatin. This misidentified 72 hours sample will not likely affect the bioequivalence assessment of ezetimibe since:

- The 72 hours sample will not affect the ezetimibe C_{max} assessment since the observed maximum ezetimibe t_{max} was at 8 hours.
- The sample may change the GMR for ezetimibe AUC and its 90% confidence interval (CI) but the bioequivalence results will not likely be changed since the original assessment's GMR is 0.97 and its 90% CI is 0.90 – 1.04 and is well within the 0.80 – 1.25 goalpost. The total evaluable subjects participated in this treatment group was 95, which makes it difficult for 1 subject's result to affect the bioequivalence assessment.

Attachment starts here.

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: February 23, 2012

TO: Mary Parks, M.D.
Director, Division of Metabolism and Endocrinology
Products

FROM: Michael F. Skelly, Ph.D.
Bioequivalence Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

THROUGH: William H. Taylor, Ph.D., DABT
Director (Acting)
Division of Bioequivalence and GLP Compliance (DBGC)
Office of Scientific Investigations (OSI)

SUBJECT: Review of EIRs Covering NDA 200-153,
Ezetimibe/Atorvastatin Tablets, Sponsored by MSP
Singapore Company LLC.

At the request of the Division of Metabolism and Endocrinology Products (DMEP), the Division of Bioequivalence and GLP Compliance (DBGC) conducted inspections of clinical and analytical portions of the following studies:

Study P-145: "A study to evaluate the definitive bioequivalence of MK-0653C with marketed products"

Study P-183: "A study to evaluate the definitive bioequivalence of MK-0653C with marketed products"

The inspections of the clinical portions were conducted at Comprehensive Phase 1/Comprehensive NeuroScience, Inc., Miramar, FL (study P-145; inspection 1/9-1/13/2012), Comprehensive Phase 1/Comprehensive NeuroScience, Inc, Fort Myers, FL (P-145; 11/28-12/02/2011), and Sea View Research, Inc. (P-183; 1/23-1/26/2012). The inspections of the bioanalytical portions were conducted at (b) (4)

(b) (4)

Following the inspections Form FDA-483 was not issued at any of the sites. However, the EIR and exhibits from the inspection at Comprehensive Phase 1, Miramar (not yet received at OSI) will detail misidentification of at least one blood sample from subject 146, period 1, 72 hours, in study P-145. Further information is not available at this time. OSI recommends that data from subject 146 should be excluded from pharmacokinetic calculations.

Conclusions:

Following the inspections, DBGC recommends the following:

- Data from subject 146 in study P-145 should be excluded from pharmacokinetic calculations, in that one or more plasma samples were misidentified at the clinical site.
- All other data from studies P-145 and P-183 are acceptable for your review.

After you have reviewed this transmittal memo, please append it to the original NDA submission.

Michael F. Skelly , Ph.D.
Bioequivalence Branch, DBGC, OSI

Final Classifications:

NAI - Comprehensive Phase 1, Miramar, FL
FEI: 3006116374

NAI - Comprehensive Phase 1, Fort Myers, FL
FEI: 3007613146

NAI - Sea View Research, Inc., Miami, FL
FEI: 3005611026

NAI -  (b) (4)

NAI -  (b) (4)

cc:

OSI/Ball/Moreno

OSI/DBGC/Taylor/Haidar/Skelly/Dejernett

OND/DMEP/Parks/Johnson/Chowdhury

OCP/Johnny (S.W.) Lau

HFR-CE2545/Milazzo

HFR-CE750/Rusin

HFR-SE250/Torres

HFR-SE2560/Garmendia

HFR-SE2585/Gunn

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/s/

MICHAEL F SKELLY
02/23/2012

WILLIAM H TAYLOR
02/29/2012

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/s/

SZE W LAU
03/02/2012

JAYABHARATHI VAIDYANATHAN
03/02/2012

CLINICAL PHARMACOLOGY REVIEW

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1 Executive Summary

The sponsor is developing fixed dose combination (FDC) tablets of ezetimibe and atorvastatin calcium (EZE/ATOR) to treat hyperlipidemia. The immediate release (IR) EZE/ATOR FDC tablets have the following 4 strengths for once daily oral administration:

- 10 mg ezetimibe/10 mg atorvastatin calcium* (EZE/ATOR 10/10 mg)
- 10 mg ezetimibe/20 mg atorvastatin calcium* (EZE/ATOR 10/20 mg)
- 10 mg ezetimibe/40 mg atorvastatin calcium* (EZE/ATOR 10/40 mg)
- 10 mg ezetimibe/80 mg atorvastatin calcium* (EZE/ATOR 10/80 mg)

*The atorvastatin calcium is expressed as 10, 20, 40, and 80 mg atorvastatin.

Ezetimibe (ZETIA[®]; 10 mg IR tablet) has an approved indication to treat hyperlipidemia (NDA 21-445). Atorvastatin calcium (LIPITOR[®]; 10, 20, 40, and 80 mg IR tablets) also has an approved indication to treat hyperlipidemia (NDA 20-702).

1.1 Recommendations

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 2 (OCP/DCP2) has reviewed NDA 200-153's Clinical Pharmacology data submitted on April 29, 2011 as well as July 22, 2011 and finds that part of the data is unacceptable to support approval and have the following comments:

- Since this submission does not contain clinical efficacy and safety data for the 4 strengths of ezetimibe/atorvastatin calcium fixed dose combination tablets, bioequivalence results are fundamental to bridge all relevant data for the coadministration of individual innovator ezetimibe plus atorvastatin calcium tablets to the corresponding ezetimibe/atorvastatin calcium fixed dose combination tablets.
- The atorvastatin component of the 10 mg ezetimibe/20 mg atorvastatin calcium and 10 mg ezetimibe/40 mg atorvastatin calcium fixed dose combination tablets are not bioequivalent to the coadministration of individual innovator 10 mg ezetimibe plus 20 mg atorvastatin calcium and 10 mg ezetimibe plus 40 mg atorvastatin calcium tablets, respectively, due to the 90% confidence intervals of the geometric mean ratios for atorvastatin C_{max} fail to be within the bioequivalence goalpost of 0.8 – 1.25. However, the ezetimibe component of the 10 mg ezetimibe/20 mg atorvastatin calcium and 10 mg ezetimibe/40 mg atorvastatin calcium fixed dose combination tablets are bioequivalent to the coadministration of corresponding individual innovator 10 mg ezetimibe plus 20 mg atorvastatin calcium and 10 mg ezetimibe plus 40 mg atorvastatin calcium tablets, respectively. For the fixed dose combination tablet as a whole, the 10 mg ezetimibe/20 mg atorvastatin calcium and 10 mg ezetimibe/40 mg atorvastatin calcium fixed dose combination tablets failed the bioequivalence assessment to the coadministration of corresponding individual ezetimibe plus atorvastatin calcium tablets.
- Hence, the 10 mg ezetimibe/20 mg atorvastatin calcium and 10 mg ezetimibe/40 mg atorvastatin calcium fixed dose combination tablets may be unacceptable for the proposed indications.
- Both ezetimibe and atorvastatin components of the 10 mg ezetimibe/10 mg atorvastatin calcium and 10 mg ezetimibe/80 mg atorvastatin calcium fixed dose combination tablets are bioequivalent to the coadministration of corresponding individual innovator 10 mg ezetimibe plus 10 mg atorvastatin calcium and 10 mg ezetimibe plus 80 mg atorvastatin calcium tablets, respectively. Hence, the 10 mg ezetimibe/10 mg atorvastatin calcium and 10 mg ezetimibe/80 mg atorvastatin calcium fixed dose combination tablets are acceptable for the proposed indications. However, these two strengths of fixed dose combination tablets do not offer the different dosing options for patients.

The sponsor may reformulate the 10 mg ezetimibe/20 mg atorvastatin calcium and 10 mg ezetimibe/40 mg atorvastatin calcium fixed dose combination tablets so as to demonstrate bioequivalence for both atorvastatin and ezetimibe to the coadministration of corresponding individual innovator ezetimibe plus atorvastatin calcium tablets.

There Office of Scientific Investigation results are pending.

1.2 Post Marketing Requirement

None.

1.3 Summary of Important Clinical Pharmacology Findings

The EZE/ATOR 10/10 mg and EZE/ATOR 10/80 mg FDC tablets are bioequivalent for both ezetimibe and atorvastatin components to the coadministration of corresponding individual EZE plus ATOR tablets.

The ezetimibe component of the EZE/ATOR 10/20 mg and EZE/ATOR 10/40 mg FDC tablets are bioequivalent to the coadministration of corresponding individual EZE plus ATOR tablets. However, the atorvastatin component of the EZE/ATOR 10/20 mg and EZE/ATOR 10/40 mg FDC tablets are not bioequivalent to the coadministration of corresponding individual EZE plus ATOR tablets. The resulting atorvastatin $AUC_{0-\infty}$ and C_{max} of EZE/ATOR 10/20 mg FDC tablet is (b) (4) than those of the coadministration of individual 10 mg ezetimibe plus 20 mg atorvastatin tablets. The resulting atorvastatin $AUC_{0-\infty}$ and C_{max} of EZE/ATOR 10/40 mg FDC tablet is (b) (4) than those of the coadministration of individual 10 mg ezetimibe plus 40 mg atorvastatin tablets.

Food decreased atorvastatin $AUC_{0-\infty}$ and C_{max} 11 and 35%, respectively, of the EZE/ATOR 10/80 mg FDC tablet. Food decreased unconjugated ezetimibe AUC_{0-last} 2% and increased unconjugated ezetimibe C_{max} 10%, of the EZE/ATOR 10/80 mg FDC tablet.

S.W. Johnny Lau, R.Ph., Ph.D.
OCP/DCP2

Jee Eun Lee, Ph.D.
OCP/DCP2

FT signed by Jayabharathi Vaidyanathan, Ph.D., Acting Team Leader, _____ 12/ /11

An Office Level Clinical Pharmacology Briefing for NDA 200-153 was conducted on December 1, 2011; participants included D. Abernethy, K. Reynolds, S. Robertson, M. Mehta, A. Rahman, D. Bashaw, K. Krudys, S. Brar, J. Liu, R. Jin, C. Shukla, D. Tran, J. Shon, D. Lee, B. Yu, Y. Fan, I Zdrojewski, L. Jain, Z Li, L. Zhao, E. Pfuma, K. Johnson (via phone), I. Chowdhury, I. Antonipillai, J. Leginus, C. Sahajwalla, S. Doddapaneni, J. Vaidyanathan, J-E Lee, and J. Lau.

2 Question-Based Review

2.1 Background

The sponsor is developing the EZE/ATOR 10/10, EZE/ATOR 10/20, EZE/ATOR 10/40, and EZE/ATOR 10/80 mg FDC oral IR tablets to provide a more convenient single tablet for the combination of ezetimibe and atorvastatin calcium.

The sponsor submitted this 505(b)(2) New Drug Application (NDA) to seek marketing approval for the 4 strengths of FDC tablets without conducting clinical efficacy and safety study to treat hyperlipidemia. However, the sponsor conducted 2 pivotal bioequivalence studies (P145 and P183) between the EZE/ATOR 10/10, EZE/ATOR 10/20, and EZE/ATOR 10/80, as well as EZE/ATOR 10/40 FDC IR tablets and the coadministration of corresponding individual innovator ezetimibe plus atorvastatin calcium IR oral tablets so as to bridge the clinical efficacy and safety data for the coadministration of individual innovator ezetimibe plus atorvastatin calcium tablets (data in NDA 21-445) to the corresponding FDC tablets. Thus, the bioequivalence data are fundamental to this NDA submission.

The sponsor claimed that the EZE/ATOR FDC tablets' development program is to assess PK bioequivalence, to evaluate the PK results with respect to safety and to predict efficacy thru modeling in order to establish comparable safety and efficacy between the FDC tablets and the coadministration of corresponding individual EZE and ATOR tablets. The sponsor performed the PK/PD modeling to salvage the failed atorvastatin bioequivalence results for the EZE/ATOR 10/20 and EZE/ATOR 10/40 mg FDC tablets. However, the regulatory decision for this NDA are based on the bioequivalence assessment results and not based on the PK/PD modeling.

The sponsor also conducted a food effect study (P146) for the highest strength of to-be-marketed EZE/ATOR 10/80 mg FDC tablet and a pilot bioequivalence study (P9396-001) for the development of atorvastatin formulation to support the Clinical Pharmacology data of this NDA.

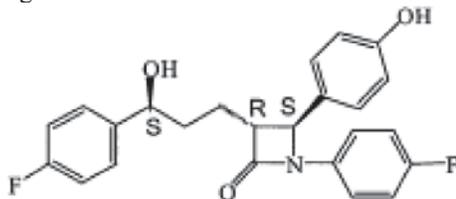
The sponsor conducted the following clinical studies with the coadministration of individual ezetimibe and statins: short-term factorial study (P0692) and Study 2154 (692's extension as long-term blinded comparator study). The sponsor conducted short-term add-on studies (P2173 and P040). The sponsor conducted short-term add-on titration studies (P079, P090, P112, and P693). The sponsor conducted the short-term study (P1030) and long-term study (P1417) in homozygous familial hypercholesterolemia patients.

The sponsor's first submission of this NDA was on September 2, 2009. However, the Division of Metabolism and Endocrinology Products refused to file this NDA due to chemistry, manufacturing, and control issues such as the manufacturing and testing facilities were not ready for GMP inspections. The sponsor resubmitted this NDA on April 29, 2011.

2.2 General Attributes

2.2.1 What are ezetimibe and atorvastatin calcium's key physicochemical properties?

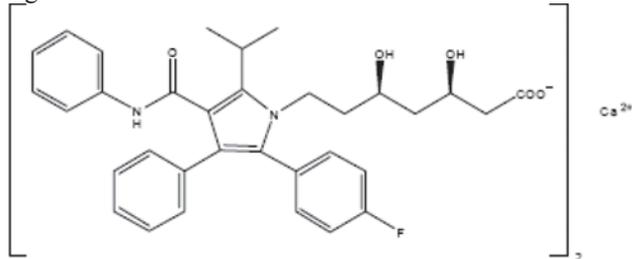
Figure 1. Ezetimibe's molecular structure.



Ezetimibe has a molecular weight of 1155.36, empirical formula of $C_{24}H_{21}F_2NO_3$, and is insoluble in water, but soluble in acetonitrile and freely soluble in ethanol and methanol. Ezetimibe has a pK_a of 9.75.

Ezetimibe's n-octanol:0.1 N HCl partition coefficient (log P) is 4.52 and n-octanol:pH 7 buffer log P is 4.51.

Figure 2. Atorvastatin calcium's molecular structure.



Atorvastatin calcium has a molecular weight of 409.4, empirical formula of $(C_{33}H_{34}FN_2O_5)_2Ca$, and is very slightly soluble in water, but insoluble in acetonitrile and soluble in methanol. Atorvastatin calcium has a pK_a of 4.46. Atorvastatin calcium's octanol:water log P is 5.6.

2.2.2 What is the formulation for the to-be-marketed ezetimibe and atorvastatin fixed dose combination (EZE/ATOR FDC) oral tablet?

Table 1 below details the formulation of the to-be-marketed EZE/ATOR FDC oral tablets.

Table 1. The to-be-marketed EZE/ATOR FDC tablets' formulations.

Components	Compendial Testing	Function	Unit Strength (Ezetimibe/Atorvastatin)			
			10/10 mg/mg	10/20 mg/mg	10/40 mg/mg	10/80 mg/mg
(b) (4)			mg/tablet			
Ezetimibe (SCH58235),	(b) (4)	Active		10.00		(b) (4)
[Redacted]						
Atorvastatin Calcium§ (amorphous)	---	Active	10.34	20.68	41.36	82.73
(equivalent free acid)¶			(10.00)	(20.00)	(40.00)	(80.00)
[Redacted]						
Coating:	(b) (4)					
[Redacted]						
Total Coated Tablet Wt.:			624.0 mg	364.1 mg	519.7 mg	830.3 mg
[Redacted]						

Additional information on the EZE/ATOR FDC tablets' formulation follows:

- The atorvastatin calcium for the EZE/ATOR FDC tablets is amorphous, whereas the atorvastatin calcium for the innovator's tablet is crystalline.
- The tablet manufacturing process (b) (4)
- (b) (4)

2.2.3 How does EZE/ATOR FDC tablet work for the proposed indications?

Ezetimibe is a cholesterol absorption inhibitor in the gastrointestinal tract, whereas atorvastatin competitively inhibits HMG-CoA reductase, which is a rate-limiting enzyme in cholesterol biosynthesis in the liver.

2.2.4 What are the sponsor's proposed indication and dosing regimen for EZE/ATOR FDC tablet?

EZE/ATOR FDC tablets' proposed indication is an adjunctive therapy to diet to:

- reduce elevated total cholesterol (total-C), LDL-C, apolipoprotein B, triglycerides, and non-high-density lipoprotein cholesterol, and to increase high-density lipoprotein cholesterol in patients with primary (heterozygous familial and non-familial) hyperlipidemia or mixed hyperlipidemia
- reduce elevated total-C and LDL-C in patients with homozygous familial hypercholesterolemia, as an adjunct to other lipid-reduction treatments

EZE/ATOR FDC tablets' proposed dosing regimen follows:

- Dosage range is 10/10 – 10/80 mg/mg once daily anytime of the day with or without food.
- The recommended starting dose is 10/10 or 10/20 mg/mg daily.

2.3 General Clinical Pharmacology

2.3.1 What are ezetimibe and atorvastatin's clinical pharmacokinetic (PK) characteristics?

Besides ezetimibe and atorvastatin calcium's product labels, the following publications also detail ezetimibe and atorvastatin's clinical PK:

- Kosoglou et al. Ezetimibe: A review of its metabolism, pharmacokinetics and drug interactions. *Clin Pharmacokinet* 2005;44: 467-94.
- Lennernäs. Clinical pharmacokinetics of atorvastatin. *Clin Pharmacokinet* 2003;42:1141-60.

2.3.2 Are ezetimibe and atorvastatin's PK dose-proportional upon oral administration?

The ezetimibe PK does not show substantial deviation from dose proportionality between 5 and 20 mg ezetimibe when administered alone [ezetimibe product label].

Atorvastatin PK is nonlinear, as reflected thru a greater than proportional increase in C_{max} and AUC with increasing single and multiple doses of 0.5 – 80 mg atorvastatin/day. This increase is consistent with saturable hepatic first-pass metabolism [Cilla et al. Multiple-dose pharmacokinetics, pharmacodynamics, and safety of atorvastatin, an inhibitor of HMG-CoA reductase, in healthy subjects. *Clin Pharmacol Ther* 1996;60:687-95].

2.3.3 Do multiple oral administrations alter EZE/ATOR FDC tablet's PK?

This submission does not contain data for the assessment of ezetimibe and atorvastatin PK upon multiple EZE/ATOR FDC tablet administrations.

2.3.4 How are the proposed daily EZE/ATOR FDC tablet dosing regimen determined for hypercholesterolemic patients?

The recommended ezetimibe dosage is 10 mg once daily taken with or without food [ezetimibe product label]. The recommended atorvastatin dosage range is 10 – 80 mg once daily taken with or without food anytime of the day [atorvastatin product label]. Moreover, the ezetimibe product label states the responses of LDL-C reduction upon coadministration of individual innovator 10 mg ezetimibe tablet plus 10, 20, 40, or 80 mg atorvastatin tablet.

2.3.5 Exposure-Response

What is the evidence of exposure-response relationship for EZE/ATOR FDC tablet?

As indicated in Section 2.1 that the regulatory decision for this NDA is based on the results of bioequivalence studies. The modeling approaches to exposure-response were reviewed under the consideration for potential evidence to support the sponsor's claim.

See this review's Sections 2.1 and 2.6 for this question's background.

(b) (4)

[Redacted]

(b) (4)

[Redacted]

2.3.6 Does EZE/ATOR FDC tablet prolong the QT or QTc interval?

This submission does not contain QTc data for the assessment of QT prolongation.

2.4 Intrinsic Factors**2.4.1 What intrinsic factors may affect the use of EZE/ATOR FDC tablet?**

This submission does not contain pediatric, geriatric, and pharmacogenomic data. See the individual ezetimibe and atorvastatin calcium product labelings for further details.

02.5 Extrinsic Factors

2.5.1 How does food affect ezetimibe and atorvastatin's bioavailability (BA)?

Study P-146 examined the effect of food on the to-be-marketed EZE/ATOR 10/80 mg FDC tablet's bioavailability as a single-dose, 2-treatment, 2-period, crossover study. Twenty-eight randomized healthy men and women participated in the study. Participants orally received the following 2 treatments in a 1:1 distribution of participants:

- Treatment A: 1 EZE/ATOR 10/80 mg FDC tablet after at least a 10 hours overnight fast
- Treatment B: 1 EZE/ATOR 10/80 mg FDC tablet 30 minutes after eating a high fat breakfast

The high fat breakfast's content is consistent with the Food-Effect Bioavailability and Fed Bioequivalence Studies Guidance's recommendation. Serial plasma samples were collected predose and 96 hours postdose to determine unconjugated and total ezetimibe as well as predose and 48 hours postdose to determine atorvastatin and its ortho- and para-hydroxy metabolites via validated LC-MS/MS assays.

Figure 5 (left). Mean plasma atorvastatin concentration-time profiles upon dosing of the EZE/ATOR 10/80 mg FDC tablet under fasted and fed conditions. Figure 6 (right). Mean plasma unconjugated ezetimibe concentration-time profiles upon dosing of the EZE/ATOR 10/80 mg FDC tablet under fasted and fed conditions.

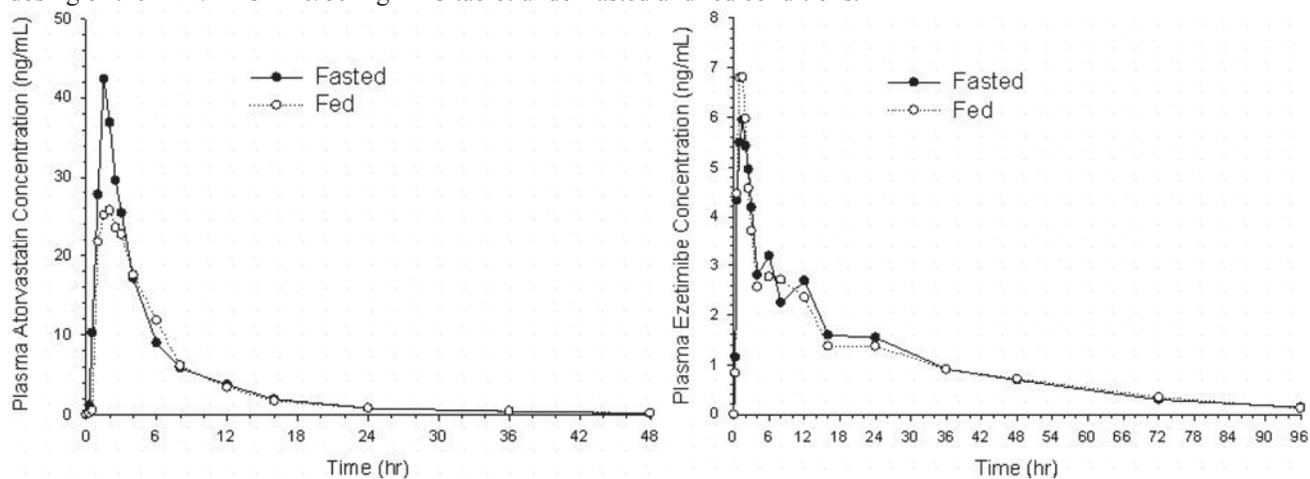


Table 3. Statistics of primary PK parameters upon single doses administration of EZE/ATOR 10/80 mg FDC tablet with a high fat breakfast and in the fasted state in healthy men (N=28).

Parameter	Least Square Geometric Mean (95% CI)		Estimated GMR (90% CI) Fed/Fasted
	Fed	Fasted	
Atorvastatin			
AUC _{0-∞} (ng*hr/mL)	156.26 (132.38, 184.43)	175.52 (148.70, 207.16)	0.89 (0.79, 1.01)
C _{max} (ng/mL)	29.51 (22.45, 38.78)	45.36 (34.51, 59.61)	0.65 (0.48, 0.87)
Unconjugated Ezetimibe			
AUC _{0-last} (ng*hr/mL)	87.77 (74.19, 103.84)	89.16 (75.36, 105.48)	0.98 (0.91, 1.07)
C _{max} (ng/ml)	8.00 (6.41, 9.99)	7.25 (5.81, 9.05)	1.10 (0.91, 1.34)

Food decreased atorvastatin AUC_{0-∞} and C_{max} 11 and 35%, respectively. Food decreased unconjugated ezetimibe AUC_{0-last} 2% and increased ezetimibe C_{max} 10%.

This reviewer's (Lau) statistical analyses results are consistent with the sponsor's analyses. This reviewer used the SAS PROC GLM procedure to calculate the GMR and confidence interval (CI), whereas the sponsor used the SAS PROC MIXED procedure. This reviewer observed only slight differences after the decimal point for the estimated GMR and 90% CI but these differences do not alter the results' interpretation.

2.5.2 What is the potential for mutual interactions between ezetimibe and atorvastatin?

Per Dr. Wei Qiu's NDA 21-445 Clinical Pharmacology review on Study P00460 and ZETIA® label, daily coadministration of 10 mg ezetimibe and 10 mg atorvastatin for 14 days showed the following changes but are not clinically significant mutual interaction

[http://www.accessdata.fda.gov/drugsatfda_docs/nda/2002/21445_Zetia_biopharmr_P1.pdf]:

- total ezetimibe C_{max} increased 12% and total ezetimibe AUC decreased 2%
- unconjugated ezetimibe C_{max} increased 31% and unconjugated ezetimibe AUC increased 21%
- atorvastatin C_{max} increased 7% and atorvastatin AUC decreased 4%

2.6 General Biopharmaceutics

What is the relative bioavailability of the EZE/ATOR FDC tablets to the coadministration of corresponding individual innovator EZE plus ATOR tablets?

Study P145 is a pivotal bioequivalence study of the to-be-marketed EZE/ATOR 10/10, 10/20, and 10/80 mg FDC tablets (at least 1/10 of the proposed commercial batch size for each strength of tablets) versus coadministration of corresponding individual ezetimibe plus atorvastatin calcium tablets. The design was an open label, randomized 3-part, 2-period, crossover study. A minimum of 14-day washout separated the 2 single-dose oral administrations. Two hundred eighty eight healthy volunteers participated in either Part 1, 2, or 3. The 3 Parts were:

- 1) single doses of coadministration of 10 mg EZE tablet plus 10 mg ATOR tablet compared to a single dose of the to-be-marketed EZE/ATOR 10/10 mg FDC tablet under fasting
- 2) single doses of coadministration of 10 mg EZE tablet plus 20 mg ATOR tablet compared to a single dose of the to-be-marketed EZE/ATOR 10/20 mg FDC tablet under fasting
- 3) single doses of coadministration of 10 mg EZE tablet plus 80 mg ATOR tablet compared to a single dose of the to-be-marketed EZE/ATOR 10/80 mg FDC tablet under fasting

Serial plasma samples were collected predose and 96 hours postdose to determine unconjugated and total ezetimibe as well as predose and 48 hours postdose to determine atorvastatin and its ortho- and para-hydroxy metabolites via validated LC-MS/MS assays.

Figure 7 (left). Mean plasma atorvastatin concentration-time profiles upon dosing of the EZE/ATOR 10/10 mg FDC tablet versus coadministration of individual 10 mg EZE plus 10 mg ATOR tablets under fasting. Figure 8 (right). Mean plasma unconjugated ezetimibe concentration-time profiles upon dosing of the EZE/ATOR 10/10 mg FDC tablet versus coadministration of individual 10 mg EZE plus 10 mg ATOR tablets under fasting.

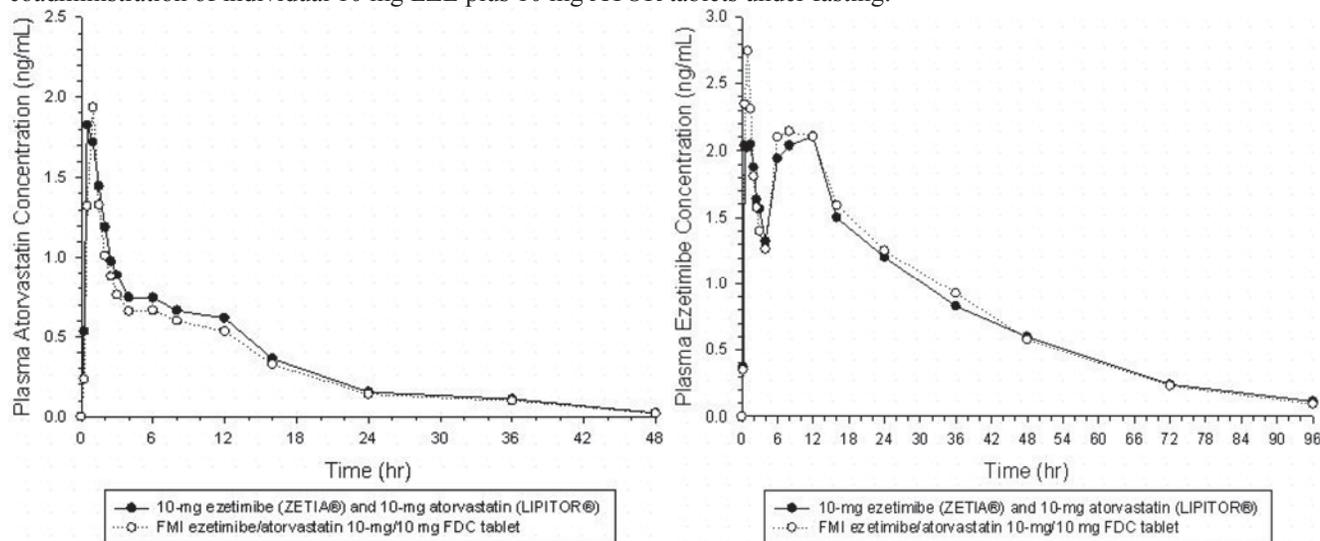


Table 4. Statistical comparisons of atorvastatin and unconjugated ezetimibe PK upon the EZE/ATOR 10/10 mg FDC tablet administration versus the coadministration of individual 10 mg EZE plus 10 mg ATOR tablets.

Analyte	Parameter	LS Geometric Mean (95% CI)		Estimated GMR (90% CI) FDC Tablet/ Coadministration
		FDC Tablet	Coadministration	
Atorvastatin	AUC _{0-∞} (ng*hr/mL)	14.38 (12.96, 15.96)	15.43 (13.91, 17.12)	0.93 (0.86, 1.01)
	C _{max} (ng/mL)	2.13 (1.92, 2.37)	2.37 (2.14, 2.64)	0.90 (0.81, 0.99)
Unconjugated Ezetimibe	AUC _{0-last} (ng*hr/mL)	65.2 (58.5, 72.6)	63.3 (56.8, 70.5)	1.03 (0.99, 1.07)
	C _{max} (ng/ml)	3.5 (3.1, 3.9)	3.1 (2.8, 3.5)	1.13 (1.05, 1.22)

The 90% CI of atorvastatin AUC_{0-∞} GMR and atorvastatin C_{max} GMR show that the atorvastatin component of EZE/ATOR 10/10 mg FDC tablet is bioequivalent to the coadministration of individual 10 mg ezetimibe plus 10 mg atorvastatin calcium tablets since the 90% CIs are within the 0.8 and 1.25 bioequivalence goalpost.

The 90% CI of unconjugated ezetimibe AUC_{0-∞} GMR and unconjugated ezetimibe C_{max} GMR show that the ezetimibe component of EZE/ATOR 10/10 mg FDC tablet is bioequivalent to the coadministration of individual 10 mg ezetimibe plus 10 mg atorvastatin calcium tablets since the 90% CIs are within the 0.8 and 1.25 bioequivalence goalpost.

Figure 9 (left). Mean plasma atorvastatin concentration-time profiles upon dosing of the EZE/ATOR 10/20 mg FDC tablet versus coadministration of individual 10 mg EZE plus 20 mg ATOR tablets under fasting. Figure 10 (right). Mean plasma unconjugated ezetimibe concentration-time profiles upon dosing of the EZE/ATOR 10/20 mg FDC tablet versus coadministration of individual 10 mg EZE plus 20 mg ATOR tablets under fasting.



Table 5. Statistical comparisons of atorvastatin and unconjugated ezetimibe PK upon the EZE/ATOR 10/20 mg FDC tablet administration versus the coadministration of individual 10 mg EZE plus 20 mg ATOR tablets.

Analyte	Parameter	LS Geometric Mean (95% CI)		Estimated GMR (90% CI) FDC Tablet/ Coadministration
		FDC Tablet	Coadministration	
Atorvastatin	AUC _{0-∞} (ng*hr/mL)			(b) (4)
	C _{max} (ng/mL)			
Unconjugated Ezetimibe	AUC _{0-last} (ng*hr/mL)			(b) (4)
	C _{max} (ng/mL)			

The 90% CI of atorvastatin AUC_{0-∞} GMR and atorvastatin C_{max} GMR show that the atorvastatin component of EZE/ATOR 10/20 mg FDC tablet is not bioequivalent to the coadministration of individual 10 mg ezetimibe plus 20 mg atorvastatin calcium tablets since the 90% CIs are outside of the 0.8 and 1.25

bioequivalence goalpost. The resulting atorvastatin $AUC_{0-\infty}$ and C_{max} of EZE/ATOR 10/20 mg FDC tablet is ^{(b) (4)} than those of the coadministration of individual 10 mg ezetimibe plus 20 mg atorvastatin calcium tablets.

The 90% CI of unconjugated ezetimibe $AUC_{0-\infty}$ GMR and unconjugated ezetimibe C_{max} GMR show that the ezetimibe component of EZE/ATOR 10/20 mg FDC tablet is bioequivalent to the coadministration of individual 10 mg ezetimibe plus 20 mg atorvastatin calcium tablets since the 90% CIs are within the 0.8 and 1.25 bioequivalence goalpost.

Figure 11 (left). Mean plasma atorvastatin concentration-time profiles upon dosing of the EZE/ATOR 10/80 mg FDC tablet versus coadministration of individual 10 mg EZE plus 80 mg ATOR tablets under fasting. Figure 12 (right). Mean plasma unconjugated ezetimibe concentration-time profiles upon dosing of the EZE/ATOR 10/80 mg FDC tablet versus coadministration of individual 10 mg EZE plus 80 mg ATOR tablets under fasting.

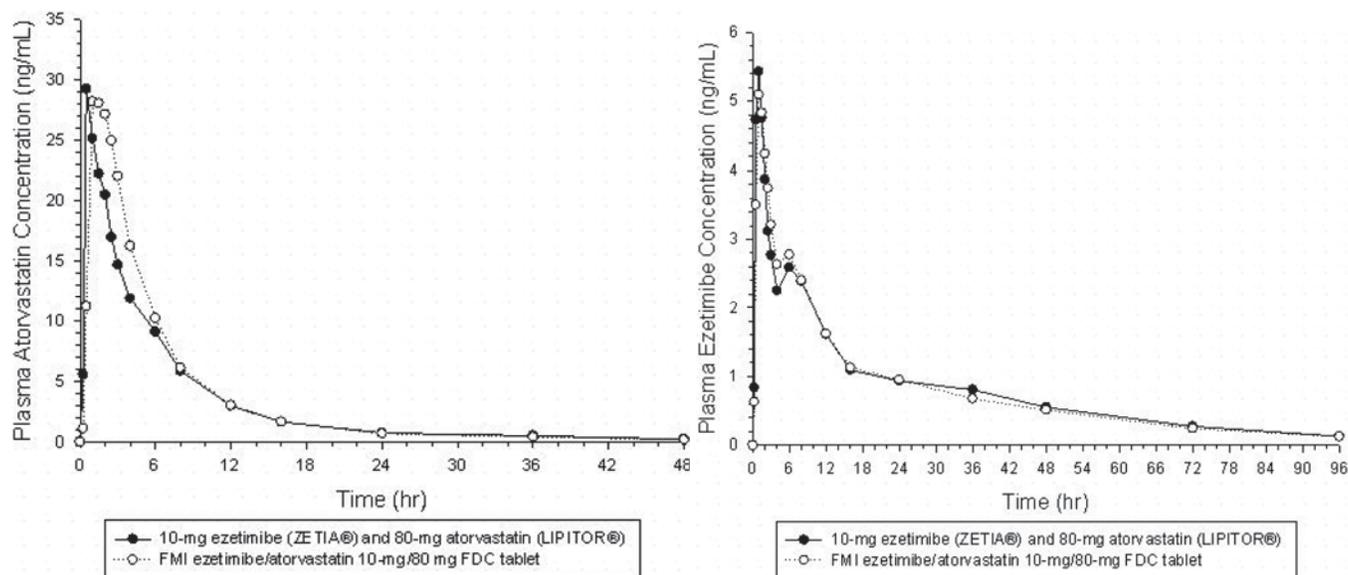


Table 6. Statistical comparisons of atorvastatin and unconjugated ezetimibe PK upon the EZE/ATOR 10/80 mg FDC tablet administration versus the coadministration of individual 10 mg EZE plus 80 mg ATOR tablets.

Analyte	Parameter	LS Geometric Mean (95% CI)		Estimated GMR (90% CI)
		FDC Tablet	Coadministration	FDC Tablet/ Coadministration
Atorvastatin	$AUC_{0-\infty}$ (ng*hr/mL)	162.04 (149.01, 176.21)	145.54 (133.83, 158.26)	1.11 (1.06, 1.17)
	C_{max} (ng/mL)	38.00 (33.91, 42.58)	34.91 (31.15, 39.12)	1.09 (0.99, 1.20)
Unconjugated Ezetimibe	AUC_{0-last} (ng*hr/mL)	66.8 (61.0, 73.1)	68.5 (62.6, 75.0)	0.97 (0.93, 1.02)
	C_{max} (ng/mL)	5.8 (5.2, 6.5)	5.9 (5.3, 6.6)	0.99 (0.92, 1.06)

The 90% CI of atorvastatin $AUC_{0-\infty}$ GMR and atorvastatin C_{max} GMR show that the atorvastatin component of EZE/ATOR 10/80 mg FDC tablet is bioequivalent to the coadministration of individual 10 mg ezetimibe plus 80 mg atorvastatin calcium tablets since the 90% CIs are within the 0.8 and 1.25 bioequivalence goalpost.

The 90% CI of unconjugated ezetimibe $AUC_{0-\infty}$ GMR and unconjugated ezetimibe C_{max} GMR show that the ezetimibe component of EZE/ATOR 10/80 mg FDC tablet is bioequivalent to the coadministration of individual 10 mg ezetimibe plus 80 mg atorvastatin calcium tablets since the 90% CIs are within the 0.8 and 1.25 bioequivalence goalpost.

Study P183 is a pivotal bioequivalence study of the to-be-marketed EZE/ATOR 10/40 mg/mg FDC tablet (at least 1/10 of the proposed commercial batch size) versus the coadministration of individual 10 mg ezetimibe plus 10 mg atorvastatin calcium tablets. The design was an open-label, randomized, 2-period crossover study. Ninety six fasted subjects participated into to the study. A minimum of 14-day washout separated the 2 single-dose oral administrations.

Serial plasma samples were collected predose and 96 hours postdose to determine unconjugated and total ezetimibe as well as predose and 48 hours postdose to determine atorvastatin and its ortho- and para-hydroxy metabolites via validated LC-MS/MS assays.

Figure 13 (left). Mean plasma atorvastatin concentration-time profiles upon dosing of the EZE/ATOR 10/40 mg FDC tablet versus coadministration of individual 10 mg EZE plus 40 mg ATOR tablets under fasting. Figure 14 (right). Mean plasma unconjugated ezetimibe concentration-time profiles upon dosing of the EZE/ATOR 10/40 mg FDC tablet versus coadministration of individual 10 mg EZE plus 40 mg ATOR tablets under fasting.



Table 7. Statistical comparisons of atorvastatin and unconjugated ezetimibe PK upon the EZE/ATOR 10/40 mg FDC tablet administration versus the coadministration of individual 10 mg EZE plus 40 mg ATOR tablets.

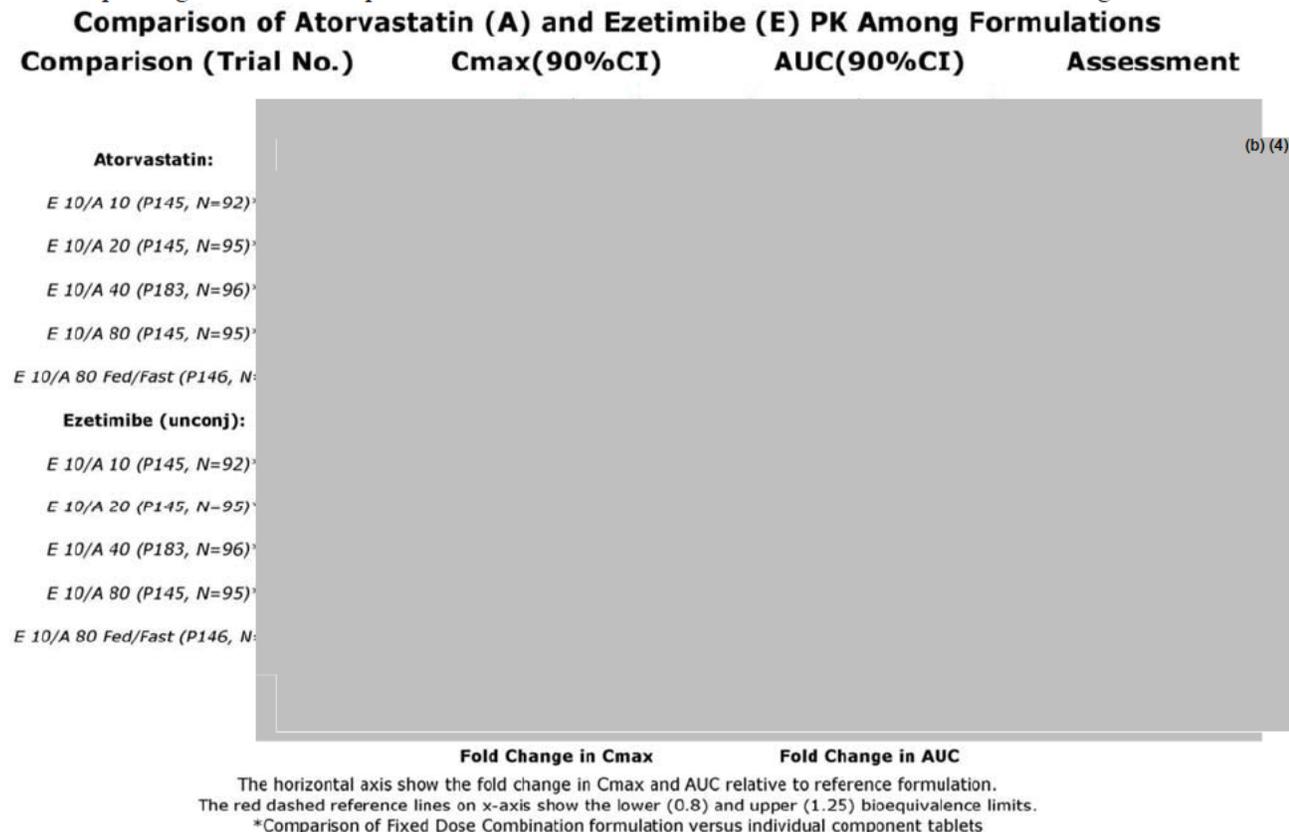
Analyte	Parameter	LS Geometric Mean (95% CI)		Estimated GMR (90% CI) FDC Tablet/ Coadministration
		FDC Tablet	Coadministration	
Atorvastatin	AUC _{0-∞} (ng*hr/mL)	(b) (4)		(b) (4)
	C _{max} (ng/mL)			
Unconjugated Ezetimibe	AUC _{0-last} (ng*hr/mL)	(b) (4)		(b) (4)
	C _{max} (ng/mL)			

The 90% CI of atorvastatin AUC_{0-∞} GMR and atorvastatin C_{max} GMR show that the atorvastatin component of EZE/ATOR 10/40 mg FDC tablet is not bioequivalent to the coadministration of individual 10 mg ezetimibe plus 40 mg atorvastatin calcium tablets since the 90% CIs are outside of the 0.8 and 1.25 bioequivalence goalpost. The resulting atorvastatin AUC_{0-∞} and C_{max} of EZE/ATOR 10/40 mg FDC tablet is (b) (4) than those of the coadministration of individual 10 mg ezetimibe plus 40 mg atorvastatin calcium tablets.

The 90% CI of unconjugated ezetimibe AUC_{0-∞} GMR and unconjugated ezetimibe C_{max} GMR show that the ezetimibe component of EZE/ATOR 10/40 mg FDC tablet is bioequivalent to the coadministration of individual 10 mg ezetimibe plus 40 mg atorvastatin calcium tablets since the 90% CIs are within the 0.8 and 1.25 bioequivalence goalpost.

This reviewer's (Lau) statistical analyses results are consistent with the sponsor's analyses. This reviewer used the SAS PROC GLM procedure to calculate the GMR and CI, whereas the sponsor used the SAS PROC MIXED procedure. This reviewer observed only slight differences after the decimal point for the estimated GMRs and 90% CIs but these differences do not alter the results' interpretation.

Figure 15. Forest plot of the bioequivalence data between the 4 strengths of EZE/ATOR FDC tablets and the coadministration of corresponding individual EZE plus ATOR tablets as well as food effect on the EZE/ATOR 10/80 mg FDC tablet.



Of note, the GMRs for atorvastatin C_{max} and for atorvastatin AUC shift upward for the comparison of EZE/ATOR 10/20, EZE/ATOR 10/40, and EZE/ATOR 10/80 mg FDC tablets versus the coadministration of corresponding individual innovator EZE plus ATOR tablets. The sponsor studied at least 95 participants for each strength of these FDC tablets in the 2 bioequivalence studies that are more than the usual number of participants (< 50) in a bioequivalence study. Also, the sponsor studied EZE/ATOR 10/20 and EZE/ATOR 10/40 mg FDC tablets in different:

- studies (P145 and P183)
- investigators (Maria Gutierrez plus Melanie Fein for Study P145 and Audrey Martinez for Study P183)
- sites (Miramar, FL plus Fort Meyers, FL for Study P145 and Miami, FL for Study P183)
- time (November 11, 2008 to January 12, 2009 for Study P145 and October 19, 2009 to December 24, 2009 for Study P183).

Yet, the atorvastatin C_{max} for the EZE/ATOR 10/20 and EZE/ATOR 10/40 mg FDC tablets consistently failed the bioequivalence assessment. Since this submission does not contain clinical efficacy and safety data for the 4 strengths of EZE/ATOR FDC tablets, bioequivalence results are fundamental to bridge all relevant data for the coadministration of individual innovator EZE plus ATOR tablets to the corresponding EZE/ATOR FDC tablets. Hence, the sponsor may reformulate the EZE/ATOR 10/20 and EZE/ATOR 10/40 mg FDC tablets so as to demonstrate bioequivalence for both atorvastatin and ezetimibe to the coadministration of corresponding individual innovator EZE plus ATOR tablets.

The sponsor justified the insignificance of decreased atorvastatin C_{max} (inequivalence) via:

-
-
-
-

(b) (4)

See Question 2.3.5 above for the discussion on PK/PD modeling to justify the failed bioequivalence of atorvastatin.

The EZE/ATOR 10/10 mg and EZE/ATOR 10/80 mg FDC tablets are bioequivalent for both ezetimibe and atorvastatin components to the coadministration of corresponding individual EZE plus ATOR tablets. Thus, the EZE/ATOR 10/10 mg and EZE/ATOR 10/80 mg FDC tablets may be recommended for approval. However, the EZE/ATOR 10/10 mg and EZE/ATOR 10/80 mg FDC tablets do not allow dose adjustment for ATOR between these 2 dosage strengths. Even though the dose and LDL-C reduction curve is rather flat between 10 mg and 80 mg atorvastatin that may allow atorvastatin dose to increase from 10 mg to 80 mg immediately, the prescriber must consider the safety of the rapid increase from 10 mg to 80 mg atorvastatin since statins' muscle adverse events are generally dose dependent.

The EZE/ATOR FDC tablets are not medical necessity products since the approved individual innovator products are still available from the market and the EZE/ATOR FDC tablets are only for convenience. Moreover, there are other options for the treatment of hyperlipidemia. There are also 6 other available statins as alternatives. Generic statins (fluvastatin sodium, lovastatin, pravastatin sodium, and simvastatin) including atorvastatin calcium are also available.

This reviewer (Lau) did not review Study P9396-001 since it is a pilot study on the bioavailability of atorvastatin only so as to develop the atorvastatin formulation for later studies.

2.7 Bioanalytical

Are the bioanalytical methods properly validated for this NDA?

Yes.

Table 8. Validation of unconjugated and total ezetimibe's bioanalytical assays

	Unconjugated Ezetimibe		Total Ezetimibe	
	n	Mean (%)	n	Mean (%)
Intraday Accuracy with Calibration Standards	8	99 – 100	6	98 - 100
Intraday Precision (CV) with Calibration Standards	8	0.9 – 5.0	6	1.1 – 3.9
Intraday Accuracy with Quality Control Samples	6	97 - 100	6	94 - 100
Intraday Precision (CV) with Quality Control Samples	6	1.7 – 7.9	6	1.6 – 3.8
Interday Accuracy with Quality Control Samples	24	94 - 100	18	97 - 100
Interday Precision (CV) with Quality Control Samples	24	2.5 – 5.5	18	1.8 – 5.4
Interday Accuracy with Calibration Standards#	156 - 164	98 - 100	151 - 158	96 - 99
Interday Precision (CV) with Calibration Standards#	156 - 164	2.7 – 7.4	151 - 158	3.0 – 4.7
Interday Accuracy with Quality Control Samples#	164	99 -100	158	93 - 98
Interday Precision (CV) with Quality Control Samples#	164	3.1 – 6.9	158	3.6 – 5.2
Extraction Recovery of Analytes	6	91 -98	6	103
Extraction Recovery of Internal Standard	6	92 - 98	6	113 - 120
Relative Matrix Effect of Analytes	6	92 - 95	6	104 - 108
Relative Matrix Effect of Internal Standard	6	91 - 94	6	117 -128
Accuracy of Dilution Integrity (4X)	6	99	6	98
Precision (CV) of Dilution Integrity (4X)	6	1.4	6	2.5
Accuracy of Dilution Integrity (10X)	6	99	6	98
Precision (CV) of Dilution Integrity (10X)	6	1.3	6	3.7
Accuracy of Reinjection Integrity after 107 hours at 15°C Unconjugated Ezetimibe; 100 hours for Total Ezetimibe##	6	98 - 100	6	96 - 99
Precision (CV) of Reinjection Integrity after 107hours at 15°C Unconjugated Ezetimibe; 100 hours for Total Ezetimibe ##	6	2.0 – 4.7	6	0.5 – 3.3
Accuracy of Processed Samples after 140 Hours at 15°C for Unconjugated Ezetimibe; 125 Hours for Total Ezetimibe	6	97 - 99	6	96 - 100
Precision (CV) of Processed Samples after 140 Hours at 15°C Unconjugated Ezetimibe; 125 Hours for Total Ezetimibe	6	1.6 – 3.8	6	2.9 – 3.8
Accuracy of Quality Control Samples after 3 Freeze/Thaw Cycles	6	94 - 95		
Precision (CV) of Quality Control Samples after 3 Freeze/Thaw Cycles	6	6.1 – 7.8		
Accuracy of Quality Control Samples after 4 Freeze/Thaw Cycles	6	97 - 98	6	93 - 99
Precision (CV) of Quality Control Samples after 4 Freeze/Thaw Cycles	6	2.6 – 4.0	6	1.7 – 2.6
Accuracy of Samples Assayed after 4 hours at Room Temperature	6	97 - 98		
Precision (CV) of Samples Assayed after 4 hours at Room Temperature	6	4.3 – 5.8		
Accuracy of Quality Control Samples Spiked with Concomitant Medications	3	95 - 98	6	97 - 99
Precision (CV) of Quality Control Samples Spiked with Concomitant Medications	3	2.0 – 4.5	6	1.6 – 4.9
Incurred Sample Re-analysis (% within specification)	1072	98.7	1063	99.6

Data from Assay Validation Reports for Unconjugated and Total Ezetimibe.
Representative data from Study #145 (~10253 samples in 82 analytical runs).
Per (b) (4) SOP, reinjection reproducibility testing is performed to determine if an analytical run can be reanalyzed.
It is not time dependent and does not establish extract stability.

Table 9. Validation of atorvastatin and its metabolites' bioanalytical assays

	Atorvastatin		o-OH- Atorvastatin	p-OH- Atorvastatin
	N	Mean (%)	Mean (%)	Mean (%)
Interday Accuracy with Calibration Standards	20-22	98.42-101.85	98.67-102.20	98.49-102.15
Interday Precision (CV) with Calibration Standards	20-22	1.41-4.38	1.60-5.83	1.88-4.56
Intraday Accuracy with Quality Control Samples	6	99.92-102.08	99.54-103.09	98.35-104.11
Intraday Precision (CV) with Quality Control Samples	6	1.23-4.91	1.72-14.95	0.85-4.28
Interday Accuracy with Quality Control Samples	66	101.18-101.80	101.05-102.55	100.34-100.87
Interday Precision (CV) with Quality Control Samples	66	2.00-4.07	2.22-5.47	3.21-5.42
Interday Accuracy with Calibration Standards#	164-194	98.15-101.83	98.81-101.19	99.04-101.39
Interday Precision (CV) with Calibration Standards#	164-194	2.67-5.71	2.38-8.07	3.22-6.75
Interday Accuracy with Quality Control Samples#	87-97	99.53-101.79	99.88-101.62	96.68-102.09
Interday Precision (CV) with Quality Control Samples#	87-97	3.24-5.48	3.28-7.30	3.72-5.81
Extraction Recovery of Analytes	6	96.31-105.26	97.65-107.60	92.52-104.78
Extraction Recovery of Internal Standard		91.81	95.15	92.62
Relative Matrix Effect of Analytes	10	≤20% LLOQ response	≤20% LLOQ response	≤20% LLOQ response
Relative Matrix Effect of Internal Standard	10	≤5% mean IS response	≤5% mean IS response	≤5% mean IS response
Accuracy of Dilution Integrity (2X)	6	101.60	102.41	101.97
Precision (CV) of Dilution Integrity (2X)	6	1.49	2.05	2.52
Accuracy of Dilution Integrity (20X)	6	100.30	101.92	101.91
Precision (CV) of Dilution Integrity (20X)	6	1.89	2.83	3.81
Accuracy of Reinjection Integrity after 58 hours at 4 °C	6	101.32-103.80	100.74-101.57	101.96-103.23
Precision (CV) of Reinjection Integrity after 58 hours at 4 °C	6	1.73-2.37	0.74-2.05	1.53-4.51
Accuracy of Processed Samples after 88 Hours at 4 °C and 28 Hours at Room Temperature	6	100.79-102.01	100.57-104.53	95.36-100.32
Precision (CV) of Processed Samples after 88 Hours at 4 °C and 28 Hours at Room Temperature	6	1.26-1.64	2.55-5.34	2.00-3.37
Accuracy of Quality Control Samples after 3 Freeze/Thaw Cycles – Storage at -20 °C	6	100.52-101.46	101.30-101.49	101.07-104.43
Precision (CV) of Quality Control Samples after 3 Freeze/Thaw Cycles – Storage at -20 °C	6	1.35-3.78	1.47-4.76	2.35-3.09
Accuracy of Quality Control Samples after 3 Freeze/Thaw Cycles – Storage at -80 °C	6	102.78-104.79	98.03-104.10	102.87-103.26
Precision (CV) of Quality Control Samples after 3 Freeze/Thaw Cycles – Storage at -80 °C	6	1.58-3.08	2.28-4.22	2.98-5.91
Accuracy of Quality Control Samples Assayed after 2 hours at Room Temperature	6	102.98-103.46	104.68-106.62	103.74-105.38
Precision (CV) of Quality Control Samples Assayed after 2 hours at Room Temperature	6	2.67-3.68	1.22-1.76	1.08-5.74
Accuracy of Quality Control Samples Spiked with Concomitant Medications	3	89.84-112.84	95.66-112.03	91.18-108.41
Incurred Sample Re-analysis (% within specification)#	~909	95.20	93.03	90.34

Data from Assay Validation Reports for Atorvastatin, o-Hydroxy-Atorvastatin and p-Hydroxy-Atorvastatin
Representative data from Study #145 (~9088 samples in up to 97 analytical runs).

3. Labeling Comments

This review will not discuss labeling comments since OCP recommends NDA 200-153's clinical pharmacology data unacceptable to support approval.

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/s/

S. W. JOHNNY W LAU
12/07/2011

JEE E LEE
12/07/2011

JAYABHARATHI VAIDYANATHAN
12/07/2011

NDA BIOPHARMACEUTICS REVIEW
Office of New Drug Quality Assessment

Application No.	NDA 200-153	Reviewer	Deepika Arora Lakhani, Ph.D
Division	Division of Medical Imaging and Hematology Products		
Sponsor	MSP (Merck)	Team Leader	Angelica Dorantes, Ph.D
Trade Name	Atozet	Supervisor	
Generic Name	Ezetimibe/Atorvastatin combination tablet (10/10, 10/20, 10/40, 10/80)	Date Assigned	May 11, 2011
Indication	Primary hypercholesterolemia and homozygous familial hypercholesterolemia	Date of Review	October 12, 2011
Formulation	Tablet		
Route of Administration	Oral		

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Submission Date	CDER Stamp Date	Date of Informal/ Formal Consult	Internal Meeting
April 28, 2011	April 29, 2011	NA	NA
Type of Submission	Original NDA 505 b(2)		

REVIEW SUMMARY:

The submission is a 505(b)(2) application with the Pfizer “atorvastatin calcium” as the RLD. The ezetimibe/atorvastatin combination product contains ezetimibe, a selective inhibitor of intestinal cholesterol and related phytosterol absorption, and atorvastatin, a 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor. The primary strategy of the Ezetimibe/Atorvastatin FDC Tablet product development program was to provide a combination tablet demonstrating bioequivalence to FDA-approved ezetimibe and atorvastatin calcium monotherapy. The drug product is supplied as a film-coated, (b) (4) tablet. The four strengths developed were 10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg and 10 mg/80 mg (ezetimibe/ atorvastatin).

BIOPHARMACEUTICS:

From the Biopharmaceutics perspective, the following proposed in-vitro dissolution test for Ezetimibe/Atorvastatin FDC Tablets (10 mg/10 mg, 10 mg/20 mg and 10 mg/80 mg) is deemed acceptable.

From the Biopharmaceutics perspective, a single combined method to assay the dissolution of both ezetimibe and atorvastatin calcium has been developed. The following in-vitro dissolution method proposed in the submission is deemed acceptable.

- Apparatus: USP apparatus 2 (paddles)
- Paddle Speed: 75 rpm
- Dissolution medium: 900 mL of Phosphate Buffer, pH 6.8 with 0.2% w/v Tween 80
- Sinker: 7-coil helical sinker (for 10 mg/ 20 mg tablets only)
- Analysis: HPLC method.

The Applicant proposed a dissolution acceptance criterion of $Q = (b) (4)$ at 30 minutes for each component of their product and based upon the data provided in the application, this value was deemed adequate. Dissolution method development was provided and reviewed. The method was shown to be discriminating between tablets (b) (4) and inclusion/exclusion of a sinker for 10/20 mg strength of the drug product.

RECOMMENDATION:

From a Biopharmaceutics perspective, NDA 200-153 is recommended for approval.

The dissolution method is deemed adequate to support the dissolution of the immediate-release Ezetimibe/Atorvastatin FDC Tablets (10 mg/10 mg, 10 mg/20 mg and 10 mg/80 mg). The selected method uses USP apparatus 2 (paddles) at a paddle speed at 75 rpm in 900 mL of Phosphate Buffer, pH 6.8 with 0.2% w/v Tween 80. The final dissolution acceptance criterion for each drug is $Q = \text{(b) (4)}$ at 30 minutes.

Deepika Arora Lakhani, Ph.D.

Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Angelica Dorantes, Ph.D.

Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

cc: List electronically filed in DARRTS

1.0 INTRODUCTION

The primary strategy of the Ezetimibe/Atorvastatin FDC Tablet product development program was to provide a physically and chemically stable formulation with the intended biopharmaceutical properties; a combination tablet demonstrating bioequivalence to FDA-approved ezetimibe and atorvastatin calcium monotherapy tablets. The four strengths developed were 10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg and 10 mg/80 mg (ezetimibe/ atorvastatin). The submission is a 505(b)(2) application with the Pfizer “atorvastatin calcium” as the RLD. The ezetimibe/atorvastatin combination product contains ezetimibe, a selective inhibitor of intestinal cholesterol and related phytosterol absorption, and atorvastatin, a 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor. The proposed market composition of the Ezetimibe/Atorvastatin FDC Tablet is:

Components	Compendial Testing	Function	Unit Strength (Ezetimibe/Atorvastatin)			
			10/10 mg/mg	10/20 mg/mg	10/40 mg/mg	10/80 mg/mg
(b) (4)						
Ezetimibe (SCH58235), (b) (4)	---	Active	mg/tablet 10.00			
(b) (4)						
Atorvastatin Calcium [§] (amorphous) (equivalent free acid) (b) (4)	---	Active	10.34 (10.00)	20.68 (20.00)	41.36 (40.00)	82.73 (80.00)
(b) (4)						
Film-Coating: (b) (4)						
(b) (4)						
Total Coated Tablet Wt.:			624.0 mg	364.1 mg	519.7 mg	830.3 mg (b) (4)
(b) (4)						

Relevant communication regarding Biopharmaceutics issues are summarized below:

- IR dated 29-JUN-2011 (NDA Review): During review, the following four comments were forwarded to the applicant:
 1. Confirm the dissolution medium composition that is proposed to be used for dissolution testing.
 2. Submit the pH solubility profile for the two drug substances.
 3. To enable comparison, resubmit the dissolution method development results (effect of paddle rotation speed, bath temperature, pH of medium, buffer concentration of medium, surfactant concentration of medium etc.) as graphical representation between the % dissolved and sampling time.
 4. Submit dissolution data for the 10/20 tablet for atorvastatin after the use of a sinker.
 5. State where in the application the discriminating capabilities of the proposed dissolution method have been addressed.

Response was obtained in the 22-JULY-2011 Quality amendment and upon review, was deemed to be acceptable. Details are provided in the review.

- IR dated 4-OCT-2011 (NDA Review): During review, the following four comments were forwarded to the applicant:
 1. As per the data submitted in the NDA, a surfactant is not needed for the dissolution of atorvastatin calcium. Please justify the use of 0.2% tween in the dissolution method for atorvastatin calcium.
 2. We acknowledge your response to our previous IR (dated 6-July-2011) regarding the discriminating capabilities of the proposed dissolution method. You provided dissolution data generated from tablets manufactured (b) (4) only for the atorvastatin calcium component of your proposed product. Please provide information regarding ezetimibe for the same parameter or justify the lack of the same.
 3. We consider that the provided information demonstrating the discriminating capability of the proposed dissolution method is very limited. Therefore, explain if you have performed any further investigations (for both atorvastatin calcium and ezetimibe components) demonstrating that your proposed dissolution method is discriminating.

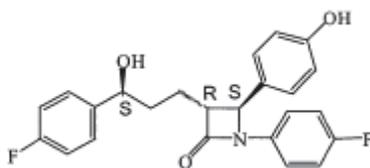
Response was obtained in the 11-OCT-2011 Quality amendment and upon review, was deemed to be acceptable. Details are provided in the review.

2.0 BIOPHARMACEUTICS QUALITY ASSESSMENT

2.1 GENERAL PROPERTIES

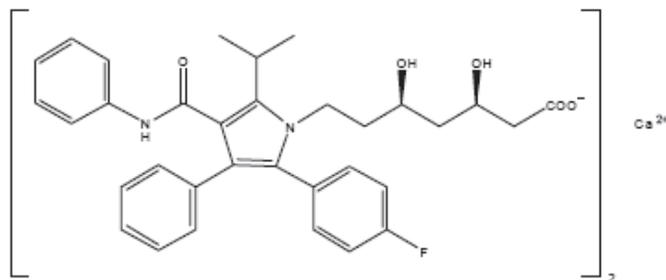
2.1.1 Structure

INN: Ezetimibe



Molecular Formula: C₂₄H₂₁F₂NO₃
Molecular Weight: 409.4 g/mole

INN: Atorvastatin



Molecular Formula: (C₃₃H₃₄FN₂O₅)₂Ca
Molecular Weight: 1155.36 g/mole

Reviewer's Comments: Ezetimibe is a white, crystalline powder that is freely to very soluble in ethanol, methanol and acetone and practically insoluble in water. Atorvastatin calcium is a white to off-white amorphous powder that is very slightly soluble in water, practically insoluble in acetonitrile and freely soluble in methanol.

2.1.2 Solubility and Other Characteristics

The Applicant has cross-referenced sponsor's approved NDA 21-445 for ezetimibe and DMF 18468 for atorvastatin.

Reviewer's Comments: The following IR was communicated to the Applicant.

IR dated 29-JUNE-2011 (NDA Review):

IR Comment

Submit the pH solubility profile for the two drug substances.

Applicant's Response:

Ezetimibe: Both the neutral and acidic conditions yielded solubility results approximately ten times below the USP limit of insoluble defined as <0.10 mg/mL (solubility results ~0.01 mg/mL). In addition, there is no pH effect on the solubility of ezetimibe since it does not contain ionizable moieties.

Atorvastatin:

pH	Solution Preparation	Solubility (mg/mL)
3.0	50.0 mL of 0.2 M Potassium biphthalate solution and 22.3 mL of 0.2 M HCl diluted to 200 mL with water	<0.10
5.0	50.0 mL of 0.2 M Potassium biphthalate solution and 22.6 mL of 0.2 M NaOH diluted to 200 mL with water	<0.10
7.0	50.0 mL of 0.2 M Potassium dihydrogen phosphate solution and 29.1 mL of 0.2 M NaOH diluted to 200 mL with water	0.10
8.0	50.0 mL of 0.2 M Boric acid solution and 50 mL of 0.2 M KCl solution and 3.9 mL of 0.2 M NaOH diluted to 200 mL with water	0.10

Evaluation: Adequate. Both compounds are insoluble to slightly soluble in water. Further references to NDA 21-445 for ezetimibe and DMF 18468 for atorvastatin are provided.

2.2 DISSOLUTION METHOD DEVELOPMENT

2.2.1 Drug Product Composition

ATOZET™ is formulated as a fixed dose combination, immediate-release, film-coated (b)(4) tablet for oral administration containing two drug substances, ezetimibe and atorvastatin calcium (amorphous). Four dosage strengths containing a fixed dose of ezetimibe and a variable dose of atorvastatin have been developed. Tablets contain 10 mg ezetimibe and 10, 20, 40 or 80 mg of atorvastatin (calculated as the free acid) and are represented as follows:

Ezetimibe/Atorvastatin 10 mg/10 mg Ezetimibe/Atorvastatin 10 mg/20 mg
 Ezetimibe/Atorvastatin 10 mg/40 mg Ezetimibe/Atorvastatin 10 mg/80 mg.

Composition of ATOZET Tablets (all strengths):

Components	Compendial Testing	Function	Unit Strength ^a (Ezetimibe/Atorvastatin)			
			10/10 mg/mg	10/20 mg/mg	10/40 mg/mg	10/80 mg/mg
(b)(4)						
Ezetimibe (SCH58235) (b)(4)	---	Active	mg/tablet 10.00			
Atorvastatin Calcium [§] (amorphous) (equivalent free acid) (b)(4)	---	Active	10.34 (10.00)	20.68 (20.00)	41.36 (40.00)	82.73 (80.00)
Film-Coating: (b)(4)						
Total Coated Tablet Wt.:			624.0 mg	364.1 mg	519.7 mg	830.3 mg (b)(4)

2.2.2 Dissolution Method Development

A single combined method to assay the dissolution of both ezetimibe and atorvastatin calcium was developed:

Apparatus: USP Apparatus II (paddles)

Speed: 75 rpm

Medium: phosphate buffer (20mM NaH₂PO₄, pH 6.8) with 0.2% w/v Tween 80

Medium Volume: 900 mL

Medium Temperature: 37 ± 0.5°C

Sinker: 7-coil helical sinker (for 10 mg/ 20 mg tablets only)

Sampling Volume: Approximately 1.3 - 6 mL

Sampling Time: 30 minutes

Analysis: HPLC method

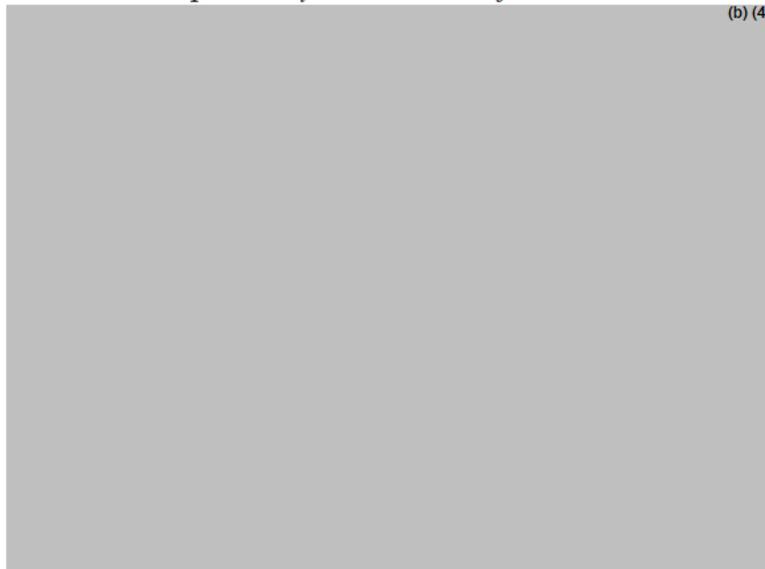
Dissolution Media: Ezetimibe drug substance is virtually insoluble across the physiological pH range in aqueous media while Atorvastatin has adequate aqueous solubility from pH 1.2 to pH 6.8; however, the stability of atorvastatin decreases significantly upon lowering the pH. Based upon the testing in various media, dissolution media of 20 mM NaH₂PO₄ (pH 6.8) was selected. The pH choice of 6.8 is also consistent with what is used to monitor atorvastatin calcium mono-therapy tablets as per the FDA-recommended dissolution method, as per the Office of Generic Drugs., Division of Bioequivalence.

IR dated 04-OCT-2011 (NDA Review)

IR Comment

As per the data submitted in the NDA, a surfactant is not needed for the dissolution of atorvastatin calcium. Please justify the use of 0.2% tween in the dissolution method for atorvastatin calcium.

Applicant's Response: *The Applicant agreed that a surfactant is not needed for atorvastatin. However, data provided demonstrates that the rate of dissolution of atorvastatin calcium is not impacted by the addition of 0.2% tween:*



Because the addition of 0.2% tween shows no impact on the rate of dissolution of atorvastatin calcium and is needed for dissolution of the ezetimibe component of the fixed dose combination tablet, a single combined method was developed to assay the dissolution of both ezetimibe and atorvastatin calcium.

Evaluation: Adequate. It must be noted that though the surfactant is not needed for Atorvastatin, the Applicant uses the same to enable a single dissolution method to analyze both the APIs. The reviewer has deemed this Acceptable as the dissolution profile of Atorvastatin generated with or without the 0.2% surfactant is super imposable.

Equipment/Apparatus and Agitation Speed: USP Apparatus 2 was selected and tested (b) (4) 75 rpm Paddle Speed and Varying Surfactant Concentration.

Figure 1: Ezetimibe Dissolution Profile 10/80 mg tablets (b) (4) and 75 rpm Paddle Speed and Varying Surfactant Concentration



Figure 2: Atorvastatin Dissolution Profile 10/80 mg tablets (b) (4) and 75 rpm Paddle Speed and Varying Surfactant Concentration



Robustness during Routine Use:

- No significant effect on the dissolution profiles were seen while changing the following slightly (within working conditions):
 - Bath Temperature
 - pH of medium
 - Buffer Concentration of medium,
 - Surfactant Concentration of medium
 - Bath manufacturer

Figure 3: Ezetimibe Dissolution Profiles Varying Paddle Rotation Speed, Bath Temperature, pH of medium, Buffer Concentration of medium, Surfactant Concentration of medium, and bath manufacturer



Figure 4: Atorvastatin Dissolution Profiles Varying Paddle Rotation Speed, Bath Temperature, pH of medium, Buffer Concentration of medium, Surfactant Concentration of medium, and bath manufacturer



Reviewer's Comment: The selection of 75 rpm with 0.2% tween is based on ezetimibe dissolution as dissolution of atorvastatin is not affected by the % tween in the medium. The experiments conducted using USP apparatus II at 75 rpm demonstrated that atorvastatin calcium was fully released and there was no visual observation of coning occurring in the dissolution vessel (b) (4) The robustness of method is

demonstrated by varying bath temperature, pH of medium, buffer concentration of medium, surfactant concentration of medium and bath manufacturer. The Applicant was sent the following IR:

IR dated 29-JUNE-2011 (NDA Review)

IR Comment

To enable comparison, resubmit the dissolution method development results (effect of paddle rotation speed, bath temperature, pH of medium, buffer concentration of medium, surfactant concentration of medium etc.) as graphical representation between the % dissolved and sampling time.

Applicant's Response: Graphical representation of requested data are provided.

Evaluation: Adequate. The figures provided are Figs 1-4, as seen above.

Use of a Sinkers: A minor change in shape was implemented for the 10 mg/ 20 mg potency to allow better individual layer weight control. (b) (4)

Dissolutions conducted on the first batches manufactured using the new image showed a significant depression in the release of ezetimibe, while showing a similar release profile of atorvastatin compared to previously manufactured tablets, as shown in Figs 5 and 6 below.

Figure 5: Release of Ezetimibe from 10 mg/ 20 mg Ezetimibe/Atorvastatin FDC Tablet Formulations without the use of sinkers

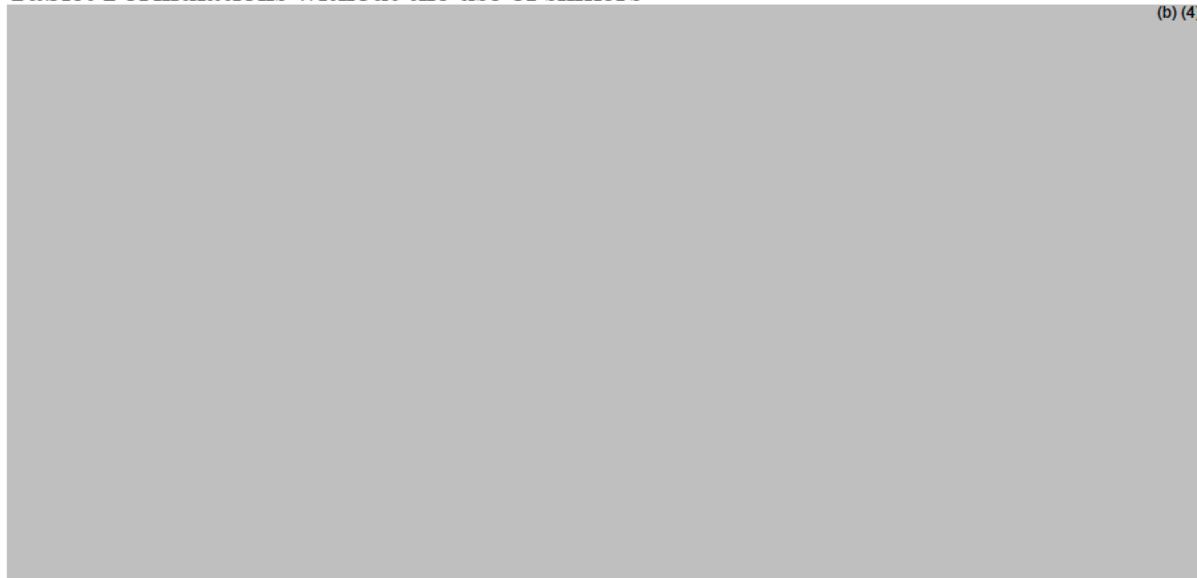


Figure 6: Release of Ezetimibe from 10 mg/ 20 mg Ezetimibe/Atorvastatin FDC Tablet Formulations with the use of a 7 coil helical sinker



Figure 7: Atorvastatin Dissolution Profile from 10 mg/20 mg Ezetimibe/Atorvastatin FDC Tablet Formulations with use of a 7 coil helical sinker



Figure 8: Atorvastatin Dissolution Profile from 10 mg/20 mg Ezetimibe/Atorvastatin FDC Tablet Formulations without use of a Sinkers



Reviewer's Comment: The use of sinkers does not seem to impact the dissolution of atorvastatin and only aids the dissolution of ezetimibe, by slightly decreasing variability. Statistical analysis is provided supporting that Q value is not impacted, with or without the inclusion of sinkers, for ezetimibe and atorvastatin. The Applicant was sent the following IR:

IR dated 29-JUNE-2011 (NDA Review)

IR Comment

Submit dissolution data for the 10/20 tablet for atorvastatin after the use of a sinker.

Applicant's Response: Figure 7 (shown above) was submitted.

Evaluation: Adequate.

Discriminating Power:

- Tablets [REDACTED] (b) (4) (Atorvastatin)

Figure 9: Atorvastatin Dissolution Profile from 10 mg/80 mg Ezetimibe/Atorvastatin FDC Tablet [REDACTED] (b) (4)



- Inclusion of sinker (Ezetimibe)

Figs 5 and 6 as shown above are referenced. The Applicant states that the method is discriminating for ezetimibe for inclusion and exclusion of a sinker for the 10/20 mg tablet.

Reviewer's Comment: *The Applicant was sent the following IR:*

IR dated 29-JUNE-2011 (NDA Review)

IR Comment

State where in the application are the discriminating capabilities of the proposed dissolution method have been addressed.

Applicant's Response

Evaluation: *Adequate.*

IR dated 4-OCT-2011 (NDA Review)

IR Comment

We acknowledge your response to our previous IR (dated 6-July-2011) regarding the discriminating capabilities of the proposed dissolution method. You provided dissolution data generated from tablets manufactured (b) (4), only for the atorvastatin calcium component of your proposed product. Please provide information regarding ezetimibe for the same parameter or justify the lack of the same.

Applicant's Response: *The ezetimibe dissolution data (b) (4) show similar release profiles. The rate of release of ezetimibe in the fixed dose combination product is consistent with the rate of ezetimibe from ZETIA™ and VYTORIN™.*

Evaluation: *Adequate.*

IR Comment

We consider that the provided information demonstrating the discriminating capability of the proposed dissolution method is very limited. Therefore, explain if you have performed any further investigations (for both atorvastatin calcium and ezetimibe components) demonstrating that the proposed dissolution method is discriminating.

Applicant's Response: *Information not provided in the 6-JULY-2011 response regarding the discriminating capability of the method:*

Dissolution rate difference for uncoated (core tablets) vs. film coated tablets: *The data show an average (b) (4) in dissolution at the 10 minute timepoint for the film coated tablet versus the uncoated (core tablet):*

Atorvastatin:

Lot Number	Strength	Uncoated (Core) Tablets 10 min % Atorvastatin	Film Coated Tablets 10 min % Atorvastatin	Difference
WL00031690	10 mg/10 mg	(b) (4)		
WL00031197	10 mg/20 mg			
WL00034555	10 mg/40 mg			
WL00031198	10 mg/80 mg			

NDA 200-153
Atozet (FDC) Tablets, MSP (Merck)

Ezetimibe:

Lot Number	Strength	Uncoated (Core) Tablets 10 min % Ezetimibe	Film Coated Tablets 10 min % Ezetimibe	Difference
WL00031690	10 mg/10 mg	(b) (4)		
WL00031197	10 mg/20 mg			
WL00034555	10 mg/40 mg			
WL00031198	10 mg/80 mg			

Dissolution rate difference due to variation in the amount of disintegrant level in atorvastatin: The data supported that the dissolution method could detect these differences:

(b) (4)

Dissolution rate difference due to an alternate film coat vs. uncoated (core tablets) tablets: The data showed that alternate coat (composed of (b) (4)) slowed the dissolution at various time points for both APIs:

Atorvastatin:

(b) (4)

Ezetimibe:



Evaluation: Adequate. The IR response satisfactorily addressed the concerns regarding the lack of discriminatory capability of the dissolution method. Though, the information provided is limited, it still supports the discriminatory capability of the method.

2.2.2 Dissolution Method Validation

Validation of the RP-HPLC method used for the determination of dissolved ezetimibe and atorvastatin is performed to demonstrate:

- Specificity/Selectivity
 - Linearity and Range
 - Accuracy
 - Precision
 - Intermediate Precision
 - Reproducibility
- Robustness

The analytical procedures used for detection are:

Content Determination by RP-HPLC:

Column: [redacted] (b) (4)
[redacted]
Column Temperature: [redacted] (b) (4)
Mobile Phase: [redacted] (b) (4)
Flow Rate: [redacted] (b) (4)
Detection: [redacted] (b) (4)
Injection Volume: [redacted] (b) (4)
Run Time: [redacted] (b) (4)

Reviewer's Comments: The methods are validated with respect to specificity, linearity, accuracy, precision, range and robustness. Analytical data are provided under Section 3.2.P.5.3. The drug substances atorvastatin and ezetimibe are analyzed in one combined analytical method such that atorvastatin appears on the chromatogram before (retention time around [redacted] (b) (4)) and ezetimibe appears later (retention time around [redacted] (b) (4)). The results show good agreement and the method of analyses does not impact the dissolution

data collected. Further data are provided to support the suitability of filter units used and supports that the filters do not adsorb the drug substance. The solution stability is assessed and the standard and sample solutions were found to be stable for at least (b) (4) respectively, when stored at ambient laboratory conditions.

2.2 DISSOLUTION ACCEPTANCE CRITERIA AND ITS JUSTIFICATION

2.3.1 Establishing Dissolution Acceptance Criteria



Figure 6: Dissolution Profiles of all Clinical and Primary Stability Batches of Ezetimibe/Atorvastatin Film-Coated Tablets (10/10, 10/20, 10/80 mg)

Based upon the above data, the applicant proposed a $Q = (b) (4)$ at 30 mins.

Reviewer's Comments: The dissolution data support the proposed dissolution acceptance criteria for each component of this immediate release tablet for all strengths.

2.3.2 Dissolution Data Over Stability

Dissolution data were generated with the current method using the proposed dissolution method generated on the 9 formal stability batches of Ezetimibe/Atorvastatin FDC Tablets (10 mg/10 mg, 10 mg/20 mg and 10 mg/80 mg) stored at 25°C/60% RH and 40°C/75% RH. The data were obtained after 10, 15, 20, 30, 45 and 60 minutes in this medium at the 3, 6, 9, 12, 18, and 24 month stability time points, and also on the initial time points. The data were statistically evaluated and the proposed dissolution acceptance criterion of (b) (4) ($Q = (b) (4)$) dissolved in 30 minutes is appropriate for both ezetimibe and atorvastatin. The dissolution rate showed no change during storage.

Reviewer's Comment: The 24 months of stability data clinical and primary stability batches stored at 25°C/60% R.H., and for 6 months at 40°C/75% R.H support that the dissolution rate showed no change on storage.

3.0 REGULATORY ISSUES

All the issues with respect to setting the dissolution acceptance criteria for each component of the Ezetimibe/Atorvastatin FDC Tablets (10 mg/10 mg, 10 mg/20 mg and 10 mg/80 mg) have been resolved. A validated dissolution method using USP apparatus 2 (paddles) with Paddle Speed: 75 rpm and Dissolution medium: 900 mL of phosphate buffer (20mM NaH₂PO₄) with 0.2% w/v Tween 80 at pH 6.8 has been developed. The method is deemed acceptable. A dissolution acceptance criterion of Q= (b) (4) at 30 mins has been established for Ezetimibe as well as for Atorvastatin (each strength of the fixed combination drug product).

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/s/

DEEPIKA LAKHANI

10/28/2011

NDA is recommended for Approval, from a Biopharmaceutics perspective.

ANGELICA DORANTES

10/28/2011

BIOPHARMACEUTICS FILING REVIEW
Office of New Drugs Quality Assessment

Application No.:	NDA 200153	Reviewer: Deepika Arora Lakhani, PhD
Submission Date:	April 28, 2011	
Division:	Division of Medical Imaging and Hematology Products	Team Lead: Angelica Dorantes, PhD
Sponsor:	MSP (Merck)	Supervisor: Patrick Marroum, PhD
Trade Name:	Atozet FDC/ (b) (4)	Date Assigned: May 11, 2011
Generic Name:	Ezetimibe/Atorvastatin combination tablet (10/10, 10/20, 10/40, 10/80)	Date of Review: June 24, 2011
Indication:	Primary hypercholesterolemia and homozygous familial hypercholesterolemia	Type of Submission: New Drug Application 505b(2)
Formulation/ strengths	Tablet	
Route of Administration	Oral	

SUBMISSION:

The submission is a 505(b)(2) application with the Pfizer “atorvastatin calcium” as the RLD. The ezetimibe/atorvastatin combination product contains ezetimibe, a selective inhibitor of intestinal cholesterol and related phytosterol absorption, and atorvastatin, a 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor. The primary strategy of the Ezetimibe/Atorvastatin FDC Tablet product development program was to provide a combination tablet demonstrating bioequivalence to FDA-approved ezetimibe and atorvastatin calcium monotherapy. The drug product is supplied as a film-coated, (b) (4) tablet. The four strengths developed were 10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg and 10 mg/80 mg (ezetimibe/ atorvastatin).

BIOPHARMACEUTICS:

A single combined method to assay the dissolution of both ezetimibe and atorvastatin calcium has been developed. The dissolution method proposed in the submission is:

Apparatus: No. 2 (paddles)

Rotation Speed: 75 rpm

Dissolution Medium: Phosphate Buffer, pH 6.8 with 0.2% w/v Tween 80 (*the composition of the dissolution medium is not clear with respect to use of surfactant (tween or (b) (4) and will be clarified as a comment to be communicated to the applicant)*)

Medium Volume: 900 mL

Medium Temperature: 37 ± 0.5°C

Sinker: 7-coil helical sinker (for 10 mg/ 20 mg tablets only)

Sampling Volume: Approximately 1.3 - 6 mL

Sampling Time: 30 minutes

The effect of paddle rotation speed, bath temperature, pH of medium, buffer concentration of medium, surfactant concentration of medium, and bath manufacturer was studied as part of the validation of the dissolution method.

The applicant has proposed the same specification for both ezetimide and atorvastatin at release and over stability. The proposed specification is Q=(b) (4) at 30 mins. The batch analyses and stability data supports the proposal.

The applicant has proposed the use of sinkers for the 10/20 mg tablet. The supportive data are provided for dissolution profile with/without sinker for ezetimide and without sinker for atorvastatin for the 10/20 mg tablet. The acceptability of this will be a subject of review of the data.

Dissolution data comparison are provided to bridge the commercial site of manufacturing for site stability and the material manufactured for Biobatch/FSS based on f2 value calculation. The acceptability of this will be a review issue.

The application contains most of the information needed to justify the selection of the dissolution conditions; however, the graphical representation of the dissolution profiles is missing to enable a comparison between the tested conditions and will be requested as a part of the comments to be communicated to the applicant.

RECOMMENDATION:

The ONDQA/Biopharmaceutics team upon review of NDA 200153 for filing purposes, found the application to be fileable, from Biopharmaceutics perspective. The below clarification comments need to be communicated to the applicant:

- Confirm the dissolution medium composition that is proposed to be used for dissolution testing.
- Submit the pH solubility profile for the two drug substances.
- Please re-submit the dissolution method development results (effect of paddle rotation speed, bath temperature, pH of medium, buffer concentration of medium, surfactant concentration of medium etc.) as graphical representation between the % dissolved and sampling time to enable comparison.
- Submit dissolution data for the 10/20 mg tablet for atorvastatin after the use of a sinker.
- Refer the reviewer to the relevant part of the application; where in the discriminating capabilities of the proposed dissolution method have been addressed.

Deepika Arora Lakhani, Ph.D.
Biopharmaceutics Reviewer
Office of New Drugs Quality Assessment

Angelica Dorantes, Ph.D.
Biopharmaceutics Team Leader or Supervisor
Office of New Drugs Quality Assessment

cc: P. Marroum

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/s/

DEEPIKA LAKHANI

06/29/2011

NDA is fileable from Biopharmaceutics perspective.

ANGELICA DORANTES

06/29/2011

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING CHECKLIST FOR NDA 200-153

NDA Number: 200-153

Applicant: Merck Sharp & Dohme Stamp Date: April 29, 2011 Corp.

Drug Name: ezetimibe + atorvastatin calcium

NDA Type: 505 (b)(2) Standard

On initial overview of the NDA application for RTF:

	Content Parameter	Yes	No	Comment
Criteria for Refusal to File (RTF)				
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	X		
2	Has the applicant provided metabolism and drug-drug interaction information?			Not applicable, since the 2 drugs are approved drugs
Criteria for Assessing Quality of an NDA				
Data				
3	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g. CDISC)?			Not applicable
4	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			Not applicable
Studies and Analyses				
5	Has the applicant made an appropriate attempt to determine the reasonable dose individualization strategy for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			Not applicable
6	Did the applicant follow the scientific advice provided regarding matters related to dose selection?			Not applicable
7	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted in a format as described in the Exposure-Response guidance?	Yes		Sponsor did modeling and simulation on the dose and LDL lowering of atorvastatin.
8	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			Not applicable
9	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			Not applicable
10	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			Not applicable
11	Is the appropriate pharmacokinetic information submitted?	Yes		
12	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	Yes		
General				
13	On its face, is the clinical pharmacology and biopharmaceutical section of the NDA organized in a	Yes		

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING CHECKLIST FOR NDA 200-153**

	manner to allow substantive review to begin?			
14	Is the clinical pharmacology and biopharmaceutical section of the NDA indexed and paginated in a manner to allow substantive review to begin?	Yes		
15	On its face, is the clinical pharmacology and biopharmaceutical section of the NDA legible so that a substantive review can begin?	Yes		
16	Are the clinical pharmacology and biopharmaceutical studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	Yes		
17	Was the translation from another language important or needed for publication?			Not applicable

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

___ Yes ___

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

S. W. Johnny Lau, R.Ph., Ph.D.

Reviewing Pharmacologist

Date

Jayabharathi Vaidyanathan, Ph.D.

Acting Team Leader

Date

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING CHECKLIST FOR NDA 200-153**

Office of Clinical Pharmacology				
<i>New Drug Application Filing and Review Form</i>				
General Information About the Submission				
	Information		Information	
NDA	200-153	Brand Name	ATOZET™	
OCP Division	2	Generic Name	Ezetimibe + atorvastatin calcium	
Medical Division	DMEP, HFD-510	Drug Class	Cholesterol Absorption Inhibitor + HMG-CoA Reductase Inhibitor	
OCP Reviewer	S.W. Johnny Lau	Indication(s)	Treat hypercholesterolemia	
OCP Team Leader (Acting)	Jayabharathi Vaidyanathan	Dosage Form	Immediate release tablet	
Date of Submission	29-APRIL-2011	Dosing Regimen	10/10 mg/day to 10/80 mg/day	
Estimated Due Date of OCP Review	6-JAN-2012	Route of Administration	Oral	
PDUFA Due Date	29-FEB-2012	Sponsor	Merck Sharp & Dohme Corp.	
Division Due Date	20-JAN-2012	Priority Classification	Standard	
Clin. Pharm. and Biopharm. Information				
	“X” if included at filing	Number of studies submitted	Number of studies reviewed	Comments (Study number)
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X	1		annotated
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
In vivo mass balance:				
In vitro isozyme characterization:				
In vitro metabolite Identity				
In vitro metabolism inhibition:				
In vitro mechanism of uptake in human liver				
In vitro plasma protein binding:				
Blood/plasma ratio:				
Pharmacokinetics (e.g., Phase I) -				
Dose proportionality, healthy volunteers – fasting & non-fasting single and multiple doses:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
pediatrics:				
gender & geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 1:				
Phase 3:				
PK/PD:				
Phase 2, dose ranging studies:				
Phase 3 clinical STUDIES:	X	12		Studies P0692, P0693, P1030, P2154, P2173, P2173R, P040, P079, P090, P112, P1417, and P1418
Population Analyses -				
Meta-analysis:				
NONMEM:				

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING CHECKLIST FOR NDA 200-153

II. Biopharmaceutics				
Absolute bioavailability:				
Bioequivalence studies – traditional design	X	2		Studies P145 and P183 (definitive)
Relative bioavailability	X	1		Study P9396-001 (pilot);
alternate formulation as reference:				
Food-drug interaction studies:	X	1		Study P146
Absorption site				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Phenotype studies:				
Chronopharmacodynamics				
Pediatric development plan				
Literature References				
QT prolongation assessment				
Total Number of Studies		16		
Fileability and QBR comments				
	“X” if yes	Comments		
Application fileable?	Yes			
Comments to be sent to firm? (if this NDA were fileable)		Please provide the electronic data files or point to the location of such files in NDA 200-153 for the modelina and simulation of: <ul style="list-style-type: none"> • (b) (4) • 		
QBR questions (key issues to be considered; if this NDA were fileable)		In Study P145, the 90% CI of the ratio of atorvastatin C_{max} is not within the 0.8 to 1.25 bioequivalence goalpost for the 10/20 fixed dose combination tablet to coadministration of individual tablets. In Study P183, the 90% CI of the ratio of atorvastatin C_{max} is not within the 0.8 to 1.25 bioequivalence goalpost for the 10/40 fixed dose combination tablet to coadministration of individual tablets. Understanding of the exposure and LDL-C lowering relationship of atorvastatin and ezetimibe.		

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING CHECKLIST FOR NDA 200-153

<p>Other comments or information not included above (if this NDA were fileable)</p>	<p>Studies P145 and P183 are the pivotal studies that link the fixed dose combination ezetimibe/atorvastatin tablets to the coadministered ezetimibe and atorvastatin tablets. Thus, a DSI inspection on Studies P145 and P183 (A Study to Evaluate the Definitive Bioequivalence of MK-0653C with Marketed Products) is in order.</p> <p>Study P145's 2 Clinical Sites: #145-0001: Maria J. Gutierrez, M.D. Comprehensive Phase One 3400 Enterprise Way, Miramar, FL 33025</p> <p>#145-0002: Melanie Fein, M.D. Comprehensive Phase One 3745 Broadway Ave, Suite 100, Fort Myers, FL 33901</p> <p>Study P145's Bioanalytical sites: (b) (4)</p> <div style="background-color: #cccccc; height: 100px; width: 100%;"></div> <p>Study P183's Clinical Site: Audrey E. Martinez, M.D. SeaView Research, Inc. 3898 NW 7th St. Miami, FL 33126</p> <p>Study P183's Bioanalytical sites: (b) (4)</p> <div style="background-color: #cccccc; height: 100px; width: 100%;"></div>
<p>Primary reviewer Signature and Date</p>	
<p>Secondary reviewer Signature and Date</p>	

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING CHECKLIST FOR NDA 200-153

Filing Memo

CLINICAL PHARMACOLOGY

NDA: 200-153
Compound: Ezetimibe and atorvastatin calcium (ATOZET™; 10/10, 10/20, 10/40, and 10/80 [mg ezetimibe/mg atorvastatin] fixed dose combination immediate release tablet)
Sponsor: Merck Sharp & Dohme Corp.
Submission Date: April 29, 2011
Relevant IND: 101,953
From: S.W. Johnny Lau, R.Ph., Ph.D.

Background

The sponsor submits a 505 (b)(2) NDA 200-153 to seek marketing approval for the 10/10, 10/20, 10/40, and 10/80 (mg ezetimibe/mg atorvastatin) fixed dose combination (FDC) oral immediate release (both drugs) film-coated (b)(4) tablets as an adjunct to diet so as to reduce total cholesterol, LDL-cholesterol, apolipoprotein B, and triglycerides as well as to increase HDL-cholesterol in adult patients with primary hypercholesterolemia and mixed dyslipidemia.

The Food and Drug Administration approved ezetimibe (NDA 21-445 on October 25, 2002) and atorvastatin calcium (NDA 20-702 on December 17, 1996) for the treatment of hypercholesterolemia. Ezetimibe is available in the US as 10 mg oral immediate release tablet (ZETIA®). Atorvastatin is available in the US as 10, 20, 40, and 80 mg oral immediate release tablets (LIPITOR®). Ezetimibe and simvastatin fixed dose combination oral immediate tablets (10/10, 10/20, 10/40, and 10/80 [mg ezetimibe/mg simvastatin]; VYTORIN®) are also available in the US (NDA 21-687 approved on July 23, 2004).

The goal of the ezetimibe/atorvastatin clinical development program is to demonstrate bioequivalence of the ezetimibe/atorvastatin FDC tablets (10/10, 10/20, 10/40, and 10/80 mg) to the corresponding coadministered ezetimibe + atorvastatin individual tablets to support bridging of the ezetimibe/atorvastatin FDC tablet to the ezetimibe + atorvastatin coadministration clinical efficacy and safety data in the original ezetimibe NDA as well as to additional coadministration studies completed since marketing approval.

The atorvastatin in the FDC is amorphous, whereas the atorvastatin in the reference tablets is crystalline. The ezetimibe (b)(4) is the same among the 4 strengths. (b)(4)

This is a resubmission. The sponsor originally submitted this NDA on September 2, 2009. The Division of Metabolism and Endocrinology Products refused to file the submission mainly due to CMC issues. The sponsor resubmitted this NDA to rectify the refusal to file.

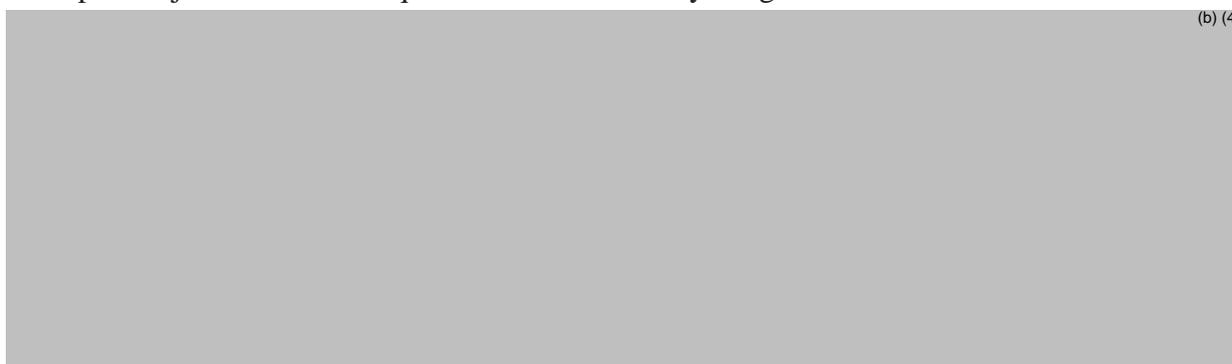
Findings

To support NDA 200-153's Clinical Pharmacology and Biopharmaceutics sections, the sponsor submitted studies' results as indicated in the table above. The findings' highlights follow:

- submitted annotated proposed labeling

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING CHECKLIST FOR NDA 200-153

- submitted bioanalytical and validation reports for Studies P9396-001, P145, P146, and P183 for unconjugated ezetimibe, total (unconjugated + conjugated) ezetimibe, atorvastatin, ortho-hydroxy atorvastatin, and para-hydroxy atorvastatin
- Study P145 is the definitive study intended to show bioequivalence for the following tablets:
 - 10 mg ezetimibe/10 mg atorvastatin FDC vs. 10 mg ZETIA[®] + 10 mg LIPITOR[®]
 - 10 mg ezetimibe/20 mg atorvastatin FDC vs. 10 mg ZETIA[®] + 20 mg LIPITOR[®]
 - 10 mg ezetimibe/80 mg atorvastatin FDC vs. 10 mg ZETIA[®] + 80 mg LIPITOR[®]
- Study P145's treatment design satisfies CFR 320.25 (g)(1).
- For Study P145, both ezetimibe and atorvastatin are bioequivalent between the 10/10 and 10/80 FDC tablets and the corresponding coadministered individual tablets except atorvastatin C_{max} for the 10/20 FDC tablet [(b) (4)] as GMR and 90% CI] (the 90% CI of the ratio of atorvastatin $AUC_{0-\infty}$ for the 10/20 FDC tablet is within the 0.8 -1.25 equivalence goalpost). The sponsor justified this "inequivalence" as clinically insignificant since:



This "inequivalence" will be a review issue.

- Per Dr. Wei Qiu's NDA 21-445 Clinical Pharmacology review on Study P00460 and ZETIA[®] label, daily coadministration of 10 mg ezetimibe and 10 mg atorvastatin for 14 days showed the following changes but are not significant mutual interaction:
 - total ezetimibe C_{max} increases 12% and total ezetimibe AUC decreases 2%
 - unconjugated ezetimibe C_{max} increases 31% and unconjugated ezetimibe AUC increases 21%
 - atorvastatin C_{max} increases 7% and atorvastatin AUC decreases 4%
- Since there is no significant mutual interaction between ezetimibe and atorvastatin (per ZETIA[®] label), Study P145's results can be interpreted as there is a lack of formulation interaction effects for ezetimibe and atorvastatin.
- The sponsor claimed that the ezetimibe/atorvastatin 10/10, 10/20, 10/40, and 10/80 FDC tablets used for the bioequivalence studies are the same as the to-be-marketed FDC formulations (Section 2.2.1 of Pharmaceutical Development, page 4/18). The sponsor also claimed that the manufacturing methodology used for these clinically tested formulations was representative and at least 1/10th the size of the commercial manufacturing process (Section 2.7.1.1.1.3 of Summary of Biopharmaceutical Studies and Associated Analytical Methods, page 12/57). These tablets were manufactured at the West Point, PA R&D site.
- Study P183 is the definitive study intended to show bioequivalence for the following tablets:
 - 10 mg ezetimibe/40 mg atorvastatin FDC vs. 10 mg ZETIA[®] + 40 mg LIPITOR[®]
- Study P183's treatment design satisfies CFR 320.25 (g)(1).
- For Study P183, both ezetimibe and atorvastatin are bioequivalent between the 10/40 FDC tablet and the corresponding coadministered individual tablets except atorvastatin C_{max} (b) (4)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING CHECKLIST FOR NDA 200-153

(b) (4) as GMR and 90% CI] (the 90% CI of the ratio of atorvastatin $AUC_{0-\infty}$ for the 10/40 FDC tablet is within the 0.8 -1.25 equivalence goalpost).

- Study P9396-001 is the pilot biocomparison study between 2 amorphous 40 mg atorvastatin test formulations (A and B) and the reference of marketed 40 mg atorvastatin tablet.
- Study P146 examined the following treatments:
 - 10 mg ezetimibe/80 mg atorvastatin FDC tablet after a high-fat breakfast
 - 10 mg ezetimibe/80 mg atorvastatin FDC tablet under fasting
- Study P146 showed that the GMR of fed:fasted atorvastatin C_{max} was 0.65 and its 90% CI was 0.48 – 0.87. The GMR of fed:fasted atorvastatin $AUC_{0-\infty}$ was 0.89 and its 90% CI was 0.79 – 1.01. The GMR of fed:fasted unconjugated ezetimibe C_{max} was 1.10 and its 90% CI was 0.91 – 1.34. The GMR of fed:fasted total ezetimibe C_{max} was 1.18 and its 90% CI was 1.03 – 1.34. All other parameters were within the bioequivalence goalpost.
- Food decreases atorvastatin C_{max} and $AUC_{0-\infty}$ 25 and 9%, respectively per the LIPITOR[®] label. Food increases unconjugated ezetimibe C_{max} 38% and increases total ezetimibe C_{max} 3% per NDA 21-445 Study P00460. Study P146's results are consistent with the LIPITOR[®] and ZETIA[®] labels.
- The sponsor conducted the short-term factorial study (P0692) and Study 2154 (692's extension as long-term blinded comparator study). The sponsor conducted short-term add-on studies (P2173 and P040). The sponsor conducted short-term add-on titration studies (P079, P090, P112, and P693). The sponsor conducted the short-term study (P1030) and long-term study (P1417) in homozygous familial hypercholesterolemia patients.

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/s/

S. W. JOHNNY W LAU
06/28/2011

JAYABHARATHI VAIDYANATHAN
06/28/2011

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING CHECKLIST FOR NDA 200-153

NDA Number: 200-153

Applicant: Merck & Co. Inc.

**Stamp Date: September 2,
2009**

**Drug Name: ezetimibe +
atorvastatin**

NDA Type: 505 (b)(2) Standard

On **initial** overview of the NDA application for RTF:

	Content Parameter	Yes	No	Comment
Criteria for Refusal to File (RTF)				
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?		No	The sponsor has not provided the multipoint dissolution profiles between the clinical batches and the to-be-marketed products.
2	Has the applicant provided metabolism and drug-drug interaction information?			Not applicable
Criteria for Assessing Quality of an NDA				
Data				
3	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g. CDISC)?			Not applicable
4	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			Not applicable
Studies and Analyses				
5	Has the applicant made an appropriate attempt to determine the reasonable dose individualization strategy for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			Not applicable
6	Did the applicant follow the scientific advice provided regarding matters related to dose selection?			Not applicable
7	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted in a format as described in the Exposure-Response guidance?			Not applicable
8	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			Not applicable
9	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			Not applicable
10	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			Not applicable
11	Is the appropriate pharmacokinetic information submitted?	Yes		
12	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	Yes		

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING CHECKLIST FOR NDA 200-153**

General				
13	On its face, is the clinical pharmacology and biopharmaceutical section of the NDA organized in a manner to allow substantive review to begin?	Yes		
14	Is the clinical pharmacology and biopharmaceutical section of the NDA indexed and paginated in a manner to allow substantive review to begin?	Yes		
15	On its face, is the clinical pharmacology and biopharmaceutical section of the NDA legible so that a substantive review can begin?	Yes		
16	Are the clinical pharmacology and biopharmaceutical studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	Yes		
17	Was the translation from another language important or needed for publication?			Not applicable

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? ___No___

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

The application did not include any information to bridge the performance of the clinically tested batches to the commercial products (such as multipoint *in vitro* dissolution profiles).

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

S. W. Johnny Lau, R.Ph., Ph.D.

Reviewing Pharmacologist Date

Sally Y. Choe, Ph.D.

Team Leader/Supervisor Date

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING CHECKLIST FOR NDA 200-153**

Office of Clinical Pharmacology <i>New Drug Application Filing and Review Form</i>				
General Information About the Submission				
	Information	Brand Name	Information	
NDA	200-153		(b) (4)®	
OCP Division	2	Generic Name	Ezetimibe + atorvastatin calcium	
Medical Division	DMEP, HFD-510	Drug Class	Cholesterol Absorption Inhibitor + HMG-CoA Reductase Inhibitor	
OCP Reviewer	S.W. Johnny Lau	Indication(s)	Treat hypercholesterolemia	
OCP Team Leader	Sally Y. Choe	Dosage Form	Immediate release tablet	
Date of Submission	2-SEP-2009	Dosing Regimen	10/10 mg/day to 10/80 mg/day	
Estimated Due Date of OCP Review		Route of Administration	Oral	
PDUFA Due Date		Sponsor	Merck & Co., Inc.	
Division Due Date		Priority Classification	Standard	
Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Comments (Study number)
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X	1		annotated
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
In vivo mass balance:				
In vitro isozyme characterization:				
In vitro metabolite Identity				
In vitro metabolism inhibition:				
In vitro mechanism of uptake in human liver				
In vitro plasma protein binding:				
Blood/plasma ratio:				
Pharmacokinetics (e.g., Phase I) -				
Dose proportionality, healthy volunteers – fasting & non-fasting single and multiple doses:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
pediatrics:				
gender & geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 1:				
Phase 3:				
PK/PD:				
Phase 2, dose ranging studies:				
Phase 3 clinical STUDIES:	X	13		Studies P0692, P0693, P1030, P2154, P2173/2246, P2173/2246a P040, P051, P079, P090, P112, P1417, and P1418
Population Analyses -				
Meta-analysis:				
NONMEM:				

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING CHECKLIST FOR NDA 200-153

II. Biopharmaceutics				
Absolute bioavailability:				
Bioequivalence studies – traditional design	X	1		Study P145 (definitive)
Relative bioavailability	X	1		Study P9396-001 (pilot);
alternate formulation as reference:				
Food-drug interaction studies:	X	1		Study P146
Absorption site				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Phenotype studies:				
Chronopharmacodynamics				
Pediatric development plan				
Literature References				
QT prolongation assessment				
Total Number of Studies		16		
Filability and QBR comments				
	“X” if yes	Comments		
Application fileable?	No	See page 2 above.		
Comments to be sent to firm? (if this NDA were fileable)	X	You should electronically submit plasma unconjugated ezetimibe, total ezetimibe, atorvastatin, o-hydroxy atorvastatin, and p-hydroxy atorvastatin concentrations data as well as their pharmacokinetic parameters for Study P145.		
QBR questions (key issues to be considered; if this NDA were fileable)		In Study P145, the 90% CI of the ratio of atorvastatin C _{max} is not within the 0.8 to 1.25 bioequivalence goalpost for the 10/20 fixed dose combination tablet.		
Other comments or information not included above (if this NDA were fileable)		<p>Study P145 is the pivotal study that links the fixed dose combination ezetimibe/atorvastatin tablets to the coadministered ezetimibe and atorvastatin tablets. Thus, a DSI inspection on Study P145 (A Study to Evaluate the Definitive Bioequivalence of MK-0653C with Marketed Products) is in order.</p> <p>Clinical Sites: Maria J. Gutierrez, M.D. Comprehensive Phase One 3400 Enterprise Way, Miramar, FL 33025</p> <p>Melanie Fein, M.D. Comprehensive Phase One 3745 Broadway Ave, Suite 100, Fort Myers, FL 33901</p> <p>Bioanalytical sites: <div style="background-color: #cccccc; width: 100%; height: 40px; margin-top: 5px;"></div> (b) (4)</p>		
Primary reviewer Signature and Date				
Secondary reviewer Signature and Date				

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING CHECKLIST FOR NDA 200-153**

Filing Memo

CLINICAL PHARMACOLOGY

NDA: 200-153
Compound: Ezetimibe and atorvastatin calcium ((b)(4)®; 10/10, 10/20, 10/40, and 10/80 [mg ezetimibe/mg atorvastatin] fixed dose combination immediate release tablet)
Sponsor: Merck & Co., Inc.
Submission Date: September 2, 2009
Relevant IND: 101,953
From: S.W. Johnny Lau, R.Ph., Ph.D.

Background

The sponsor submits a 505 (b)(2) NDA 200-153 to seek marketing approval for the 10/10, 10/20, 10/40, and 10/80 (mg ezetimibe/mg atorvastatin) fixed dose combination (FDC) oral immediate release (both drugs) tablets as an adjunct to diet so as to reduce total cholesterol, LDL-cholesterol, apolipoprotein B, and triglycerides as well as to increase HDL-cholesterol in adult patients with primary hypercholesterolemia and mixed dyslipidemia.

The Food and Drug Administration approved ezetimibe (NDA 21-445 on October 25, 2002) and atorvastatin calcium (NDA 20-702 on December 17, 1996) for the treatment of hypercholesterolemia. Ezetimibe is available in the US as 10 mg oral immediate release tablet (ZETIA®). Atorvastatin is available in the US as 10, 20, 40, and 80 mg oral immediate release tablets (LIPITOR®). Ezetimibe and simvastatin fixed dose combination oral immediate tablets (10/10, 10/20, 10/40, and 10/80 [mg ezetimibe/mg simvastatin]; VYTORIN®) are also available in the US (NDA 21-687 approved on July 23, 2004).

The goal of the ezetimibe/atorvastatin clinical development program is to demonstrate bioequivalence of the ezetimibe/atorvastatin FDC tablets (10/10 mg, 10/20 mg, 10/80 mg) to the corresponding coadministered ezetimibe + atorvastatin individual tablets to support bridging of the ezetimibe/atorvastatin FDC tablet to the ezetimibe + atorvastatin coadministration clinical efficacy and safety data in the original ezetimibe NDA as well as to additional coadministration studies completed since marketing approval.

The ezetimibe/atorvastatin FDC is an immediate release (both drugs) film-coated (b)(4) tablet. The atorvastatin in the FDC is amorphous, whereas the atorvastatin in the reference tablets is crystalline. The ezetimibe (b)(4) is the same among the 4 strengths. (b)(4)

Thus, the sponsor proposed the bracketing approach to demonstrate bioequivalence of the 10/20 and 10/80 mg strengths to individually coadministered 10 + 20 and 10 + 80 mg ezetimibe and atorvastatin so as to apply for biowaiver for the 10/40 strength. This proposal is generally acceptable per Dr. Tein-Mein Chen's review of ONDQA Biopharmaceutics [IND 101,953 (SN-006) June 24, 2009].

Findings

To support NDA 200-153's Clinical Pharmacology and Biopharmaceutics sections, the sponsor submitted studies' results as indicated in the table above. The findings' highlights follow:

- submitted annotated proposed labeling

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING CHECKLIST FOR NDA 200-153

- submitted bioanalytical and validation reports for Studies P9396-001, P145, and P146 for unconjugated ezetimibe, total (unconjugated + conjugated) ezetimibe, atorvastatin, ortho-hydroxy atorvastatin, and para-hydroxy atorvastatin
- Study P145 is the definitive study intended to show bioequivalence for the following tablets:
 - 10 mg ezetimibe/10 mg atorvastatin FDC vs. 10 mg ZETIA[®] + 10 mg LIPITOR[®]
 - 10 mg ezetimibe/20 mg atorvastatin FDC vs. 10 mg ZETIA[®] + 20 mg LIPITOR[®]
 - 10 mg ezetimibe/80 mg atorvastatin FDC vs. 10 mg ZETIA[®] + 80 mg LIPITOR[®]
- Study P145's treatment design satisfies CFR 320.25 (g)(1).
- See Dr. Lucan Bi's Clinical Pharmacology review of Study P145's protocol under IND 101,953 Serial 0001 dated September 16, 2008.
- For Study P145, both ezetimibe and atorvastatin are bioequivalent between the 10/10 and 10/80 FDC tablets and the corresponding coadministered individual tablets except atorvastatin C_{max} for the 10/20 FDC tablet (b) (4) as GMR and 90% CI] (the 90% CI of the ratio of atorvastatin $AUC_{0-\infty}$ for the 10/20 FDC tablet is within the 0.8 -1.25 equivalence goalpost). The sponsor justified this "inequivalence" as clinically insignificant since:

(b) (4)

This "inequivalence" will be a review issue.

- Per ZETIA[®] label, daily coadministration of 10 mg ezetimibe and 10 mg atorvastatin for 14 days showed the following changes but are not significant mutual interaction:
 - total ezetimibe C_{max} increases 12% and total ezetimibe AUC decreases 2%
 - unconjugated ezetimibe C_{max} increases 31% and unconjugated ezetimibe AUC increases 21%
 - atorvastatin C_{max} increases 7% and atorvastatin AUC decreases 4%
- Since there is no significant mutual interaction between ezetimibe and atorvastatin (per ZETIA[®] label), Study P145's results can be interpreted as there is a lack of formulation interaction effects for ezetimibe and atorvastatin.
- The sponsor claimed that the ezetimibe/atorvastatin 10/10, 10/20 and 10/80 FDC tablets tested in Study P145 are the same as the to-be-marketed FDC formulations (Section 2.2.1 of Pharmaceutical Development). The sponsor also claimed that the manufacturing methodology used for these clinically tested formulations was representative and at least 1/10th (b) (4) the size of the commercial manufacturing process (Section 2.7.1.1.1.3 of Summary of Biopharmaceutic Studies and Associated Analytical Methods). These tablets were manufactured at the West Point, PA R&D site. However, the sponsor has not provided the multipoint in vitro dissolution profiles comparison between the clinically-tested formulation and the to-be-marketed product (not yet manufactured).
- Per the reviewing chemist, there is no commercial manufacturing site and appears that no product has been manufactured at the commercial site. Thus, there is no CMC information for the biobatches to be compared with the commercial product. This situation may be handled as a manufacturing site change from the R&D to the commercial manufacturing site. Applying SUPAC-IR principles, in vivo bioequivalence study is not necessary for the FDC tablets

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING CHECKLIST FOR NDA 200-153

between these 2 manufacturing sites provided the sponsor uses the same formulation, manufacturing process, and machines as well as similarity of the multipoint in vitro dissolution profiles for the FDC manufactured at the R&D site to that at the commercial site.

- Per the Division of Metabolism and Endocrinology Products' October 2, 2009 e-mail request, the sponsor responded that the equipment, environmental controls, and in-process controls for the to-be-marketed product are the same as that used for the batches in the bioequivalence study and the formal stability studies via e-mail on October 5, 2009. The sponsor also explained that there was a minor change in the ezetimibe (b) (4) between the clinically-tested batch and the commercial batch. The CMC reviewer considers this minor change should not affect the outcome.
- Study P9396-001 is the pilot biocomparison study between 2 amorphous 40 mg atorvastatin test formulations (A and B) and the reference of marketed 40 mg atorvastatin tablet.
- Study P146 examined the following treatments:
 - 10 mg ezetimibe/80 mg atorvastatin FDC tablet after a high-fat breakfast
 - 10 mg ezetimibe/80 mg atorvastatin FDC tablet under fasting
- Study P146 showed that the GMR of fed:fasted atorvastatin C_{max} was 0.65 and its 90% CI was 0.48 – 0.87. The GMR of fed:fasted atorvastatin $AUC_{0-\infty}$ was 0.89 and its 90% CI was 0.79 – 1.01. The GMR of fed:fasted unconjugated ezetimibe C_{max} was 1.10 and its 90% CI was 0.91 – 1.34. The GMR of fed:fasted total ezetimibe C_{max} was 1.18 and its 90% CI was 1.03 – 1.34. All other parameters were within the bioequivalence goalpost.
- Food decreases atorvastatin C_{max} and $AUC_{0-\infty}$ 25 and 9%, respectively per LIPITOR[®] label. Food increases unconjugated ezetimibe C_{max} 38% and increases total ezetimibe C_{max} 3% per ZETIA[®] label. Study P146's results are consistent with the LIPITOR[®] and ZETIA[®] labels.
- Per ZETIA[®] label, daily coadministration of 10 mg ezetimibe and 10 mg atorvastatin for 14 days showed the following changes but are not significant:
 - total ezetimibe C_{max} increases 12% and total ezetimibe AUC decreases 2%
 - unconjugated ezetimibe C_{max} increases 31% and unconjugated ezetimibe AUC increases 21%
 - atorvastatin C_{max} increases 7% and atorvastatin AUC decreases 4%
- The sponsor conducted the short-term factorial study (P0692) and Study 2154 (692's extension as long-term blinded comparator study). The sponsor conducted short-term add-on studies (P2173 and P040). The sponsor conducted short-term add-on titration studies (P079, P090, P112, and P693). The sponsor conducted the short-term study (P1030) and long-term study (P1417) in homozygous familial hypercholesterolemia patients.

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/s/

S. W. JOHNNY W LAU
10/30/2009

SALLY Y CHOE
10/30/2009