

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
200153Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 200153

SUPPL #

HFD # 510

Trade Name Liptruzet

Generic Name ezetimibe and atorvastatin

Applicant Name MSD International GmbH

Approval Date, If Known 5/3/2013

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES X NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(2) NDA

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES X NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO X

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO X

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO X

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES X NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 21445 Zetia (ezetimibe) Tablets

NDA# 20702 Lipitor (atorvastatin) Tablets

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a)

is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES X NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES X NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO X

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO X

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

P185-A Randomized, Double-Blind, Active-Controlled, Multicenter, Crossover Study to Evaluate the Efficacy and Safety of Ezetimibe/Atorvastatin 10/20 Fixed Dose Combination Tablet Compared to Co-administration of Marketed Ezetimibe 10 mg and Atorvastatin 20 mg in Patients with Primary Hypercholesterolemia

P190-A Randomized, Double-Blind, Active-Controlled, Multicenter, Crossover Study to Evaluate the Efficacy and Safety of Ezetimibe/Atorvastatin 10/40 Fixed Dose Combination Tablet Compared to Co-administration of Marketed Ezetimibe 10 mg and Atorvastatin 40 mg in Patients with Primary Hypercholesterolemia

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO X

Investigation #2 YES NO X

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO X

Investigation #2 YES NO X

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

P185-A Randomized, Double-Blind, Active-Controlled, Multicenter, Crossover Study to Evaluate the Efficacy and Safety of Ezetimibe/Atorvastatin 10/20 Fixed Dose Combination Tablet Compared to Co-administration of Marketed Ezetimibe 10 mg and Atorvastatin 20 mg in Patients with Primary Hypercholesterolemia

P190-A Randomized, Double-Blind, Active-Controlled, Multicenter, Crossover Study to Evaluate the Efficacy and Safety of Ezetimibe/Atorvastatin 10/40 Fixed Dose Combination Tablet Compared to Co-administration of Marketed Ezetimibe 10 mg and Atorvastatin 40 mg in Patients with Primary Hypercholesterolemia

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
!
IND # 101953 YES X ! NO
! Explain:

Title: Project Manager
Date: May 3, 2013

Name of Office/Division Director signing form: Eric Colman, MD
Title: Deputy Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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

/s/

KATI JOHNSON
05/03/2013

ERIC C COLMAN
05/03/2013

Johnson, Kati

From: Greeley, George
Sent: Friday, December 02, 2011 11:08 AM
To: Johnson, Kati
CC: Mathis, Lisa; Addy, Rosemary; Suggs, Courtney; Lee, Catherine S.; Parks, Mary H
Subject: NDA 200-253 Atozet

Importance: High

Attachments: 1_Pediatric_Record.pdf

Hi Kati,

The email serves as confirmation of the review for the Atozet (ezetimibe/atorvastatin calcium amorphous) product conducted by the PeRC PREA Subcommittee on November 30, 2011.

(b) (4)

The PeRC instead agreed with the Division to grant a full waiver for this product.

The amended pediatric record is attached for Atozet.



1_Pediatric_Record.pdf (67 KB).

Thanks,

George Greeley
Regulatory Health Project Manager
Pediatric and Maternal Health Staff
FDA/CDER/OND
10903 New Hampshire Avenue
Bldg. 22, Room 6467
Silver Spring, MD 20993-0002
Phone: 301.796.4025
Email: george.greeley@fda.hhs.gov

Please consider the environment before printing this e-mail.

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 200153 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type:
Proprietary Name: Liptruzet Established/Proper Name: ezetimibe and atorvastatin Dosage Form: Tablets		Applicant: MSD International GmbH Agent for Applicant (if applicable): Merck Sharp & Dohme Corp.
RPM: Kati Johnson		Division: Division of Metabolism and Endocrinology Products
<p><u>NDA and NDA Efficacy Supplements:</u></p> <p>NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>	<p><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u></p> <p>Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):</p> <p>NDA 20702, Lipitor (atorvastatin) Tablets</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p>This is a fixed dose combination of ezetimibe and atorvastatin</p> <p><input type="checkbox"/> This application does not rely upon a listed drug. <input type="checkbox"/> This application relies on literature. <input type="checkbox"/> This application relies on a final OTC monograph. <input type="checkbox"/> This application relies on (explain)</p> <p><u>For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></p> <p><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></p> <p>X No changes <input type="checkbox"/> Updated Date of check: 5/3/2013</p> <p>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</p>	
❖ Actions		
<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is <u>5/4/2013</u> 	X AP <input type="checkbox"/> TA <input type="checkbox"/> CR	
<ul style="list-style-type: none"> • Previous actions (<i>specify type and date for each action taken</i>) 	<input type="checkbox"/> None RTF 10/29/2009 CR 2/29/2012	

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists the documents to be included in the Action Package.

² For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

<p>❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____</p>	<input type="checkbox"/> Received
<p>❖ Application Characteristics³</p>	
<p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only):</p> <p> <input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC </p> <p> NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies </p> <p> <input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC <input type="checkbox"/> Submitted in response to a Pediatric Written Request </p> <p> BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart H <input type="checkbox"/> Approval based on animal studies </p> <p> REMS: <input type="checkbox"/> MedGuide <input type="checkbox"/> Communication Plan <input type="checkbox"/> ETASU <input type="checkbox"/> MedGuide w/o REMS <input type="checkbox"/> REMS not required </p> <p>Comments:</p>	
<p>❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)</p>	<input type="checkbox"/> Yes, dates
<p>❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)</p>	<input type="checkbox"/> Yes <input type="checkbox"/> No
<p>❖ Public communications (<i>approvals only</i>)</p>	
<ul style="list-style-type: none"> Office of Executive Programs (OEP) liaison has been notified of action 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> Press Office notified of action (by OEP) 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> Indicate what types (if any) of information dissemination are anticipated 	<input checked="" type="checkbox"/> None <input type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? 	X No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i> 	X No <input type="checkbox"/> Yes If, yes, NDA/BLA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	X No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	X No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	X No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	X No <input type="checkbox"/> Yes If yes, NDA # _____ and date 10-year limitation expires: _____
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. 	X Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. 	21 CFR 314.50(i)(1)(i)(A) X Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). 	X No paragraph III certification Date patent will expire _____
<ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i> 	<input type="checkbox"/> N/A (no paragraph IV certification) X Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

Yes No
For the following:
5,686,104
5,969,156
6,126971

Yes No

Yes No

For patent 5,969,156

Yes No

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p> <p>NOTE: FDA was notified in an April 16, 2012 submission that they had been granted a license by Pfizer and that the litigation was settled.</p>	<p><input checked="" type="checkbox"/> Yes <input type="checkbox"/> No For patent 5,969,156</p>
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CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist ⁴	X
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	X Included
Documentation of consent/non-consent by officers/employees	X Included
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s) RTF 10/29/2009 CR 2/29/2012 AP 5/3/2013
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> • Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	

⁴ Fill in blanks with dates of reviews, letters, etc.

<ul style="list-style-type: none"> ❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>) 	<input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	
<ul style="list-style-type: none"> ❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>) 	
<ul style="list-style-type: none"> • Most-recent draft labeling 	
<ul style="list-style-type: none"> ❖ Proprietary Name <ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) • <i>Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.</i> 	<p>Atozet acceptable 9/26/2011 Atozet unacceptable 2/19/2013 Liptruzet acceptable 4/26/2013</p> <p>Letters issued 9/26/2011, 2/19/2013, and 4/29/2013</p>
<ul style="list-style-type: none"> ❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>) 	<input type="checkbox"/> RPM <input checked="" type="checkbox"/> DMEPA 1/27/2012, 4/1/2013 <input checked="" type="checkbox"/> DMPP/PLT (DRISK) 2/14/2012, 3/27/2013 <input checked="" type="checkbox"/> ODPD (DDMAC) 5/2/2013 <input checked="" type="checkbox"/> SEALD 4/29/2013 <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
Administrative / Regulatory Documents	
<ul style="list-style-type: none"> ❖ Administrative Reviews (<i>e.g., RPM Filing Review⁵/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>) 	11/18/2011
<ul style="list-style-type: none"> ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte 	<input type="checkbox"/> Not a (b)(2) 2/13/2012, 4/29/2013
<ul style="list-style-type: none"> ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>) 	<input type="checkbox"/> Not a (b)(2) 5/3/2013
<ul style="list-style-type: none"> ❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>) 	X Included
<ul style="list-style-type: none"> ❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm 	
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes X No
<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not an AP action

⁵ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC <u>11/30/2011</u> If PeRC review not necessary, explain: _____ • Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>) 	X Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>)	X Verified, statement is acceptable
❖ Outgoing communications (<i>letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons</i>)	X
❖ Internal memoranda, telecons, etc.	X
❖ Minutes of Meetings	
• Regulatory Briefing (<i>indicate date of mtg</i>)	X No mtg
• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)	<input type="checkbox"/> N/A or no mtg 12/18/2009
• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	X No mtg
• EOP2 meeting (<i>indicate date of mtg</i>)	X No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)	
❖ Advisory Committee Meeting(s)	X No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available (<i>do not include transcript</i>)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	X None
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 5/3/2013
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	X None
PMR/PMC Development Templates (<i>indicate total number</i>)	X None
Clinical Information⁶	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	N/A
• Clinical review(s) (<i>indicate date for each review</i>)	4/10/2013, 1/20/2012, 10/9/2009
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	X None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	See page 15 of 1/20/2012 clinical review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	X None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	X Not applicable

⁶ Filing reviews should be filed with the discipline reviews.

❖ Risk Management <ul style="list-style-type: none"> REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>) REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) 	X None
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	X None requested
Clinical Microbiology X None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	X None
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	X None
Statistical Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 4/3/2013, 1/6/2012, 6/21/2011, 10/7/2009
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	X None
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	X None
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 3/2/2012, 12/7/2011, 6/28/2011, 10/30/2009
❖ DSI Clinical Pharmacology Inspection Review Summary (<i>include copies of OSI letters</i>)	<input type="checkbox"/> None 2/29/2012
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	X None
• Supervisory Review(s) (<i>indicate date for each review</i>)	X None
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	<input type="checkbox"/> None 2/2/2012
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	X None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	X No carc
❖ ECAC/CAC report/memo of meeting	X None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary (<i>include copies of OSI letters</i>)	X None requested

Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	X None
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	X <input type="checkbox"/> None
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	<input type="checkbox"/> None CMC-5/3/2013, 12/6/2011, 8/23/2011, 6/27/2011, 10/7/2009 BIOPHARM-10/28/2011, 6/29/2011
❖ Microbiology Reviews <input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i> <input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>	X Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	X None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	See page 87 of 8/23/2011 CMC review
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>	
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>	
❖ Facilities Review/Inspection	
<input type="checkbox"/> NDAs: Facilities inspections (include EER printout) <i>(date completed must be within 2 years of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁷)</i>	Date completed: 5/2/2013 X Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER <i>(date of most recent TB-EER must be within 30 days of action date) (original and supplemental BLAs)</i>	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i>	<input type="checkbox"/> Completed <input type="checkbox"/> Requested X Not yet requested <input type="checkbox"/> Not needed (per review)

⁷ I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

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/s/

KATI JOHNSON
05/03/2013

Johnson, Kati

From: Kohler, Catherine leomy [catherine.kohler@merck.com]
Sent: Friday, May 03, 2013 12:42 PM
To: Johnson, Kati
Subject: RE: NDA 200153, Liptruzet (ezetimibe and atorvastatin) Tablets, AP letter

Dear Kati,

The proofing is complete. No content differences between our documents and the FDA's documents.

Thank you very much and enjoy your vacations next week.

Best regards,
Catherine

From: Kohler, Catherine leomy
Sent: Friday, May 03, 2013 11:41 AM
To: 'Johnson, Kati'
Subject: RE: NDA 200153, Liptruzet (ezetimibe and atorvastatin) Tablets, AP letter

Dear Kai,

This email is to confirm receipt of the Liptruzet approval letter.

We are still proof reading and I will send you a follow up message shortly.

Thank you very much,
Best regards,
Catherine

From: Johnson, Kati [mailto:Kati.Johnson@fda.hhs.gov]
Sent: Friday, May 03, 2013 10:51 AM
To: Kohler, Catherine leomy
Subject: NDA 200153, Liptruzet (ezetimibe and atorvastatin) Tablets, AP letter

Please confirm receipt.
Thanks, Kati

Kati Johnson
Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
301-796-1234 (Phone)

Notice: This e-mail message, together with any attachments, contains information of Merck & Co., Inc. (One Merck Drive, Whitehouse Station, New Jersey, USA 08889), and/or its affiliates Direct contact information for affiliates is available at

5/1/2013

MEMORANDUM OF MEETING

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

INTERNAL MEETING MINUTES

Pre-decisional Agency Information

Meeting Date: April 25, 2013

Time: 1:24 p.m. – 1:26 p.m.

Location: CDER WO 3276, Building 51

NDA: 200153

Drug: LIPTRUZET™ (ezetimibe and atorvastatin) Tablets

MA: 3

Meeting Chair: Kendra Y. Jones, Regulatory Review Officer, Office of Prescription Drug Promotion (OPDP)

Meeting Recorder: Kendra Y. Jones

External Participant Lead: Renee Ambrosio, Associate Director, Office of Promotion and Advertising Review, Merck & Co., Inc.

OPDP Attendees: Kendra Y. Jones

External Attendees: Renee Ambrosio

Background:

On March 8, 2013, Merck & Co., Inc. (Merck) submitted to the Office of Prescription Drug Promotion (OPDP) a proposed launch packaging sheet for LIP TRUZET™ (ezetimibe and atorvastatin) Tablets for advisory comments.

OPDP issued an advisory letter on April 12, 2013, that communicated that the proposed packaging sheet was misleading because it failed to communicate the full indication as well as any important risk information associated with the use of ezetimibe and atorvastatin tablets.

On April 23, 2013, Merck asked for clarity with respect to what specifically within the proposed packaging sheet makes representation about the product.

Meeting Objectives:

The purpose of this meeting was to provide Merck with additional perspective on OPDP's April 12, 2013, advisory letter.

Discussion Points:

1. OPDP stated that the proposed packaging sheet includes claims regarding the storage and handling of Liptruzet that makes representations about the use of drug product.
2. Merck thanked OPDP for the explanation.

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/s/

KENDRA Y JONES
05/01/2013



DEPARTMENT OF HEALTH AND HUMAN
SERVICES

Food and Drug
Administration Silver
Spring MD 20993

NDA 200153

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

MSD International GmbH
c/o Merck Sharp & Dohme Corp.
P.O. Box 1000
North Wales, PA 19454

Attention: Catherine L. Kohler, PharmD
Director, Regulatory Affairs
Agent for MSD International GmbH

Dear Dr. Kohler:

Please refer to your New Drug Application (NDA) dated April 28, 2011, received April 29, 2011, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Ezetimibe and Atorvastatin Tablets, 10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg, and 10 mg/80 mg. Please also refer to your Class 2 Resubmission dated and received November 5, 2012.

We also refer to your submission dated and received February 25, 2013, requesting review of your proposed proprietary name, Liptruzet. We also refer to your proprietary name amendment dated and received March 06, 2013.

We have completed our review of the proposed proprietary name, Liptruzet, and have concluded that it is acceptable.

The proposed proprietary name, Liptruzet, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your February 25, 2013, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Margarita Tossa, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4053. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager Kati Johnson, at (301) 796-1234.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
04/29/2013



4/12/2013

Food and Drug Administration
Silver Spring, MD 20993

Renee Ambrosio, Associate Director
Office of Promotion and Advertising Review
Merck & Co., Inc.
UG3BC-10, P.O. Box 1000
North Wales, PA 19454-1099

RE: NDA 200153
ezetimibe and atorvastatin tablets
MA #3

Dear Ms. Ambrosio:

This letter responds to Merck & Co., Inc.'s, (Merck) March 8, 2013, request to the Office of Prescription Drug Promotion (OPDP) for advisory comments on a proposed launch packaging sheet for ezetimibe and atorvastatin tablets. The submission included the draft ezetimibe and atorvastatin tablets Patient Information (PPI), 10 mg/20 mg trade foil pouch, 10 mg/20 mg trade case and the following promotional materials:

- Packaging Sheet, Pharmacy (CARD-1069484-0000)

Reference is made to a teleconference between OPDP (Kendra Jones) and Merck (Sandra Kerr) on March 29, 2013, during which OPDP requested that Merck submit the draft product labeling (PI) for ezetimibe and atorvastatin tablets. Reference is further made to Merck's March 29, 2013, submission of the draft PI for ezetimibe and atorvastatin tablets.

OPDP's comments reflect the version of the draft product labeling (PI) that was included in the March 29, 2013, submission and the PPI from the March 8, 2013, submission. These comments are tentative pending finalization of the ezetimibe and atorvastatin tablets product labeling (PI). The proposed packaging sheet, as well as future promotional materials, should be updated to reflect the final approved PI for ezetimibe and atorvastatin tablets.

OPDP has reviewed the proposed packaging sheet and we offer the following comments, which should be applied to this submission and to all current and future promotional materials for ezetimibe and atorvastatin tablets that contain the same or similar claims or representations.

Inappropriate Reminder Labeling/ Omission of Indication and Risk Information

Reminder labeling is labeling that calls attention to the name of the drug product, but does not include its indication, or dosage recommendations, or other representations or

suggestions relating to the drug product. Reminder labeling may contain only the proprietary name and established names of the drug product and may contain information relating to quantitative ingredient statements, dosage form, quantity of package contents, price, the name and address of the manufacturer, or other written, printed, or graphic matter which contain no representation or suggestion relating to the advertised drug product. (See 21 CFR 201.100(f)).

Although the proposed packaging sheet does not state the drug product's indication, the claims presented make representations about ezetimibe and atorvastatin tablets' use. As such, the proposed packaging sheet is misleading because it fails to communicate the full indication as well as any important risk information associated with the use of ezetimibe and atorvastatin tablets. In addition, the proposed packaging sheet fails to provide adequate directions for use of ezetimibe and atorvastatin tablets.

If you have any questions or comments, please direct your response to the undersigned by facsimile at (301) 847-8444, or at the **Food and Drug Administration, Center for Drug Evaluation and Research, Office of Prescription Drug Promotion, 5901-B Ammendale Road, Beltsville, Maryland 20705-1266**. To ensure timely delivery of your submissions, please use the full address above and include a prominent directional notation (e.g. a sticker) to indicate that the submission is intended for OPDP. Please refer to the MA #3 in addition to the NDA number in all future correspondence relating to this particular matter. OPDP reminds you that only written communications are considered official.

Sincerely,

{See appended electronic signature page}

Kendra Y. Jones
Regulatory Review Officer
Office of Prescription Drug Promotion

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

/s/

KENDRA Y JONES
04/12/2013



DEPARTMENT OF HEALTH AND HUMAN
SERVICES

2/19/2013

Food and Drug
Administration Silver
Spring MD 20993

NDA 200153

PROPRIETARY NAME REQUEST
UNACCEPTABLE

MSD International GmbH
c/o Merck Sharp & Dohme Corp
P.O. Box 1000
North Wales, PA 19454

Attention: Catherine L. Kohler, PharmD, US Agent
Director, Regulatory Affairs

Dear Dr. Kohler:

Please refer to your New Drug Application (NDA) dated April 28, 2011, received April 29, 2011 submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Ezetimibe and Atorvastatin Tablets, 10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg, and 10 mg/80 mg. Please also refer to your Class 2 Resubmission dated and received November 5, 2012.

We also refer to:

- Your initial proprietary name submission, dated July 7, 2011, requesting review of your proposed proprietary name Atozet;
- Our initial correspondence dated September 26, 2011, finding your proposed proprietary name Atozet, conditionally acceptable;
- Your submission dated and received December 14, 2012, requesting re-review of your proposed proprietary name, Atozet.
- The amendment to request for proprietary name review dated February 7, 2013 which includes the external study conducted by (b) (4) for the proposed proprietary name.

We have completed our review of the proposed proprietary name, Atozet, and have concluded that this name is unacceptable because Atozet is phonetically similar to the currently marketed product, Aricept (donepezil).

We acknowledge that this determination differs from our previous evaluation and conclusion communicated in the letter dated September 26, 2011. We further acknowledge that this determination differs from the external proprietary name risk assessment conducted by (b) (4) (b) (4) dated March 4, 2011 and submitted on February 7, 2013 that concludes that Atozet "may be able" to safely exist in the market for which it was tested.

The reason we have reached a different determination with respect to the safety of your proposed name is based upon the new safety information identified in the voice simulation studies, which was confirmed by our phonetic analysis of the Aricept/Atozet name pair. The details of our findings are described below.

In our current evaluation of your proposed name, one participant in the voice simulation study misinterpreted Atozet as Aricept. In our previous evaluation, the misinterpretation of Atozet as “Aricept” **did not occur in the simulation studies** that were conducted as part of that evaluation. Several reasons could explain why the misinterpretation did not occur in one simulation study versus another. The simulation studies were performed using different handwriting and voice samples of the proposed name and the participants responding to the simulation studies differed. Both or either of these changes could explain differences in the qualitative findings of the simulation studies. Additionally, name simulation studies are not designed to provide conclusive evidence that a proposed name does not pose a risk of confusion given the small sample size used in these studies. Therefore, a negative finding (i.e. no name confusion) from the previous series of prescription simulation studies does not supersede a positive finding (i.e. name confusion) from this subsequent series of simulation studies. Conversely, a positive finding does supersede any previous findings since such a finding is an indication of the vulnerability of a proposed name to confusion.

Thus, the new information garnered from the simulation studies caused us to revisit in this evaluation our previous Failure Modes and Effects Analysis of the Aricept/Atozet pair. Our previous conclusion that Atozet was conditionally acceptable was based on the fact that the name was not thought to present a risk for confusion with any marketed or pending drug or biologic names. Our FMEA did consider whether Atozet might be confused with Aricept, but at the time of that review we determined that phonetic differences in the names would distinguish these names in verbal communication. The evaluator in the first safety review, conducted for the letter dated September 26, 2011 letter, concluded the following phonetic differences would prevent the names from being confused. Specifically, that reviewer asserted that the names were **distinguishable when spoken because the first syllable in Atozet ends with a “t” sound versus the “r” sound in Aricept and the final syllable in Atozet does not have a “p” sound vs. Aricept has the sound “p”.** However, the misinterpretation in the voice simulation studies conducted as part of this review now provides reason to conclude that this analysis and conclusion was incorrect.

With respect to the phonetic similarity of Atozet and Aricept, both names have 3 syllables with the stress placed on the first syllable. Within each syllable there are similarities as follows:

- First syllable: Although the *intended* pronunciation of the first vowel sound in both names differ (AT vs. Air; or /ə/ vs. /eɪ/), it is possible that both vowel sounds be pronounced as /ə/. The second sounds in both names are alveolar/post-alveolar. Therefore, the first syllables of both names are stressed, may begin with the same vowel sound /ə/ and end with an alveolar sound.
- Second syllable: The second syllable in both names are short weak syllables (oh vs. eh), that are influence by the sounds around them and may blend with either the previous and following sounds.
- Third syllable: The first sounds (/z/ vs. /s/) are affricative/fricative and alveolar, which may cause voicing assimilation and sound the same. The second sounds are

the same (/ɛ/). The last sound (/t/ vs. /pt/) may sound the same as voice assimilation may occur between the /p/ and /t/ since both are plosive sounds. Therefore, the last syllables in both names may sound the same.

In addition to the phonetic similarity of Atozet and Aricept, we note that these products share a number of product characteristics that would lead to errors in the usual practice setting. Both Aricept and Atozet are oral tablets that can be administered once daily. We note that Atozet has two ingredients, ezetimibe and atorvastatin, with the following strengths: 10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg, and 10 mg/80 mg. However, since the 10 mg of ezetimibe is common to all four strengths and the atorvastatin component varies across the four strengths, there is potential for this product to be prescribed and ordered referencing only the atorvastatin component (e.g. Atozet 10 mg). Med-ERRS, a subsidiary for the Institute for Safe Medication Practices, published responses to a questionnaire posed to health care practitioners specifically related to the prescribing and dispensing of combination products¹ and confirmed this practice does occur in the clinical setting. Aricept is a single ingredient product with the strengths 5 mg and 10 mg; thus, we find that there is a potential overlap of 10 mg between the two products if ordered as “Atozet 10 mg” or “Aricept 10 mg”. In this situation, an order for Atozet 10 mg daily could be misinterpreted as Aricept 10 mg daily by a pharmacist, nurse, or other practitioner who receives a verbal order or prescription thus resulting in a medication error. Our analysis is informed by our post-marketing surveillance of medication errors involving other drug products. Specifically, we are aware of post-marketing reports of errors that have occurred between combination drug products and single ingredient drug products that have similar names and overlapping or similar strengths.

Collectively, our post-marketing experience with other drug products and the voice simulation study misinterpretation lead us to conclude that the name Atozet is vulnerable to confusion with Aricept. Specifically, we have concern that practitioners may order Atozet 10mg/10mg as “Atozet 10 mg,” and that such verbal orders may be mistakenly interpreted as Aricept 10mg resulting in a medication error.

We further acknowledge that our determination also differs from the external proprietary name risk assessment conducted by (b) (4). This report was not submitted by you for consideration in our previous review, but was carefully evaluated as part of this review. (b) (4) concluded in their report that Atozet “may be able” to safely exist in the market for which it was tested.

In the report, (b) (4) describes Atozet as having “slight sound-alike similarity” with Aricept. (b) (4) did not detail what attributes of the name they used to determine that this “sound-alike” similarity exists, nor do they describe how they determined this similarity to be “slight”. Notwithstanding, we find that the phonetic similarity of Atozet and Aricept to be demonstrated by the misinterpretation recorded in our voice simulation study and our phonetic analysis of the name pair. We agree with (b) (4) that the 10 mg strength of Aricept “may be confused with the ezetimibe 10 mg/atorvastatin 10 mg strength of Atozet” based upon the fact that the atorvastatin portion (e.g., 10 mg) of Atozet may be the only portion expressed on prescriptions or orders. It is unclear why, in the face of this identified risk of name confusion, (b) (4) determined that the name Atozet “may be able” to safely exist in the market for which it was tested. Aricept is an actively marketed drug, and there conclusion appears at odds with their

¹ <http://www.med-errs.com/Question/Resulterr0408.asp>, accessed October 18, 2012

safety finding. Given this inconsistency, we are unable to explain why our conclusions differ with (b) (4) determination.

We note that you have not proposed an alternate proprietary name for review. If you intend to have a proprietary name for this product, we recommend that you submit a new request for a proposed proprietary name review. (See the Guidance for Industry, *Complete Submission for the Evaluation of Proprietary Names*, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf> and “PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012”.)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Margarita Tossa, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4053. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager Kati Johnson at (301) 796-1234.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
02/19/2013



1/15/2013

Food and Drug Administration
Silver Spring, MD 20993

Renee Ambrosio, Associate Director
Office of Promotion and Advertising Review
Merck & Co., Inc.
UG3BC-10, P.O. Box 1000
North Wales, PA 19454-1099

RE: NDA #200153
ATOZET™ (ezetimibe and atorvastatin) tablets
MA #1

Dear Ms. Ambrosio:

This letter responds to Merck & Co., Inc.'s (Merck) December 11, 2012, request to the Division of Professional Drug Promotion (DPDP) in the Office of Prescription Drug Promotion (OPDP) for comments on a proposed Health Care Provider (HCP) Coming Soon Journal Advertisement (CARD-1054163-0000) (coming soon ad) for ATOZET™ (ezetimibe and atorvastatin) tablets (Atozet).

DPDP has reviewed the proposed HCP coming soon ad and offers the following comments. These comments should be applied to this submission and all future promotional materials that contain the same or similar claims.

General

The proposed HCP coming soon ad includes a reference to the website (b) (4) DPDP cannot comment on the content of this link because the website was not submitted for our review.

DPDP has no further comments at this time.

If you have any questions or comments, please direct your response to the undersigned by facsimile at (301) 847-8444, or at the **Food and Drug Administration, Center for Drug Evaluation and Research, Office of Prescription Drug Promotion, Division of Professional Drug Promotion, 5901-B Ammendale Road, Beltsville, Maryland 20705-1266**. To ensure timely delivery of your submissions, please use the full address above and include a prominent directional notation (e.g. a sticker) to indicate that the submission is intended for OPDP. Please refer to the MA #1 in addition to the NDA number in all future correspondence relating to this particular matter. DPDP reminds you that only written communications are considered official.

Ms. Renee Ambrosio
Merck & Co., Inc.
NDA #200153/MA #1

Page 2

Sincerely,

{See appended electronic signature page}

Samuel M. Skariah, Pharm.D.
LCDR, USPHS
Regulatory Review Officer
Division of Professional Drug Promotion
Office of Prescription Drug Promotion

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/s/

SAMUEL M SKARIAH
01/15/2013



NDA 200153

**ACKNOWLEDGE –
CLASS 2 RESPONSE**

Merck Sharp & Dohme Corp.
Agent for MSD International GmbH
Attention: Catherine Kohler, PharmD
Director, Worldwide Regulatory Affairs
P.O. Box 1000, UG2D-027
North Wales, PA 19454

Dear Dr. Kohler:

We acknowledge receipt on November 5, 2012, of your November 5, 2012, resubmission of your new drug application submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for ATOZET (ezetimibe/atorvastatin) Tablets, 10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg, and 10 mg/80 mg.

We consider this a complete, class 2 response to our February 29, 2012, action letter. Therefore, the user fee goal date is May 5, 2013.

If you have any questions, call me at (301) 796-1234.

Sincerely,

{ See appended electronic signature page }

Kati Johnson
Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

KATI JOHNSON
11/21/2012



NDA 200153

GENERAL ADVICE

Merck Sharp & Dohme Corp.
Attention: Catherine Kohler, PharmD
Director, Worldwide Regulatory Affairs
P.O. Box 1000, UG2D-027
North Wales, PA 19454

Dear Dr. Kohler:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Atozet (ezetimibe/atorvastatin) Tablets.

In your April 28, 2011 amendment, you included revised carton and container labeling. We have completed our review of this material and have the following comments and requests:

A. General Comments (All Labels and Strengths)

1. Remove or decrease the size of the graphic shape that appears prior to the proprietary name as this could be confused as a letter, i.e. "V", in the proprietary name.
2. Revise the strength presentations so that the strengths for both ingredients are presented in the same color.
3. Remove the color block at the bottom of the labels and relocate the color block so that it appears around the strength statement in order to visually highlight the strength differentiation.
4. Increase the prominence of the established name and dosage form to ensure that it is in accordance with CFR 201.10(g)(2).
5. Delete the tablet graphic that appears on the principal display panel and replace with an actual image of the Atozet tablet.

B. Sample Blister (All Strengths)

1. (b) (4)
Present the name, Atozet, in a neutral color, such as black to avoid confusion among strengths or alternatively, utilize a different color for 10 mg/20 mg strength.
2. Relocate the strength so that it appears below or adjacent to the dosage form.
3. Remove the (b) (4)
statement that appears above the storage information because it adds clutter to the principal display panel.
4. Relocate the Atozet...each tablet contains statements so that it appears at the bottom of the principal display panel or the backside of the sample blister.

5. Relocate the temperature recommendations so that they appear at the end of the storage recommendations and increase visibility of the important instructions to avoid moisture and light.

C. Sample Foil Pouch (All Strengths)

1. See comments B1 through B5.
2. Relocate the instructions to protect from moisture so that it appears in the white area of the principal display panel and appears in bold black font.

D. Sample Carton Labeling (All Strengths)

1. See comments B1 through B4.
2. Revise the contents of the carton statement to state:
This carton contains 4 patient pouches.
Each pouch contains 7 tablets

In addition, increase the font of the contents statements and relocate to the top the carton, so that it is more visible.

3. Relocate the statements, (b) (4) After the foil pouch is opened, protect Atozet from moisture and light' to the area in white and revise the statement so that it appears in black font and the font is more prominent. Additionally, these storage recommendations should appear on more than one panel.

E. HUD Foil pouch (All Strengths)

1. See comments B1 through B5 and D3.

F. HUD Blister (All Strengths)

1. Relocate the strength so that it appears below dosage form.
2. Consider reorienting one side of the pouch so both sides are oriented in the same manner (as opposed to one side upside down).

G. Plastic Case (front)

1. See comments B1 through B4.
2. Relocate the 'After the pouch is opened...' statement so that it appears in the white area in black font. Additionally, increase the font size to ensure that this important information is communicated to the patient.
3. Communicate to patients how to protect Atozet from moisture and light. Does this include keeping the tablets in the plastic case? Please provide specific instructions.
4. Relocate the 'Each tablet contains...' statement so that it appears at the bottom or back (if possible).

H. Carton Labeling, 30 and 90 count (All Strengths)

1. See comments B1 through B5, D2 and D3.

If you have any questions, call Kati Johnson, Regulatory Project Manager, at (301) 796-1234.

Sincerely,

{See appended electronic signature page}

Eric Colman, MD
Deputy Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

ERIC C COLMAN
01/31/2012



NDA 200-153

INFORMATION REQUEST

Merck Sharp & Dohme Corp.
Agent for MSP Singapore Company, LLC
Attention: Catherine Kohler, PharmD
Director, Worldwide Regulatory Affairs
P.O. Box 1000, UG2CD-48
North Wales, PA 19454

Dear Dr. Kohler:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ezetimibe/Atorvastatin tablets.

We are reviewing the Biopharmaceutics section of your submission and have the following comments and information requests. We request a prompt written response within one week (October 11th, 2011) in order to continue our evaluation of your NDA.

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 [REDACTED] ^{(b) (4)} only for the atorvastatin calcium component of your proposed product . Please provide information regarding ezetimide 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 ezetimide components) demonstrating that you proposed dissolution method is discriminating.

If you have any questions, call Khushboo Sharma, Regulatory Project Manager, at (301) 796-1270.

Sincerely,

{See appended electronic signature page}

Ali Al Hakim, Ph.D.
Branch Chief, Branch VII
Division of New Drug Quality Assessment III
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

ALI H AL HAKIM
10/04/2011



NDA 200153

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

MSP Singapore Company, LLC
c/o Jeffrey R. Tucker, MD.
US Agent
P.O. Box 1000, UG2CD-48
North Wales, PA 19454-1099

Attention: Jeffrey R. Tucker, M.D.
Senior Director, Regulatory Affairs

Dear Dr. Tucker:

Please refer to your New Drug Application (NDA) dated April 28, 2011, received April 29, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ezetimibe and Atorvastatin Tablets, 10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg, and 10 mg/80 mg.

We also refer to your July 7, 2011, correspondence, received July 7, 2011, requesting review of your proposed proprietary name, Atozet. We have completed our review of the proposed proprietary name, Atozet and have concluded that it is acceptable.

The proposed proprietary name, Atozet, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your July 7, 2011, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Margarita Tossa, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4053. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager Kati Johnson at (301) 796-1234.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology

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/s/

CAROL A HOLQUIST
09/26/2011



NDA 200153

DISCIPLINE REVIEW LETTER

Merck Sharp & Dohme Corp.
Attention: Catherine Kohler, PharmD
Director, Worldwide Regulatory Affairs
P.O. Box 1000, UG2CD-48
North Wales, PA 19454

Dear Dr. Kohler:

Please refer to your April 28, 2011 New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Atozet (ezetimibe/atorvastatin) Tablets.

We also refer to your amendment dated July 22, 2011, containing chemistry, manufacturing and controls (CMC) information as a partial response to our letter dated July 6, 2011.

Our review of the CMC section of your submission is complete, and we have identified the following deficiencies:

1. Provide a schematic drawing (with dimensions) for each of the four strength tablets.
2. Provide an explanation for the (b) (4)
[REDACTED]
3. Provide a single acceptance criterion for each test in the drug product specifications. Having two sets of acceptance criteria (release and stability) for tests in the drug product specification for non-protein products is not acceptable. As described in ICH Q6A, acceptance criteria for assay and impurity (degradation product) levels are the same from release throughout shelf life. However, in-house criteria for alternate limits for these tests are acceptable.
4. Include batch release results for moisture content in development, clinical and stability batch analyses showing compliance with the drug product specifications.
5. Provide schematic drawings (with dimensions) of the blister cards for both the multi-unit and unit dose container for Ezetimibe/Atorvastatin Tablets.
6. (b) (4)
[REDACTED]

(b) (4)

7.

(b) (4)

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Kati Johnson, Regulatory Project Manager, at (301) 796-1234.

Sincerely,

{See appended electronic signature page}

Enid Galliers
Chief, Project Management Staff
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

ENID M GALLIERS
08/24/2011



NDA 200153

FILING COMMUNICATION

Merck Sharp & Dohme Corp.
Agent for MSP Singapore Company, LLC
Attention: Jeffrey R. Tucker, MD
Senior Director, Worldwide Regulatory Affairs
P.O. Box 1000, UG2CD-48
North Wales, PA 19454

Dear Dr. Tucker:

Please refer to your New Drug Application (NDA) dated April 28, 2011, received April 29, 2011 submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Atozet (ezetimibe/atorvastatin) Tablets, 10/10, 10/20, 10/40, and 10/80.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is **February 29, 2012**.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, midcycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by **February 1, 2012**.

During our filing review of your application, we identified the following potential review issues. Please provide the following information:

Clinical Statistical

For Study P0693, please provide analysis files with the following information, or, if this information is available in the submission, state its location:

1. Subject-specific: indicator variable(s) that code for each analysis population, such as full analysis-set and per-protocol.

2. Visit-specific:
 - a. indicator variable(s) that code for the primary endpoint in its final form
 - b. indicator variable(s) that code for the derivation status of the primary endpoint, i.e., whether it is measured or derived

Office of New Drug Quality Assessment Biopharmaceutics

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 mg 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 addresses.

Clinical Pharmacology

Please provide the electronic data files in SAS transport file (.XPT) format, or point to the location of such files in application, for the modeling and simulation of:

1. The impact of regimen and formulation on the LDL-C dose response relationship of statins
2. The potential impact of changes in exposure of atorvastatin and ezetimibe on LDL-C dose response relationship

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

If you have any questions, call Kati Johnson, Regulatory Project Manager, at (301) 796-1234.

Sincerely,

{See appended electronic signature page}

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

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/s/

KATI JOHNSON
07/06/2011
signing for Mary Parks, MD



NDA 200153

**ACKNOWLEDGE RESUBMISSION
AFTER REFUSE-TO-FILE**

Merck Sharp & Dohme Corp.
Agent for MSP Singapore Company, LLC
Attention: Jeffrey R. Tucker, MD
Senior Director, Regulatory Affairs
P.O. Box 1000, UG2CD-48
North Wales, PA 19454

Dear Dr. Tucker:

We have received your new drug application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act in response to our October 29, 2009, refusal to file letter for the following:

Name of Drug Product: Atozet™ (Ezetimibe/Atorvastatin) Tablets, 10 mg/10 mg,
10 mg/20 mg, 10 mg/40 mg, 10 mg/80 mg

Review Priority Classification: Standard

Date of Application: April 28, 2011

Date of Receipt: April 29, 2011

Our Reference Number: NDA 200153

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on June 28, 2011, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be February 29, 2012.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirements. We acknowledge receipt of your request for a waiver of pediatric studies for this application. Once the application has been filed we will notify you whether we have waived the pediatric study requirement for this application.

Please cite the NDA number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, call me at 301-796-1234.

Sincerely,

{See appended electronic signature page}

Kati Johnson
Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

KATI JOHNSON
05/09/2011



NDA 200153

MEETING MINUTES

Merck & Co., Inc.
Attention: Sandra Mackenzie
Director, Worldwide Regulatory Affairs
P.O. Box 2000, RY 33-208
Rahway, NJ 07065-0900

Dear Ms. McKenzie:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (b)(4) (ezetimibe/atorvastatin) Tablets.

We also refer to the telecon between representatives of your firm and the FDA on December 3, 2009. The purpose of the meeting was to clarify issues in both the October 29, 2009 "refuse to file" and the November 3, 2009 "general advice" letters.

A copy of the official minutes of the telecon is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at 301-796-1234.

Sincerely,

{See appended electronic signature page}

Kati Johnson
Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type A
Meeting Category: Following Refuse to File letter
Meeting Date and Time: Thursday, December 3, 2009
Meeting Location: Telephone Number: 1-877-423-2663, (b) (4)
Application Number: NDA 200153
Product Name: (b) (4) (ezetimibe/atorvastatin) Tablets
Indication: Dyslipidemia
Sponsor/Applicant Name: Merck & Co., Inc.
Meeting Chair: Suong Tran, PhD
Meeting Recorder: Kati Johnson

FDA ATTENDEES

Division of Metabolism & Endocrinology Products
Eric Colman, MD-Deputy Director, Lipid Team Leader
Katrina Rhodes, MD-Clinical Reviewer
Eileen Craig, MD-Clinical Reviewer
Kati Johnson-Project Manager

Office of Translational Sciences, Office of Clinical Pharmacology
Sally Choe, PhD-Team Leader
S.W. "Johnny" Lau, PhD-Clinical Pharmacology Reviewer

Office of New Drug Quality Assessment
Prasad Peri, PhD-Branch Chief (Acting), ONDQA, Division 1 Branch II
Su Tran, PhD-Product Assessment Lead, Division of Pre-marketing Assessment I

SPONSOR ATTENDEES

Ganapathy Mohan	Pharmaceutical CMC
Cheryl Emery	Pharmaceutical CMC
Sandra Mackenzie	Regulatory Affairs
Robert Silverman	Regulatory Affairs
Andrew Tershakovec	Clinical Research
Arthur Bergman	Clinical PK/PD
Gail Murphy	Clinical Pharmacology

Martin Behm	Clinical Pharmacology
Richard Clay	Safety Assessment
Ronald Garutti	Regulatory Affairs
Diane Zezza	Regulatory Affairs CMC

1.0 BACKGROUND

(b) (4) (ezetimibe/atorvastatin) was submitted September 2, 2009, proposing to market 10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg, and 10 mg/80 mg tablets for the treatment of primary hyperlipidemia and Homozygous Familial Hypercholesterolemia (HoFH). The application was refused for filing on October 29, 2009 with a separate letter containing additional (not refuse to file) comments issuing November 3, 2009.

For completeness, copies of these two letters are appended to these meeting minutes.

2. DISCUSSION

NOTE: The comments conveyed in the two FDA letters are in regular text. The sponsor's position and subsequent question are in *italics*, our preliminary response is **bolded**, and any meeting discussion **bolded and underlined**

1. Refusal to File Issue #3

The primary stability batches were manufactured at a Research and Development (R&D) facility. Provide stability data to bridge the R&D manufacturing to the commercial manufacturing (i.e., data for three commercial batches with at least three months of long term and accelerated data) as well as multipoint dissolution profiles.

Sponsor's Position

The primary stability batches were manufactured at a GMP pilot facility in West Point, PA, within the Merck Manufacturing Division and not at an R&D facility. The West Point pilot facility used equipment that is of the same design and operating principles as those at the proposed manufacturing sites. The resubmitted NDA will contain up to 12 months of long term and 6 months of accelerated stability data from three primary stability batches for each of the 3 strengths in the formal stability study (10 mg/10 mg, 10 mg/20 mg and 10 mg/80 mg). Two of the three primary stability batches for each strength were manufactured at 1/10th of the commercial scale or greater on a per unit operation basis consistent with the ICH Q1A(R2) guidance. Additionally, the composition of the formal stability study batches is the same as the composition of the proposed commercial product. The primary stability batches are fully representative of the intended commercial batches. The drug substances used in the manufacture of the primary stability study batches were obtained from the respective commercial suppliers. The unit operations for the MK-653c tablet manufacturing process include: (b) (4)

The remaining steps were performed at the Merck Manufacturing Division GMP

pilot facility in West Point, PA. The manufacturing equipment in this facility consists of fully qualified production equipment, established to be fundamentally scalable to the commercial sites. In the case of the (b) (4) the same equipment model is used in all facilities. A comparison of equipment used for each unit operation of the manufacture of the primary stability batches and for production batches can be found in the Table 1.

Table 1: Comparison of Equipment Used for the Primary Stability Batches and Production Batches for Ezetimibe + Atorvastatin Tablet

Unit Operation	Process Equipment	
	Primary Stability Batches [†] – Merck, West Point, PA	Commercial Facilities specified in the NDA
(b) (4)		
[†] Includes pivotal bioequivalence batch		

Question 1

MSP believes that the refiled NDA containing a detailed review of the process development, the 12 months of stability data from the primary stability study and the commitment to supply additional stability data and multipoint dissolution profiles within 6 months of product launch (as described, above) will satisfy the Agency's identified deficiency in the prior NDA.

Does the Agency concur with this proposal?

FDA's response: No, we do not concur with this proposal. The primary stability batches, including the batches also used in the pivotal bioequivalence study, were fully manufactured at the facility in West Point PA. (b) (4)

(b) (4)

Your proposal to submit no testing data of any product manufactured by any one of these manufacturing site combinations for us to review prior to taking an action on the NDA is not acceptable. In order for us to determine an expiration dating period for the to-be-marketed product, at minimum 3-month accelerated stability data will be required for one product lot manufactured by each one of the manufacturing site combinations, and the data will be used to bridge to the data of the primary stability batches. In addition, multipoint *in vitro* dissolution profiles will be required for one product lot manufactured by each manufacturing site combination, and the data will be used to bridge to the data of the pivotal bioequivalence batches.

(b) (4)

2. Refusal to File Issue #4

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

Sponsor's Position

The batches used in the clinical bioequivalence study were included as part of the formal stability study program. No other clinical studies presented in the submission were conducted with any other batches of the fixed dose combination tablet. Additionally, the NDA contains a biowaiver for the 10 mg/40 mg tablet, which includes dissolution profiles demonstrating similarity via f_2 between the 10 mg/40 mg tablet and both the 10 mg/20 mg and the 10 mg/80 mg biobatch tablets.

Please refer to the preceding response for the our discussion of the similarities in composition, manufacturing equipment, environmental conditions and process, and the rationale for why comparative data between the formal stability study batches, including the biobatches, and the commercial batches were not provided in the NDA. For the reasons cited in the preceding response, we did not provide data to compare the biobatches to the commercial product.

As part of process validation, comparative multipoint dissolution profiles will be generated between the process validation batches at each proposed manufacturing site with the data from the biobatches as a measure of successful validation. The multipoint dissolution profiles for the process validation batches will be included as a component of the post-approval commitment for providing commercial site stability data within 6 months post-launch.

Question 2

MSP believes that based on the information presented, historical experience, conformance to the available guidances, MSP's commitment to compare data from the validation batches to the biobatches and provide the validation batch data within 6 months of launch will satisfy the Agency's identified deficiency in the prior NDA.

Does the Agency concur with this proposal?

FDA's Response: No, see Response to Question 1.

Meeting Discussion:

The sponsor said they understood the agency's position

(b) (4)

In response to a question from the firm regarding submitting stability data for the commercial product during the review cycle, the agency said that the NDA should be complete upon submission for filing. Therefore, all stability data (especially for the commercial product) should be included in the resubmission with no agreement on submitting stability data amendments during the NDA review, as per GRMPPs.

Following a brief discussion, it was agreed that the NDA would be resubmitted with the following chemistry information.

**-12 months of formal ICH stability data for the pilot batches and
-3 months room temperature and 3 months accelerated temperature for 1 batch of each strength tablet manufactured at the proposed commercial site and scale.**

3. Non-filing issue #6

In addition to the comparative impurity results submitted in your October 27, 2009 communication, provide physicochemical data as requested by FDA on June 30, 2009 to compare the atorvastatin used in the toxicology studies, the atorvastatin used in the commercial product, and the atorvastatin used in the RLD Lipitor. This information is required in support of the 505(b)(2) application.

Sponsor's Position

Using the information contained in Warner-Lambert Patent 5,969,156 regarding crystalline atorvastatin Form I and the FDA-approved LIPITOR label, MSP can provide the following comparative physicochemical data on the amorphous atorvastatin drug substance used in our FDC product and in our impurity qualification toxicology studies to the previously generated data on crystalline atorvastatin drug substance used in LIPITOR. This data will be included in the resubmission.

- *Appearance*
- *Solubility in various solvents*
- *X-ray Powder Diffraction*
- *Solid state ¹³C NMR*

Additionally, the impurity profile comparisons between our product and the RLD LIPITOR, demonstrating similarity between the products and submitted in the October 27, 2009 correspondence, will be provided in the resubmission.

Due to the inherent physical differences in the amorphous and crystalline forms, some physical characterization techniques are expected to demonstrate a difference between the forms. However, based on the information available in FOI documents from the LIPITOR NDA, where comparability of safety was established between the amorphous and crystalline forms, MSP believes that the

inherent differences in physicochemical characteristics of amorphous and crystalline atorvastatin would not present any clinical implications. This rationale will be provided in the submission.

Question 3

MSP believes this information will meet the requirements of 505(b)(2) referred to by the Agency in their comment. Does the Agency concur?

FDA's response: This is a review issue.

Meeting Discussion:

In response to the firm's question, they were told that their proposal appeared reasonable, but that this was clearly a review issue.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

None

4.0 ACTION ITEMS

None

5.0 ATTACHMENTS AND HANDOUTS

None

8 Pages Have Been Withheld As A Duplicate Copy Of The "Refuse to File Letter" dated October 29, 2009 and "Separate Letter Containing Additional Comments" dated November 3, 2009 Which Are Located In This Same Section Of This NDA Approval Package.

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-200153

GI-1

MSP SINGAPORE
CO LLC

(b) (4) (ezetimibe/atorvastatin
calcium amorphous) Tablet Fixed
dose combination

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/s/

KATI JOHNSON
12/18/2009



NDA 200153

REFUSAL TO FILE

Merck & Co., Inc.
Agent for MSP Singapore LLC
Attention: Sandra Mackenzie
Director, Regulatory Affairs
P.O. Box 2000, RY 33-208
Rahway, NJ 07065

Dear Ms. Mackenzie:

Please refer to your September 2, 2009 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (b) (4) (ezetimibe/atorvastatin) tablets, 10/10 mg, 10/20 mg, 10/40 mg and 10/80 mg.

After a preliminary review, we find your application is not sufficiently complete to permit a substantive review. Therefore, we are refusing to file this application under 21 CFR 314.101(d) for the following reasons:

Filing deficiencies:

1. You state that the manufacturing and testing facilities are currently not ready for GMP inspections. Therefore, this NDA is considered to be incomplete and cannot be filed until all facilities involved in the manufacturing and testing of the commercial product are ready for GMP inspections.
2. The application did not include the proposed or actual master production record for the manufacture of the commercial product in support of your 505(b)(2) application as per 21 CFR 314.54.
3. The primary stability batches were manufactured at a Research and Development (R&D) facility. Provide stability data to bridge the R&D manufacturing to the commercial manufacturing (i.e., data for three commercial batches with at least three months of long term and accelerated data) as well as multipoint dissolution profiles.
4. The application did not include any information to bridge the performance of the clinically tested batches to the commercial products (e.g., multipoint *in vitro* dissolution profiles).

We will refund 75% of the total user fee submitted with the application.

Within 30 days of the date of this letter, you may request in writing a meeting about our refusal to file the application. To file this application over FDA's protest, you must avail yourself of this informal conference.

If, after the meeting, you still do not agree with our conclusions, you may request that the application be filed over protest. In that case, the filing date will be 60 days after the date you requested the meeting. The application will be considered a new original application for user fee purposes, and you must remit the appropriate fee.

If you have any questions, call Kati Johnson, Regulatory Project Manager, at (301) 796-1234.

Sincerely yours,

{See appended electronic signature page}

Eric Colman, M.D.
Deputy Division Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-200153

ORIG-1

MSP SINGAPORE
CO LLC

(b) (4) (ezetimibe/atorvastatin
calcium amorphous) Tablet Fixed
dose combination

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/s/

ERIC C COLMAN
10/29/2009



NDA 200153

GENERAL ADVICE

Merck & Company
Agent for MSP Singapore LLC
Attention: Sandra Mackenzie
Director, Regulatory Affairs
P.O. Box 2000, RY33-208
Rahway, NJ 07065

Dear Ms. Mackenzie:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (b) (4) (ezetimibe/atorvastatin) Tablets.

We also refer to the October 29, 2009 letter notifying you that the application was not sufficiently complete to permit a substantive review, and therefore we were refusing to file the application.

We also have the following non-filing issues that should be address in a future submission:

Chemistry, Manufacturing and Controls (CMC)

1. We remind you that, regarding the reference to CMC information in NDA 21445 (Zetia), only the approved information can be referenced.
2. Provide samples of the container closure system, including the vented blister, plastic case, and foil pouch.
3. Clarify whether the materials of construction are the same for all packaging systems (commercial, hospital use, and sample) and indicate the tablet counts in the sample packaging.
4. A complete NDA should be submitted with at least 12-month primary stability data at the long term storage condition. Your NDA is submitted with 26 weeks of stability data at the long term storage condition of 25° C/60% RH and at the accelerated condition of 40° C/75% RH. While we may attempt to review unsolicited amendments submitted during the review cycle, the review of such amendments will depend on the timeliness of the submission, extent of the submitted data, and available resources. Therefore, in accordance with Good Review Management Principles and Practices (GRMPPs) timelines, we cannot guarantee that we will review unsolicited amendments such as your proposed stability update.

5. Your primary stability batches and clinical batches used in the pivotal bioequivalence studies were manufactured at an R&D facility. Provide multipoint dissolution profiles comparing these batches and the to-be-marketed product.
6. In addition to the comparative impurity results submitted in your October 27, 2009 communication, provide physicochemical data as requested by FDA on June 30, 2009 to compare the atorvastatin used in the toxicology studies, the atorvastatin used in the commercial product, and the atorvastatin used in the RLD Lipitor. This information is required in support of the 505(b)(2) application.

Pharmacology/Toxicology

Provide your justification for providing a combination toxicology study with atorvastatin and MK-6213 (a cholesterol absorption inhibitor which is not ezetimibe) in a 3-month toxicity study in dogs (with MK-6213/L000776336, study TT #07-6039).

Clinical

1. Please provide, or indicate location in the submission, subject accountability by individual investigators for all randomized subjects in tabular format for the following protocols: 079, 090, 112,145, and 051.

(b) (4) MK-0653C: Subject Accountability by Selected Investigators (All Randomized Subjects Per Individual Protocol)

Investigator (Site #) Treatment	# Subjects Randomized	# Subjects Treated	# Subjects Discontinue d	% of Randomized Subjects that Discontinued
Per Protocol				
EZ/Atorva 10/10 mg				
EZ/Atorva 10/20 mg				
EZ/Atorva 10/40 mg				
EZ/Atorva 10/80 mg				
Atorvastatin				
Ezetimibe				
Total				
Per Investigator				
EZ/Atorva 10/10 mg				
EZ/Atorva 10/20 mg				
EZ/Atorva 10/40 mg				
EZ/Atorva 10/80 mg				
Atorvastatin				
Ezetimibe				
Total				

2. Regarding Protocol P051, please provide, or indicate location in submission, financial disclosure information and an explanation of why this study is not included in the safety or efficacy analysis.

3. Regarding individual study AE datasets and ISS AE dataset, please identify, or provide location in submission, coding dictionary for mapping terms (i.e.: MedDRA Version used).
4. Please provide, or indicate location in the submission, datasets (as SAS transport files) for the following protocol(s):

Protocol	Title
051	A multicenter, randomized, double-blind, 8 arm parallel group 6-week study. Following a 4-week placebo run-in period, patients were randomized to 1 of 8 treatment groups: the ezetimibe/simvastatin combination tablet at doses of 10/10, 10/20, 10/40, or 10/80 mg/mg, or atorvastatin alone at doses of 10, 20, 40, or 80 mg for 6 weeks.
01418 (x693; 032)	Long Term, Open-Label, Safety and Tolerability Study of Ezetimibe in Addition to Atorvastatin in Subjects with Coronary Heart Disease or Multiple Risk Factors and with Primary Hypercholesterolemia Not Controlled by a Starting Dose (10 mg) of Atorvastatin
O1417 (x1030; 019)	Long-Term, Open-Label, Safety and Tolerability Study of SCH 58235 in Addition to Atorvastatin or Simvastatin in the Therapy of Homozygous Familial Hypercholesterolemia
02173R/ 02246 (Reversability Period 02173)	A Multicenter, Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Lipid-Altering Efficacy, Safety and Tolerability of SCH 58235 (Ezetimibe 10 mg) When Added to Ongoing Therapy With an HMG-CoA Reductase Inhibitor (Statin) in Patients With Primary Hypercholesterolemia, Known Coronary Heart Disease or Multiple Cardiovascular Risk Factors

5. Please add the following variables to ISS datasets (ADSL/AE/LB): 1) unique subject identifier (in the same format as individual studies' variable 'USUBJID' (Char40)) (ADSL/AE/LB); 2) MedDRA hierarchy terms for LLT, HLT, and HLG (AE); 3) concomitant medications (ADSL/AE); 4) vitals (LB); and 5) Creatinine (LB).
6. Please provide, or identify location in submission, any publications based on newly submitted clinical studies post-approval of Zetia (NDA 21,445).

Clinical Statistics

Submit the analysis data files for study P693 (A Phase 3 double-blind efficacy and safety study of ezetimibe 10 mg in addition to atorvastatin in subjects with coronary heart disease or multiple cardiovascular risk factors and with primary hypercholesterolemia not controlled by a starting dose (10 mg) of atorvastatin). We could only locate the data listings.

Regulatory

In your amendment dated September 11, 2009, you clarified that the applicant for NDA 200153 is MSP Singapore Company, LLC. However, the letters of authorization submitted as part of

NDA 200-153 generally authorize Merck & Co., Inc. to incorporate by reference certain information in specified Drug Master Files into certain drug applications filed by Merck & Co., Inc. These letters of authorization are inadequate for an application submitted by MSP Singapore Company, LLC. If MSP Singapore Company, LLC intends to rely upon certain information in Drug Master Files, an adequate letter of authorization to each DMF is required (see 21 CFR 314.420).

If you have any questions, call Kati Johnson, Regulatory Project Manager, at (301) 796-1234.

Sincerely,

{See appended electronic signature page}

Eric Colman, M.D.
Deputy Division Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Application
Type/Number

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ORIG-1

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/s/

ERIC C COLMAN
11/03/2009



NDA 200153

NDA ACKNOWLEDGMENT

Merck & Co., Inc.
Agent for MSP Singapore Company, LLC
Attention: Sandra Mackenzie
Director, Regulatory Affairs
P.O. Box 2000, RY 33-208
Rahway, NJ 07065

Dear Ms. Mackenzie:

We have received your new drug application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: (b) (4) (Ezetimibe/Atorvastatin) Tablets, 10/10 mg, 10/20 mg, 10/40 mg and 10/80 mg

Date of Application: September 2, 2009

Date of Receipt: September 2, 2009

Our Reference Number: NDA 200153

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on **November 1, 2009** in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size.

Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>

If you have any questions, call me at (301) 796-1234.

Sincerely,

{See appended electronic signature page}

Kati Johnson
Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
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/s/

KATI JOHNSON
10/27/2009