

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
200153Orig1s000

OTHER REVIEW(S)

505(b)(2) ASSESSMENT

Application Information		
NDA # 200153	NDA Supplement #: S- N/A	Efficacy Supplement Type SE- N/A
Proprietary Name: Liptruzet Established/Proper Name: Ezetimibe/Atorvastatin Dosage Form: Tablets Strengths: 10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg, 10 mg/80 mg		
Applicant: MSD International GmbH		
Date of Receipt: 11/5/2012		
PDUFA Goal Date: 5/4/2013		Action Goal Date (if different): 5/3/2013
Proposed Indication(s): 1. reduce elevated total-C, LDL-C, Apo B, TG, and non-HDL-C, and to increase HDL-C in patients with primary (heterozygous familial and non-familial) hyperlipidemia or mixed hyperlipidemia. 2. reduce elevated total-C and LDL-C in patients with homozygous familial hypercholesterolemia (HoFH), as an adjunct to other lipid-lowering treatments.		

GENERAL INFORMATION

1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product OR is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES NO

If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.



**INFORMATION PROVIDED VIA RELIANCE
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. (*If not clearly identified by the applicant, this information can usually be derived from annotated labeling.*)

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
Lipitor (NDA 20702)	Clinical, Clinical Pharmacology, Pharmacology/Toxicology, Quality

*each source of information should be listed on separate rows

- 3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific “bridge” to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

For strengths 10/10 and 10/80-bridge thru BE

For strengths 10/20 and 10/40-the sponsor provided evidence that the fixed dose combinations were equivalent for LDL-C lowering when compared with coadministered ezetimibe with atorvastatin 20 mg and 40 mg.

RELIANCE ON PUBLISHED LITERATURE

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES NO

If “NO,” proceed to question #5.

- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES NO

If “NO,” proceed to question #5.

If “YES”, list the listed drug(s) identified by name and answer question #4(c).

- (c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES NO

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

- 5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES NO

If "NO," proceed to question #10.

- 6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)
Lipitor	NDA 20702	Y

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A YES NO

If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".

If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 8) Were any of the listed drug(s) relied upon for this application:

- a) Approved in a 505(b)(2) application?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved in a 505(b)(2) application:

- b) Approved by the DESI process?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved via the DESI process:

- c) Described in a monograph?

YES NO

If “YES”, please list which drug(s).

Name of drug(s) described in a monograph:

d) Discontinued from marketing?

YES NO

If “YES”, please list which drug(s) and answer question d) i. below.

If “NO”, proceed to question #9.

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES NO

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, “This application provides for a new indication, otitis media” or “This application provides for a change in dosage form, from capsule to solution”).

This application proposes a combination product containing the 505(b)(2) product, Lipitor (atorvastatin) and Zetia (ezetimibe).

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered YES to question #1, proceed to question #12; if you answered NO to question #1, proceed to question #10 below.

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c)).

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.

YES NO

If "**NO**" to (a) proceed to question #11.
If "**YES**" to (a), answer (b) and (c) then proceed to question #12.

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

YES NO

If "**YES**" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.

If "**NO**" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.

YES NO

If "**NO**", proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

YES NO

If "**YES**" and there are no additional pharmaceutical alternatives listed, proceed to question #12.

If "**NO**" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in

the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s): 5,686,104
5,969,156
6,126,971

No patents listed proceed to question #14

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES X NO

If "NO", list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

X 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s): 5,273,995
RE40,667

21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s):

X 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification*

- was submitted, proceed to question #15.*
- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*
- 21 CFR 314.50(i)(1)(ii): No relevant patents.
- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):
Method(s) of Use/Code(s):

15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s): 5,686,104; 5,969,156; 6,126,971

(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]? YES X NO
If "NO", please contact the applicant and request the signed certification.

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt. YES X NO
If "NO", please contact the applicant and request the documentation.

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s): 7/7/2011

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.

YES X NO Patent owner(s) consent(s) to an immediate effective date of approval
For patent 5,969,156 only

NOTE: In a 4/16/2012 submission, the Agency was notified that MSD International GmbH was granted a nonexclusive license by Pfizer to make, use, formulate, package, import, export, offer to sell, and sell the Ezetimibe/Atorvastatin product that is the subject of NDA 200153.

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

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: May 2, 2013

To: Kati Johnson, Regulatory Project Manager
Division of Metabolism and Endocrinology Products (DMEP)

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

Subject: NDA 200153 LIPTRUZET™ (ezetimibe and atorvastatin) Tablets

OPDP has reviewed the proposed Prescribing Information (PI) and Patient Information (PPI) for LIPTRUZET™ (ezetimibe and atorvastatin) Tablets submitted for consult on March 21, 2013.

OPDP's comments on the proposed draft PI and PPI are based on the version sent via email from Kati Johnson (RPM) on April 30, 2013, and are provided directly on the marked version provided below.

Thank you for the opportunity to comment on this label. If you have any questions regarding this proposed draft label, please contact Kendra Jones at 301-796-3917 or Kendra.jones@fda.hhs.gov.

29 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

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
05/02/2013

SEALD Director Sign-Off Review of the End-of-Cycle Prescribing Information: Outstanding Format Deficiencies

Product Title	LIPTRUZET (ezetimibe and atorvastatin) tablets, for oral use
Applicant	Merck Sharp and Dohme, Corp.
Application/Supplement Number	NDA 200153
Type of Application	Original Submission
Indication(s)	As adjunctive therapy to diet to: <ul style="list-style-type: none"> • reduce elevated total-C, LDL-C, Apo B, TG, and non-HDL-C, and to increase HDL-C in patients with primary (heterozygous familial and non-familial) hyperlipidemia or mixed hyperlipidemia. • reduce elevated total-C and LDL-C in patients with homozygous familial hypercholesterolemia (HoFH), as an adjunct to other lipid-lowering treatments.
Established Pharmacologic Class ¹	A cholesterol absorption inhibitor and a HMG-CoA reductase inhibitor (statin)
Office/Division	ODE II/DMEP
Division Project Manager	Kati Johnson
Date FDA Received Application	November 5, 2012
Goal Date	May 5, 2013
Date PI Received by SEALD	April 24, 2013
SEALD Review Date	April 25, 2013
SEALD Labeling Reviewer	Jeanne M. Delasko
SEALD Division Director	Laurie Burke

PI = prescribing information

¹ The established pharmacologic class (EPC) that appears in the final draft PI.

This Study Endpoints and Labeling Development (SEALD) Director Sign-Off review of the end-of-cycle, draft prescribing information (PI) for critical format elements reveals **outstanding labeling format deficiencies that must be corrected** before the final PI is approved. After these outstanding labeling format deficiencies are corrected, the SEALD Director will have no objection to the approval of this PI.

The critical format elements include labeling regulation (21 CFR 201.56 and 201.57), labeling guidance, and best labeling practices (see list below). This review does not include every regulation or guidance that pertains to PI format.

Guide to the Selected Requirements of Prescribing Information (SRPI) Checklist: For each SRPI item, one of the following 3 response options is selected:

- **NO**: The PI **does not meet** the requirement for this item (**deficiency**).
- **YES**: The PI **meets** the requirement for this item (**not a deficiency**).
- **N/A** (not applicable): This item does not apply to the specific PI under review.

Selected Requirements of Prescribing Information

Highlights (HL)

GENERAL FORMAT

- NO** 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment: Top margin is 1 inch, instead of 1/2 inch.

- YES** 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period (for RPMs)**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of Cycle Period (for SEALD reviewers)**

- The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment: HL is > 1/2 page. DMEP will grant a waiver.

- NO** 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment: Use in Specific Populations heading is not presented in the center of the horizontal line.

- YES** 4. White space must be present before each major heading in HL.

Comment:

- NO** 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment: Information under Use in Specific Populations heading in HL must reference (8.6) in the FPI. The reference is missing.

- YES** 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required

Selected Requirements of Prescribing Information

• Boxed Warning	Required if a Boxed Warning is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state “None.”)
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

NO

7. A horizontal line must separate HL and Table of Contents (TOC).

Comment: *There is a small line fragment. A complete horizontal line must be inserted.*

HIGHLIGHTS DETAILS

Highlights Heading

YES

8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: “**HIGHLIGHTS OF PRESCRIBING INFORMATION**”.

Comment:

Highlights Limitation Statement

YES

9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: “**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**”

Comment:

Product Title

YES

10. Product title in HL must be **bolded**.

Comment:

Initial U.S. Approval

NO

11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Comment: *Must insert "2013" for 4-digit year and not "XXXX."*

Boxed Warning

N/A

12. All text must be **bolded**.

Comment:

N/A

13. Must have a centered heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Selected Requirements of Prescribing Information

Comment:

- N/A** 14. Must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” in *italics* and centered immediately beneath the heading.

Comment:

- N/A** 15. Must be limited in length to 20 lines (this does not include the heading and statement “*See full prescribing information for complete boxed warning.*”)

Comment:

- N/A** 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

- N/A** 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

- N/A** 18. Must be listed in the same order in HL as they appear in FPI.

Comment:

- N/A** 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Dosage and Administration, Coronary Stenting (2.2) --- 3/2012”.

Comment:

- N/A** 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage

- YES** 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

Comment:

Dosage Forms and Strengths

- N/A** 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Contraindications

- YES** 23. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known.

Comment:

YES

Selected Requirements of Prescribing Information

24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

Adverse Reactions

- YES** 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

Patient Counseling Information Statement

- YES** 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product does not have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product has FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**”

Comment:

Revision Date

- NO** 27. **Bolded** revision date (i.e., “**Revised: MM/YYYY or Month Year**”) must be at the end of HL.

Comment: *Must read "Revised: April 2013," if approved in April or "Revised: May 2013" if approved in May, not "Revised: XX/XXXX."*

Contents: Table of Contents (TOC)

GENERAL FORMAT

- YES** 28. A horizontal line must separate TOC from the FPI.

Comment:

- NO** 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”.

Comment:

- NO** 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment: *Subsection 7.5 in the TOC reads "Fenofibrates" but subsection 7.5 in the FPI reads (b) (4) The TOC heading must match the FPI heading.*

- N/A** 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Comment:

- YES** 32. All section headings must be **bolded** and in UPPER CASE.

Selected Requirements of Prescribing Information

Comment:

YES 33. All subsection headings must be indented, not bolded, and in title case.

Comment:

YES 34. When a section or subsection is omitted, the numbering does not change.

Comment:

YES 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “**FULL PRESCRIBING INFORMATION: CONTENTS**” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”

Comment:

Full Prescribing Information (FPI)

GENERAL FORMAT

YES 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: “**FULL PRESCRIBING INFORMATION**”.

Comment:

YES 37. All section and subsection headings and numbers must be **bolded**.

Comment:

YES 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action

Selected Requirements of Prescribing Information

12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- NO** 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment: *FDA-approved patient labeling (Patient Information) does not appear at the end of the PI.*

- YES** 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, “[see Warnings and Precautions (5.2)]”.

Comment:

- N/A** 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

- N/A** 42. All text is **bolded**.

Comment:

- N/A** 43. Must have a heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Comment:

- N/A** 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

- N/A** 45. If no Contraindications are known, this section must state “None”.

Comment:

Adverse Reactions

- YES** 46. When clinical trials adverse reactions data is included (typically in the “Clinical Trials Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

Selected Requirements of Prescribing Information

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”

Comment:

- YES** 47. When postmarketing adverse reaction data is included (typically in the “Postmarketing Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

Patient Counseling Information

- YES** 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:
- “See FDA-approved patient labeling (Medication Guide)”
 - “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information)”
 - “See FDA-approved patient labeling (Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

Comment:

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/s/

JEANNE M DELASKO
04/25/2013

LAURIE B BURKE
04/29/2013

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label and Labeling Memo

Date: March 27, 2013

Reviewer: Reasol S. Agustin, PharmD
Division of Medication Error Prevention and Analysis

Team Leader Lubna Merchant, MS, PharmD
Division of Medication Error Prevention and Analysis

Drug Name: Ezetimibe and Atorvastatin Tablets, 10 mg/10 mg, 10 mg/20 mg,
10 mg/40 mg, 10 mg/80 mg

Application Type/Number: NDA 200153

Applicant/sponsor: Merck and Co, Inc

OSE RCM #: 2012-2941

*** This document contains proprietary and confidential information that should not be released to the public.***

1 INTRODUCTION

This review evaluates the revised container labels, carton, and insert labeling for Atozet (Ezetimibe and Atorvastatin) Tablets for NDA 200153 for areas of vulnerability that could lead to medication errors. The Applicant initially submitted labels and labeling on July 7, 2011 and the Division of Medication Error Prevention and Analysis (DMEPA) provided comments and recommendations in OSE Review #2011-2459, dated January 26, 2012.

On February 29, 2012, the application received a Complete Response (CR) Letter due to bioequivalence issues. On November 5, 2012, Merck resubmitted the proposed container labels, carton, and insert labeling for Atozet (Ezetimibe and Atorvastatin) Tablets.

2 MATERIAL REVIEWED

The proposed container label and carton labeling submitted to the Agency on November 5, 2012 (See Appendices) and OSE Review 2011-2459, dated January 26, 2012, were evaluated to assess whether the recommendations adequately addressed our concerns from a medication error perspective.

3 CONCLUSIONS AND RECOMMENDATIONS

The container labels and carton labeling submitted on November 5, 2012, addressed most of DMEPA's concerns. However, upon further evaluation, we have the following recommendations.

A. All Labels and Labeling

Update all labels and labeling to remove reference to the proprietary name, 'Atozet' as this name has been denied.

B. Insert Labeling

Revise the strength presentation to read "XX mg/XX mg" (i.e. 10 mg/10 mg)

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review.

If you have further questions or need clarifications, please contact OSE Regulatory Project Manager Margarita Tossa at 301-796-4053.

12 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS)
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/s/

REASOL AGUSTIN
03/29/2013

LUBNA A MERCHANT
04/01/2013

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs**

PATIENT LABELING REVIEW

Date: March 27, 2013

To: Mary Parks, MD
Director
**Division of Metabolism and Endocrinology Products
(DMEP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)
Robin Duer, MBA, BSN, RN
Senior Patient Labeling Reviewer,
Division of Medical Policy Programs (DMPP)

From: Shawna Hutchins, MPH, BSN, RN
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Subject: DMPP Review of Patient Labeling: Patient Package Insert
(PPI)

Drug Name (established name): ATOZET (ezetimibe/atorvastatin)

Dosage Form and Route: Tablets

Application Type/Number: NDA 200-153

Applicant: Merck Sharp & Dohme Corporation

1 INTRODUCTION

On November 05, 2012, Merck Sharp & Dohme Corporation re-submitted for the Agency's review a New Drug Application (NDA 200-153) for ATOZET (ezetimibe/atorvastatin) Tablets. ATOZET (ezetimibe/atorvastatin) contains a cholesterol absorption inhibitor and an HMG-CoA reductase inhibitor (statin) and is indicated as adjunctive therapy to diet to:

- reduce elevated total-C, LDL-C, Apo B, TG, and non-HDL-C, and to increase HDL-C in patients with primary (heterozygous familial and non-familial) hyperlipidemia or mixed hyperlipidemia.
- reduce elevated total-C and LDL-C in patients with homozygous familial hypercholesterolemia (HoFH) as an adjunct to other lipid-lowering treatments.

ATOZET was originally submitted on April 29, 2011. On February 29, 2012, the Agency issued a Complete Response (CR) letter citing clinical pharmacology and safety deficiencies.

On March 19, 2013, the Division of Metabolism and Endocrinology Products (DMEP) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Patient Package Insert (PPI) for ATOZET (ezetimibe/atorvastatin) Tablets. This review is written in response to the request by DMEP for DMPP to review the Applicant's proposed Patient Package Insert (PPI) for ATOZET (ezetimibe/atorvastatin) Tablets.

2 MATERIAL REVIEWED

- Draft ATOZET (ezetimibe/atorvastatin) PPI received on November 05, 2013 and received by DMPP on March 21, 2013
- Draft ATOZET (ezetimibe/atorvastatin) Prescribing Information (PI) received on November 05, 2012, revised by the Review Division throughout the review cycle, and received by DMPP on March 21, 2013
- Approved VYTORIN (ezetimibe/simvastatin) comparator labeling dated October 31, 2012

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APFont to make medical information more accessible for patients with vision loss. We have reformatted the PPI document using the Verdana font, size 11.

In our review of the PPI we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI is consistent with the approved comparator labeling where applicable

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our review of the PPI is appended to this memorandum. Consult DMPP regarding any additional revisions made to the Package Insert (PI) to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/

SHAWNA L HUTCHINS
03/27/2013

ROBIN E DUER
03/27/2013

LASHAWN M GRIFFITHS
03/27/2013

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs**

REVIEW DEFERRAL MEMO

Date: February 14, 2012

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

Through: LaShawn Griffiths, RN, MSHS-PH, BSN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Melissa Hulett, RN, BSN, MSBA
Team Leader, Patient Labeling Team
Division of Medical Policy Programs

From: Sharon W. Williams, MSN, BSN, RN
Patient Labeling Reviewer
Division of Medical Policy Programs

Subject: DMPP Review Deferred: Patient Package Insert (PPI)

Drug Name(s): Atozet (ezetimibe/atorvastatin)

Application Type/Number: NDA 200153

Applicant/Sponsor: Merck Sharp & Dohme Corp.

OSE RCM #: 2011-2458

This memorandum documents the deferral of our review of our review of Atozet (ezetimibe/atorvastatin). On July 7, 2011 the Division of Metabolism and Endocrinology Products requested that DMPP review the Patient Package Insert (PPI).

Due to outstanding Clinical and Chemistry deficiencies, the Division of Metabolism and Endocrinology Products plans to issue a Complete Response (CR) letter.

Therefore, DMPP defers comment on the sponsor's Patient Labeling at this time. A final review will be performed after the Applicant submits a Complete Response to the Complete Response letter. Please send us a new consult request at such time.

Please notify us if you have any questions.

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/s/

SHARON W WILLIAMS
02/14/2012

MELISSA I HULETT
02/14/2012

LASHAWN M GRIFFITHS
02/14/2012

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label and Labeling Review

Date: January 26, 2012

Reviewer: Anne C. Tobenkin, PharmD
Division of Medication Error Prevention and Analysis

Team Leader: Lubna Merchant, PharmD, M.S.
Division of Medication Error Prevention and Analysis

Deputy Director: Kellie Taylor, PharmD, MPH

Division Director: Carol Holquist, R.Ph.
Division of Medication Error Prevention and Analysis

Drug Name(s) and Strengths: Atozet (Ezetimibe and Atorvastatin) Tablets, 10 mg/10 mg,
10 mg/20 mg, 10 mg/40 mg, 10 mg/80 mg

Application Type/Number: NDA 200153

Applicant/sponsor: MSP Singapore, Inc.

OSE RCM #: 2011-2459

*** This document contains proprietary and confidential information that should not be released to the public.***

1 INTRODUCTION

This review evaluates the proposed container labels, carton and insert labeling for Atozet (Ezetimibe and Atorvastatin) Tablets for NDA 200153 for areas of vulnerability that could lead to medications errors. The review responds to a request from the Division of Metabolism and Endocrinology Products (DMEP). The proposed proprietary name, Atozet, was found acceptable in OSE review # 2011-2469.

1.1 PRODUCT INFORMATION

The following product information is provided in the July 7, 2011 proprietary name submission.

- Established Name: Ezetimibe and Atorvastatin
- Indication of Use: Reduction of cholesterol in primary hyperlipidemia and homozygous familial hypercholesterolemia
- Route of administration: oral
- Dosage form: tablet
- Dose: One tablet (10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg, 10 mg/80 mg)
- How Supplied: Physician samples of 7 tablets per packet, Hospital unit dose, plastic packs of 10, packaged in 3
- Storage: Store in original pouch at room temperature, protect from moisture and light
- Container and Closure System: Foil pouches, not child resistant

2 METHODS AND MATERIALS REVIEWED

Using Failure Mode and Effects Analysis¹, and postmarketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted July 7, 2011
- Carton Labeling submitted July 7, 2011
- Insert Labeling submitted July 7, 2011

3 CONCLUSIONS AND RECOMMENDATIONS

The proposed labels and labeling introduce vulnerability that can lead to medication errors because of a prominent graphic on the principal display panel as well as information presented in a cluttered manner which detracts from important information. We recommend the following revisions be implemented prior to the approval of this NDA:

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

A. *Insert Labeling*

1. Revise the strength statement throughout the labeling so that both strengths are followed by ‘mg’.
2. The symbols ‘<’ and ‘>’ are utilized throughout the Dosage and Administration section of the labeling are dangerous symbols that appear on the ISMP List of Error-Prone Abbreviations, Symbols, and Dose Designations². These symbols are often mistaken and used as opposite of intended. Replace all instances of the symbol ‘<’ with phrase “less than” and symbol ‘>’ with phrase “greater than.”

B. *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 table graphic that appears on the principal display panel and replace with an actual image of the Atozet tablet.

C. *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
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 bottle of the principal display panel or the backside of the sample blister.

² Institute for Safe Medication Practices, “List of Error-Prone Abbreviations, Symbols, and Dose Designations. www.ismp.org.

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.

D. Sample Foil Pouch (All Strengths)

1. See C1 through C5.
2. Relocate the instructions to protect from moisture so that it appears in the white area of the principal display panel and appear in bold black font.

E. Sample Carton Labeling (All Strengths)

1. See C1 through C4.
2. Revise the contents of the carton statement to state:
This carton contains 4 patient pouches.
Each pouch contains 7 tablets
Additionally, increase the font of the 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.

F. HUD Foil pouch (All Strengths)

1. See C1 through C5 and E3

G. 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).

H. Plastic Case (front)

1. See comments C1 through C4.
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

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

1. See C1 through C5, E2 and E3.

If you have further questions or need clarifications, please contact OSE Project Manager, Margarita Tossa, at 301-796-4053.

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/s/

ANNE C TOBENKIN
01/26/2012

LUBNA A MERCHANT
01/26/2012

KELLIE A TAYLOR
01/27/2012

CAROL A HOLQUIST
01/27/2012

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements (except SE8 and SE9)

Application Information		
NDA # 200153 BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: Atozet Established/Proper Name: ezetimibe/atorvastatin Dosage Form: Tablets Strengths: 10/10, 10/20, 10/40, 10/80		
Applicant: MSP Singapore Company, LLC Agent for Applicant (if applicable): Merck & Co.		
Date of Application: 4/28/2011 Date of Receipt: 4/29/2011 Date clock started after UN: N/A		
PDUFA Goal Date: 2/29/2012	Action Goal Date (if different):	
Filing Date: 6/28/2011	Date of Filing Meeting: 6/27/2011	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 4		
Proposed indication(s)/Proposed change(s): ATOZET, which contains a cholesterol absorption inhibitor and an HMG-CoA reductase inhibitor (statin), is indicated as adjunctive therapy to diet to: -reduce elevated total-C, LDL-C, Apo B, TG, and non-HDL-C, and to increase HDL-C in patients with primary (heterozygous familial and non-familial) hyperlipidemia or mixed hyperlipidemia. -reduce elevated total-C and LDL-C in patients with homozygous familial hypercholesterolemia (HoFH), as an adjunct to other lipidlowering treatments.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at:</i> http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html <i>and refer to Appendix A for further information.</i>		
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input checked="" type="checkbox"/>	
Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i> N/A	<input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Drug/Device <input type="checkbox"/> Biologic/Device	
<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation N/A	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR]	

<input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other: N/A	314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (<i>if OTC product</i>):		N/A		
List referenced IND Number(s): 101953				
Goal Dates/Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			Revise tradename is under review.
Are all classification properties [e.g., orphan drug, 505(b)(2)] entered into tracking system? <i>If not, ask the document room staff to make the appropriate entries.</i>	X			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm		X		
If yes, explain in comment column.				
If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:			X	
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			
<u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send UN letter and contact user fee staff.</i>	Payment for this application: X Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>	Payment of other user fees: X Not in arrears <input type="checkbox"/> In arrears			

Note: 505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. All 505(b) applications, whether 505(b)(1) or 505(b)(2), require user fees unless otherwise waived or exempted (e.g., small business waiver, orphan exemption).

505(b)(2) (NDAs/NDA Efficacy Supplements only)		YES	NO	NA	Comment
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?			X		
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).			X		
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))? <i>Note: If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).</i>			X		
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm If yes, please list below:					There is no unexpired Hatch Waxman exclusivity but pediatric studies have extended the patent life.
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration		
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>					
Exclusivity		YES	NO	NA	Comment
Does another product have orphan exclusivity for the same indication? Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm			X		
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)</i>					
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (NDAs/NDA efficacy supplements only) If yes, # years requested: <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>			X		

Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?		X		
If yes , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i>				

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission , which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission , does it follow the eCTD guidance ¹ ? If not , explain (e.g., waiver granted).	X			
Index : Does the submission contain an accurate comprehensive index?	X			
Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including: <input type="checkbox"/> legible <input type="checkbox"/> English (or translated into English) <input type="checkbox"/> pagination <input type="checkbox"/> navigable hyperlinks (electronic submissions only) If no , explain.	X			
Controlled substance/Product with abuse potential : Is an Abuse Liability Assessment, including a proposal for scheduling, submitted? <i>If yes, date consult sent to the Controlled Substance Staff:</i>		X		
BLAs only : Companion application received if a shared or divided manufacturing arrangement? If yes , BLA #			X	

Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature? <i>If foreign applicant, both the applicant and the U.S. agent must sign the form.</i>	X			
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a?	X			
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature? <i>Forms must be signed by the APPLICANT, not an Agent.</i> <i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>	X			
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	X			
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? (<i>Certification is not required for supplements if submitted in the original application</i>) <i>If foreign applicant, both the applicant and the U.S. Agent must sign the certification.</i> <i>Note: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i>	X			

Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>			X	

Pediatrics	YES	NO	NA	Comment
<p><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	X			
<p>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>	X			
<p>If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?</p> <p><i>If no, request in 74-day letter</i></p>			X	
<p>If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3)</p> <p><i>If no, request in 74-day letter</i></p>	X			
<p><u>BPCA</u> (NDAs/NDA efficacy supplements only):</p> <p>Is this submission a complete response to a pediatric Written Request?</p> <p><i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)</i></p>		X		

Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that it is submitted as a separate document and routed directly to OSE/DMEPA for review.</i>	X			
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input checked="" type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request in 74-day letter.</i>	X			
Is the PI submitted in PLR format?	X			
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request PLR format in 74-day letter.</i>			X	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?		X		Will be consulted when there is a "substantially complete" PI
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)			X	PPI will be consulted to OSE/DRISK when there is a "substantially complete" PI
REMS consulted to OSE/DRISK?			X	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA?	X			Carton/Immediate container labels sent
OTC Labeling	X Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			

	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>				

Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>		X		

Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): <i>If yes, distribute minutes before filing meeting</i>		X		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): <i>If yes, distribute minutes before filing meeting</i>		X		
Any Special Protocol Assessments (SPAs)? Date(s): <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>		X		

¹<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

ATTACHMENT

MEMO OF FILING MEETING

DATE: June 27, 2011

BLA/NDA/Supp #: NDA 200153

PROPRIETARY NAME: Atozet

ESTABLISHED/PROPER NAME: ezetimibe/atorvastatin

DOSAGE FORM/STRENGTH: Tablets, 10/10, 10/20, 10/40, 10/80

APPLICANT: MSD International GmbH

PROPOSED INDICATION(S)/PROPOSED CHANGE(S):

ATOZET, which contains a cholesterol absorption inhibitor and an HMG-CoA reductase inhibitor (statin), is indicated as adjunctive therapy to diet to:

- reduce elevated total-C, LDL-C, Apo B, TG, and non-HDL-C, and to increase HDL-C in patients with primary (heterozygous familial and non-familial) hyperlipidemia or mixed hyperlipidemia.
- reduce elevated total-C and LDL-C in patients with homozygous familial hypercholesterolemia (HoFH), as an adjunct to other lipidlowering treatments.

BACKGROUND:

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Kati Johnson	Y
	CPMS/TL:		
Cross-Discipline Team Leader (CDTL)	Eric Colman		Y
Clinical	Reviewer:	Iffat Chowdhury	Y
	TL:		
Social Scientist Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
Clinical Microbiology (<i>for antimicrobial</i>)	Reviewer:		

<i>products)</i>			
	TL:		
Clinical Pharmacology	Reviewer:	Johnny Lau	Y
	TL:	Jaya Vaidyanathan	Y
Biostatistics	Reviewer:	Janice Derr	Y
	TL:	Todd Sahlroot	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Indra Antonipillai	Y
	TL:	Karen Davis Bruno	Y
Statistics (carcinogenicity) N/A	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>) N/A	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Joe Leginus Biopharm=Deepika Lakhani	N
	TL:	Suong Tran	Y
Quality Microbiology (<i>for sterile products</i>) N/A	Reviewer:		
	TL:		
CMC Labeling Review (<i>for BLAs/BLA supplements</i>) N/A	Reviewer:		
	TL:		
Facility Review/Inspection N/A	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Anne Tobenkin	N
	TL:	Lubna Merchant	N
OSE/DRISK (REMS) N/A	Reviewer:		
	TL:		
Bioresearch Monitoring (DSI)	Reviewer:		

BE Study Inspectors TBD			
	TL:		

Other reviewers: Maternal Health	Millie Wright	Y
Other attendees		

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> 505(b)(2) filing issues? <p>If yes, list issues:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Electronic Submission comments <p>List comments:</p>	<input checked="" type="checkbox"/> Not Applicable
<p>CLINICAL</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain: Most of the studies were already conducted under NDA 21445 (Zetia)</p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure,</i> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:

<i>mitigation, treatment or prevention of a disease</i>	
<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>PRODUCT QUALITY (CMC)</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE

Comments:	<input type="checkbox"/> Review issues for 74-day letter
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? If no, was a complete EA submitted? If EA submitted, consulted to EA officer (OPS)? <p>Comments:</p>	<input type="checkbox"/> Not Applicable X YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments:</p>	X Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? <p>Comments:</p>	<input type="checkbox"/> Not Applicable X YES <input type="checkbox"/> NO X YES <input type="checkbox"/> NO
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	X Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>CMC Labeling Review (BLAs/BLA supplements only)</u></p> <p>Comments:</p>	<input type="checkbox"/> Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Eric Colman	
21st Century Review Milestones (see attached) (optional):	
Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
X	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p>X Review issues have been identified for the 74-day letter. List (optional):</p> <p><u>Review Classification:</u></p> <p>X Standard Review</p> <p><input type="checkbox"/> Priority Review</p>
ACTIONS ITEMS	
<input type="checkbox"/>	Ensure that the review and chemical classification properties, as well as any other pertinent properties (e.g., orphan, OTC) are correctly entered into tracking system.
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	<p>If priority review:</p> <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify DMPQ (so facility inspections can be scheduled earlier)
<input type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original 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) 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, or
- (3) 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) 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, and.
- (3) 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) 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, or
- (3) 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 OND ADRA or OND IO.

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
11/18/2011

MEMORANDUM

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

DATE: August 8, 2011

TO: Associate Director
International Operations Drug Group
Division of Foreign Field Investigations

Director, Investigations Branch
Florida District Office (FLA-DO)
555 Winderly Place, Suite 200
Maitland, FL 32751

Director, Investigations Branch
Baltimore District Office (BLT-DO)
6000 Metro Drive, Suite 101
Baltimore, MD 21215

FROM: Martin K. Yau, Ph.D.
Acting Team Leader—Bioequivalence Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

SUBJECT: FY 2011, **High Priority CDER NDA Pre-Approval Data
Validation Inspection**, Bioresearch Monitoring, Human
Drugs, CP 7348.001

RE: NDA 200-153
DRUG: ATOZET (EZETIMIBE/ATORVASTATIN) TABLETS, 10/10,
10/20, 10/40, 10/80 (mg/mg)

SPONSOR: MSP Singapore Company LLC.
300 Beach Road #12-08
The Concourse
Singapore 199555
TEL: Not available
FAX: Not available
EMAIL ADDRESS: Not available

U.S. AGENT: Jeffrey R. Tucker, M.D.,
Sen. Dir., Regulatory Affairs
P.O. Box 1000

UG2CD-48, North Wales, PA 19454-1099
TEL: 267-305-6715
FAX: 267-305-6406
EMAIL ADDRESS: Not available

This memo requests an inspection of the clinical and analytical portions of the following bioequivalence studies. **Due to the 'User Fee' due date, this inspection should be completed before 12/13/2011.**

Study P-145:

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

Clinical Site P-145-01:

Comprehensive Phase 1
Comprehensive NeuroScience, Inc.
3400 Enterprise Way
Miramar, FL 33025

Principal Clinical Investigator at Clinical Site P-145-01:

Maria J. Gutierrez, M.D., F.A.C.R., CPI
TEL: 954-266-1000
FAX: Not available
E-Mail Address: Not available

Clinical Site P-145-02:

Comprehensive Phase 1
Comprehensive NeuroScience, Inc.
3745 Broadway Avenue, Suite 100
Fort Myers, FL 33901

Principal Clinical Investigator at Clinical Site P-145-02:

Melanie Fein, M.D., DABFM, CPI
TEL: 239-461-8600
FAX: Not available
E-Mail Address: Not available

Study P-183:

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

Clinical Site P-183:

Sea View Research Inc.
3898 NW 7th Street
Miami, FL 33126

Principal Clinical Investigator at Clinical Site P-183:

Audrey E. Martinez, MD
TEL: 305-665-6074
FAX: Not available
E-Mail Address: Not available

Please check the batch numbers of the test and reference formulations used in Study P-145 and Study P-183 with the descriptions in documents submitted to the Agency. Please confirm whether reserve samples were retained as required by 21 CFR Parts 320.38 and 320.63. Samples of the test and reference drug formulations should be collected and mailed to the Division of Pharmaceutical Analysis, St. Louis, MO, for screening.

Please note that the Study P-145 was conducted in three parts (Part I, II, and III) and 96 subjects were enrolled for each part (i.e., total of 288 subjects for the study P-145). The Part I and II (i.e., a total of 192 subjects were enrolled) were conducted at the clinical site 145-01 and part III (i.e., 96 subjects were enrolled) was conducted at the clinical site 145-02. In the study P-183, a total of 96 subjects were enrolled.

Please collect the records of at least 50 % of 96 subjects enrolled in each part of the Study P-145 and Study P-183 audited. The subject records in the NDA submission should be compared to the original documents at the firm. In addition to the standard investigation involving the source documents, case report forms, adverse events, concomitant medications, number of evaluable subjects, drug accountability, etc., the files of communication between the clinical site and the sponsor should be examined for their content. Please confirm the presence of 100% of the signed and dated informed consent forms, and comment on this informed

consent check in the EIR. Please determine if the subjects met the protocol inclusion/exclusion criteria. Also, please verify that the subjects were compliant with the trial regimen.

Analytical Site 1:

(b) (4)
[Redacted])

Principal Bioanalytical Investigator at the analytical site 1:

(b) (4)
[Redacted]

Analytical Site 2:

(b) (4)
[Redacted]

Principal Bioanalytical Investigator at the analytical site 2:

(b) (4)
Ann Levesque (for Study P-183)

Analytical Method: LC-MS/MS

Please note that the analytical site 1, i.e., (b) (4), performed the assay for unconjugated and total ezetimibe, and the analytical site 2, i.e., (b) (4), performed the assay for atorvatatin, o-hydroxy atorvatatin, and p-hydroxy atorvastatin.

All pertinent items related to the analytical method should be examined and the sponsor's data should be audited. The

Page 5 - BIMO Assignment, NDA 200-153 ATOZET
(EZETIMIBE/ATORVASTATIN) TABLETS, 10/10, 10/20, 10/40,
10/80

analytical data provided in the NDA submission should be compared with original documents at the firm. The method validation and the actual assay of the subject plasma samples, as well as the variability between and within runs, QCs, stability, the number of repeat assays of the subject plasma samples, and the reason for such repetitions should be examined. The SOPs for various procedures must also be scrutinized. In addition to the standard investigation involving the source documents, the files of communication between the analytical site and the sponsor should be examined for their content.

Following identification of the investigator background material will be forwarded directly. **A DSI scientist with specialized knowledge may participate in the inspection of the analytical site to provide scientific and technical expertise.**

Headquarters' Contact Person

For Foreign inspection: Michael F. Skelly, Ph.D. (301)796-3375

For Domestic inspection: Young M. Choi, Ph.D. (301)796-1516

cc:

CDER DSI PM TRACK

DSI/Choi/Dejernett/skelly/CF

HFC-130/ORA HQ DFFI IOB BIMO

HFR-CE250 BLT-DO

HFR-SE200 FLA-DO

OND/DMEP/ Mary H. Parks/Kati Johnson/Iffat Chowdhury

OCP/Johnny (S.W.) Lau

Draft: YMC 8/8/11

Edit: MKY 8/9/11

DSI: 6245; O:\BE\assigns\bioN200153.doc

FACTS: 1313583

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

/s/

YOUNG M CHOI
08/09/2011

MARTIN K YAU
08/09/2011