Trade Name: Vytorin

Generic Name: Ezetimibe and simvastatin

Sponsor: MSD International GmbH

Approval Date: 01/18/2017

Indications: VYTORIN, 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 lipid-lowering treatments.
**CONTENTS**

**Reviews / Information Included in this NDA Review.**

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<td>Other Review(s)</td>
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<td>Administrative/Correspondence Document(s)</td>
<td>X</td>
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</tbody>
</table>
APPLICATION NUMBER:
021687Orig1s057

APPROVAL LETTER
APPROVAL LETTER

MSD International GmbH
C/o Merck Sharp & Dohme Corp. U.S. Agent for MSD International GmbH
Attention: Catherine Kohler, PharmD
Director, Global Regulatory Affairs
351 N. Sumneytown Pike
P.O. Box 1000, UG 2D027
North Wales, PA 19454-2505

Dear Dr. Kohler:

Please refer to your Supplemental New Drug Applications (sNDA) dated July 18, 2016, received July 18, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

<table>
<thead>
<tr>
<th>NDA #</th>
<th>Supplement #</th>
<th>Drug Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>21445</td>
<td>041</td>
<td>Zetia (ezetimibe) Tablets, 10mg</td>
</tr>
<tr>
<td>21687</td>
<td>057</td>
<td>Vytorin (ezetimibe and simvastatin) Tablets</td>
</tr>
<tr>
<td>200153</td>
<td>004</td>
<td>Liptruzet (ezetimibe and atorvastatin) Tablets</td>
</tr>
</tbody>
</table>

These “Changes Being Effected in 30 days” supplemental new drug applications provide for changes to the Ezetimibe drug substance and drug product specifications and analytical procedures to align with the current USP monographs for Ezetimibe and Ezetimibe tablets.

We have completed our review of these supplemental new drug applications. These supplements are approved.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Teicher Agosto, Regulatory Project Manager, at (240) 402-3777.
Sincerely,

{See appended electronic signature page}

Ramesh Raghavachari, Ph.D.
Chief, Branch I
Division of Post-Marketing Activities 1
Office of Lifecycle Drug Products
Center for Drug Evaluation and Research
Office of Lifecycle Drug Products  
Division of Post-Marketing Activities I  
Review of Chemistry, Manufacturing, and Controls

1. NDA Supplement Number: NDA 21445 S-41 (lead), NDA 21687 S-57, NDA 200153 S-4

2. Submission(s) Being Reviewed:

<table>
<thead>
<tr>
<th>NDA</th>
<th>Submission Type</th>
<th>Submission Date</th>
<th>CDER Stamp Date</th>
<th>Assigned Date</th>
<th>PDUFA Goal Date</th>
<th>Review Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>21445</td>
<td>Original Supplement</td>
<td>07/18/2016</td>
<td>07/18/2016</td>
<td>09/04/2016</td>
<td>01/18/2017</td>
<td>01/16/2017</td>
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<tr>
<td>21687</td>
<td>Original Supplement</td>
<td>07/18/2016</td>
<td>07/18/2016</td>
<td>09/04/2016</td>
<td>01/18/2017</td>
<td>01/16/2017</td>
</tr>
<tr>
<td>200153</td>
<td>Original Supplement</td>
<td>07/18/2016</td>
<td>07/18/2016</td>
<td>09/04/2016</td>
<td>01/18/2017</td>
<td>01/16/2017</td>
</tr>
</tbody>
</table>

3. Provides For:

Changes to the Ezetimibe drug substance and drug product specifications and analytical procedures to align with the current USP monographs for Ezetimibe and Ezetimibe tablets.

4. Review #: 1

5. Clinical Review Division: DMEP

6. Name and Address of Applicant:

   For NDA 21445 and NDA 21687
   MSD International GmbH
   Weystrasse 20
   Lucerne 6000, Switzerland

   Authorized U.S. Agent:
   Attn: Catherine Kohler, Pharm. D.
   Director, Regulatory Affairs
   351 N. Sumneytown Pike
   P.O. Box 1000, UG2D-027
   North Wales, PA
   (267)305-3510 (voice)
catherine.kohler@merck.com

   For NDA 200153
   Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
   1 Merck Drive
   P.O. Box 100
   Whitehouse Station, NJ, 08889
   Attn:
   Catherine Kohler, Pharm. D.
   Director, Regulatory Affairs
7. Drug Product:

<table>
<thead>
<tr>
<th>NDA</th>
<th>Drug Name</th>
<th>Dosage Form</th>
<th>Strength (mg)</th>
<th>Route of Administration</th>
<th>Rx or OTC</th>
<th>Special Product</th>
</tr>
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<tbody>
<tr>
<td>21445</td>
<td>ZETIA (Ezetimibe tablet)</td>
<td>Tablet</td>
<td>10</td>
<td>Oral</td>
<td>Rx</td>
<td>No</td>
</tr>
<tr>
<td>21687</td>
<td>VYTORIN (Ezetimibe/Simvastatin Combination Tablet)</td>
<td>Tablet</td>
<td>Ezetimibe: 10 Simvastatin: 10, 20, 40, 80</td>
<td>Oral</td>
<td>Rx</td>
<td>No</td>
</tr>
<tr>
<td>200153</td>
<td>Liptruzet (Ezetimibe/Atorvastatin Combination Tablet)</td>
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<td>Ezetimibe: 10 Atorvastatin: 10, 20, 40, 80</td>
<td>Oral</td>
<td>Rx</td>
<td>No</td>
</tr>
</tbody>
</table>

8. Chemical Name and Structure of Drug Substance:

- **USAN: Ezetimibe**
  - Chemical name: 1-(4-fluorophenyl)-3(R)-[3-(4-fluorophenyl)-3(S)-hydroxypropyl]4(S)-(4-hydroxyphenyl)-2-azetidinone
  - Molecular formula: C_{24}H_{21}F_{2}NO_{3}
  - MW: 409.4

- **USAN: Simvastatin**
  - Chemical name: butanoic acid, 2,2-dimethyl-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4hydroxy-6-oxo-2H-pyran-2-yl)-ethyl]-1-naphthalenyl ester, [1S-[1α,3α,7β,8β(2S*,4S*),-8αβ]]
  - Molecular formula: C_{25}H_{38}O_{5}
  - MW: 418.57

- **USAN: Atorvastatin**
  - Chemical name: [R-(R*, R*)]-2-(4-fluorophenyl)-β, δ,-dihydroxy-5-(1-methyl ethyl)-3-phenyl-4[(phenylamino) carbonyl]-1H-pyrrole-1-heptanoic acid, calcium salt (2:1) trihydrate
  - Molecular formula: C_{66}H_{68}CaF_{2}N_{4}O_{10}.3H_{2}O
  - MW: 1209.36

9. Indication:
   Treatment of primary hypercholesterolemia and homozygous familial hypercholesterolemia
10. **Supporting/Relating Documents:** Pages 4-7.

11. **Consults:** None.

12. **Executive Summary:**
   
   This bundled supplemental submission proposes changes to Ezetimibe drug substance and drug product specifications and analytical procedures to ensure conformance to the newly published USP monographs. The applicant has provided adequate justification for the removal or addition of specifications/methods for Ezetimibe DS and DP. Additionally, for the remaining differences between the NDA and the USP monographs, the applicant has provided justification as to why the currently approved methods/conditions are equivalent and/or superior and not expected to impact the testing outcome of the analytical procedures. Overall, the proposed changes are unlikely to have negative impact on the quality of the drug substance and drug product.

13. **Conclusions & Recommendations:**

   This bundled supplement is recommended for approval.

14. **Comments/Deficiencies to Be Conveyed to Applicant:** None.

15. **Primary Reviewer:**

   Wei-Hua Emily Wu, Ph.D., CMC reviewer, Branch 1, DPMAI, OLDP, OPQ

16. **Secondary Reviewer:**

   Ramesh Raghavachari, Ph.D., Branch Chief, Branch 1, DPMA I, OLDP, OPQ

3 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page
Evaluation: Adequate.

5) 1.12.14 Environmental Analysis

Comments: The applicant stated that the supplement meets the requirements of a categorical exclusion under 21 CFR §25.31(a) because it will not increase the use of the drug.

Evaluation: Adequate.

Summary: The applicant has provided adequate justification for the removal or addition of specifications/methods for Ezetimibe DS and DP to ensure conformance to the currently published USP monographs for Ezetimibe and Ezetimibe tablets. Additionally, for the remaining differences between the NDA and the USP monographs, the applicant has provided justification as to why the currently approved methods/conditions are equivalent and/or superior and not expected to impact the testing outcome of the analytical procedures. Overall, the proposed changes are unlikely to have negative impact on the quality of the drug substance and drug product. Hence, this bundled supplemental submission is recommended for approval.
APPLICATION NUMBER:
021687Orig1s057

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS
NDAs 21445/S-041, 21687/S-057 and 200153/S-004

CBE SUPPLEMENT –
ACKNOWLEDGEMENT

MSD International GmbH
C/o Merck Sharp & Dohme Corp. U.S. Agent for MSD International GmbH
Attention: Catherine Kohler, PharmD
Director, Global Regulatory Affairs
351 N. Sumneytown Pike
P.O. Box 1000, UG 2D027
North Wales, PA 19454-2505

Dear Dr. Kohler:

We have received your Supplemental New Drug Application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

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These supplemental applications, submitted as a “Changes Being Effected in 30 days” supplement, provides for United States Pharmacopoeia (USP) monograph for ezetimibe drug substance and drug product.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we have filed the application on September 16, 2016 in accordance with 21 CFR 314.101(a).

If the application is filed, the user fee goal date will be January 18, 2017.

Cite the application 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:
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, see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

If you have questions, call me at (240) 402-3777.

Sincerely,

{See appended electronic signature page}

Teicher N. Agosto, Pharm D, RPh
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
Food and Drug Administration