CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

021687Orig1s057

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.

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APPLICATION NUMBER:

021687Orig1s057

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

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

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 July18, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

NDA #	Supplement #	Drug Product
21445	041	Zetia (ezetimibe) Tablets, 10mg
21687	057	Vytorin (ezetimibe and simvastatin) Tablets
200153	004	Liptruzet (ezetimibe and atorvastatin) Tablets

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

APPEARS THIS WAY ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021687Orig1s057

CHEMISTRY REVIEW(S)

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**:

NDA	Submission	Type	Submission Date	CDER Stamp Date	Assigned Date	PDUFA Goal Date	Review Date
21445	Original Supplement	CBE-30	07/18/2016	07/18/2016	09/04/2016	01/18/2017	01/16/2017
21687	Original Supplement	CBE-30	07/18/2016	07/18/2016	09/04/2016	01/18/2017	01/16/2017
200153	Original Supplement	CBE-30	07/18/2016	07/18/2016	09/04/2016	01/18/2017	01/16/2017

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

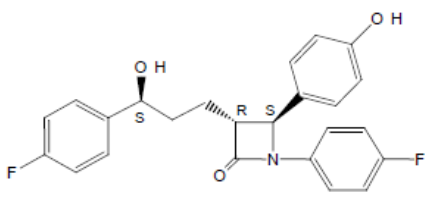
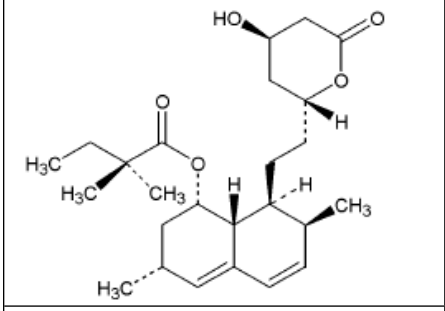
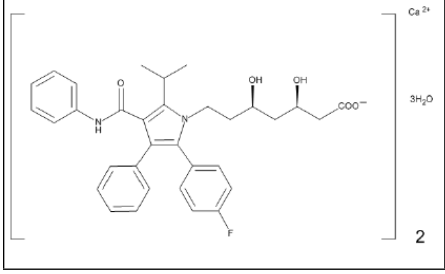
   For NDA 200153
   Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
   1 Merck Drive
   P.O. Box 100
   Whitehouse Station, NJ, 08889
   Attn:
   Catherine Kohler, Pharm. D.
   Director, Regulatory Affairs

351 N. Sumneytown Pike
P.O. Box 1000, UG2D-027
North Wales, PA
(267)305-3510 (voice)
catherine.kohler@merck.com

7. Drug Product:

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

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: $C_{24}H_{21}F_2NO_3$ 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-2*H*-pyran-2-yl)-ethyl]-1-naphthalenyl ester, [1*S*-[1α,3α,7β,8β(2*S**,4*S**),-8aβ]] Molecular formula: $C_{25}H_{38}O_5$ MW: 418.57
	USAN: Atorvastatin Chemical name: [R-(R*, R*)]-2-(4-fluorophenyl)-ß, δ,-dihydroxy-5-(1-methylethyl)-3-phenyl-4[(phenylamino) carbonyl]-1H-pyrrole-1-heptanoic acid, calcium salt (2:1) trihydrate Molecular formula: $C_{66}H_{68}CaF_2N_4O_{10}.3H_2O$ 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

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(b) (4)

[redacted]

***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.

Ramesh Raghavachari

Digitally signed by Ramesh Raghavachari
Date: 1/17/2017 11:29:22PM
GUID: 502d0913000029f375128b0de8c50020

Wei-Hua Emily Wu

Digitally signed by Wei-Hua Emily Wu
Date: 1/17/2017 10:43:06PM
GUID: 563bb552005070f99249ecb1733e3b79

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021687Orig1s057

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

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:

NDA/ Supplement	Drug Products	Date of Submission	Date of Receipt
21445/S-041	Zetia (ezetimibe) tablets, 10mg	July 18, 2016	July 18, 2016
21687/S-057	Vytorin (ezetimibe and simvastatin) Tablets	July 18, 2016	July 18, 2016
200153/S-004	Liptruzet (ezetimibe and atorvastatin) Tablets	July 18, 2016	July 18, 2016

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:

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

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, 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

Teicher Agosto

Digitally signed by Teicher Agosto
Date: 9/21/2016 03:56:38PM
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