CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213072Orig1s000

OTHER REVIEW(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs
Division of Pediatric and Maternal Health
Silver Spring, MD 20993
Telephone 301-796-2200
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M E M O R A N D U M

From: Ndidi Nwokorie, MD Medical Officer
Division of Pediatric and Maternal Health (DPMH)
Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine (ORPURM)
Office of New Drugs (OND)

Through: Mona Khurana, MD, Pediatric Team Leader
DPMH, ORPURM, OND

John J. Alexander, MD, MPH, Deputy Director
DPMH, ORPURM, OND

To: Division of Diabetes, Lipid Disorders, and Obesity (DDLO)

Subject: Pediatric Labeling Review and Development of Post-Marketing Requirements under the Pediatric Research Equity Act

Applicant: Althera Life Sciences, LLC

Application number: NDA 213072

Drug: Roszet (rosuvastatin and ezetimibe fixed-dose combination [FDC])

Drug Class: Cholesterol Absorption Inhibitor and 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) Reductase Inhibitor

Proposed Indication: In adults:

- As an adjunct to diet in patients with primary non-familial hyperlipidemia to reduce low density lipoprotein cholesterol (LDL-C)
- Alone or as an adjunct to other LDL-C-lowering therapies in patients with homozygous familial hypercholesterolemia (HoFH) to reduce LDL-C

Route of administration: Oral

Dosage Form: (b) (4) film-coated tablets

Dosage Strengths: 5/10, 10/10, 20/10, 40/10 rosuvastatin mg/ezetimibe mg

Proposed Adult Dosage: 5/10 mg daily to 40/10 mg daily

Consult Request:
DDLO consulted DPMH on January 2021 to review the proposed labeling for this product to determine if the (b) (4) language proposed by the Applicant is appropriate.

Materials Reviewed:

- The following documents entered into DARRTS under NDA 213072
  - Pediatric Administrative Information submitted into Module 1.9 - October 29, 2019
  - Information Request – January 16, 2020
  - DPMH Memorandum - May 1, 2020
  - Complete Response Letter - May 26, 2020
  - Type A Meeting Minutes - June 29, 2020
- Crestor Labeling NDA 012366 approved 2003
- Zetia Labeling NDA 021445 approved in 2002

I. Regulatory History of this Application

This is a class 2 resubmission of an NDA seeking approval under the 505(b)(2) regulatory pathway for a FDC of two lipid-lowering agents that are each FDA approved

as single ingredient products.[1] The Applicant is seeking to rely on FDA's previous findings of safety and effectiveness for the following two listed drugs (LD): Crestor (rosuvastatin calcium) and (2) Zetia (ezetimibe). In Section 1 of the Applicant's annotated draft labeling, the proposed indications include primary non-familial hyperlipidemia (b) (4) and HoFH. DDLO received the application on September 23, 2020, and the Prescription Drug user Fee Act (PDUFA) goal date is March 23, 2021.

The Applicant originally submitted an NDA for the proposed product on July 29, 2019 seeking approval under the 505(b)(2) regulatory pathway for the same two adult indications being proposed in the resubmission. DDLO had consulted DPMH during the first review cycle for assistance with development of post-marketing requirements (PMR) under the Pediatric Research Equity Act (PREA). At that time, DPMH noted that the proposed product represents a novel combination that is considered a new active ingredient under PREA and, therefore, the application is subject to pediatric study requirements under PREA for the same indications being sought in adults.

The Applicant had submitted the original NDA without an Agreed initial Pediatric Study Plan or a pediatric assessment, but DDLO filed the application and opted to consider PREA PMR development during the NDA review. DPMH recommended the Applicant submit a PSP to inform PREA PMR development during the application review. In the PSP, [2] the Applicant stated its plan to (b) (4) .

DPMH discussions with DDLO during the first review cycle centered around how the Applicant could provide a scientific bridge to the approved pediatric use information for the (b) (4) HoFH indications in approved labeling for the two LDs upon which the Applicant was relying. [3] Given the opportunity to require studies under PREA for this product, DPMH discussed with DDLO the type of data that might be needed from pediatric clinical trials to demonstrate that each drug component contributes to each claimed effect as well as the most appropriate lower age limit for which a pediatric assessment should be required. The Division tentatively concluded that, in lieu of conducting new pediatric clinical trials, a more comprehensive review of published data could enable the Applicant to obtain sufficient data to support pediatric approval of

[1] Crestor (NDA 012366) approved 2003 and Zetia (NDA 021445) approved in 2002

[2] October 29. 2019 submission into Module 1.9 Pediatric Administrative Information to DARRTS under NDA 213072

[3] May 1, 2020 DPMH Memorandum in DARRTS under NDA 213072

(b) (4) HoFH in patients (b) (4) years of age and older. DDLO issued a Complete Response (CR) Letter, citing multiple deficiencies related to qualities and facilities inspections,[4] hence DDLO did not proceed with issuing any PREA PMRs during the first review cycle. The Applicant subsequently met with DDLO to discuss the deficiencies outlined in the letter.[5]

II. DPMH Review of Current Resubmission

DDLO initially consulted DPMH for assistance with the NDA resubmission to opine on whether or not the Applicant's proposed (b) (4) language in labeling was appropriate. Specifically, the Applicant included the following language in Section 1 (Indications and Usage) of the proposed annotated labeling:

"(b) (4)
"

The Applicant did not attempt to submit an iPSP to reach agreement prior to the NDA resubmission but was not advised to do so in the CR Letter. Therefore, the NDA resubmission does not include an Agreed iPSP.

During internal meetings, DDLO stated the submission contains (b) (4) to support the safety and efficacy of extending the HoFH indication to the pediatric population down to (b) (4) years of age. Based on the Division's assessment, DPMH focused on (b) (4) the unexpired exclusivity rights for one of the LDs (Crestor). FDA granted Crestor pediatric exclusivity for the HeFH indication, resulting in extension of patent protection to June 2022. Notably, the Written Request (WR) for Crestor included a randomized, double-blind, placebo-controlled, parallel group 12-week trial in patients down to 10 years of age with HeFH. (b) (4)

[4] May 26, 2020 Complete Response Letter in DARRTS under NDA 213072

[5] June 29, 2020 Type A Meeting Minutes in DARRTS under NDA 213072

Given the existing patent protection for Crestor and the separate existing orphan drug exclusivity also granted by FDA to Crestor to support the HoFH indication as well as lack of alignment between the Applicant's patent certifications with the proposed indications in labeling, DDLO issued an Information Request[6] and held a teleconference with the Applicant on March 1, 2021 for clarification on the precise adult indications the Applicant is seeking in the resubmission. Based on discussion at the teleconference, the Applicant resubmitted proposed labeling on March 10, 2021, confirming it is seeking the following indications in adults: (1) primary non-familial hyperlipidemia; and (2) HoFH. The Applicant stated (b) (4) .

Based on the adult indications being sought by the Applicant, DPMH had discussed with DDLO during the first review cycle that the required pediatric assessment for primary non-familial hyperlipidemia could be fully waived on the basis that the product fails to represent a meaningful therapeutic benefit over existing therapies and is unlikely to be used in substantial number of all pediatric age groups. DPMH agreed with DDLO that a deferred assessment for the HoFH indication was appropriate because the product is ready for approval in adults. Based on discussions with DDLO during the first review cycle regarding the level of evidence needed and most appropriate age cut-off to study, DPMH agreed with DDLO that PREA study requirements should be partially waived for the HoFH indication in patients less than (b) (4) years of age because studies are impossible or highly impractical due to the few numbers of patients. DPMH stated that (b) (4)

DDLO discussed this application and the planned PREA PMR for the HoFH indication with the Pediatric Review Committee (PeRC) on March 16, 2021. The PeRC agreed with the Division's plan for full waiver for the primary non-familial hyperlipidemia indication, but discussion centered on the information needed (b) (4) to support a pediatric HoFH indication and the most appropriate lower age cut-off for the assessment. The Division noted that Zetia labeling has limited pediatric information about HoFH and this application provides an opportunity to collect more information on not only Zetia but also this novel combination in pediatric patients with HoFH. The PeRC also discussed the utility of this product in patients less than (b) (4) years of age with HoFH. (b) (4) The Division also stated that clinical guidelines for pediatric patients with HoFH recommended screening and initiating treatment in patients starting at 2 years of age. The PeRC recommended the

[6] February 22, 2021 Information Request issued via email correspondence and entered into DARRTS under NDA 213072

Division issue a PREA PMR containing broad, general language in patients 2 to 17 years of age with HoFH to allow the Division and the Applicant flexibility to determine the best approach to fulfilling the PMR.

Following the PeRC discussion, DPMH queried the WR and PeRC databases to identify WR issued and pediatric assessments discussed at the PeRC for pediatric HoFH programs over the past 5 years. See Table 1 and 2. Based on these other programs, the lower age limit for study inclusion does vary, and the precise age cut-off may be product-specific.

Table 1. FDA Issued WR for Studies to Support a Pediatric HoFH Indication

Active Moiety	NDA/IND#	Pediatric age group to be studied for HoFH	Date Issued
NON-RESPONSIVE			
lomitapide	NDA 203858	NON-RESPONSIVE	1/20/2015

Table 2. Pediatric Assessments Discussed at the PeRC for Pediatric HoFH Programs

Product	NDA/IND#	Pediatric age group to be studied for HoFH	PeRC Mgt date
NON-RESPONSIVE			

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

PATIENT LABELING REVIEW

Date:	March 19, 2021
To:	Martin White, M.S Regulatory Project Manager **Division of Diabetes, Lipid Disorders, and Obesity (DDLO)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Kelly Jackson, PharmD Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Ankur Kalola, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	ROSZET (rosuvastatin and ezetimibe)
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	NDA 213072
Applicant:	Althera Life Sciences, LLC

1 INTRODUCTION

On September 23, 2020, Althera Life Sciences, LLC submitted for the Agency's review a resubmission of New Drug Application (NDA) 213072 for ROSZET (rosuvastatin and ezetimibe) after being issued a Complete Response (CR) letter dated May 26, 2020. The proposed indication for ROSZET (rosuvastatin and ezetimibe) tablets, for oral use is for the treatment of primary ((b) (4) non-familial) hyperlipidemia (b) (4) and homozygous familial hypercholesterolemia (HoFH).

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Diabetes, Lipid Disorders, and Obesity (DDLO) on October 5, 2020, respectively, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for ROSZET (rosuvastatin and ezetimibe) tablets, for oral use.

2 MATERIAL REVIEWED

- Draft ROSZET (rosuvastatin and ezetimibe) PPI received on September 23, 2020, and received by DMPP and OPDP on March 17, 2021.
- Draft ROSZET (rosuvastatin and ezetimibe) Prescribing Information (PI) received on September 23, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on March 17, 2021.

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.

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 APHont to make medical information more accessible for patients with vision loss. We reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we:

- 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 is free of promotional language or suggested revisions to ensure that it is free of promotional language

- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the 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/

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

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

Memorandum

Date: March 18, 2021

To: Martin White, Regulatory Project Manager
Division of Diabetes, Lipid Disorders, and Obesity (DDLO)

Monika Houstoun, Associate Director for Labeling, (DDLO)

From: Ankur Kalola, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Melinda McLawhorn, Team Leader, OPDP

Subject: OPDP Labeling Comments for ROSZET (rosuvastatin and ezetimibe) tablets, for oral use

NDA: 213072

In response to DDLO's consult request dated October 5, 2020, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI), and carton and container labeling for the NDA submission for ROSZET (rosuvastatin and ezetimibe) tablets, for oral use.

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DDLO on March 17, 2021, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed PPI will be sent under separate cover.

(b) (4) **Container Labeling**: OPDP has reviewed the attached proposed (b) (4) container labeling received by electronic mail form DDLO on March 17, 2021, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Ankur Kalola at (301) 796-4530 or Ankur.Kalola@fda.hhs.gov.

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ANKUR S KALOLA
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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	February 9, 2021
Requesting Office or Division:	Division of Diabetes, Lipid Disorders, and Obesity (DDLO)
Application Type and Number:	NDA 213072
Product Name and Strength:	Roszet (rosuvastatin and ezetimibe) tablet, 5 mg/10 mg, 10 mg/10 mg, 20 mg/10 mg, and 40 mg/10 mg
Applicant/Sponsor Name:	Althera Life Sciences, LLC (Althera)
OSE RCM #:	2019-1642-4
DMEPA Safety Evaluator:	Ariane O. Conrad, PharmD, BCACP, CDCES
DMEPA Team Leader:	Idalia E. Rychlik, PharmD

1 PURPOSE OF MEMORANDUM

Althera submitted revised container labels for Roszet (rosuvastatin and ezetimibe), on February 3, 2021. Division of Diabetes, Lipid Disorders, and Obesity (DDLO) requested that we review the revised labels for Roszet (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

We reviewed the resubmitted labels for Roszet to determine if they are acceptable from a medication error perspective. We confirmed that Althera addressed our prior labeling recommendations and we have no additional recommendations at this time.

[a] Conrad, A. Review of Revised Label and Labeling Review Memorandum for Roszet (NDA 213072). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 Jan 28. RCM No. 2019-1642-3.

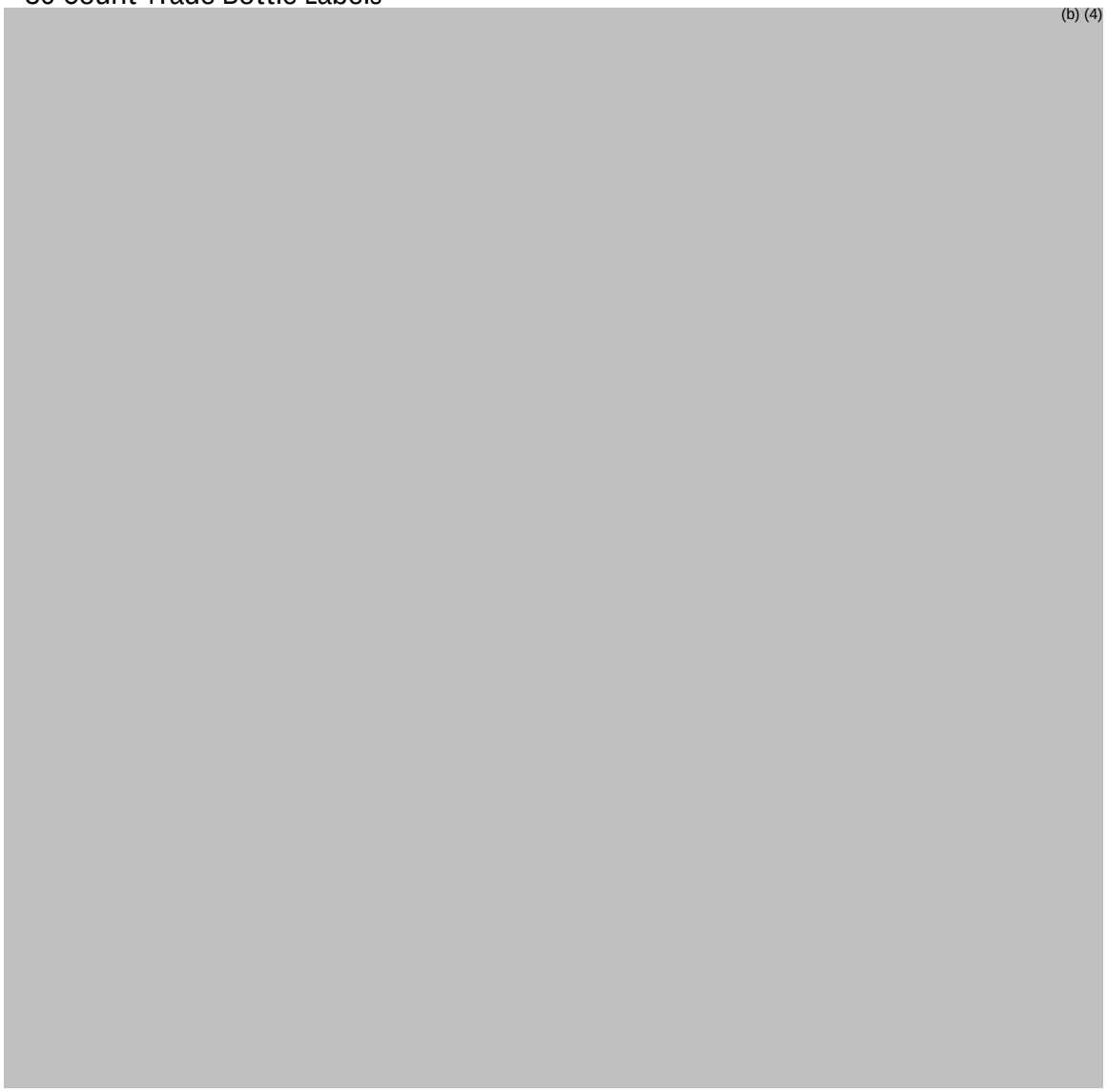
APPENDIX A. LABEL AND LABELING RECEIVED ON FEBRUARY 3, 2021

Using the principles of human factors and Failure Mode and Effects Analysis, along with postmarket medication error data, we reviewed the following Roszet labels and labeling submitted by Althera.

Container labels:

30 Count Trade Bottle Labels

(b) (4)



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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	January 28, 2021
Requesting Office or Division:	Division of Diabetes, Lipid Disorders, and Obesity (DDLO)
Application Type and Number:	NDA 213072
Product Name and Strength:	Roszet (rosuvastatin and ezetimibe) tablet, 5 mg/10 mg, 10 mg/10 mg, 20 mg/10 mg, and 40 mg/10 mg
Applicant/Sponsor Name:	Althera Life Sciences, LLC (Althera)
OSE RCM #:	2019-1642-3
DMEPA Safety Evaluator:	Ariane O. Conrad, PharmD, BCACP, CDCES
DMEPA Team Leader:	Idalia E. Rychlik, PharmD

1 PURPOSE OF MEMORANDUM

Althera submitted revised container labels for Roszet (rosuvastatin and ezetimibe), on January 27, 2021. Division of Diabetes, Lipid Disorders, and Obesity (DDLO) requested that we review the revised labels for Roszet (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a] We note that the sponsor responded to each our labeling recommendations for the trade container labels, (b) (4) [b]

2 CONCLUSION

We reviewed the resubmitted labels for Roszet to determine if they are acceptable from a medication error perspective. We confirmed that Althera addressed our prior labeling recommendations; however, we did identify additional areas of vulnerability that may lead to

[a] Conrad, A. Review of Revised Label and Labeling Review Memorandum for Roszet (NDA 213072). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 Jan 11. RCM No. 2019-1642-2.
[b] Althera Life Sciences LLC. Response to DMEPA Information Request for Roszet (NDA 213072). Submitted to FDA January 27, 2021. Available via: \\CDSESUB1\evsprod\nda213072\0028\m1\us\12-cover-letters\response-to-dmepa-information-request.pdf.

medication errors with the Roszet trade container labels. We provide recommendations in Section 3.

3 RECOMMENDATIONS FOR ALTHERA LIFE SCIENCES, LLC

We recommend the following be implemented prior to approval of this NDA:

A. Trade Bottle Labels

1. We note that the proprietary name was revised to appear in (b) (4) font in response to our prior comment recommending the use of one unique color. However, we recommend that you consider the use of another color which may help users differentiate the name from the other information on the label. In addition, please ensure that the color selected does not overlap with any other colors utilized in highlighting the product strengths.
2. To improve readability and clarity, we recommend revising the storage recommendations to read as follows: “Store at 20 to 25°C (68 to 77°F)”.

APPENDIX A. LABEL AND LABELING RECEIVED ON JANUARY 27, 2021

Using the principles of human factors and Failure Mode and Effects Analysis, along with postmarket medication error data, we reviewed the following Roszet labels and labeling submitted by Althera.

Container labels:

30 Count Trade Bottle Labels

(b) (4)

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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	January 11, 2021
Requesting Office or Division:	Division of Diabetes, Lipid Disorders, and Obesity (DDLO)
Application Type and Number:	NDA 213072
Product Name and Strength:	Roszet (rosuvastatin and ezetimibe) tablet, 5 mg/10 mg, 10 mg/10 mg, 20 mg/10 mg, and 40 mg/10 mg
Applicant/Sponsor Name:	Althera Life Sciences, LLC (Althera)
OSE RCM #:	2019-1642-2
DMEPA Safety Evaluator:	Ariane O. Conrad, PharmD, BCACP, CDCES
DMEPA Team Leader:	Idalia E. Rychlik, PharmD

1 PURPOSE OF MEMORANDUM

Althera submitted their response to a complete response (CR) letter for Roszet (rosuvastatin and ezetimibe), under NDA 213072, on September 23, 2020. In addition, Althera resubmitted proposed labels and labeling for Roszet (Appendix A) with their response to the CR, which we reviewed to determine if they are acceptable from a medication error perspective. Of note, we evaluated the proposed labels and labeling for Roszet in prior labeling reviews completed before the NDA received a complete response (CR) on May 27, 2020.[a,b] Our reviews determined that (b) (4) container labels were acceptable at that time; however, we confirmed that our comments for the prescribing information (PI) were not communicated to the sponsor.

2 CONCLUSION

We reviewed the resubmitted labels and labeling for Roszet to determine if they are acceptable from a medication error perspective. After communicating the comments documented in our

[a] Fanari, M. Label and Labeling Review for Roszet (NDA 213072). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 Jan 3. RCM No. 2019-1642.
[b] Fanari, M. Review of Revised Label and Labeling Memorandum for Roszet (NDA 213072). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 Jan 27. RCM No. 2019-1642-1.

prior labeling review to the review team again[a], we determined that the PI is acceptable. Our review of the resubmitted container labels (b) (4) determined that our prior labeling recommendations were addressed. However, we did identify additional areas of vulnerability that may lead to medication errors with the Roszet trade container labels, sample container labels (b) (4) and we provide recommendations in Section 3.1.

3 RECOMMENDATIONS FOR ALTHERA LIFE SCIENCES, LLC

We recommend the following be implemented prior to approval of this NDA:

A. Trade Bottle Labels

1. We recommend that the proprietary name appears in one unique color to improve readability of the name and ensure the color does not overlap with any other colors utilized in highlighting the product strengths.
2. To improve readability and clarity, we recommend revising the established name to read as follows "rosuvastatin and ezetimibe tablets".
3. Consider reorienting the linear barcode to a vertical position to improve the ability to scan the barcode. Barcodes placed in a horizontal position may not scan due to bottle curvature.[c]
4. To ensure consistency with the Prescribing Information, revise the statement, "(b) (4)" to read "Recommended Dosage: See prescribing information."
5. We note that there is inadequate space between the numerical dose and unit of measure in some areas of the label. Place adequate space between the numerical dose and unit of measure to improve readability (e.g., revise 10mg to read 10 mg).
6. As currently presented, the format for the expiration date is not acceptable. To minimize confusion and reduce the risk for deteriorated drug medication errors, we recommend that you modify the format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a slash or a hyphen be used to separate the portions of the expiration date.
7. Increase the amount of space separating the net quantity statement and the product strength on the principal display panel. From post-marketing experience, the risk of numerical confusion between the strength and net

[c] Neuenschwander M. et al. Practical guide to bar coding for patient medication safety. Am J Health Syst Pharm. 2003 Apr 15;60(8):768-79.

quantity increases when the net quantity statement is located in close proximity to the strength statement.

B. Sample Container Labels

1. We recommend revising the product strength statements to clearly communicate that the designated strength is per unit. For example, we recommend revising "20 mg/10 mg" to read "20 mg/10 mg per tablet".
2. We note that there is inadequate space between the numerical dose and unit of measure in some areas of the label. Place adequate space between the numerical dose and unit of measure to improve readability (e.g., revise 10mg to read 10 mg).
3. To improve readability and clarity, we recommend revising the established name to read as follows "rosuvastatin and ezetimibe tablets".

APPENDIX A. LABEL AND LABELING RECEIVED ON SEPTEMBER 23, 2020

Using the principles of human factors and Failure Mode and Effects Analysis, along with postmarket medication error data, we reviewed the following Roszet labels and labeling submitted by Althera.

Prescribing Information: \\CDSESUB1\evsprod\nda213072\0023\m1\us\114-labeling\draft\labeling\spl\package-insert-pdf.pdf

Container labels

30 Count Trade Bottle Labels

(b) (4)

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

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

Memorandum

Date: May 27, 2020

To: Richard Whitehead, Regulatory Project Manager
Division of Diabetes, Lipid Disorders, and Obesity (DDLO)

Monika Houstoun, Associate Director for Labeling, (DDLO)

From: Ankur Kalola, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Melinda McLawhorn, Team Leader, OPDP

Subject: OPDP Labeling Comments for ROSZET (rosuvastatin and ezetimibe) tablets

NDA: 213072

This memo is in response to DDLO's labeling consult request dated August 1, 2019. Reference is made to a Complete Response letter that was issued on May 26, 2020. Therefore, OPDP defers comment on the proposed labeling at this time, and request that DDLO submit a new consult request during the subsequent review cycle. If you have any questions, please contact Ankur Kalola at (301) 796-4530 or Ankur.Kalola@fda.hhs.gov.

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ANKUR S KALOLA
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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
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M E M O R A N D U M

From: Ndidi Nwokorie, MD, Medical Officer

Division of Pediatric and Maternal Health (DPMH)
Office of Rare Diseases, Pediatrics, Urologic & Reproductive Medicine (ORPURM)
Office of New Drugs (OND)

Through: Mona Khurana, MD, Pediatric Team Leader

John J. Alexander, MD, MPH, Deputy Director
DPMH, ORPURM, OND

To: Division of Diabetes, Lipid Disorders, and Obesity (DDLO)

Subject: Development of Post-Marketing Requirements under the Pediatric Research Equity Act

Application: NDA 213072

Applicant: **Althera Life Sciences, LLC**

Drug: Ezetimibe and rosuvastatin fixed-dose combination (FDC)

Dosage Form: (b) (4) Film-Coated Tablets

Route of Administration: Oral

Dosage Strengths: Rosuvastatin mg/ezetimibe mg
5/10, 10/10, 20/10, 40/10

Proposed Adult Dosage: 5/10 mg daily to 40/10 mg daily

Proposed Adult Indications: 1. Primary (b) (4) Hyperlipidemia

Reduce (b) (4) LDL-C, (b) (4) in patients with primary ((b) (4) non-familial) hyperlipidemia (b) (4) .

2. Homozygous Familial Hypercholesterolemia (HoFH)

Reduce elevated (b) (4) LDL-C in patients with HoFH, as an adjunct to other (b) (4) lowering treatments.

Proposed Pediatric Indication: None

Consult Request:

DDLO consulted DPMH to opine on a path forward regarding the development of a pediatric assessment plan for the FDC product, Roszet.

Materials Reviewed:

Tracked under NDA 21366 in DARRTS

- DPMH Pediatric Consult Crestor® entry date August 3, 2015
- Approval Letter for Crestor® entry date November 20, 2015
- Approval Letter for Crestor® entry date May 27, 2016
- Clinical Filing Checklist for Crestor® entry date September 10, 2015

Tracked under NDA 21445 in DARRTS

- Clinical Review of Zetia® entry date June 05, 2008
- Primary Medical Officer Filing Memo for Zetia® entry date February 06, 2008

Tracked under IND 136378 in DARRTS and EDR

- P-IND Meeting Minutes entry date November 02, 2017
- P-IND Meeting Background Materials (eCTD #0001) Submitted October17, 2018

Tracked under NDA 213072 in DARRTS and EDR

- Summary of Biopharmaceutic Studies and Associated Analytical Methods (eCTD #0001) Submitted July 29, 2019
- Information Request (IR) entry date January 16, 2020
- Under eCTD# 0016 Submitted February 24, 2020
    - Pediatric Study Plan-other
    - Request for waiver of Pediatric Studies
    - Request for deferral of Pediatric Studies

Drugs@FDA accessed on April 8, 2020

- Approved Zetia® Labeling
- Approved Crestor® Labeling
- Approval Letters for the original and subsequent approvals for Crestor®

Accessed from Orange Book on April 8, 2020

- Patents and Exclusivity Information for Crestor®
- Patents and Exclusivity Information for Zetia®

I. Background of Disease

Familial Hypercholesterolemia (FH) is a genetic disorder that causes high plasma cholesterol levels, especially elevated Low-Density Lipoprotein Cholesterol (LDL-C). This disorder causes premature and progressive cardiovascular disease (CVD) that are clinically evident as early as in childhood and adolescence. FH belongs to the family of primary dyslipidemias and is inherited in an autosomal dominant pattern.[1] The homozygous form (HoFH) is exceedingly rare and affects approximately 1 in a million people worldwide. The heterozygous form (HeFH) is quite common and occurs in 1 in 200-250 persons; affecting an estimated 6.8-8.5 million children and adolescents worldwide. Patients with HoFH present with high LDL-C levels from birth, which explains the early course of major complications of the disease. HoFH patients may experience the first adverse cardiovascular event in adolescence, but symptoms, such as angina pectoris, have been reported early in childhood. Untreated patients often do not reach the second decade of their life.[1]

II. Submission Strategy for NDA 213072

The Applicant submitted NDA 213072 through the 505(b)(2) pathway, relying on FDA's previous findings of safety and effectiveness for the following two listed drugs (LDs): (1) rosuvastatin calcium (Crestor®); and (2) ezetimibe (Zetia®).

Crestor is a 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor (statin). FDA approved Crestor for the following use in pediatric patients:

- Treatment of HeFH in patients 10 to 17 years of age in 2009 with expansion of the indication down to 8 years of age and older in 2014
- Treatment of HoFH in patients 7 years of age and older

Two pivotal studies formed the bases of FDA approval of Crestor for the treatment of HeFH in pediatric patients. The first was a double-blind randomized, placebo-controlled trial in 176 children ages 10-17-years receiving Rosuvastatin 5, 10, or 20 mg daily. Rosuvastatin significantly reduced LDL-C, Total-C, and ApoB levels at each dose compared to placebo. See Table 1.

[1]Familial Hypercholesterolemia in Children and Adolescents: Diagnosis and Treatment (Maliachova & Stabouli, 2018)

Table 1: Percentage of Patients Achieving LDL-C goal of less than 110 mg/dL after 12 weeks[2]

Dosage	n	LDL-C %
Placebo	46	0
5 mg	42	12
10 mg	44	41
20 mg	44	71

A 2-year open label, titration to goal trial of rosuvastatin conducted in patients 8 to 17 years of age and starting from a daily dose of 5 mg to 10 mg in patients less than 10 years and 5 mg to 20 mg in patients over 10 years formed the second pivotal trial. The trial enrolled 175 patients. The reduction of LDL-C from baseline was consistent not only across all age groups but to previous experience in adult and pediatric controlled trials.[2] FDA granted Crestor pediatric exclusivity for the HeFH indication that will expire June 2022.[3]

FDA approved Crestor for the treatment of HoFH in 2015 (HYDRA Study) for patients 7 years and older based on a 6-week randomized, double-blind, placebo-controlled, crossover study in 14 patients aged 7-15 years; followed by 12 weeks of open-label treatment. 13 patients completed the study. Rosuvastatin significantly reduced LDL-C, total-C, ApoB, and non-HDL-C compared to placebo. See Table 2. FDA granted Crestor pediatric orphan exclusivity for HoFH. This orphan exclusivity expires May 2023.[3]

Table 2: Lipid-modifying Effects of Rosuvastatin in Pediatric Patients 7 to 15 years of Age with Homozygous Familial Hypercholesterolemia After 6 Weeks[2]

	Placebo (N=13)	**CRESTOR 20 mg (N=13)**	**Percent difference (95% CI)**
LDL-C (mg/dL)	481	396	-22.3% (-33.5, -9.1)
Total-C (mg/dL)	539	448	-20.1% (-29.7, -9.1)
Non-HDL-C	505	412	-22.9% (-33.7, -10.3)
ApoB (mg/dL)	268	235	-17.1% (-29.2, -2.9)

Zetia, ezetimibe, is in a class of lipid-lowering compounds that selectively inhibits the intestinal absorption of cholesterol and related phytosterols. In 2008, FDA approved ezetimibe 10 mg to be co-administered with approved pediatric doses of a statin in pediatric patients 10 to 17 years of

[2] Crestor Label Drugs@FDA accessed 4/8/2020

[3] Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book); https://www.accessdata.fda.gov/scripts/cder/ob/index.cfm accessed 4/8/2020

age with HeFH who, because of an inadequate response to treatment with an optimal dose of a statin, required additional lipid lowering therapy.[4] Approval of Zetia for co-administration with a statin was based on a randomized, double-blind, controlled, parallel-group, phase 3 trial to evaluate the efficacy and safety of the co-administration of ezetimibe 10 mg/day plus simvastatin 10 mg/day, 20 mg/day, or 40 mg/day vs simvastatin 10 mg/day, 20 mg/day, or 40 mg/day as monotherapy on LDL-C reduction for up to one year in 248 adolescent patients 10 to 17 years of age with HeFH. After 6 weeks of treatment, the difference in the primary efficacy of mean percent change from baseline LDL-C between the ezetimibe/simvastatin group and the simvastatin monotherapy group was approximately 15%. This represented a statistically significant ($p<0.01$) finding deemed by FDA to be clinically meaningful. There were statistically significant decreases in mean percent changes in Total-C, Apo-B, Non-HDL-C, and Triglycerides. These findings remained consistent through week 53.[4]

To date, ezetimibe has not been approved either as monotherapy or for co-administration with statins for the treatment of pediatric patients with HoFH. Therefore, there is no approved pediatric use information for Zetia for the treatment of HoFH.

NDA 213072 is a new FDC product of once daily rosuvastatin and ezetimibe proposed for the treatment of primary (b) (4) hyperlipidemia and homozygous hyperlipidemia in adults. The Applicant plans to show bioequivalence of its FDC product with co-administered rosuvastatin and ezetimibe in a bridging study to show its product is bioequivalent to Crestor and Zetia co-administered.

III. DPMH Discussion

The Applicant submitted NDA 213072 on July 2019 without an Agreed iPSP or a pediatric assessment. DDLO filed the application on September 2019, electing to treat the pediatric drug development as a review matter. DDLO consulted DPMH to opine on a path forward and answer key clinical and regulatory questions concerning the development of a pediatric drug program for this product. The Applicant plans to (b) (4) .

DDLO asked DPMH to consider the following questions:

1. Are plans to waive assessment in children less than (b) (4) years and defer assessment in children over (b) (4) years until Crestor® exclusivity expires (b) (4) sufficient to support safety and efficacy in HoFH patients?
2. What recommendations does DPMH have to ensure compliance with PREA for (b) (4) non-Familial hyperlipidemia (FH)?
3. Once Crestor® exclusivity expires, would (b) (4) ?

[4] Clinical Review for sNDA 21445 Zetia® DARRTS June 5, 2008

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.[5] This proposed product contains a novel combination which is considered to be a new active ingredient under PREA. Therefore, the Applicant is required to submit a pediatric assessment with the adult NDA or an Agreed initial Pediatric Study Plan (iPSP) describing how it plans to evaluate dosing, safety, and efficacy of this product in the pediatric population, including any plans to request partial waivers and/or deferral of PREA study requirements for a specific pediatric age group.

Given the lack of both a pediatric assessment and Agreed iPSP in this NDA submission, DPMH focused on (b) (4) HoFH, and how the Applicant could provide a scientific bridge to the approved pediatric use information for each indication in approved labeling for the two listed drugs (LD) the Applicant is relying upon to support this 505(b)(2) NDA.

In HoFH patients, a partial waiver of PREA study requirements in pediatric patients less than (b) (4) years of age is (b) (4) for other drugs approved for the same indication, but a PREA post-marketing requirement (PMR) will be needed to either evaluate this product or to provide information about the concomitant use of both components in pediatric patients greater than (b) (4) years of age. Data sources to provide the latter include data from the relied-upon LDs, Crestor and Zetia, drug utilization data, published data, and analysis of registry data supporting the pediatric dosing, safety, and efficacy of this novel combination in pediatric patients with HoFH. Zetia has no pediatric use information for HoFH in labeling, so FDA has no previous findings of safety and effectiveness of Zetia for HoFH patients upon which this Applicant can rely. Hence, if the Applicant is unable to provide sufficient data from the aforementioned sources on the use of ezetimibe in pediatric patients with HoFH, it will need to conduct new pediatric studies to fulfill PREA requirements for this indication.

In non-FH patients, a full waiver in all pediatric ages of PREA study requirements is reasonable and consistent with action taken for other drugs approved for the same indication. Because diet and life-style modification rather than pharmacologic treatment are the mainstay of therapy for these patients, this product will not provide any meaningful benefit over existing therapies and is unlikely to be used in substantial numbers for the treatment of non-FH.

(b) (4)

[5] https://www.congress.gov/108/plaws/publ155/PLAW-108publ155.pdf

(b) (4)

Note for an FDC product, the Applicant must provide evidence that each drug component contributes to each claimed effect.

DPMH conveyed these recommendations to the division during an internal meeting between DDLO and DPMH on January 9, 2020. DDLO sent an Information Request (IR) to the Applicant requesting it submit a Pediatric Plan-Other.[6]

IV. DPMH Review of Applicant's IR Response

Althera Life Sciences, LLC submitted a Pediatric Study Plan (PSP)-Other as requested in the IR. In the PSP, the Applicant specified which FDA's findings of safety and effectiveness for Crestor and Zetia it plans to rely upon to support pediatric approval of this product and how it plans to bridge data gaps (b) (4) to support safety and efficacy of this product for (b) (4) pediatric patients (b) (4) years of age and older with HoFH.

The Applicant cites the pivotal trial used to approve Crestor for pediatric HoFH, the HYDRA Study,[7] in which 57% (8 of 13) of patients in the trial were concurrently on ezetimibe. See Figure 1. Neither the Applicant's IR response nor the trial report included data comparing patients receiving ezetimibe with those who did not. The Applicant states that adverse events were few and not serious. The Applicant also referenced the pivotal trial described in Zetia labeling that supported approval of Zetia to be co-administered with statins for treatment of HoFH in adult patients.[8] The Applicant cites that in this trial, 33 patients received either atorvastatin or simvastatin in conjunction with ezetimibe. Out of these 33 patients, 5 were under 18 years of age. The Applicant provided no further analysis of the trial in the IR response.

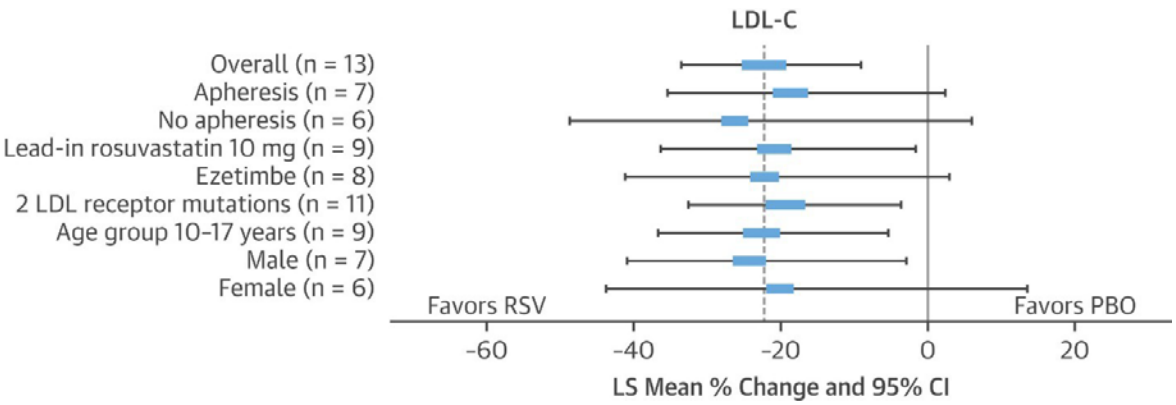
The Applicant states lack of additional available data due to the overall small number of patients with HoFH, citing the prevalence of HoFH as 1 in 0.16 million to 1 million. The Applicant further stated that drug utilization query is not feasible as US International Classification of Disease (ICD) does not differentiate HoFH from FH.

[6] Information Request tracked under NDA 213072 in DARRTS January 16, 2020

[7] Stein et al. *Efficacy of Rosuvastatin in Children with Homozygous Familial Hypercholesterolemia and Association with Underlying Genetic Mutations* JACC Vol. 70 2017

[8] Gagne et al. *Efficacy and Safety of ezetimibe co-administered with atorvastatin or simvastatin in patients with Homozygous Familial Hypercholesterolemia*. Circulation 2002

Figure 1: LDL-C Response by Subgroups



FDA approved Crestor for treatment of HoFH in pediatric patients 7 years of age and older on the basis of a single trial in 13 pediatric patients 7 to 15 years of age. Of note, the adult approval was based on a trial that enrolled 40 patients aging 8-63 years old.**Error! Bookmark not defined.** The Applicant should attempt to retrieve data from a comparable number of patients from publicly available sources or sources for which the Applicant can obtain right of reference to demonstrate the safety and efficacy of concomitant ezetimibe and statin use in patients down to (b) (4) years of age with HoFH. The Applicant should consider disease registries such as the CAscade SCreening for Awareness and DEtection of Familial Hypercholesterolemia (CASCADE FH) patient registry which is maintained by the FH Foundation. Such data sources should be able to accurately capture LDL-C levels at baseline and at specific timepoints after statin and ezetimibe treatment have been initiated.

The Applicant identified two published trials (b) (4) in the literature. One publication describes a 12-week, randomized, double-blind, placebo-controlled trial, enrolling 138 patients, 6 to 10 years of age with elevated LDL-C while on a lipid lowering diet for ≥ 3 months. The investigators randomized patients 2:1 to daily ezetimibe 10 mg (n = 93) or placebo (n = 45) for 12 weeks. Ninety percent of patients had HeFH. After 12 weeks, ezetimibe significantly reduced LDL-C by 27% (P < .001). Patients tolerated ezetimibe well with similar safety profile to older children and adults.[9] The second publication describes a retrospective study designed to compare the age of initiation and impact of treatment in 3,064 children (age range 3-11 years at diagnosis) with HeFH, in medical centers from 8 European countries. The median follow-up period was 6 years. The authors assessed age at diagnosis, age of initiation of treatment and baseline change in LDL-C levels after treatment initiation. The analysis showed greater baseline reduction in LDL-C with early statin use or statin in combination with ezetimibe. One subgroup of interest (n = 801) received statin and ezetimibe. Mean % LDL-C reduction in

[9] Kuster, DM, et al. *Efficacy and Safety of Ezetimibe Monotherapy in Children with Heterozygous Familial or Nonfamilial Hypercholesterolemia.* The Journal of Pediatrics.2015;166:1377-84.

this subgroup was 56.9% compared to 35.4% in those treated with a statin alone. Baseline LDL-C in the ezetimibe group was 254 compared to 215 mg/dl in those without ezetimibe.[10]

These publications suggest that (b) (4)

V. DPMH Conclusions

Because DDLO plans to issue a Complete Response (CR) to this application for CMC related deficiencies, PREA PMRs will not be issued during this review cycle. If the Applicant resubmits the NDA addressing the CMC deficiencies and continues to seek approval only in adults, DPMH recommends issuing PREA PMRs with adult approval of the NDA resubmission. DPMH agrees with DDLO that the PREA PMR's should consist of the following: (b) (4) assessment of Roszet (rosuvastatin and ezetimibe) for the treatment of homozygous familial hypercholesterolemia in pediatric patients (b) (4) to 17 years of age (inclusive). These PMRs should be due shortly before the corresponding exclusivities expire for Crestor.

DPMH recommends the pediatric assessment for (b) (4) HoFH indications include a comprehensive review of all published data as outlined in Section IV of this review. The Applicant must submit the pediatric assessments as an Efficacy Supplement to the approved NDA. DPMH recommends that the Applicant submit its Efficacy Supplement at least 6 months before exclusivities expire, which will be (b) (4) on or after November 2022 for HoFH to fulfill its PREA requirements and to support expansion (b) (4) to the pediatric population.

[10] Ramaswami U, et al. *Comparison of the characteristics at diagnosis and treatment of children with heterozygous familial hypercholesterolaemia (FH) from eight European countries*. Atherosclerosis 292 (2020) 178–187,

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/s/

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JOHN J ALEXANDER
05/01/2020 04:07:21 PM

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 MEMORANDUM

Date:	April 28, 2020
To:	Richard Whitehead, MS Regulatory Project Manager **Division of Diabetes, Lipid Disorders, and Obesity (DDLO)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Kelly Jackson, PharmD Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
Subject:	Review Deferred: Package Insert (PPI)
Drug Name (established name):	ROSZET (rosuvastatin and ezemtimibe)
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	NDA 213072
Applicant:	Althera Life Sciences, LLC

1 INTRODUCTION

On July 29, 2019, Althera Life Sciences, LLC submitted for the Agency's review an original New Drug Application (NDA 213072) for ROSZET (rosuvastatin and ezemtimibe) tablets, for oral use which contains a cholesterol absorption inhibitor and an HMG-CoA reductase inhibitor (statin) indicated (b) (4) to:

- reduce (b) (4) LDL-C, (b) (4) in patients with primary ((b) (4) non-familial) hyperlipidemia (b) (4).
- reduce (b) (4) LDL-C in patients with homozygous familial hypercholesterolemia (HoFH), as an adjunct to other (b) (4) lowering treatments.

On August 1, 2019, the Division of Diabetes, Lipid Disorders, and Obesity (DDLO) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Patient Package Insert (PPI) for ROSZET (rosuvastatin and ezemtimibe).

This memorandum documents the DMPP review deferral of the Applicant's proposed PPI for ROSZET (rosuvastatin and ezemtimibe).

2 CONCLUSIONS

Due to outstanding Chemical Manufacturing and Controls (CMC) deficiencies, DDLO plans to issue a Complete Response (CR) letter. Therefore, DMPP defers comment on the Applicant's patient labeling at this time. A final review will be performed after the Applicant submits a complete response to the Complete Response (CR) letter. Please send us a new consult request at such time.

Please notify us if you have any questions.

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/s/

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M E M O R A N D U M

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

DATE: April 16, 2020

TO: Bing Li, Ph.D.
Director (Acting)
Office Bioequivalence
Office of Generic Drugs

Lisa Yanoff, M.D.
Director (Acting)
Division of Diabetes, Lipid Disorders, and Obesity
Office of Cardiology, Hematology, Endocrinology, and Nephrology
Office of New Drugs

FROM: Hasan Irier, Ph.D.
Division of Generic Drug Study Integrity (DGDSI)
Office of Study Integrity and Surveillance (OSIS)

Li-Hong Yeh, Ph.D.
Division of New Drug Study Integrity (DNDSI)
OSIS

THROUGH: Seongeun Cho, Ph.D.
Director
DGDSI
OSIS

SUBJECT: Surveillance inspection of (b) (4)

1. Inspection Summary

The Office of Study Integrity and Surveillance (OSIS) inspected the analytical portion of studies (b) (4)-083-18, (b) (4)-084-18, and (b) (4)-085-18(NDA 213072, Rosuvastatin/Ezetimibe), NON-RESPONSIVE conducted at (b) (4).

We did not observe objectionable conditions and did not issue Form FDA 483 at the inspection close-out. The final inspection classification is No Action Indicated (NAI).

1.1. Recommendation

Based on our review of the inspectional findings, we conclude the data from the audited studies are reliable to support a regulatory decision.

2. Inspected Studies

Study [redacted]-083-18 (NDA 213072)
"A randomized, balanced, open label, two treatment, two period, two sequence, single dose, crossover, pivotal bioequivalence study of fixed dose combination of Rosuvastatin 40 mg/Ezetimibe 10 mg tablets manufactured on behalf of [redacted], at Piramal Enterprises Limited, Pithampur, India, with co-administration of CRESTOR® (rosuvastatin calcium) tablets 40 mg of AstraZeneca Pharmaceuticals LP Wilmington, DE 19850, and ZETIA® (ezetimibe) Tablets 10 mg of Merck & Co., INC, Whitehouse Station, NJ08889, USA, in healthy human adult male and/or female subjects under fasting condition."
Sample Analysis Period: 04/25/2019 – 05/09/2019

Study [redacted]-084-18 (NDA 213072)
"A randomized, balanced, open label, two treatment, two period, two sequence, single dose, crossover, pivotal bioequivalence study of fixed dose combination of Rosuvastatin 40 mg/Ezetimibe 10 mg tablets manufactured on behalf of [redacted], at Piramal Enterprises Limited, Pithampur, India, with co-administration of CRESTOR® (rosuvastatin calcium) tablets 40 mg of AstraZeneca Pharmaceuticals LP Wilmington, DE 19850, and ZETIA® (ezetimibe) Tablets 10 mg of Merck & Co., INC, Whitehouse Station, NJ08889, USA, in healthy human adult male and/or female subjects under fed condition."
Sample Analysis Period: 04/10/2019 – 04/25/2019

Study [redacted]-085-18 (NDA 213072)
"A randomized, balanced, open label, two treatment, two period, two sequence, single dose, crossover, pivotal bioequivalence study of fixed dose combination of Rosuvastatin 5 mg/Ezetimibe 10 mg tablets manufactured on behalf of [redacted], at Piramal Enterprises Limited, Pithampur, India, with co-administration of CRESTOR® (rosuvastatin calcium) tablets 5 mg of AstraZeneca Pharmaceuticals LP Wilmington, DE 19850, and ZETIA® (ezetimibe) Tablets 10 mg of Merck & Co., INC, Whitehouse Station, NJ08889, USA, in healthy human adult male and/or female subjects under fasting condition."

Sample Analysis Period: 05/07/2019 - 05/22/2019

NON-RESPONSIVE

2. Scope of Inspection

OSIS scientists Hasan A. Irier and Li-Hong Yeh audited the analytical portion of the above studies at [redacted] (b) (4)

(b) (4) from (b) (4) .

The inspection included a thorough examination of study records, facilities, laboratory equipment, method validation, and sample analysis, and interviews with the firm's management and staff.

4. Inspectional Findings

At the conclusion of the inspection, we did not observe objectionable conditions. We did not issue Form FDA 483 to (b) (4). There were no formal discussion items at the inspection closing meeting.

5. Conclusion

After review of the inspectional findings, we conclude that the analytical data from the audited studies are reliable. In addition, data from studies not audited but submitted to pending applications (**Attachment 1**) are reliable for Agency review.

Studies using similar methods conducted between the previous inspection (b) (4) and the end of the current surveillance interval should be considered reliable without an inspection.

Final Classification:

NAI – (b) (4)

cc: OTS/OSIS/Kassim/Folian/Mitchell/Fenty-Stewart/Haidar/Mirza
OTS/OSIS/DNDSI/Bonapace/Dasgupta/Ayala/Biswas/Yeh
OTS/OSIS/DGDSI/Cho/Choi/Skelly/Au/Irier

Draft: HAI 4/7/2020, PY 04/14/2020
Edit: YMC 4/15/2020; JC 4/15/2020

ECMS:
http://ecmsweb.fda.gov:8080/webtop/drl/objectId/0b0026f881a09352

OSIS File #: BE 8706 (NDA 213072), NON-RESPONSIVE

FACTS: (b) (4)

Attachment 1. List of studies ***not audited*** but submitted to pending applications

Applicable study number	Analyte(s)	Sponsor/applicant	Application number
NON-RESPONSIVE			

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/s/

HASAN A IRIER
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SEONGEUN CHO
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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	January 27, 2020
Requesting Office or Division:	Division of Metabolism and Endocrinology Products (DMEP)
Application Type and Number:	NDA 213072
Product Name and Strength:	Roszet (rosuvastatin and ezetimibe) tablet, 5 mg/10 mg, 10 mg/10 mg, 20 mg/10 mg, and 40 mg/10 mg
Applicant/Sponsor Name:	Althera
OSE RCM #:	2019-1642-1
DMEPA Safety Evaluator:	Melina Fanari, R.Ph.
DMEPA Team Leader:	Sevan Kolejian, PharmD, MBA

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on January 17, 2020 for Roszet. The Division of Metabolism and Endocrinology Products (DMEP) requested that we review the revised container labels and carton labeling for Roszet (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The revised carton and container labels are acceptable from a medication error perspective and we have no additional recommendations at this time.

[a] Fanari, M. Label and Labeling Review for Roszet (NDA 213072). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 Jan 3. RCM No.: 2019-1642.

5 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

MELINA N FANARI
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SEVAN H KOLEJIAN
01/28/2020 12:36:52 PM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	January 3, 2020
Requesting Office or Division:	Division of Metabolism and Endocrinology Products (DMEP)
Application Type and Number:	NDA 213072
Product Name and Strength:	Roszet (rosuvastatin and ezetimibe) tablet, 5 mg/10 mg, 10 mg/10 mg, 20 mg/10 mg, and 40 mg/10 mg
Product Type:	Multi-Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Althera
FDA Received Date:	July 29, 2019, November 14, 2019 and November 27, 2019
OSE RCM #:	2019-1642
DMEPA Safety Evaluator:	Melina Fanari, R.Ph.
DMEPA Team Leader:	Sevan Kolejian, PharmD, MBA

1 REASON FOR REVIEW

As part of the approval process for Roszet (rosuvastatin and ezetimibe) tablet, the Division of Metabolism and Endocrinology Products (DMEP) requested that we review the proposed Roszet prescribing information (PI), container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B-N/A
ISMP Newsletters	C-N/A
FDA Adverse Event Reporting System (FAERS)*	D-N/A
Other	E-N/A
Labels and Labeling	F

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 FINDINGS AND RECOMMENDATIONS

Tables 2 and 3 below include the identified medication error issues with the submitted prescribing information (PI), container labels, and carton labeling, our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 2. Identified Issues and Recommendations for Division of Metabolism and Endocrinology Products (DMEP)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Prescribing Information – General Issues			
1.	The symbols “>” and “≥” are utilized in the Dosage and Administration	Prevent misinterpretation and confusion.	Consider replacing the symbols “>” and “≥” with their intended meanings.

Table 2. Identified Issues and Recommendations for Division of Metabolism and Endocrinology Products (DMEP)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
	sections of highlights and full PI.		
2.	Numerical dose is not consistently followed by unit of measure.	Prevent wrong dose errors.	The product strength presentation in all sections of the PI should be revised as follows: XX mg/XX mg
Full Prescribing Information – Section 16 How Supplied/Storage and Handling			
3.	Inadequate space between numerical dose and unit of measure.	Improve readability.	Place adequate space between the numerical dose and unit of measure (e.g. 10 mg instead of 10mg).

Table 3. Identified Issues and Recommendations for Althera (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
ALL Carton Labeling and Container Labels ((b) (4))			
1.	Inadequate space between numerical dose and unit of measure.	Improve readability.	Place adequate space between the numerical dose and unit of measure (e.g. 10 mg instead of 10mg).
2.	Inappropriate use of (b) (4) and use of (b) (4) in the proprietary name.	Improve readability.	Revise the proprietary name as follows: 'Roszet' In addition, we recommend that the proprietary name appear in its own unique color and ensure the color does not overlap with any other colors utilized in highlighting the strengths.

Table 3. Identified Issues and Recommendations for Althera (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
3.	The expiration date is absent.	Minimize risk for deteriorated drug medication errors.	We request that you add the expiration date. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.
4.	The lot number is absent.	The lot number statement is required per 21 CFR 201.10(i)(1).	We request that you add the lot number statement. Ensure that there are no other numbers located in close proximity to the lot number and clearly differentiate the lot number from the expiration date.
5.	Manufacturer name on principle display panel competes with prominence of the	Takes readers attention away from important information.	Decrease prominence of or remove the manufacturer name from the principle display panel. We note this

Table 3. Identified Issues and Recommendations for Althera (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
	proprietary and established name and strength statement.		information already exists on the side panels
	(b) (4) Container Labels for 30 (b) (4) count bottles		
1.	The product identifier required under the drug supply chair security act (DSCSA) is missing.	DSCSA requires manufacturers and repackages, respectively, to affix or imprint a product identifier to each package and homogeneous case of a product intended to be introduced in a transaction in (to) commerce beginning November 27, 2017, and November 27, 2018, respectively.	We recommend that you review the draft guidance to determine if the product identifier requirements apply to your product's labeling. The draft guidance is available from: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf
3.	Net quantity statement is too prominent.	Numerical confusion can occur between product strength and net quantity statement.	Decrease the prominence of and relocate the net quantity statement to the bottom of the principle display panel.
4.	Rx Only statement is too prominent.	Takes readers attention away from important information.	Decrease the prominence of the Rx Only statement.
(b) (4)			

4 CONCLUSION

Our evaluation of the proposed Roszet prescribing information (PI), container labels, and carton labeling identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 2 for the Division and Table 3 for the Applicant. We ask that the Division convey Table 3 in its entirety to Althera so that recommendations are implemented prior to approval of this NDA.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Error! Reference source not found. presents relevant product information for Roszet received on November 14, 2019 from Althera, and the listed drugs (LD).

Table 2. Relevant Product Information for Roszet and the Listed Drugs

Product Name	Roszet	Zetia[a]	Crestor[b]
Initial Approval Date	N/A	2002	2003
Active Ingredient	rosuvastatin and ezetimibe	ezetimibe	rosuvastatin
Indication	Adjunct to diet to: - reduce (b) (4) LDL-C (b) (4) in patients with primary ((b) (4) non-familial) hyperlipidemia (b) (4) . - reduce (b) (4) LDL-C in patients with homozygous familial hypercholesterolemia (HoFH), as an adjunct to other (b) (4) -lowering treatments	Adjunct to diet to: -Reduce elevated total-C, LDL-C, Apo B, and non-HDL-C in patients with primary hyperlipidemia, alone or in combination with an HMG-CoA reductase inhibitor (statin) -Reduce elevated total-C, LDL-C, Apo B, and non-HDL-C in patients with mixed hyperlipidemia in combination with fenofibrate -Reduce elevated total-C and LDL-C in patients with homozygous familial hypercholesterolemia	-adult patients with primary hyperlipidemia and mixed dyslipidemia as an adjunct to diet to reduce elevated total-C, LDL-C, ApoB, nonHDL-C, and TG levels and to increase HDL-C -pediatric patients 8 to 17 years of age with heterozygous familial hypercholesterolemia (HeFH) to reduce elevated total-C, LDL-C and ApoB after failing an adequate trial of diet therapy -pediatric patients 7 to 17 years of age with homozygous familial hypercholesterolemia (HoFH) to reduce LDL-C, total-C, nonHDL-C and ApoB as an adjunct to

[a] Zetia [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. 2012 Jan 24. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021445s033lbl.pdf

[b] Crestor [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. 2018 Nov 09. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/021366s038lbl.pdf.

		(HoFH), in combination with atorvastatin or simvastatin -Reduce elevated sitosterol and campesterol in patients with homozygous sitosterolemia (phytosterolemia)	diet, either alone or with other lipid-lowering treatments -adult patients with hypertriglyceridemia as an adjunct to diet adult patients with primary dysbetalipoproteinemia (Type III hyperlipoproteinemia) as an adjunct to diet -adult patients with homozygous familial hypercholesterolemia (HoFH) to reduce LDL-C, total-C, and ApoB slowing the progression of atherosclerosis as part of a treatment strategy to lower total-C and LDL-C as an adjunct to diet -risk reduction of MI, stroke, and arterial revascularization procedures in patients without clinically evident CHD, but with multiple risk factors
Route of Administration	oral	Oral	Oral
Dosage Form	tablet	tablet	tablet
Strength	5 mg/10 mg, 10 mg/10 mg, 20 mg/10 mg, and 40 mg/10 mg	10 mg	5 mg, 10 mg, 20 mg and 40 mg
Dose and Frequency	One tablet daily	One tablet daily	5 mg to 40 mg once daily
How Supplied	Bottles of 30 (b) (4)	Bottles of 30, 90, 500 and 5000 count tablets. Unit dose packages of 100.	Bottle of 30 tablets (only 40 mg), 90 tablets (5 mg, 10 mg, and 20 mg) and

	(b) (4)		100 tablets (10 mg and 20 mg)
Storage	Store at controlled room temperature, 20ºC -25ºC (68-77ºF) [see USP Controlled Room Temperature]. Protect from moisture.	Store at 25ºC, excursions permitted to (15ºC -30ºC (59ºF - 86ºF) [see USP Controlled Room Temperature]. Protect from moisture.	Store at room temperature, 20ºC -25ºC (68 ºF -77ºF) [see USP Controlled Room Temperature]. Protect from moisture.

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[c] along with postmarket medication error data, we reviewed the following Roszet labels and labeling submitted by Althera.

- Container label received on November 14, 2019
- (b) (4) received on November 14, 2019
- (b) (4) received on November 14, 2019
- Prescribing Information (Image not shown) received on November 14, 2019, available from \\cdsesub1\evsprod\nda213072\0009\m1\us\114-labeling\draft\annotated\package-insert-ms-word.docx

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

6 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

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M E M O R A N D U M

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

DATE: 9/20/2019

TO: Division of Metabolism and Endcrinology Products
Office of Drug Evaluation II

FROM: Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct an on-site inspection**

RE: NDA 213072

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) determined that an inspection is not warranted at this time for the site listed below. The rationale for this decision is noted below.

Rationale

The Office of Regulatory Affairs (ORA) inspected the site in June 2019, which falls within the surveillance interval. The inspection was conducted under the following submissions: NON-RESPONSIVE NON-RESPONSIVE

The final classification for the inspection was No Action Indicated (NAI).

Therefore, based on the rationale described above, an inspection is not warranted at this time.

Inspection Site

Facility Type	Facility Name	Facility Address
Clinical	Syngene International, Ltd.	Human Pharmacology Unit, Tower I, Semicon Park, Electronic City, Phase II Hosur Road, Bangalore, Karnataka, India

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/s/

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