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Morristown, NJ 07960

**RE: NDA 213072**  
ROSZET (rosuvastatin and ezetimibe) tablets, for oral use  
MA 4

Dear Dr. Medley:

The Office of Prescription Drug Promotion (OPDP) of the U.S. Food and Drug Administration (FDA) has reviewed the promotional communication, a professional “Roszet Doctor Info Letter Size” (ROS-0009-001) for ROSZET (rosuvastatin and ezetimibe) tablets, for oral use (Roszet) submitted by Althera Pharmaceuticals, LLC (Althera) under cover of Form FDA 2253. This promotional communication makes false or misleading claims and representations about the risks and the efficacy of Roszet. Thus, the promotional communication misbrands Roszet within the meaning of the Federal Food, Drug and Cosmetic Act (FD&C Act) and makes its distribution violative. 21 U.S.C. 352(a); 321(n); 331(a). *C.f.* 21 CFR 202.1 (e)(3)(i); (e)(5); (e)(7)(viii). These violations are especially concerning from a public health perspective because the promotional communication creates a misleading impression regarding the safety and effectiveness of Roszet, which is a drug with multiple serious and potentially life-threatening risks. High cholesterol is a significant public health concern that affects millions of adults in the United States. Consumers and patients who seek assistance with managing their high cholesterol should receive truthful and non-misleading information regarding the serious risks and expected benefits associated with the use of a cholesterol lowering prescription drug product, such as Roszet.

## Background

Below are the indication and summary of the most serious and most common risks associated with the use of Roszet.<sup>1</sup> According to the INDICATIONS AND USAGE section of the FDA-approved prescribing information (PI):

Roszet is indicated 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

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<sup>1</sup> This information is for background purposes only and does not necessarily represent the risk information that should be included in the promotional piece cited in this letter.

homozygous familial hypercholesterolemia (HoFH) to reduce LDL-C.

Roszet is contraindicated in patients with acute liver failure or decompensated cirrhosis and in patients with hypersensitivity to rosuvastatin, ezetimibe, or any excipients in Roszet. The PI for Roszet includes warnings and precautions regarding myopathy and rhabdomyolysis, immune-mediated necrotizing myopathy, hepatic dysfunction, proteinuria and hematuria, and increases in HbA1c and fasting serum glucose levels. The most common adverse reactions reported with rosuvastatin were headache, nausea, myalgia, arthralgia, dizziness, asthenia, constipation, and abdominal pain; and with ezetimibe were upper respiratory tract infection, diarrhea, arthralgia, sinusitis, pain in extremity, fatigue, and influenza. The most common adverse reactions reported with ezetimibe co-administered with a statin were nasopharyngitis, myalgia, upper respiratory tract infection, arthralgia, diarrhea, back pain, influenza, pain in extremity, and fatigue.

### **False or Misleading Claims about Efficacy**

Prescription drug advertisements and labeling (promotional communications) misbrand a drug if they are false or misleading with respect to efficacy. The determination of whether a promotional communication is misleading includes, among other things, not only representations made or suggested in the promotional communication, but also the extent to which the promotional communication fails to reveal facts material in light of the representations made or with respect to consequences that may result from the use of the drug as recommended or suggested in the promotional communication.

The promotional communication includes the following claims (emphasis original):

- **“TOTAL\* LDL-C REDUCTIONS**
  - Roszet 10 mg/10 mg **64%**
  - Roszet 20 mg/10 mg **66%**
  - Roszet 40 mg/10 mg **72%**”
  
- “Roszet 5 mg/10 mg total LDL-C reduction is 59%\*.”

These claims about the effect of Roszet, attributing specific levels of LDL-C reductions to the drug product at various dosages, are misleading. Specifically, as reflected in an asterisked note on these claims,<sup>2</sup> the LDL-C reductions claimed in the promotional communication are not the findings of any study of Roszet. Rather, the analysis used to generate these percentages combines the results of two separate and unrelated studies from the CLINICAL

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<sup>2</sup> The asterisk on the claims cited above refers to a note that states: “\*Roszet LDL-C reductions calculated from baseline. E.g. 64% reduction indicates final LDL-C is at 36% of the original baseline level i.e.  $(1-52\%)*(1-25\%) = 36\%$ . [LDL-C reductions: rosuvastatin 10 mg = 52%; ezetimibe 10 mg = incremental 25% reduction].” Inclusion of this note does not mitigate the misleading claims given that they are based on a scientifically unsound analysis as discussed above.

STUDIES section of the Roszet PI: 1) a monotherapy study that evaluated rosuvastatin in patients with hyperlipidemia and 2) a combination study that evaluated ezetimibe added to ongoing statin therapy in patients with primary hyperlipidemia, known coronary heart disease or multiple cardiovascular risk factors who were already receiving statin monotherapy, but who had not met their target LDL-C goal. The LDL-C reductions represented in the claims above that are attributed to Roszet actually depict numbers that were retrospectively calculated by combining the results of these two unrelated studies, neither of which evaluated the specific combination of rosuvastatin and ezetimibe (i.e., Roszet). In fact, rosuvastatin was not actually one of the statins used in the study of ezetimibe added to ongoing statin therapy. The LDL-C reductions claimed in the promotional communication for each dose of Roszet were calculated by taking the percent change from baseline LDL-C reduction observed in the rosuvastatin monotherapy study and then applying an additional 25% LDL-C reduction which was observed in the separate ezetimibe added to ongoing statin therapy study. FDA is not aware of a scientific basis for combining study results in this manner.

Furthermore, these studies differed in patient population and type and dose of statin(s), as well as duration (i.e., 6 weeks for the rosuvastatin monotherapy study and 8 weeks for the ezetimibe added to ongoing statin therapy study). Such differences between studies limit the interpretability of any cross-study comparisons and any analysis combining the results of these studies. Thus, such an analysis does not support these claims that attribute specific levels of LDL-C reductions to each dose of Roszet. The clinical studies described in the Roszet PI and cited in the promotional communication support FDA's finding of safety and efficacy of the drug with respect to its labeled indication, involving the reduction of LDL-C in certain patients, but not in achieving the specific levels of LDL-C reductions claimed. Thus, the promotional communication creates a misleading impression regarding the effect of Roszet.

The promotional communication also includes the following claims and presentations (emphasis original):

- **“Patients Can Get Below 70 mg/dL with One Pill Daily”**
- “Mean LDL-C Reductions Achieved in Clinical Trials”
  - **“GRAVITY<sup>3</sup> Study**
    - Baseline LDL-C **163** mg/dl → Final LDL-C **65** mg/dl after 12 weeks (Dose: rosuvastatin/ezetimibe 10 mg/10 mg)
    - Baseline LDL-C **165** mg/dl → Final LDL-C **59** mg/dl after 12 weeks (Dose: rosuvastatin/ezetimibe 20 mg/10 mg)”

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<sup>3</sup> Ballantyne CM, et al. Efficacy, safety and effect on biomarkers related to cholesterol and lipoprotein metabolism of rosuvastatin 10 or 20 mg plus ezetimibe 10 mg vs. simvastatin 40 or 80 mg plus ezetimibe 10 mg in high risk patients: Results of the GRAVITY randomized study. *Atherosclerosis* 2014; 232:86-93.

- **“EXPLORER<sup>4</sup> Study**
  - Baseline LDL-C **189** mg/dl → Final LDL-C **57** mg/dl after 6 weeks (Dose: rosuvastatin/ezetimibe 40 mg/10 mg)”

These claims and presentations create a misleading impression regarding the efficacy of Roszet in achieving specific levels of LDL-C reduction over specific periods of time. There are multiple limitations to the cited studies<sup>3,4</sup> that preclude drawing conclusions regarding the quantitative treatment effect of Roszet on LDL-C based on these studies.

For example, both the GRAVITY and EXPLORER studies conducted analyses in a modified intent-to-treat population (mITT) that excluded subjects with no post-baseline measurements from the efficacy analyses and only used the last observation carried forward (LOCF) method to impute missing data. Both LOCF and mITT introduce bias in the estimation of the treatment effect and increase the chance of committing a Type I error (i.e., falsely concluding a treatment effect). The use of the mITT population biases the estimate of the treatment effect of the drug because excluding patients after randomization could undermine the integrity of randomization. Similarly, the use of LOCF to account for patients with missing data further biases the estimate of the treatment effect of the drug because it relies on the unlikely assumption that outcomes after treatment discontinuation remain constant. Also, the use of LOCF does not account for the uncertainty of the imputed values for missing data. Thus, the use of the mITT population and LOCF introduce bias into the study results and limit the conclusions that can be drawn regarding the quantitative treatment effect based on these studies.

Additionally, the promotional communication includes claims and presentations that misleadingly imply that the GRAVITY and EXPLORER studies establish that patients can get their LDL-C below 70 mg/dL with Roszet. The primary endpoints in GRAVITY and EXPLORER studies were mean percent reduction in LDL-C from baseline to week 12 and the proportion of patients who achieved LDL-C <100 mg/dL at week 6, respectively. However, the proportion of patients achieving LDL-C <70 mg/dL was only one of numerous secondary endpoints in these studies and, the study publications do not discuss, and the FDA is not aware of, any methods taken to control for multiplicity testing of secondary endpoints in these studies. As the number of endpoints analyzed in a single study increases, the likelihood of making false conclusions about a drug's effects with respect to one or more of those endpoints becomes a concern if there is not appropriate adjustment for multiplicity. Basing a conclusion on an analysis where the risk of false conclusions has not been appropriately controlled can lead to false or misleading representations regarding a drug's effects. If you have information on any methods taken to control for multiplicity testing of secondary endpoints in these studies, please submit to FDA for review.

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<sup>4</sup> Ballantyne CM, et al. Efficacy and safety of rosuvastatin 40 mg alone or in combination with ezetimibe in patients at high risk of cardiovascular disease (results from the EXPLORER study). *Am J Cardiol* 2007; 99:673-80.

Lastly, the promotional communication misleadingly implies that the results for the GRAVITY study represent 12 weeks of treatment with ROSZET. However, this study was not designed to demonstrate the effect of the combination of rosuvastatin and ezetimibe on LDL-C after 12 weeks of treatment. Rather, patients were first treated with 6 weeks of rosuvastatin 10 mg or 20 mg monotherapy (Weeks 0 to 6) followed by 6 weeks of rosuvastatin plus ezetimibe 10 mg (Weeks 7 to 12). The effects on LDL-C seen at Week 12 are the result of 6 weeks of monotherapy *followed by* 6 weeks of combination therapy, *not* 12 weeks of combination therapy. Therefore, this study does not support the claimed efficacy of the combination of rosuvastatin plus ezetimibe after 12 weeks of treatment.

Therefore, due to multiple limitations of design and analytic strategy, these studies do not support claims and presentations regarding the magnitude of treatment effect of Roszet on LDL-C.

The claims and presentations regarding Roszet's effect on LDL-C such as, "**Roszet Delivers Powerful LDL-C Reductions**" and "**Patients Can Get Below 70 mg/dL with One Pill Daily**," are also misleading because they omit material information from the full indication about the relative effect of diet (emphasis original). According to the INDICATIONS AND USAGE section of the PI, one of Roszet's indications is as an adjunct to diet to reduce LDL-C in patients with primary non-familial hyperlipidemia. OPDP acknowledges that the full indication is included at the bottom of page one of the promotional communication. However, unlike the benefit claims in the promotional communication, which utilize significant white space and large colorful font, the full indication is included under an "**Important Safety Information**" header in paragraph format in a much smaller font size and with minimal white space at the bottom of the page (emphasis original). Therefore, this does not mitigate the misleading impression. By omitting this information from these claims, this presentation misleadingly suggests that Roszet alone, in the absence of diet, provides these benefits to patients with primary non-familial hyperlipidemia when this has not been demonstrated.

### **False or Misleading Risk Presentation**

Promotional communications misbrand a drug if they are false or misleading with respect to risk. The determination of whether a promotional communication is misleading includes, among other things, not only representations made or suggested in the promotional communication, but also the extent to which the promotional communication fails to reveal facts material in light of the representations made or with respect to consequences that may result from the use of the drug as recommended or suggested in the promotional communication.

The promotional communication is misleading because it fails to present information relating to the contraindications and warnings and precautions for Roszet with a prominence and readability reasonably comparable with the presentation of information relating to the benefits of Roszet. Factors impacting prominence and readability include typography, layout, contrast, headlines, paragraphing, white space, and other techniques apt to achieve

emphasis. Specifically, benefit claims for Roszet are presented in conjunction with colorful graphics and large bolded headlines, with significant white space. However, risk information regarding some of the contraindications is relegated to the bottom of the first page and the remaining contraindications and warnings and precautions are presented on a subsequent page. This risk information is also presented in small font and in paragraph format. We note that some of the most common adverse reactions are presented in the body of the promotional communication in table format under the header “**Safety and Tolerability**” (emphasis original). However, only presenting common adverse reactions associated with Roszet under this header and relegating the serious risks (i.e., contraindications and warnings and precautions) to the bottom of the page and subsequent page in small font and paragraph format creates a misleading impression regarding the risk profile of Roszet. For example, event rates for myalgia are prominently presented under the header “**Safety and Tolerability**,” however the warning and precaution for myopathy and rhabdomyolysis is relegated to the subsequent page in small font and paragraph format (emphasis original). The overall effect of disclosing risk information in this manner undermines the communication of risk information and thereby misleadingly minimizes the risks associated with the use of Roszet.

### **Conclusion and Requested Action**

For the reasons discussed above, the letter misbrands Roszet within the meaning of the FD&C Act and makes its distribution violative. 21 U.S.C. 352(a); 321(n); 331(a). *C.f.* 21 CFR 202.1 (e)(3)(i); (e)(5); (e)(7)(viii).

This letter notifies you of our concerns and provides you with an opportunity to address them. OPDP requests that Althera cease any violations of the FD&C Act. Please submit a written response to this letter within 15 working days from the date of receipt, addressing the concerns described in this letter, listing all promotional communications (with the 2253 submission date) for Roszet that contain representations like those described above, and explaining any plan for discontinuing use of such communications, or for ceasing distribution of Roszet.

If you believe that your product is not in violation of the FD&C Act, please include in your submission to us your reasoning and any supporting information for our consideration within 15 working days from the date of receipt of this letter.

The concerns discussed in this letter do not necessarily constitute an exhaustive list of potential violations. It is your responsibility to ensure compliance with each applicable requirement of the FD&C Act and FDA implementing regulations.

Please direct your response to the undersigned at the **Food and Drug Administration, Center for Drug Evaluation and Research, Office of Prescription Drug Promotion, 5901-B Amundson Avenue, Beltsville, Maryland 20705-1266**. A courtesy copy can be sent by facsimile to (301) 847-8444. Please refer to MA 4 in addition to the NDA number in all future

correspondence relating to this particular matter. All correspondence should include a subject line that clearly identifies the submission as a Response to Untitled Letter. You are encouraged, but not required, to submit your response in eCTD format. All correspondence submitted in response to this letter should be placed under eCTD Heading 1.15.1.6. Additionally, the response submission should be coded as an Amendment to eCTD Sequence 0044 under NDA 213072. Questions related to the submission of your response letter should be emailed to the OPDP RPM at CDER-OPDP-RPM@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Ankur Kalola, PharmD, RAC  
Regulatory Review Officer  
Division of Advertising & Promotion Review 2  
Office of Prescription Drug Promotion

{See appended electronic signature page}

Melinda Wilson, PharmD, MPH, BCPS,  
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**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**

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/s/

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06/02/2022 02:50:30 PM

MELINDA M WILSON  
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