

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**214012Orig1s000**

**OTHER REVIEW(S)**

**Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)  
Epidemiology: ARIA Sufficiency**

Date: December 15, 2021

Reviewer(s): Po-Yin Chang, PhD  
Epidemiologist  
Division of Epidemiology I

Team Leader: Yandong Qiang, MD, PhD, MPH, MHS  
Lead Epidemiologist  
Division of Epidemiology I

Division Director: Simone Pinheiro, ScD, MSc, ALM  
Director  
Division of Epidemiology I

Subject: ARIA Sufficiency Memo for Pregnancy Safety Concerns

Drug Name(s): Inclisiran

Application Type/Number: NDA 214012

Applicant/sponsor: NOVARTIS Pharmaceuticals Corp

OSE RCM #: 2020-2159



**EXECUTIVE SUMMARY** (*place "X" in appropriate boxes*)

<b>Memo type</b>	
-Initial	X
-Interim	
-Final	
<b>Source of safety concern</b>	
-Peri-approval	X
-Post-approval	
<b>Is ARIA sufficient to help characterize the safety concern?</b>	
-Yes	
-No	X
<b>If "No", please identify the area(s) of concern.</b>	
-Surveillance or Study Population	
-Exposure	
-Outcome(s) of Interest	X
-Covariate(s) of Interest	X
-Surveillance Design/Analytic Tools	X

## 1. BACKGROUND INFORMATION

### 1.1. Medical Product

Inclisiran is a double-stranded, synthesized small interfering ribonucleic acid (siRNA) molecule that inhibits the production of proprotein convertase subtilisin/kexin type 9 (PCSK9). The Applicant submitted this New Drug Application (NDA), seeking approval of Inclisiran (LEQVIO, NDA214012)<sup>1</sup>

- as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (CVD), who require additional lowering of low-density lipoprotein cholesterol (LDL-C).

Circulating PCSK9, derived almost entirely from the liver, binds to low-density lipoprotein (LDL) receptors and increases degradation of LDL receptors. Inclisiran produces hepatocyte-specific, PCSK9-specific RNA silencing, reduces PCSK9 levels, increases the availability of LDL receptors, and subsequently reduces LDL-C levels in circulation.<sup>2</sup>

The recommended dosage of inclisiran is 284 mg, administered by subcutaneous injection initially, again at 3 months, then every 6 months.<sup>1</sup>

Lipid-lowering agents in the U.S. include statins, fibrates, niacin, ezetimibe, bile acid sequestrants, lomitapide, and PCSK9 inhibitors.

The regulatory trigger for this memo is FDA's issuance of a descriptive, single-arm pregnancy safety study as a Post Marketing Requirement (PMR) for inclisiran.

### 1.2. Describe the Safety Concern

Multiple clinical practice guidelines recommend against use of lipid-lowering drugs in pregnant women.<sup>a, 3-8</sup> Discontinuation of lipid-lowering drugs for a short period of time during pregnancy is considered to have little impact on long-term therapy for hyperlipidemia and is unlikely to affect outcomes of cardiovascular disease.<sup>9, 10</sup> Cholesterol and cholesterol derivatives are important for embryo-fetal development. During pregnancy, it is normal for total cholesterol, LDL-C, and high-density lipoprotein cholesterol (HDL-C) to increase by 25-50%, and triglycerides increase two to four times. In pregnant women, decreased levels of total cholesterol were associated with preterm birth and small-for-gestational age infants.<sup>11</sup>

In Phase 3 trials of inclisiran, three inclisiran-exposed pregnancies occurred, with treatment discontinued in all cases. One pregnancy ended with a full-term healthy baby, one pregnancy was electively terminated before 12 weeks, and one pregnancy was ongoing at the time of submission<sup>b</sup>.

Based on the Pregnancy and Lactation Labeling Rule (PLLR), the Division of Pediatric and Maternal Health (DPMH) reviewed the inclisiran submission and provided the following conclusions:<sup>10</sup>

- Because inclisiran decreases cholesterol and possibly other biological active substance derived from cholesterol, inclisiran may cause fetal harm when administered to pregnant patients based on the mechanisms of action. However, animal studies in rats and rabbit provided no evidence of embryoletality, fetotoxicity, or genotoxicity.

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<sup>a</sup> Six clinical practice guidelines recommend discontinuing lipid-lowering drugs during pregnancy, except bile acid sequestrants, and avoiding lipid-lowering drugs in women who plan to become pregnant. See References three to eight.

<sup>b</sup> Pregnancy that was electively terminated had inclisiran exposure in the first trimester. The indication for pregnancy termination was not provided and malformation was not reported. For the remaining two pregnancies, the Applicant did not report when inclisiran was administered during pregnancy.



- Because women of reproductive potential constitute a significant part of the target inclisiran users, there is a need for more information to be gathered and included in the labeling of Pregnancy and Lactation subsections.
- In humans, there are sparse data on use of inclisiran in three pregnant women. Therefore, the data are insufficient to determine a drug-associated risk for major birth defects, miscarriage, or adverse maternal or fetal outcomes.

Given potential inclisiran exposure during pregnancy and potential for fetal harm, the Division of Diabetes, Lipid Disorders, and Obesity (DDLDO) plans to issue a Postmarketing Requirement (PMR) at approval for an observational, descriptive study to assess the maternal and fetal safety associated with inclisiran exposure during pregnancy.

A descriptive pregnancy safety study is appropriate because use of lipid-lowering drugs is not recommended in pregnant women and labeling advises about discontinuation of inclisiran when pregnancy is recognized. Thus, a study sufficiently powered for a comparative analysis is not required.

The regulatory trigger for this memo is FDA's issuance of a descriptive pregnancy safety study as a PMR for inclisiran.

In the proposed product labeling, as of December 3, 2021, the Risk Summary in Section 8.1 states:





### 1.3. FDAAA Purpose (per Section 505(o)(3)(B))

- Please ensure that the selected purpose is consistent with the other PMR documents in DARRTS

*Purpose (place an "X" in the appropriate boxes; more than one may be chosen)*

Assess a known serious risk	
Assess signals of serious risk	
Identify unexpected serious risk when available data indicate potential for serious risk	X

## 2. REVIEW QUESTIONS

### 2.1. Why is pregnancy safety a safety concern for this product? Check all that apply.

- ☐ Specific FDA-approved indication in pregnant women exists and exposure is expected
- ☐ No approved indication, but practitioners may use product off-label in pregnant women
- ☒ No approved indication, but there is the potential for inadvertent exposure before a pregnancy is recognized
- ☒ No approved indication, but use in women of child bearing age is a general concern

### 2.2. Regulatory Goal

- ☒ *Signal detection* – Nonspecific safety concern with no prerequisite level of statistical precision and certainty
- ☐ *Signal refinement of specific outcome(s)* – Important safety concern needing moderate level of statistical precision and certainty. <sup>†</sup>
- ☐ *Signal evaluation of specific outcome(s)* – Important safety concern needing highest level of statistical precision and certainty (e.g., chart review). <sup>†</sup>

**2.3. What type of analysis or study design is being considered or requested along with ARIA? Check all that apply.**

- ☐ Pregnancy registry with internal comparison group
- ☐ Pregnancy registry with external comparison group
- ☐ Enhanced pharmacovigilance (i.e., passive surveillance enhanced by with additional actions)
- ☐ Electronic database study with chart review
- ☐ Electronic database study without chart review
- ☒ Other, please specify: A worldwide, descriptive pregnancy safety study which will collect prospective and retrospective data in women exposed to inclisiran during pregnancy to assess risks of maternal, fetal, and infant outcomes. The minimum number of patients will be specified in the protocol. This study will *not* require inferential analyses. A descriptive pregnancy safety study is appropriate in this case because use of lipid-lowering drugs is not recommended in pregnant women and labeling advises about discontinuation of inclisiran when pregnancy is recognized.

**2.4. Which are the major areas where ARIA not sufficient, and what would be needed to make ARIA sufficient?**

- ☐ Study Population
- ☐ Exposures
- ☒ Outcomes
- ☒ Covariates
- ☒ Analytical Tools

*For any checked boxes above, please describe briefly:*

**Outcomes:**

The ARIA system lacks access to detailed information regarding (1) accurate timing of drug exposure in relation to pregnancy onset and (2) outcomes of interest (e.g., congenital malformation). The outcomes of interest may require medical chart validation and independent review of primary sources by physicians with expertise in birth defects.

**Covariates:**

The ARIA system is unlikely to provide complete information about critical maternal covariates, such as smoking, alcohol consumption, occupational exposure, and illicit drug use.

**Analytical Tools:**

This descriptive study is being requested for broad-based surveillance of the safety of Inclisiran exposure during pregnancy, which would include multiple maternal and fetal outcomes in mother-baby pairs. ARIA might address analyses of multiple outcomes by appropriate data mining approaches. However, current ARIA analytic tools are not sufficient to assess the regulatory question of interest because data mining methods have not been tested for birth defects and other pregnancy outcomes.

## 2.5. Please include the proposed PMR language in the approval letter.

The proposed PMR language in the approval letter:

*Conduct a worldwide, descriptive study that collects prospective and retrospective data in women exposed to Leqvio during pregnancy to assess risk of pregnancy and maternal complications, adverse effects on the developing fetus and neonate, and adverse effects on the infant. Infant outcomes will be assessed through at least the first year of life. The minimum number of patients will be specified in the protocol.*

CC list:

CallowayP/WangY/MosholderA/QiangY/HuaW/SandhuS/PinheiroS/DEPI-I  
 PetruccelliM/CraigE/ChowdhuryI/HigginbothamL/HoustounM/SharrettsJ/YanoffL/DDLO  
 MastroyannisC/JohnsonT/DPMH  
 PickingR/DROCHEN  
 WoronowD/DPV  
 NgT/DRISK  
 Hamilton-StokesD/OSE

### Reference:

1. Craig E and Chowdhury I. Clinical Review for New Drug Application 214012, Inclisiran (LEQVIO). Reference ID: 4697450. November 4, 2020.
2. Ray KK, Landmesser U, Leiter LA, et al. Inclisiran in patients at high cardiovascular risk with elevated LDL cholesterol. *N Engl J Med* 2017; 376: 1430-40
3. Goldberg AC, Hopkins PN, Toth PP, et al. Familial Hypercholesterolemia: Screening, diagnosis and management of pediatric and adult patients: Clinical guidance from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. *Journal of Clinical Lipidology*. 2011;5(3, Supplement):S1-S8.
4. Grundy SM, Stone NJ, Bailey AL, et al. 2018  
 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA /ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2019;139(25):e1082-e1143.
5. Lambert CT, Sandesara P, Isiadinso I, et al. Current Treatment of Familial Hypercholesterolaemia. *Eur Cardiol*. 2014;9(2):76-81.
6. Lloyd-Jones DM, Morris PB, Ballantyne CM, et al. 2017 Focused Update of the 2016 ACC Expert Consensus Decision Pathway on the Role of Non-Statins Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk: A Report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways. *Journal of the American College of Cardiology*. 2017;70(14):1785-1822.
7. Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk: The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European





Atherosclerosis Society (EAS). *European Heart Journal*. 2019;41(1):111-188.

8. Thorogood M, Seed M, De Mott K, Group GD. Management of fertility in women with familial hypercholesterolaemia: summary of NICE guidance. *BJOG: An International Journal of Obstetrics & Gynaecology*. 2009;116(4):478-47
9. Jane Liedtka. Pregnancy and lactation labeling [prior approval supplements (PASs), pregnancy and lactation labeling rule (PLLR) conversions]. Reference ID: 4396340. February 27, 2019.
10. Mastroyannis C. Pregnancy and lactation labeling formatting recommendations for inclisiran, NDA 214012. Reference ID: 4687201. October 16, 2020.
11. Vrijkotte, TG, Krukzeiner N, Hutten BA, et al., Maternal Lipid Profile During Early Pregnancy and Pregnancy Complications and Outcomes: The ABCD Study. *J Clin Endocrinol Metab* 2012; 97: 3917-3925.

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/s/  
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SIMONE P PINHEIRO  
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12/15/2021 02:50:52 PM

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

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

## Memorandum

**Date:** December 14, 2021

**To:** Iffat N. Chowdhury, M.D., Medical Officer  
Division of Diabetes, Lipid Disorders, and Obesity (DDLO)

Ronald Picking III, Project Manager, (DGE)

Monika Houstoun, Associate Director for Labeling, (DMEP)

**From:** Charuni Shah, Regulatory Review Officer  
Office of Prescription Drug Promotion (OPDP)

**Through:** Melinda McLawhorn, Team Leader, OPDP

**Subject:** OPDP Labeling Comments for LEQVIO (inclisiran) injection, for subcutaneous use

NDA 214012

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In response to DGE's consult request dated August 16, OPDP has reviewed the proposed product labeling (PI) and Carton/Container for LEQVIO (inclisiran) injection, for subcutaneous use (Leqvio). This is a new application indicated for the reduction of LDL in adult patients with ASCVD and HeFH.

**PI, Carton/Container:** OPDP's comments on the proposed PI are based on the draft materials sent by DDLO on December 2, 2021, and are provided below.

Thank you for your consult. If you have any questions, please contact Charuni Shah at (240) 402-4997 or [charuni.shah@fda.hhs.gov](mailto:charuni.shah@fda.hhs.gov).

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

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CHARUNI P SHAH  
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MEMORANDUM  
REVIEW OF REVISED LABEL AND LABELING  
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)  
Office of Medication Error Prevention and Risk Management (OMEPRM)  
Office of Surveillance and Epidemiology (OSE)  
Center for Drug Evaluation and Research (CDER)

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Date of This Memorandum:	December 8, 2021
Requesting Office or Division:	Division of Diabetes, Lipid Disorders, and Obesity (DDLO)
Application Type and Number:	NDA 214012
Product Name and Strength:	Leqvio (inclisiran) injection, 284 mg/1.5 mL
Applicant/Sponsor Name:	Novartis Pharmaceuticals Corporation (Novartis)
OSE RCM #:	2019-2666-4
DMEPA 1 Safety Evaluator:	Ariane O. Conrad, PharmD, BCACP, CDCES
DMEPA 1 Team Leader:	Idalia E. Rychlik, PharmD

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## 1 PURPOSE OF MEMORANDUM

Novartis resubmitted carton and container labels for Leqvio (inclisiran) for review on November 29, 2021 in response to comments that were made during a previous label and labeling review.<sup>a</sup> The Division of Diabetes, Lipid Disorders, and Obesity requested that we review the labels and labeling for Leqvio (Appendix A) to determine if they are acceptable from a medication error perspective. Of note, Novartis responded to each of the comments that were made during a previous label and labeling review.<sup>b</sup>

## 2 CONCLUSION

We note that we advised Novartis to consider using one of the recommended formats for the human-readable expiration date on the Leqvio carton and container labels. However, Novartis responded with their preference to maintain their planned format ("MMM YYYY") with the understanding that they will adopt the FDA recommended format of "YYYY MMM" by 2023 in compliance with the Drug Supply Chain Security Act (DSCSA) aggregation enforcement timeline of November 27, 2023. In addition, Novartis confirmed that the linear barcode is oriented

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<sup>a</sup> Conrad, A. Review of Revised Label and Labeling Memorandum for Leqvio (NDA 214012). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2021 Oct 14. RCM No.: 2019-2666-3

<sup>b</sup> Response to Information Request (container labels and carton labeling) for NDA 214012. East Hanover (NJ): Novartis Pharmaceuticals Corporation; 2021 Nov 5. Available from: <\\CDSESUB1\evsprod\nda214012\0072\m1\us\fda-response-clinical.pdf>.

lengthwise along the syringe barrel for proper scanning, and they provided an image for reference (Appendix B).<sup>c</sup>

We determined that Novartis's response to our labeling comments is reasonable. Thus, our evaluation of the proposed Leqvio labels and labeling determined that the syringe label, syringe tray label, and carton labeling are acceptable from a medication error perspective. We have no additional recommendations at this time.

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<sup>c</sup> Attachment to Response to Information Request (container labels and carton labeling) for NDA 214012. East Hanover (NJ): Novartis Pharmaceuticals Corporation; 2021 Nov 5. Available from: <\\CDSESUB1\evsprod\nda214012\0072\m1\us\fda-response-clinical-attach1.jpg>.

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/s/  
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ARIANE O CONRAD  
12/08/2021 03:06:49 PM

IDALIA E RYCHLIK  
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MEMORANDUM  
REVIEW OF REVISED LABEL AND LABELING  
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)  
Office of Medication Error Prevention and Risk Management (OMEPRM)  
Office of Surveillance and Epidemiology (OSE)  
Center for Drug Evaluation and Research (CDER)

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Date of This Memorandum:	October 14, 2021
Requesting Office or Division:	Division of Diabetes, Lipid Disorders, and Obesity (DDLO)
Application Type and Number:	NDA 214012
Product Name and Strength:	Leqvio (inclisiran) injection, 284 mg/1.5 mL
Applicant/Sponsor Name:	Novartis Pharmaceuticals Corporation (Novartis)
OSE RCM #:	2019-2666-3
DMEPA 1 Safety Evaluator:	Ariane O. Conrad, PharmD, BCACP, CDCES
DMEPA 1 Team Leader:	Idalia E. Rychlik, PharmD

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## 1 PURPOSE OF MEMORANDUM

Novartis submitted draft carton and container labels for Leqvio (inclisiran) for review on July 1, 2021. The Division of Diabetes, Lipid Disorders, and Obesity requested that we review the labels and labeling for Leqvio (Appendix A) to determine if they are acceptable from a medication error perspective.

## 2 REGULATORY HISTORY

We evaluated the product labeling submitted for NDA 214012 in prior reviews and we found them to be acceptable.<sup>abc</sup> The NDA received a complete response (CR) on December 23, 2019 and Novartis submitted their response to the CR with revised labels and labeling for review on July 1, 2021.

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<sup>a</sup> Fanari, M. Label and Labeling Review for (b) (4) (NDA 214012). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 Mar 12. RCM No.: 2019-2666.

<sup>b</sup> Fanari, M. Review of Revised Label and Labeling for Leqvio (NDA 214012). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 Sep 15. RCM No.: 2019-2666-1.

<sup>c</sup> Fanari, M. Review of Revised Label and Labeling for Leqvio (NDA 214012). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 Oct 14. RCM No.: 2019-2666-2.



### 3 CONCLUSION

Our review of the current carton and container label submission identified some design differences when compared to the version of labels and labeling reviewed during the last review cycle (e.g., reorientation of the barcode on the syringe label from a vertical position to a horizontal position). Our evaluation of the proposed labels and labeling determined that the syringe label, syringe tray label, and carton are acceptable from a medication error perspective; however, we do provide two comments requesting clarification from the sponsor in Section 4.

### 4 RECOMMENDATIONS FOR NOVARTIS PHARMACEUTICALS CORPORATION

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

#### A. General Comments (Container labels & Carton Labeling)

1. We note that your planned format for the expiration date is defined as “MMM YYYY”. 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.

#### B. Container Label

1. We note that the linear barcode on the syringe label is oriented in a horizontal position. Please confirm that the orientation of the linear barcode allows the barcode to be scanned properly. We typically recommend that the barcode is oriented lengthwise along the syringe barrel; however, it is unclear how the barcode will be oriented on your product.

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10/14/2021 11:49:02 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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Food and Drug Administration

Center for Drug Evaluation and Research  
Office of New Drugs, ORPUM  
Division of Pediatric and Maternal Health  
Silver Spring, MD 20993  
Telephone 301-796-2200  
FAX 301-796-9855

**MEMORANDUM TO FILE**

**Date of Consult Request:** November 16, 2020

**From:** Heather Buck  
Division of Pediatric and Maternal Health (DPMH)

**To:** Kati Johnson, Regulatory Project Manager

**NDA Number:** NDA 214012

**Drug:** Leqvio (inclisiran)

**Applicant:** The Medicines Co.

**Indication:** Adjunct to diet and maximally tolerated statin therapy for the treatment of adults with primary hyperlipidemia [including heterozygous familial hypercholesterolemia (HeFH)] to reduce low-density lipoprotein cholesterol (LDL-C)

The Division of Diabetes, Lipid Disorders, and Obesity (DDLO) submitted a second maternal consult request to DPMH for this NDA which is currently under review with a PDUFA goal date of December 23, 2020. The first consult was issued on January 6, 2020 for PLLR labeling (see October 19, 2020 Maternal Health review by Christos Mastroyannis). It recommends a PMR study in pregnant women (worldwide, single-arm, observational safety study of pregnant women exposed to inclisiran). At the October 13, 2020 Late-Cycle meeting, the firm inquired as to whether a program planned similar to a program in Europe called PRIM (Pregnancy Outcome Intensive Monitoring) would be acceptable. The firm submitted this amendment describing the proposed program.

Maternal Response (emailed to Kati Johnson November 25, 2020):

Novartis proposes a draft study design for consideration by the Agency to fulfill the pregnancy PMR. Novartis provides a study synopsis of a “single-arm, uncontrolled, descriptive non-interventional study using an enhanced post-marketing data collection and processing system via a set of targeted checklists,

structured follow-up, rigorous process of data entry and data quality control, and programmed aggregate analysis.”

The study synopsis captures the conceptual design of the Single-Arm Pregnancy Safety Study that is being recommended by DPMH. However, the protocol will require revisions to be consistent with the current approach. Further agreement regarding the protocol is pending Agency review of the full draft protocol. The applicant should submit the draft protocol for review at the predetermined time as recommended in the approval letter. DPMH recommends a minimum of a 6-month time period for Agency review of the draft protocol, prior to finalization.

DPMH suggested language for the PMR description and proposed milestone dates via email on December 2, 2020. DPMH also asked for at least a 6-month time period to review the draft protocol.

The goal of the study is to evaluate the long-term safety of inclisiran in women with exposure during pregnancy, including assessing risks of pregnancy complications, maternal mortality, and adverse effects on the developing fetus and neonates. Data are needed on the safe use of inclisiran during pregnancy as current clinical data is absent.

#### PMR Description

Conduct a worldwide, single-arm, descriptive study that collects prospective and retrospective data in women exposed to inclisiran during pregnancy to assess risk of pregnancy and maternal complications, adverse effects on the developing fetus and neonate, and adverse effects on the infant. Infant outcomes will be assessed through at least the first year of life. The study will collect information for a minimum of 10 years. Results will be analyzed and reported descriptively. Data collected retrospectively will be analyzed separately and reported with the interim and final study reports.

- Draft Protocol Submission: June 2021
- Final Protocol Submission: December 2021 Draft Protocol Submission
- Interim Study Report: Annually after the final protocol submission
- Study Completion: December 2032 Final Study Report: June 2033

On December 3, 2020, DPMH and DDLO further discussed the PMR and emailed the division additional comments to share with the applicant:

- Based on the proposed protocol synopsis of the non-interventional study to assess inclisiran pregnancy outcomes, the data collection schedule intends to target the following timepoints: pregnancy baseline, pregnancy outcome, infant status at 3 months and infant status at 12 months. The applicant should revise the data collection schedule to include a time mid-point during pregnancy to better capture safety information during the course of pregnancy.

- With the protocol submission, the applicant should submit a copy of the targeted questionnaires for collection of pregnancy and infant follow-up data for each timepoint. These targeted questionnaires should include data elements, such as maternal demographic information, weight, history of co-morbid medical conditions, co-morbid medical conditions in the current pregnancy, concomitant medications, prior obstetric history, family history of congenital malformations, social history such as alcohol, tobacco, drug use in pregnancy, prenatal testing performed, etc. Refer to the 2019 Draft Guidance for Industry “Postapproval Pregnancy Safety Studies” Appendix A (<https://www.fda.gov/media/124746/download>).

DPMH Maternal Health has no further comments at this time. This memorandum will close out the consult request.

DPMH Maternal Health MO Reviewer – Christos Mastroyannis  
DPMH Maternal Health Team Leader – Tamara Johnson  
DPMH RPM - Heather Buck

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/s/  
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HEATHER G BUCK  
12/06/2020 12:07:29 PM



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

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**Date:** November 30, 2020

**To:** Lisa Yanoff, M.D., *Acting Director*  
Division of Metabolism and Endocrinology Products (DMEP)

**Through:** Dominic Chiapperino, PhD, Director  
Controlled Substance Staff (CSS)

Chad Reissig, Ph.D., Supervisory Pharmacologist  
Controlled Substance Staff (CSS)

**From:** Joshua Hunt, PharmD, MPH, Senior Regulatory Reviewer  
Controlled Substance Staff (CSS)

**Subject:** **NDA 214012**  
**Drug substance:** inclisiran, a small interfering RNA (siRNA), proposed trade name: Leqvio™  
**Dosage:** 284 mg on Day 1, Day 90, and every 6 months thereafter  
**Route of Administration:** subcutaneous injection  
**Indication:** as adjunct to diet, [REDACTED] (b) (4)  
[REDACTED] for the treatment of adults with primary hyperlipidemia (including heterozygous familial hypercholesterolemia) to reduce low-density lipoprotein cholesterol LDL-C.

**Sponsor:** Novartis Pharmaceuticals Corp/The Medicine's Co.  
1 Health Plaza Bldg 315  
East Hanover, New Jersey 07936-1080

**Materials**  
**Reviewed:** Sponsor NDA submission: Integrated Summary of Safety (150 pgs)

**Review and Conclusions:**

The Division of Metabolism and Endocrinology Products (DMEP, or the Division), now the Division of Diabetes, Lipid Disorders, and Obesity (DDLO) after Office of New Drugs reorganization, sent a consult request to CSS on January 6, 2020, regarding NDA 214012. In an April 2, 2019 submission to their IND 127589, the Sponsor requested a “waiver” of the need for an assessment of abuse potential. In

a letter dated June 12, 2019, based on a June 11, 2019 CSS review (authored by Joshua Hunt PharmD, MPH), the Agency informed the Sponsor that no further *in vitro* (e.g., receptor binding /functional assays), preclinical *in vivo* (e.g., drug discrimination, self-administration, conditioned place preference), or human abuse potential testing was necessary. During the time of CSS's previous interaction with the Division, the Sponsor was conducting ongoing confirmatory phase 3 clinical trials. CSS requested that the Sponsor continue to monitor for abuse-related adverse events (AEs) in all phases of development, as part of their therapeutic development program's ongoing safety analysis. These recommendations are outlined in Section V.B. of the guidance for industry, Assessment of Abuse Potential of Drugs (2017).

Following review of the non-clinical pharmacology and summarized AE data, provided by the Sponsor, we conclude from these data that inclisiran lacks meaningful abuse-related CNS activity. Based on a review of MedDRA terms, reported neurocognitive and psychiatric events had similar frequency in treatment and placebo arms. The maximum dose of inclisiran in the clinical development program was 900 mg, and more than 100 participants received a dose higher than 300 mg. Monitoring of abuse-related AEs included the following terms: Euphoric mood, Elevated mood, Feeling abnormal, Feeling drunk, Feeling of relaxation, Dizziness, Thinking abnormal, Hallucination, and Inappropriate affect. Impairment of attention, cognition, and mood were monitored by the following terms: Somnolence or Mood disorders and disturbances. In the Sponsor's pooled safety analysis, there was no difference between treatment groups in events related to abuse liability (See Table 39 in the Sponsor's document submission entitled: *Integrated Summary of Safety*). According to AE data, inclisiran was generally well-tolerated, and the most common safety issue was injection site reactions in the phase 3 trials.

In summary, CSS has not identified any abuse- or dependence-related concerns with inclisiran, and the proposed drug product, if approved by DDLO, will not require section 9 DRUG ABUSE AND DEPENDENCE in its product labeling.



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DOMINIC CHIAPPERINO  
12/01/2020 10:05:41 AM

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

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

**Memorandum**

**Date:** November 19, 2020

**To:** Kati Johnson  
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 LEQVIO (inclisiran) injection, for subcutaneous use

**NDA:** 214012

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In response to DDLO's consult request dated November 16, 2020, OPDP has reviewed the proposed product labeling (PI) and carton and container labeling for the original NDA submission for LEQVIO (inclisiran) injection, for subcutaneous use (Leqvio).

**Labeling:** OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DDLO on November 16, 2020 and are provided below.

**Carton and Container Labeling:** OPDP has reviewed the attached proposed carton and container labeling received by electronic mail from DDLO on November 16, 2020, 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](mailto:Ankur.Kalola@fda.hhs.gov).

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

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ANKUR S KALOLA  
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**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Division of Pediatric and Maternal Health  
Office of Rare Diseases, Pediatrics, Urologic  
and Reproductive Medicine  
Office of New Drugs  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Silver Spring, MD 20993  
Tel 301-796-2200  
FAX 301-796-9744

**Division of Pediatric and Maternal Health Review**

**Date:** October 16, 2020      **Date consulted:** January 6, 2020

**From:** Christos Mastroyannis, M.D., Medical Officer, Maternal Health,  
Division of Pediatric and Maternal Health (DPMH)

**Through:** Tamara Johnson, MD, MS, Team Leader, Maternal Health, DPMH

Lynne P. Yao, MD, OND, Division Director  
Division of Pediatric and Maternal Health

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

**Drug:** Inclisiran for Subcutaneous Injection (SC)

**NDA :** 214012

**Applicant:** The Medicines Co.

**Subject:** Pregnancy and Lactation Labeling Formatting Recommendations

**Indication:** An adjunct to diet and maximally tolerated statin therapy for the treatment of adults with primary hyperlipidemia [including heterozygous familial hypercholesterolemia (HeFH)] to reduce low-density lipoprotein cholesterol (LDL-C).

**Materials Reviewed:**

- December 23, 2019 Original Submission for NDA 214012 for New Molecular Entity (NME)
- January 6, 2020 DDLO consult, DARRTS Reference ID 4542519

**Consult Question:**

Review of the FPI for PLLR compliance, and any additional labeling recommendations from the Maternal Health Team to ensure the safe use of inclisiran.

## **INTRODUCTION AND BACKGROUND**

On December 23, 2019, The Medicines Co. submitted an original NDA 214012 for inclisiran for subcutaneous (SC) injection under the 505 (b)(1) pathway. With this submission, the applicant provided labeling to comply with PLLR. The Division of Diabetes, Lipid Disorders, and Obesity (DDLO) consulted the Division of Pediatric and Maternal Health (DPMH) on January 6, 2020, to assist with the Pregnancy and Lactation subsections of labeling.

### **Drug Characteristics<sup>1</sup>**

- Inclisiran is a double-stranded small interfering ribonucleic acid (siRNA) that inhibits the production of proprotein convertase subtilisin/kexin type 9 (PCSK9).
- Provided in a single use prefilled syringe (300 mg inclisiran sodium in 1.5 mL aqueous solution containing 284 mg of inclisiran) for SC injection by a healthcare professional.
- Inclisiran is not a substrate, inhibitor or inducer of cytochrome P450 enzymes or common drug transporters, and therefore it is not expected to have clinically significant interactions with other medications. It is not expected to interact with oral contraceptives.

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<sup>1</sup> From applicant's submission, dated December 23, 2019

**Table 1: Inclisiran Drug Characteristics<sup>5,2</sup>**

Drug Class	Cholesterol-lowering
Mechanism of Action	A double-stranded small interfering ribonucleic acid (siRNA, conjugated on the sense strand with triantennary N-Acetylgalactosamine (GalNAc) to facilitate uptake specifically by hepatocytes. It utilizes the RNA interference mechanism and directs catalytic breakdown of mRNA for PCSK9, a novel mechanism. This increases LDL-C receptor recycling and expression on the hepatocyte cell surface, which increases LDL-C uptake and lowers LDL-C levels in the circulation.
Molecular Weight	(b) (4)
Terminal half life	9 hours
Bioavailability	(b) (4)
Plasma Protein Binding	87%
Carcinogenesis/Genotoxicity	No

## REVIEW

### PREGNANCY

#### Cholesterol and Triglycerides during Pregnancy

Cholesterol is important for embryo-fetal development. The conceptus derives the substantial proportion (at least 80%) of its cholesterol needs from endogenous synthesis rather than via the maternal circulation.<sup>3</sup> Across multiple species including humans, the rates of cholesterol synthesis in the fetus are much greater than in the adult.<sup>4</sup> Whether mediated by dietary intervention or by genetic mutations resulting in 50% reduction in maternal serum LDL-C, no negative effects on embryo-fetal development have been observed in children born to mothers with low cholesterol throughout pregnancy.<sup>5</sup> High synthetic rate in the conceptus and/or the placenta provides sufficient cholesterol to

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<sup>2</sup> From applicant's proposed labeling

<sup>3</sup> Bartels A and O'Donoghue K. Cholesterol in pregnancy: a review of knowns and unknowns. *Obstetric Med.* 2011; 4:147–151.

<sup>4</sup> Dietschy JM, Turley SD, and Spady DK. Role of liver in the maintenance of cholesterol and low-density lipoprotein homeostasis in different animal species, including humans. 1993; *J Lipid Res.* 34:1637-1659.

<sup>5</sup> Hormanics GE, Smith TJ, Zhang SH, et al. Targeted modification of the apolipoprotein B gene results in hypobetalipoproteinemia and developmental abnormalities in mice. *Proc. Natl. Acad. Sci. USA.* 1992; 90:2389-2393

maintain sterol-independence from maternal sources.<sup>6</sup> This finding may indicate a low risk for fetal harm in humans.

Normal pregnancy is associated with predicted changes in lipid metabolism and increases in lipid concentration as gestation progresses. During the first trimester, there is marked deposition and hypertrophy of maternal adipocytes with increased expression of insulin receptors.<sup>7,8</sup> Increase in maternal insulin in addition to production of progesterone leads to lipogenesis with diminished lipolysis, and increased production of lipids, which then are transported across the placenta and metabolized.<sup>7,8,9</sup> While both total cholesterol (TC) and triglycerides (TG) rise throughout pregnancy, TG in particular rise disproportionately in comparison to other lipid fractions reaching two to four times pre-pregnancy levels by the third trimester.<sup>10</sup> However, these changes are felt to be generally non-atherogenic, and fall precipitously to pre-pregnancy levels following delivery.<sup>7,10</sup> As TG levels increase, there is a decrease in overall LDL size with an increased proportion of smaller, denser LDL particles that are thought to be more atherogenic.<sup>11,12</sup> HDL-C levels and apolipoprotein A-I levels also increase during normal gestation, with peak levels during the second trimester. Studies have suggested a potential protective effect to the mother to offset elevations in atherogenic LDL-C and TG levels.<sup>10,11</sup>

Atherogenic lipid profiles during the first trimester confer an increased risk of adverse pregnancy outcomes including maternal morbidity, mortality, and preterm delivery.<sup>8</sup> In a large European community-based cohort study comprising nearly 4000 non-diabetic otherwise healthy women with a mean age of  $30.9 \pm 4.9$ , investigators found that elevated TG levels, but not TC levels, during the first trimester were independently associated with adverse outcomes for both the mother and the newborn.<sup>8</sup> Dyslipidemia, especially during mid-gestation, is associated with mild preeclampsia.<sup>13,14</sup> The presence in pre-pregnancy and early gestation of atherogenic dyslipidemia – characterized by high TG, small dense LDL, and low HDL-C levels – confers an increased risk of adverse pregnancy outcomes as well as cardiovascular risk later in life. Atherogenic lipid

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<sup>6</sup> Woollett LA. Maternal cholesterol in fetal development: transport of cholesterol from the maternal to the fetal circulation. *Am J Clin Nutr.* 2005; 82:1155–1161

<sup>7</sup> Hadden DR, McLaughlin C. Normal and abnormal maternal metabolism during pregnancy. *Semin Fetal Neonatal Med* 2009;14(6):401

<sup>8</sup> Vrijkotte TG, Krukziener N, Hutten BA, et al. Maternal lipid profile during early pregnancy and pregnancy complications and outcomes: the ABCD study. *J Clin Endocrinol Metab* 2012;97(11):3917-25.

<sup>9</sup> Herrera E. Lipid metabolism in pregnancy and its consequences in the fetus and newborn. *Endocrine* 2002;19:43–55

<sup>10</sup> Mukherjee M. Dyslipidemia in Pregnancy. *Clinical topics American College of Cardiology. Expert analysis.* May 19, 2014

<sup>11</sup> Belo L, Caslake M, Gaffney D, et al. Changes in LDL size and HDL concentration in normal and preeclamptic pregnancies. *Atherosclerosis* 2001;162:425-32.

<sup>12</sup> Brizzi P, Tonolo G, Esposito F, et al. Lipoprotein metabolism during normal pregnancy. *Am J Obstet Gynecol* 1999;181:430-4.

<sup>13</sup> Enquobahrie DA, Williams MA, Butler CL, et al. Maternal plasma lipid concentrations in early pregnancy and risk of preeclampsia. *Am J Hypertens* 2004;17:574-81.

<sup>14</sup> Baker AM, Klein RL, Moss KL, et al. Maternal serum dyslipidemia occurs early in pregnancy in women with mild but not severe preeclampsia. *Am J Obstet Gynecol* 2009;201:293.e1-4.

profiles during pregnancy are associated with preterm birth and newborns that are large for gestational age.<sup>10</sup> Recommendations on the treatment of significant dyslipidemia in pregnant women are limited. Further studies are needed to delineate the role of anti-hyperlipidemic therapies in pregnant women with dyslipidemia.

The guidelines published by the National Institute of Health Clinical Excellence (NICE) recommend that women should not start the lipid-lowering agent again until they have completed breastfeeding.<sup>15,16,20,17,18</sup> The reader is referred to a review by DPMH on statins for more extensive discussion.<sup>19</sup> Therefore, the current conclusion is that women who are planning pregnancy or who become pregnant should stop cholesterol-reducing drug therapy. Discontinuation of lipid-lowering medication for a short period of time during pregnancy is thought to have little impact on long-term therapy for hyperlipidemia and is unlikely to affect outcomes for cardiovascular disease.

### ***Applicant's Review***

#### **Nonclinical Data**

In animal reproduction studies, no adverse developmental effects were observed in rats and rabbits with subcutaneous administration of inclisiran during organogenesis at doses up to 5- to 10 times the maximum recommended human dose (MRHD) based on body surface area (BSA) comparison. No embryo lethality, fetotoxicity or teratogenicity were observed. In rats, inclisiran was detected in fetal plasma but not in the liver, at concentrations much lower (65-154 fold lower) compared to maternal levels. In female New Zealand White rabbits, inclisiran was not detected in fetal plasma or liver. No adverse developmental outcomes were observed in offspring of rats administered inclisiran from organogenesis through lactation at 5 times the MRHD based on BSA comparison.

No humoral immune suppression has been described with inclisiran. The applicant concludes that based on nonclinical findings, inclisiran is not expected to cross the placenta, and therefore, no fetal exposure is anticipated.

The reader is referred to the nonclinical review in DARRTS, by Elena Braithwaite PhD, for further details.

#### **Human Data**

#### **Review of Pharmacovigilance Database**

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<sup>15</sup> Manson JM et al. Post-marketing Surveillance of Lovastatin and Simvastatin Exposure during Pregnancy. *Reproductive Toxicology*. 1996; Vol. 10, No. 6, pp. 439-446.

<sup>16</sup> Thorogood, M et al., 2009, Management of fertility in women with familial hypercholesterolemia: summary of NICE guidance, *BJOG*, 116:478-479.

<sup>17</sup> AHA/ACOG PRESIDENTIAL ADVISORY Promoting Risk Identification and Reduction of Cardiovascular Disease in Women Through Collaboration With Obstetricians and Gynecologists A Presidential Advisory From the American Heart Association and the American College of Obstetricians and Gynecologists

<sup>18</sup> <https://www.acc.org/latest-in-cardiology/articles/2018/05/10/13/51/familial-hypercholesterolemia-and-pregnancy> by ACC

<sup>19</sup> Liedtka JE, Dinatale MC, Yao LP. A labeling review for Zocor (simvastatin)/Zetia (ezetimibe)/Vytorin (ezetimibe and simvastatin). In DARRTS, February 28, 2019, Reference ID: 4396340



Clinical trials conducted by the applicant excluded females who are pregnant or nursing, or who are of childbearing potential and unwilling to use at least 2 methods of highly effective contraception. There were 3 inclisiran-exposed pregnancies during the drug clinical development program. When pregnancies were identified, treatment discontinued in all cases. Of those pregnancies, 1 pregnancy went to term with delivery of a full-term healthy baby, 1 pregnancy was voluntarily terminated before 12 weeks (no indication is provided, and no malformations were reported), and 1 pregnancy was ongoing at the time of submission. There is no reporting when inclisiran was administered during pregnancy, except for the pregnancy that was voluntarily terminated where inclisiran was administered during the first trimester.

### **Drug Utilization**

This is a new drug product that has not been approved yet. Therefore, there is no drug utilization to be reported.

### **Review of Literature**

Inclisiran is an NME and, therefore, no human literature exists. The drug has not been used in pregnant women. Females who were pregnant (according to a positive pregnancy test), or were actively attempting to get pregnant, or were lactating, were to be excluded from participation in all clinical trials of inclisiran. As per the applicant, based on nonclinical findings, inclisiran is not expected to cross the placenta (see Module 2.4 Nonclinical Overview).

### ***DPMH's Review of Literature***

DPMH reviewed PubMed and Embase using the following terms: “Inclisiran and embryofetal toxicity”, “Inclisiran and fetal malformations”, “Inclisiran and spontaneous abortion”, “Inclisiran and miscarriage”, and “Inclisiran and pregnancy”. No citations were found in any of the searches. DPMH also searched Micromedex (ReproTox and TERIS). No information regarding inclisiran was found in either source.

### **Summary**

From the pharmacovigilance data on use of inclisiran, there were 3 inclisiran-exposed pregnancies during the drug clinical development program. When pregnancies were identified, treatment discontinued in all cases. Therefore, the data are insufficient to determine a drug-associated risk for major birth defects, miscarriage or adverse maternal or fetal outcomes. Nonclinical data demonstrated no evidence of embryoletality, fetotoxicity, or teratogenicity. Because the drug decreases cholesterol and possibly other biologically active substances derived from cholesterol, inclisiran may cause fetal harm when administered to pregnant patients based on the mechanism of action (inclisiran increases LDL-C uptake and lowers LDL-C levels in the circulation). In addition, treatment of hyperlipidemia is not generally necessary during pregnancy. Atherosclerosis is a chronic process and the discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hyperlipidemia for most patients. Alternatively, the prescriber should consider the ongoing therapeutic needs of the individual patient.

Because females of reproductive potential constitute a significant part of the target population of patients to be treated with inclisiran, there is need for more information to be included in the labeling for Pregnancy and Lactation subsections. Therefore, a postmarketing requirement is recommended to conduct a worldwide, single-arm, observational safety study of pregnant women exposed to inclisiran. It is a descriptive study that actively collects prospective and retrospective data in women exposed to inclisiran during pregnancy to assess risk of pregnancy and maternal complications, adverse effects on the developing fetus and neonate, and adverse effects on the infant in all exposed pregnancies of which you become aware. Infant outcomes should be assessed through at least the first year of life. The single arm pregnancy study will collect information for a minimum of 10 years from the date of market approval for inclisiran.

## ***LACTATION***

### **Nonclinical Experience**

Inclisiran is present in rat milk at all doses, but not in F1 generation pup plasma. There was no inclisiran found in fetal plasma or liver of breastfed New Zealand White rabbits.

### **Review of Pharmacovigilance Database**

There are no neonatal exposures to inclisiran through breast milk during the clinical development program.

### **Review of Literature**

There is no information available on the presence of inclisiran in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production. This is an NME and the applicant has not identified any published literature.

DPMH searched LactMed and did not find any information regarding inclisiran use during lactation. GG Briggs and RK Freeman in Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk and Hale's Medications and Mother's Milk do not have any entries on the drug.

In communication with nonclinical, we have concluded "Oligonucleotide-based products typically have poor oral bioavailability; therefore, it is considered unlikely that low milk exposure levels will adversely impact neonatal development."

## ***FEMALES AND MALES OF REPRODUCTIVE POTENTIAL***

### **Nonclinical Experience**

Inclisiran did not show positive signals for selective reproductive toxicity in fertility and early embryonic development studies conducted in rats, embryo-fetal development studies conducted in rats and rabbits, and a pre- and postnatal development study conducted in rats. Genotoxicity studies were conducted including a bacterial mutagenicity assay, an in vitro chromosome aberration assay using human peripheral lymphocytes, and an in vivo bone marrow micronucleus assay. No genotoxicity findings were identified.

### **Review of Literature**

Neither the applicant nor this reviewer identified any publications on the effects of inclisiran on the reproductive potential of females and males. There are no recommendations for contraception use with inclisiran, or pregnancy testing prior to initiating treatment with inclisiran, because no drug-associated risks to pregnant women or the fetus have been demonstrated based on the nonclinical studies and three reported human pregnancies. Therefore, the subsection 8.3 Females and Males of Reproductive Potential will be omitted because there is no information to provide to the subscriber regarding pregnancy testing, contraception or on the effects on human fertility.

### **Review of Pharmacovigilance Database**

Nothing is reported in the pharmacovigilance database during the drug development program.

## **DISCUSSION AND CONCLUSIONS**

### **Pregnancy**

- In animal reproduction studies, no evidence of teratogenic effects was observed in rats and rabbits. Also, there was no evidence of embryoletality, fetotoxicity, or genotoxicity.
- In humans, there are sparse data on use of inclisiran in three pregnant women. Therefore, the data are insufficient to determine a drug-associated risk for major birth defects, miscarriage or adverse maternal or fetal outcomes.
- There is anticipated use in females of reproductive potential and during pregnancy.
- Theoretical considerations concerning the role of cholesterol in embryofetal development plus the lack of demonstrated benefit of treating hyperlipidemia during gestation are the reasons for avoidance of cholesterol lowering drugs during pregnancy.
- Current recommendation is that women who are planning pregnancy or who become pregnant should stop cholesterol reducing drugs therapy.<sup>20</sup> Alternatively, the prescriber should consider the ongoing therapeutic needs of the individual patient.
- DPMH recommends a PMR to conduct a worldwide, single-arm, observational safety study of pregnant women exposed to inclisiran. It is a descriptive study that actively collects prospective and retrospective data in women exposed to inclisiran during pregnancy to assess risk of pregnancy and maternal complications, adverse effects on the developing fetus and neonate, and adverse effects on the infant in all exposed pregnancies of which you become aware. Infant outcomes should be assessed through at least the first year of life. The single arm pregnancy study will collect information for a minimum of 10 years from the date of market approval for inclisiran.
- Contact information for the pregnancy safety study should be added to labeling once the protocol is finalized and enrollment begins.

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<sup>20</sup> Wierzbicki AS, Humphries SE, Minhas R. Familial hypercholesterolemia: summary of NICE guidance. *BMJ* . 2008 Aug 27;337:a1095/doi: 10.1136/bmj.a1095

### **Lactation**

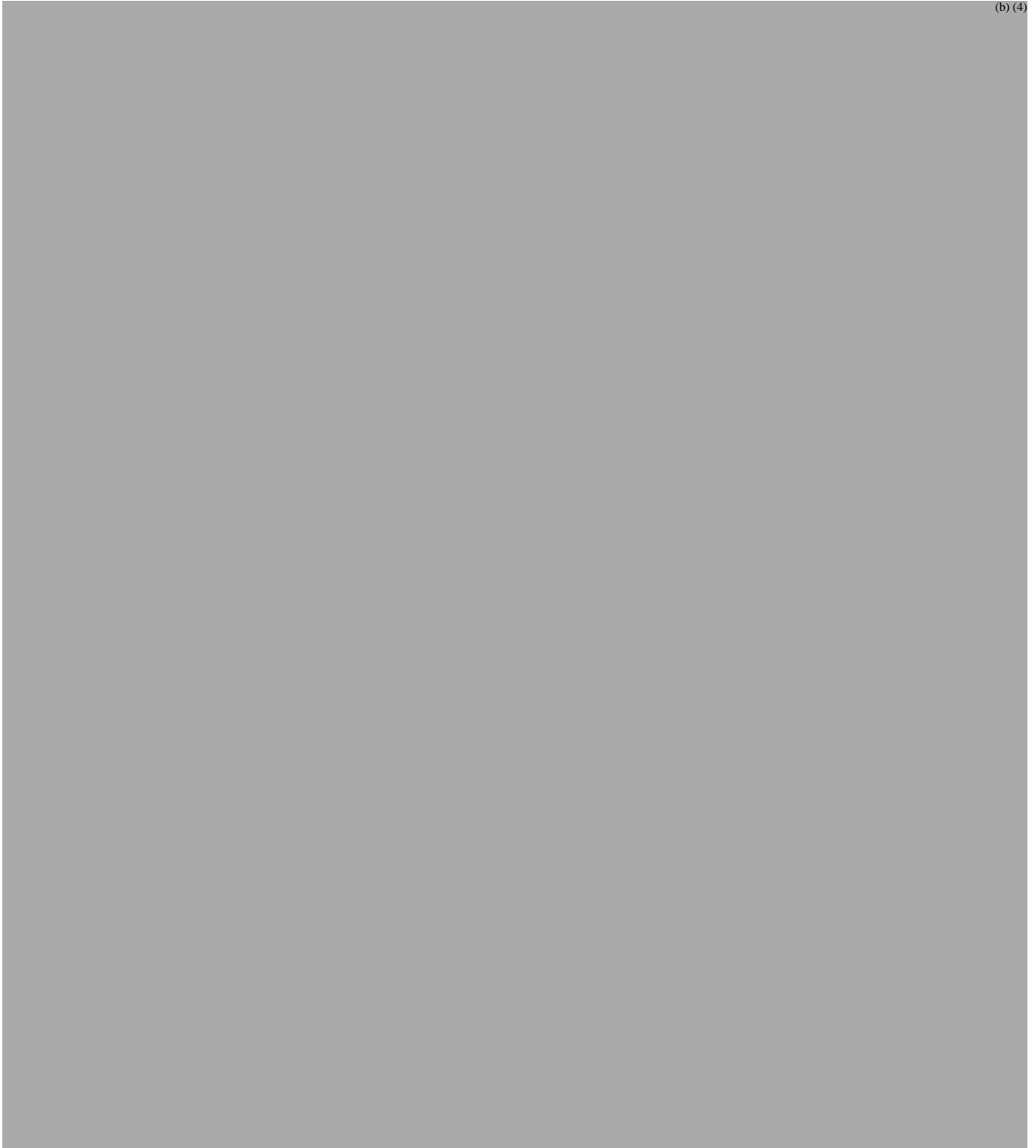
- It is not known if the drug is present in human milk. There is no information on the effects of the drug on the breastfed infant, or the effects of the drug on the milk production.
- Inclisiran is present in rat milk at all doses, but not in F1 generation pup plasma.
- Oligonucleotide-based products typically have poor oral bioavailability; therefore, it is considered unlikely that low milk exposure levels will adversely impact neonatal development.
- There was no inclisiran present in fetal plasma or liver of breastfed New Zealand White rabbits.
- As animal study findings suggest that inclisiran is not systemically absorbed by rat pups, DPMH does not recommend a PMR clinical lactation study. DPMH recommends the standard risk-benefit statement is added to subsection 8.2 of inclisiran labeling.

### **Females and Males of Reproductive Potential**

- The subsection 8.3 Females and Males of Reproductive Potential will be omitted because there is no information to provide to the prescriber regarding pregnancy testing, contraception or on the effects on fertility.

**LABELING RECOMMENDATIONS**

DPMH revised subsections 8.1 and 8.2 of labeling for compliance with the PLLR (see below). DPMH refers to the final NDA action for final labeling.

**DPMH Proposed Pregnancy and Lactation Labeling**

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10/16/2020 05:13:42 PM

LYNNE P YAO  
10/19/2020 06:26:12 AM

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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)

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Date of This Memorandum:	October 14, 2020
Requesting Office or Division:	Division of Diabetes, Lipid Disorders, and Obesity (DDLO)
Application Type and Number:	NDA 214012
Product Name and Strength:	Leqvio (inclisiran) injection, 284 mg/1.5 mL
Applicant/Sponsor Name:	Novartis Pharmaceuticals Corporation (Novartis)
OSE RCM #:	2019-2666-2
DMEPA Safety Evaluator:	Melina Fanari, R.Ph.
DMEPA Team Leader:	Sevan Kolejian, PharmD, MBA, BCPPS

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## 1 PURPOSE OF MEMORANDUM

The Applicant submitted a revised (b) (4) labeling on September 29, 2020 for Leqvio. The Division of Diabetes, Lipid Disorders, and Obesity requested that we review the revised labeling (Appendix A) to determine if it is acceptable from a medication error perspective. DMEPA had previously reviewed revised container labels and carton labeling for Leqvio and found them to be acceptable.<sup>a</sup>

## 2 CONCLUSION

The revised (b) (4) labeling contained minor format changes due to a change in the text area size and is acceptable from a medication error perspective. We have no additional recommendations at this time.

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<sup>a</sup> Fanari, M. Label and Labeling Review for Leqvio (NDA 214012). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 SEPT 15. RCM No.: 2019-2666-1.



APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON SEPTEMBER 29, 2020  
available in EDR <\\CDSESUB1\evsprod\NDA214012\0040\m1\us\114-labeling>

(b) (4)



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MELINA N FANARI  
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SEVAN H KOLEJIAN  
10/14/2020 05:41:11 PM

### Clinical Inspection Summary

<b>Date</b>	9/23/2020
<b>From</b>	Cynthia F. Kleppinger, M.D., Senior Medical Officer Min Lu, M.D., M.P.H., Team Leader Kassa Ayalew, M.D., M.P.H., Branch Chief Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
<b>To</b>	Iffat Chowdhury, M.D., Clinical Reviewer Eileen Craig, M.D., Clinical Reviewer John Sharretts, M.D., Clinical Team Leader Division of Diabetes, Lipid Disorders, and Obesity (DDLO) Kati Johnson, Senior Regulatory Project Manager Division of Regulatory Operations for Cardiology, Hematology, Endocrinology, and Nephrology
<b>NDA</b>	214012
<b>Applicant</b>	The Medicines Company (transferred to Novartis Pharmaceuticals Corporation)
<b>Drug</b>	Inclisiran sodium
<b>NME</b>	Yes
<b>Therapeutic Classification</b>	Antihyperlipidemic
<b>Proposed Indication</b>	As an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with Heterozygous Familial Hypercholesterolemia or clinical atherosclerotic cardiovascular disease who require additional lowering of low-density lipoprotein cholesterol
<b>Consultation Request Date</b>	1/24/2020
<b>Summary Goal Date</b>	10/1/2020
<b>Action Goal Date</b>	12/11/2020
<b>PDUFA Date</b>	12/23/2020

## I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The inspection for this new drug application (NDA) consisted of two domestic clinical investigator sites and one foreign clinical investigator site in addition to the sponsor.

The COVID-19 global pandemic has significantly limited the Office of Regulatory Affairs' ability to conduct onsite good clinical practice (GCP) inspections. As a result, planned foreign onsite inspections could not be completed. A remote regulatory assessment of source records was performed for Dr. Elane Van Nieuwenhuizen's site located in South Africa. The planned inspection of Dr. Anna Sidorowicz-Bialynicka's site in Poland was not conducted. Remote

regulatory assessment of source records was not feasible due to local restrictions on access to subject source records.

In general, based on the inspections of the two domestic clinical sites and the sponsor, and the remote regulatory assessment of one foreign site, the inspectional findings support validity of data as reported by the sponsor under this NDA.

## II. BACKGROUND

The Medicines Company\* submitted a new drug application (NDA) for inclisiran to be an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with Heterozygous Familial Hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (ASCVD), who require additional lowering of low-density lipoprotein cholesterol (LDL-C).

*\*In January 2020, The Medicines Company merged with Novartis Pharmaceuticals Corporation. As a result of the merger, The Medicines Company became an indirect wholly-owned subsidiary of Novartis Pharmaceuticals Corporation.*

Inclisiran is a small interfering RNA, which inhibits the production of proprotein convertase subtilisin/kexin type 9 (PCSK9) with a novel twice-a-year dosing schedule. The 300 mg dose of inclisiran sodium administered on Day 1, Day 90, and every 6 months was the chosen dose and dose regimen for the Phase III program.

Three similarly designed Phase III studies (referred to as ORION-9, ORION-10, AND ORION-11) were conducted in parallel to support approval of inclisiran. Inspections were requested for all three studies.

### ORION-9 (MDCO-PCS-17-03)

Title of Study: *A placebo-controlled, double-blind, randomized trial to evaluate the effect of 300 mg of inclisiran sodium given as subcutaneous injections in subjects with heterozygous familial hypercholesterolemia (HeFH) and elevated low-density lipoprotein cholesterol (LDL-C)*

This was an international, multicenter, Phase III, placebo-controlled, double-blind, randomized study. The study was conducted at 47 sites in 8 countries. A total of 617 subjects were screened and 482 were randomized (1:1) to receive either inclisiran sodium 300 mg or placebo on top of a maximally tolerated dose of a statin (other lipid lowering treatments including ezetimibe were allowed). Of the 482 subjects randomized, 481 subjects were treated (240 with placebo and 241 with inclisiran). The study was 18 months in duration with subjects receiving four 300 mg doses of inclisiran sodium (or placebo) on Day 1, Day 90, Day 270, and Day 450. There were 231 placebo-treated subjects and 235 inclisiran-treated subjects that completed the study.

Primary Endpoint(s):

- Percentage change in LDL-C from baseline to Day 510

- Time-adjusted percentage change in LDL-C from baseline after Day 90 and up to Day 540. This was the average percentage change in LDL-C from baseline over the period after Day 90 and up to Day 540.

#### **ORION-10 (MDCO-PCS-17-04)**

Title of Study: *A placebo-controlled, double-blind, randomized trial to evaluate the effect of 300 mg of inclisiran sodium given as subcutaneous injections in subjects with atherosclerotic cardiovascular disease (ASCVD) elevated low-density lipoprotein cholesterol (LDL-C)*

This was a multicenter, Phase III, placebo-controlled, double-blind, randomized study. The study was conducted at 146 sites in the USA. Subjects with ASCVD (coronary heart disease [CHD], cerebrovascular disease [CVD] or peripheral arterial disease [PAD]) were included in this study.

A total of 2329 subjects were screened and 1561 were randomized (1:1) to receive either inclisiran sodium 300 mg or placebo on top of a maximally tolerated dose of a statin (other lipid lowering treatments including ezetimibe were allowed). Of the 1561 subjects randomized, 1559 subjects were treated (778 subjects with placebo and 781 subjects with inclisiran). The study was 18 months in duration with subjects receiving four 300 mg doses of inclisiran sodium (or placebo) on Day 1, Day 90, Day 270, and Day 450. There were 1415 subjects that completed the study.

Primary Endpoint(s):

- Percentage change in LDL-C from baseline to Day 510
- Time-adjusted percentage change in LDL-C from baseline after Day 90 and up to Day 540. This was the average percentage change in LDL-C from baseline over the period after Day 90 and up to Day 540.

#### **ORION-11 (MDCO-PCS-17-08)**

Title of Study: *A placebo-controlled, double-blind, randomized trial to evaluate the effect of 300 mg of inclisiran sodium given as subcutaneous injections in subjects with atherosclerotic cardiovascular disease (ASCVD) or ASCVD-risk equivalents and elevated low-density lipoprotein cholesterol (LDL-C)*

This was an international (non-US), multicenter, Phase III, placebo-controlled, double-blind, randomized study. The study was conducted at 72 sites in European countries and South Africa. A total of 2381 subjects were screened and 1617 were randomized (1:1) to receive either inclisiran sodium 300 mg or placebo on top of a maximally tolerated dose of a statin (other lipid lowering treatments including ezetimibe were allowed).

Subjects with either ASCVD (coronary heart disease [CHD], cerebrovascular disease [CVD] or peripheral arterial disease [PAD]) or ASCVD risk equivalents were included in this study. ASCVD risk equivalent is defined as those subjects with type 2 diabetes mellitus, familial

hypercholesterolemia [FH], or 10-year risk of 20% or greater of having a cardiovascular (CV) event assessed by Framingham Risk Score or equivalent (target LDL-C of <100 mg/dL).

The study was 18 months in duration with subjects receiving four 300 mg doses of inclisiran sodium (or placebo) on Day 1, Day 90, Day 270, and Day 450. Of the 1617 subjects randomized, there were 1615 subjects treated and 1542 subjects completed the study.

Primary Endpoint(s):

- Percentage change in LDL-C from baseline to Day 510
- Time-adjusted percentage change in LDL-C from baseline after Day 90 and up to Day 540. This was the average percentage change in LDL-C from baseline over the period after Day 90 and up to Day 540.

### III. RESULTS (by Site)

**NOTE:** Site inspections focused on review of informed consent documents (ICDs), institutional review board (IRB)/ ethics committee (EC) correspondences, 1572s/investigator agreements, financial disclosures, training records, CVs and licenses, delegation of duties, monitoring logs and reports, inclusion/exclusion criteria, enrollment logs, subject source documents including medical history records, drug accountability, concomitant medication records, and adverse event reports. Source records were compared to the sponsor's data line listings.

**1. Ahmad A. Aslam, M.D.**  
**308 Holderrieth Boulevard**  
**Tomball, TX 77375-4536**

**Site:** 10001045

**Study:** MDCO-PCS-17-04

Dates of inspection: July 22 – 29, 2020

There were 80 subjects screened and 59 subjects enrolled into the study; 59 subjects completed the study. There were 30 subject records reviewed.

Dr. Aslam is the owner and founder in 2012 of Northwest Houston Clinical Research, Inc., the clinical site where the study was conducted and the location of his private practice. All subjects were recruited from his practice. Initially when the study began, a sub-investigator trained overseas but without a US medical license was performing clinical assessments. This was discovered by the sponsor and stopped early in the study.

The institutional review board of record was (b) (4) IRB.

The subjects' records were both hard copy and electronic, consisting of an office chart

(electronic) and study file binder with source documents. The records were legible, organized, and available. Source records were compared to the sponsor data line listings. There were no discrepancies. There was no under-reporting of adverse events.

The electronic case report forms (eCRFs) were on a thumb drive provided by the sponsor to the site with a letter indicating that the thumb drive contained the final version of the source data. The thumb drive did not contain lipid panel test results; the site was blinded to the primary endpoint LDL-C data during the study and there was no source data at the site from the central laboratory. The lab values were entered directly into the database by the central lab. The FDA inspector reviewed the lab test requisitions at the site and confirmed that the testing logistics matched the primary efficacy endpoint information.

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

**2. Kishor N. Vora, M.D.**  
**1200 Breckenridge Street**  
**Owensboro, KY 42303**

**Site:** 10001107

**Study:** MDCO-PCS-17-04

Dates of inspection: July 20 – 24, 2020

There were 33 subjects screened and 21 subjects enrolled into the study; 17 subjects completed the study. There were 33 subject records reviewed.

Dr. Vora is majority owner of Owensboro Medical Practice, which includes Research Integrity, LLC where the study was performed. Subjects were recruited primarily from Dr. Vora's private practice. A few subjects were recruited by (b) (4) a recruitment company hired by the sponsor. No handouts or advertising materials were used to recruit subjects.

The institutional review board of record was initially (b) (4) merged with (b) (4) and became (b) (4), which began serving as the IRB for the study 2/5/2018.

All source documents were hard copy. The records were attributable, legible, contemporaneous, and organized. Data captured in the source documents was transcribed into the eCRFs. The end of study (EOS) lab results for Subjects 0031 and 0032 were not in the subjects' source records; however, both subjects rolled over into the ORION 8 study and those test results (EOS) were found in the source records for the ORION 8 study; no significant findings were identified.

Source records were compared to the sponsor data line listings. There were two adverse

events found for Subject (b) (6) that were not reported by the site. Visit 8, Day 510 source records showed that the subject had acute bronchitis in (b) (6) and a separated right rotator cuff in (b) (6).

A final ECG was not performed on Subject (b) (6) at Visit 9, Day 540 because, according to the notes in the study chart, the ECG machine was not working at the time; no protocol deviation was submitted.

Subject (b) (6) failed to meet inclusion criteria #2 (history of ASCVD). The subject was enrolled into the study without the site having received the subject's medical records. When the records were received and reviewed by the site, it was noted that the subject did not meet the inclusion criteria; the subject continued to remain in the study and received all four doses of medication. This was reported as a protocol deviation.

The eCRFs were on a thumb drive provided by the sponsor to the site with a letter indicating that the thumb drive contained the final version of the source data. The thumb drive did not contain lipid panel laboratory results; the site was blinded to the primary endpoint LDL-C data during the study and there was no source data at the site from the central laboratory. The lab values were entered directly into the database by the central lab. Because several of the subjects were rolled-over into the Orion 8 study, the sponsor had not yet disclosed the lab results, other than the initial lab tests taken at screening, to the site. The FDA inspector reviewed the lab test requisitions at the site and confirmed that the testing logistics matched the primary efficacy endpoint information.

Although there were a few minor non-compliance issues noted, the inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

**3. Elane Van Nieuwenhuizen, M.D.**  
**60 Stamvrug Street**  
**Tshwane, 184**  
**South Africa**

**Site:** 90027006

**Study:** MDCO-PCS-17-03

**Site:** 11027006

**Study:** MDCO-PCS-17-08

Dates of remote assessment: July 29 – August 21, 2020

Due to the COVID-19 pandemic, travel to the site was not possible. A regulatory remote assessment was conducted as an alternative to an onsite inspection. In this alternative approach, teleconferencing via Cisco's WebEx and document sharing via an online platform (box.com) were utilized to exchange information in support of regulatory compliance review. The review was significantly limited in scope due to the logistical constraints of this information exchange. The assessment covered the review of records and procedures related to the clinical trial protocols and their amendments and administrative



changes; subject selection criteria; test article controls, including accountability and blinding; source data evaluation, including serious adverse event reporting; laboratory samples; and the comparison of source records to data submitted to the agency.

For Study MDCO-PCS-17-03, there were 38 subjects screened and 33 subjects enrolled into the study; 30 subjects completed the study. There were 10 subject records reviewed.

For Study MDCO-PCS-17-08, there were 39 subjects screened and 27 subjects enrolled into the study; 23 subjects completed the study. There were 10 subject records reviewed.

Dr. Nieuwenhuizen is a Senior Research Physician at (b) (4). (b) (4) a private facility owned by (b) (4). (b) (4) a wholly owned subsidiary (b) (4). (b) (4). All subjects were recruited through the research facility's database of research participants. No advertisements were used to recruit subjects.

Each study was approved by the local independent ethics committee Pharma-Ethics Independent Research Ethics Committee and the South Africa Health Products Regulatory Authority.

Source documents were hard copy. All paper documentation was retained in a locked room at the clinical site. Source records were compared to the sponsor data line listings. There were no discrepancies. There was no under-reporting of adverse events.

The site was still blinded to the primary endpoint LDL-C data. The sponsor did provide study data on a thumb drive; however, it does not include lipid values. Those values were entered directly into the database by the central laboratory. A review of the sample collection times and logistics in the source documents revealed no issues of concern.

The regulatory remote assessment revealed adequate adherence to the regulations and the investigational plan.

#### **4. Novartis Pharmaceuticals Corporation/ Sponsor One Health Plaza East Hanover, NJ 07936-1080**

Dates of inspection: June 22 – July 2, 2020

The inspection consisted of reviewing the organizational structure and responsibilities, transfer of obligations, contractual agreements, selection of sites, training, investigational product accountability, the evaluation of the adequacy of monitoring and corrective actions taken by the sponsor/monitor/CRO, deviations related to key safety and efficacy endpoints, quality assurance and audits, adverse events evaluation and reporting, 1572s and investigator agreements, the interactive voice/web response system, financial disclosures, standard operating procedures (SOPs), trial master file review, record retention, selection

criteria for all committee members, oversight of committees, data management, escalation of issues, and clinical trial oversight.

The Medicines Company submitted the initial application (NDA 214012) in December of 2019 and was subsequently acquired by Novartis Pharmaceuticals Corporation in January of 2020. Per Novartis Pharmaceuticals, this NDA was the only active NDA awaiting action by The Medicines Company and it does not have any clinical trials in-progress.

The FDA inspector observed that multiple subjects did not receive an End of Study (EOS) ECG across all three studies. The protocols required an ECG to be collected at baseline and EOS. If any cardiac changes were evident, the site investigators were to report them as an adverse event. The results were left to the investigators for comments, but there was no requirement by the monitors to ensure that this comparison was completed and reported. According to Novartis, there were four (4) subjects in Orion 9, 23 subjects in Orion 10, and 34 subjects in Orion 11 that did not have an in-person EOS visit, and are presumed to have not been given the terminal EOS ECG. Novartis could not confirm which subjects did and did not have an ECG. The Medicines Company did not maintain a master list of the subjects given an EOS ECG.

The data flow from the central laboratory (b) (4) to The Medicines Company was reviewed regarding management and security of the data reported by the clinical sites to (b) (4) and then to the Medicines Company. According to the data handling plan, to maintain and support the integrity of the blind, data was to remain at (b) (4) and to remain blinded to The Medicines Company until database lock. Audit trails were available for each system and showed the name of the individual entering data as well as the date and time of the initial entry and any subsequent changes.

The primary efficacy endpoint data was secured at (b) (4) and was not transferred until after database lock. Review of documents, including Data Lock Memos and the data agreement between (b) (4) and The Medicines Company, revealed no deficiencies with the data handling.

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

*{See appended electronic signature page}*

Cynthia F. Kleppinger, M.D.  
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DDLO /Team Lead/John Sharretts  
DDLO /Clinical Reviewer/ Eileen Craig  
DDLO /Clinical Reviewer/ Iffat Chowdhury  
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OSI/DCCE/GCPAB Reviewer/Cynthia Kleppinger  
OSI/DCCE/GCPAB/Program Analyst/Yolanda Patague  
OSI/DCCE/Database Project Manager/Dana Walters

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/s/  
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CYNTHIA F KLEPPINGER  
09/23/2020 08:52:32 PM

MIN LU  
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KASSA AYALEW  
09/24/2020 08:14:21 AM

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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)

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Date of This Memorandum:	September 15, 2020
Requesting Office or Division:	Division of Diabetes, Lipid Disorders, and Obesity (DDLO)
Application Type and Number:	NDA 214012
Product Name and Strength:	Leqvio (inclisiran) injection, 284 mg/1.5 mL
Applicant/Sponsor Name:	Novartis Pharmaceuticals Corporation (Novartis)
OSE RCM #:	2019-2666-1
DMEPA Safety Evaluator:	Melina Fanari, R.Ph.
DMEPA Team Leader:	Sevan Kolejian, PharmD, MBA, BCPPS

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## 1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on June 24, 2020 for Leqvio. The Division of Diabetes, Lipid Disorders, and Obesity requested that we review the revised container labels and carton labeling for Leqvio (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations we made during a previous label and labeling review.<sup>a</sup>

## 2 CONCLUSION

The revised container labels and carton labeling are acceptable from a medication error perspective. Of note, the labels and labeling include the proposed proprietary name Leqvio which was found to be acceptable.<sup>b</sup> We have no additional recommendations at this time.

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<sup>a</sup> Fanari, M. Label and Labeling Review for (b) (4) (NDA 214012). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 Mar 12. RCM No.: 2019-2666.

<sup>b</sup> Conrad, A. Proprietary Name Review for Leqvio (NDA 214012). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 Aug 31. RCM No.: 2020-40549961.

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/s/  
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MELINA N FANARI  
09/15/2020 01:37:30 PM

SEVAN H KOLEJIAN  
09/15/2020 02:36:16 PM

## Interdisciplinary Review Team for Cardiac Safety Studies

### QT Consultation Review

Submission	NDA 214012
Submission Number	001
Submission Date	12/23/2019
Date Consult Received	1/14/2020
Drug Name	Inclisiran Injection
Indication	For the treatment of hypercholesterolemia
Therapeutic dose	284 mg SC injection
Clinical Division	DMEP

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This review responds to your consult dated 1/14/2020 regarding the sponsor's QT evaluation. We reviewed the following materials:

- Previous QT-IRT review for IND-127589 dated 04/04/2017 in DARRTS ([link](#));
- Previous QT-IRT review for IND-127589 dated 12/14/2017 in DARRTS ([link](#));
- Previous QT-IRT review for IND-127589 dated 05/29/2018 in DARRTS ([link](#));
- Previous QT-IRT review for IND-127589 dated 01/29/2019 in DARRTS ([link](#));
- Sponsor's clinical study protocol # ORION-12 (SN0001 / SDN001; [link](#));
- Sponsor's clinical study report # ORION-12 (SN0001 / SDN001; [link](#));
- Sponsor's QT assessment report # ORION-12 (SN0001 / SDN001; [link](#));
- Sponsor's statistical analysis plan # ORION-12 (SN0001 / SDN001; [link](#)); and
- Sponsor's propose product label (SN0001 / SDN001; [link](#)).

## 1 SUMMARY

No significant QTc prolongation effect of inclisiran was detected in this QT assessment.

The effect of inclisiran was evaluated in a thorough QT study (Study # ORION-12), a phase I, randomized, double-blind, double-dummy, placebo- and positive-controlled, 3-way crossover study in healthy subjects. The highest dose evaluated was 900 mg single dose (administered as 3 subcutaneous injections), which covers the worst-case exposure scenario (renal impairment, section 3.1). The data were analyzed using the by-time analysis as the primary analysis, which did not suggest that inclisiran is associated with significant QTc prolonging effect (refer to section 4.3) – see Table 1 for overall results.

The study included moxifloxacin as a positive control and assay sensitivity was established using by time analysis. The findings of this analysis are further supported by the available nonclinical data (section 3.1.2) and exposure response analysis (section 4.5).

**Table 1: The Point Estimates and the 90% CIs (FDA Analysis)**

ECG parameter	Treatment	Time	$\Delta\Delta\text{QTcF}$ (msec)	90% CI (msec)
QTc	Inclisiran 900 mg	4h	2.9	(0.5 to 5.2)

*For further details on the FDA analysis please see section 4.*

#### **1.1 RESPONSES TO QUESTIONS POSED BY SPONSOR**

Not applicable.

#### **1.2 COMMENTS TO THE REVIEW DIVISION**

Not applicable.

### **2 RECOMMENDATIONS**

#### **2.1 ADDITIONAL STUDIES**

Not applicable.

#### **2.2 PROPOSED LABEL**

Below are proposed edits to the label submitted to SDN001 ([link](#)) from the IRT. Our changes are highlighted (**addition**, **deletion**). Please note, that this is a suggestion only and that we defer final labeling decisions to the Division.

(b) (4)

*We propose to use labeling language for this product consistent with the “Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format” guidance.*

### **3 SPONSOR’S SUBMISSION**

#### **3.1 OVERVIEW**

##### **3.1.1 Clinical**

Novartis Pharmaceuticals (previously with the Medicines company) is developing inclisiran as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with primary hyperlipidemia to reduce low-density lipoprotein cholesterol (LDL-C).



Inclisiran (ALN-PCSSC, PCSSC, ALN-60212, AD-60212, A05AL; MW: 17,284.72 g/mol, solidum salt) is a (chemically synthesized) double-stranded oligonucleotide covalently linked to a ligand containing three N-acetyl-galactosamine (GalNAc) residues for uptake by hepatocytes. In hepatocytes, the antisense strand is incorporated in the RNA-induced silencing complex (RISC) and directs catalytic breakdown of mRNA for pro-protein convertase subtilisin kexin type 9 (PCSK9), thereby inhibiting translation of PCSK9 protein. The reduction of intrahepatic PCSK9 levels expected to increase LDL-C receptor recycling and expression on the hepatocyte cell surface, thereby increasing LDL-C uptake and lowering LDLC levels in the circulation. The product is formulated as a sterile solution containing 284 mg inclisiran (equivalent to 300 mg inclisiran sodium salt in 1.5 mL; single-use prefilled syringe) for subcutaneous injection. The proposed dose is 284 mg to be administered as a single subcutaneous injection (by a healthcare professional into the abdomen) initially, again at 3 months, and then every 6 months. The peak concentrations of  $510 \pm 260$  ng/mL ( $T_{max}$  ~6 h; half-life ~ 10 h) are expected at steady-state with the proposed therapeutic dose and no accumulation is expected with multiple dosing with the proposed dosing regimen (Studies # ORION-6 and ORION-7).

Sponsor highlights that inclisiran primarily metabolized by nucleases to shorter nucleotides and is not a substrate, inhibitor, or inducer of cytochrome P450 enzymes or common drug transporters. No formal clinical drug interaction studies have been conducted by the sponsor. Pharmacokinetic studies indicate that  $\sim 16 \pm 5\%$  of the drug is excreted in urine (Studies # ORION-6 and ORION-7). The renal impairment study indicated that the exposures are inclisiran are increased in subjects with mild (2.3-fold), moderate (2-fold), and severe (3.3-fold) renal impairment compared to that with normal renal function (Study ORION-7). Similarly, the hepatic impairment study indicated that the exposures are inclisiran are increased in subjects with mild (1.1-fold) and moderate (2.1-fold) hepatic impairment compared to that with normal hepatic function (Study ORION-6). However, no dose adjustment is proposed by the sponsor in the subjects with reduced renal or hepatic function.

Previously, the sponsor proposed substitution of thorough QT study based on the relatively large molecular size (~17 kDa), short half-life, low systemic exposure, and lack of accumulation. The IRT reviewed the sponsor's request and recommended to characterize the effects of inclisiran on the QTc interval per the ICH E14 guideline (Dt: 04/04/2017). The sponsor planned a thorough QT study evaluating the potential of QT prolongation associated with subcutaneous administration of inclisiran at suprathreshold dose. The IRT reviewed the sponsor's clinical study protocol for thorough QT study (# MDCO-PCS-17-09; Dt: 12/14/2017). Study included a four-arm parallel design in healthy subjects (n=200) receiving single therapeutic (300 mg), suprathreshold (900 mg), moxifloxacin, and inclisiran placebo doses. The IRT provided comments on primary endpoint, study design, data modeling, and data submission. Subsequently, the sponsor submitted the revised protocol selecting QTcF as the primary endpoint and crossover design (Dt: 05/29/2018). In addition, the sponsor did not follow the recommended model by the IRT and proposed an alternative model. The protocol was amended to reflect the type of moxifloxacin tablets that will be used in the study (Dt: 01/29/2019).

Recently, the sponsor conducted thorough QT study evaluating the potential of QT prolongation associated with subcutaneous administration of 900 mg inclisiran as a single

dose (Study ORION-12). This was a phase I, randomized, double-blind, double-dummy, placebo- and positive-controlled, 3-way crossover study in healthy subjects. In this study, subjects (n=48) were randomized to receive – 1) inclisiran (900 mg as 3 SC injections; and moxi placebo); 2) matching inclisiran placebo (placebo solution, as 3 SC injections; and moxi placebo); and 3) Moxifloxacin (400 as positive control; inclisiran placebo as 3 SC injections). Moxifloxacin and its matching placebo were administered as over-encapsulated tablet (capsule size 0). Assigned doses were administered in the morning of Days 1, 9, and 17, following overnight fast with at least 7 days washout. Study included screening period, check-in period, treatment period, follow-up and post-treatment observation periods (total duration ~270 days).

Continuous ECG monitoring was performed at least 60 minutes before dosing through 48 h post-dose on Days 1, 9, and 17. PK blood samples were collected at pre-dose (60, 45, and 30 min) and 0.5, 1, 2, 4, 6, 8, 12, 24, and 48 hours after dosing. The ECG extractions were time matched to the PK samples.

The mean peak concentrations of  $2890 \pm 1360$  ng/mL ( $T_{max} \sim 4$  h) were observed following a 900 mg inclisiran injection. The peak concentrations of inclisiran observed in the study were higher than those observed with at the therapeutic doses in healthy subjects ( $C_{max}$ : 509 ng/mL) and also, in subjects with severe renal impairment ( $C_{max}$ : 1760 ng/mL; Study # ORION-7).

### 3.1.2 Nonclinical Safety Pharmacology Assessments

Refer to the sponsor's non-clinical overview ([m2.4](#)) and the previous IRT review under IND-127589 dated 04/04/2017 in DARRTS.

Animal studies did not indicate that inclisiran has an immediate or delayed effect on clinical observations, qualitative or quantitative electrocardiographic measurements, hemodynamic parameters, or respiration rate.

## 3.2 SPONSOR'S RESULTS

### 3.2.1 By Time Analysis

Sponsor's by-time analysis showed that inclisiran 900 mg excluded the 10 msec threshold at the supratherapeutic dose level for  $\Delta\Delta QTcF$ .

**Reviewer's comment:** FDA reviewer's analysis results of  $\Delta\Delta QTcF$ ,  $\Delta\Delta HR$ ,  $\Delta\Delta PR$ , and  $\Delta\Delta QRS$  are similar to the sponsor's analysis results.

#### 3.2.1.1 Assay Sensitivity

Per sponsor's analysis, assay sensitivity was established by the moxifloxacin arm.

**Reviewer's comment:** FDA reviewer's analysis shows that assay sensitivity was established by moxifloxacin arm.

##### 3.2.1.1.1 QT Bias Assessment

Not applicable.

### 3.2.2 Categorical Analysis

There were no significant outliers per the sponsor's analysis for QTcF (i.e., > 480 msec or change from baseline > 60 msec), HR (<50 or >100 bpm), PR (>220 msec and 25% more than baseline) and QRS (>120 msec and 25% more than baseline).

**Reviewer's comment:** *FDA reviewer's analysis results are similar to the sponsor's analysis results.*

### 3.2.3 Exposure-Response Analysis

As a supportive analysis, the sponsor explored PK/PD relationship between concentration of inclisiran and  $\Delta$ QTcF (change from baseline in QTcF) using a linear mixed-effects model. The model included  $\Delta$ QTcF as the dependent variable and baseline QTcF, treatment, time point, and plasma concentration as independent variables. The sponsor analysis indicated no significant relationship between inclisiran concentration and  $\Delta$ QTcF ( $p=0.0772$ ). The model-predicted  $\Delta$ QTcF was 1.9 msec (90% CI 0.64, 3.17 msec) at the mean peak concentrations of inclisiran following 900 mg single dose. Similarly, the model-predicted  $\Delta$ QTcF was 1.1 msec (90% CI 0.34, 1.92 msec) at the expected peak concentrations (1760 ng/mL) in subjects with severe renal impairment (worst-case scenario) at the proposed therapeutic doses (Study ORION-7). The results of the sponsor's analysis suggest an absence of significant QTc prolongation at the maximum proposed therapeutic dose.

**Reviewer's comment:** *The results of the reviewer's analysis agreed with the sponsor's conclusion. Please see Section 4.5 for additional details.*

### 3.2.4 Cardiac Safety Analysis

Safety data were provided from 48 subjects who received inclisiran, placebo, and moxifloxacin in a crossover fashion and who were followed for up to 180 days.

There were no severe TEAEs, deaths, treatment-emergent SAEs, or TEAEs leading to study discontinuation. There were no cardiac-related TEAEs. There were no clinically meaningful changes in safety 12-lead ECG results.

*Reviewer's comment: None of the events identified to be of clinical importance per the ICH E14 guidelines (i.e., seizure, significant ventricular arrhythmias or sudden cardiac death) occurred in this study.*

## 4 REVIEWERS' ASSESSMENT

### 4.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The sponsor used QTcF for the primary analysis, which is acceptable as no large increases or decreases in heart rate (i.e.  $|\text{mean}| < 10$  bpm) were observed (see Section 4.3.2).

### 4.2 ECG ASSESSMENTS

#### 4.2.1 Overall

Overall ECG acquisition and interpretation in this study appears acceptable.

#### 4.2.2 QT Bias Assessment

Not Applicable.

#### 4.3 BY TIME ANALYSIS

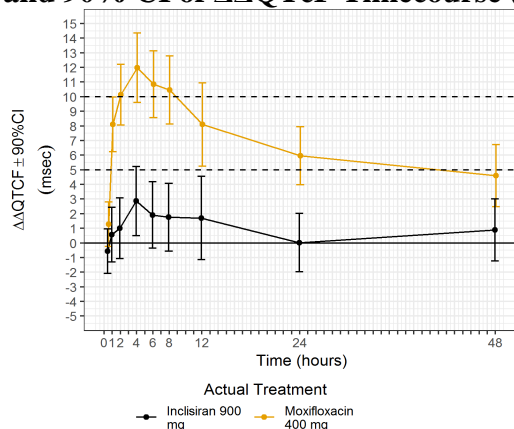
The by time analysis included all subjects with a baseline and at least one post-dose ECG.

The statistical reviewer used linear mixed model to analyze the drug effect by time for each biomarker (e.g.,  $\Delta\text{QTcF}$ ,  $\Delta\text{HR}$ ,  $\Delta\text{PR}$  and  $\Delta\text{QRS}$ ) independently. The model includes treatment, sequence, period, time (as a categorical variable), and treatment-by-time interaction as fixed effects and baseline as a covariate. The model also includes subject as a random effect and an unstructured covariance matrix to explain the associated between repeated measures within period.

##### 4.3.1 QTc

Figure 1 displays the time profile of  $\Delta\Delta\text{QTcF}$  for different treatment groups. The maximum  $\Delta\Delta\text{QTcF}$  values by treatment are shown in Table 2.

**Figure 1: Mean and 90% CI of  $\Delta\Delta\text{QTcF}$  Timecourse (unadjusted CIs).**



**Table 2: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for  $\Delta\Delta\text{QTcF}$  of Inclisiran 900 mg Arm**

N	Time (hours)	$\Delta\Delta\text{QTcF}$ (msec)	90.0% CI (msec)
48	4.0	2.9	(0.5 to 5.2)

##### 4.3.1.1 Assay sensitivity

The same model was used for assay sensitivity analysis. The time-course of changes in  $\Delta\Delta\text{QTcF}$  is shown in Figure 1 and shows the expected time-profile with a mean effect of  $> 5$  msec after Bonferroni adjustment for 4 time points (Table 3).

**Table 3: The Point Estimates and CIs Corresponding to the Largest Lower Bounds for  $\Delta\Delta\text{QTcF}$  of Moxifloxacin Arm**

N	Time (hours)	$\Delta\Delta\text{QTcF}$ (msec)	90.0% CI (msec)	97.5% CI (msec)
48	4.0	12.0	(9.6 to 14.3)	(8.7 to 15.2)

4.3.2 HR

Figure 2 displays the time profile of  $\Delta\Delta\text{HR}$  for different treatment groups. The maximum  $\Delta\Delta\text{HR}$  values by treatment are shown in Table 4.

Figure 2: Mean and 90% CI of  $\Delta\Delta\text{HR}$  Timecourse

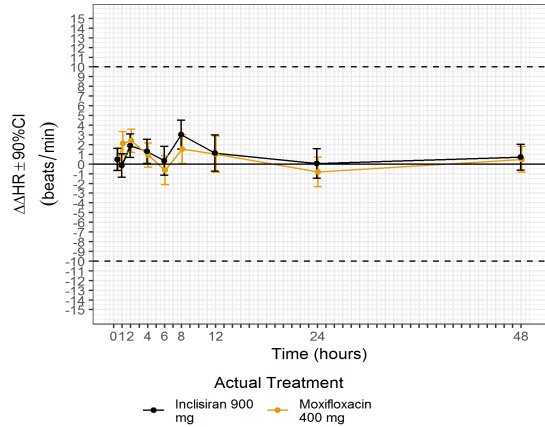


Table 4: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for  $\Delta\Delta\text{HR}$  of Incisiran 900 mg Arm

N	Time (hours)	$\Delta\Delta\text{HR}$ (beats/min)	90.0% CI (beats/min)
48	8.0	3.0	(1.5 to 4.5)

4.3.3 PR

Figure 3 displays the time profile of  $\Delta\Delta\text{PR}$  for different treatment groups. The maximum  $\Delta\Delta\text{PR}$  values by treatment are shown in Table 5.

Figure 3: Mean and 90% CI of  $\Delta\Delta\text{PR}$  Timecourse

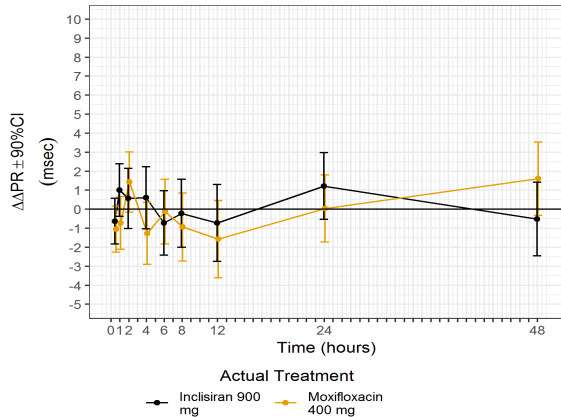


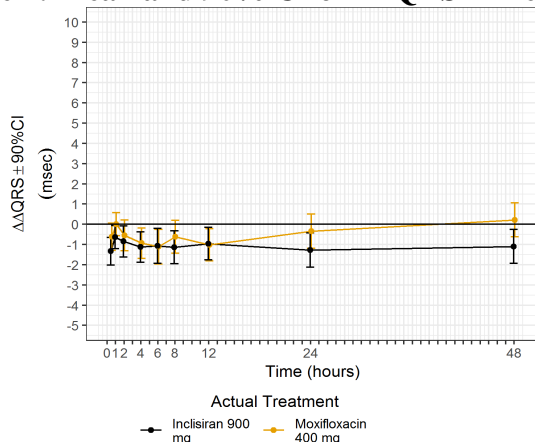
Table 5: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for  $\Delta\Delta\text{PR}$  of Incisiran 900 mg Arm

N	Time (hours)	$\Delta\Delta\text{PR}$ (msec)	90.0% CI (msec)
48	24.0	1.2	(-0.5 to 3.0)

### 4.3.4 QRS

Figure 4 displays the time profile of  $\Delta\Delta$ QRS for different treatment groups. The maximum  $\Delta\Delta$ QRS values by treatment are shown in Table 6.

**Figure 4: Mean and 90% CI of  $\Delta\Delta$ QRS Timecourse**



**Table 6: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for  $\Delta\Delta$ QRS of Inclisiran 900 mg Arm**

N	Time (hours)	$\Delta\Delta$ QRS (msec)	90.0% CI (msec)
48	1.0	-0.6	(-1.2 to -0.1)

## 4.4 CATEGORICAL ANALYSIS

Categorical analysis was performed for different ECG measurements either using absolute values, change from baseline or a combination of both. The analysis was conducted using the safety population and includes both scheduled and unscheduled ECGs.

### 4.4.1 QTcF

None of the subjects experienced QTcF values greater than 480 msec in inclisiran 900 mg group. Similarly, none of the subjects experienced  $\Delta$ QTcF values greater than 30 msec in inclisiran 900 mg group.

### 4.4.2 HR

None of the subjects experienced HR greater than 100 beats/min in inclisiran 900 mg group.

### 4.4.3 PR

None of the subjects experienced PR greater than 220 msec in inclisiran 900 mg group.

### 4.4.4 QRS

None of the subjects experienced QRS greater than 120 msec in inclisiran 900 mg group.

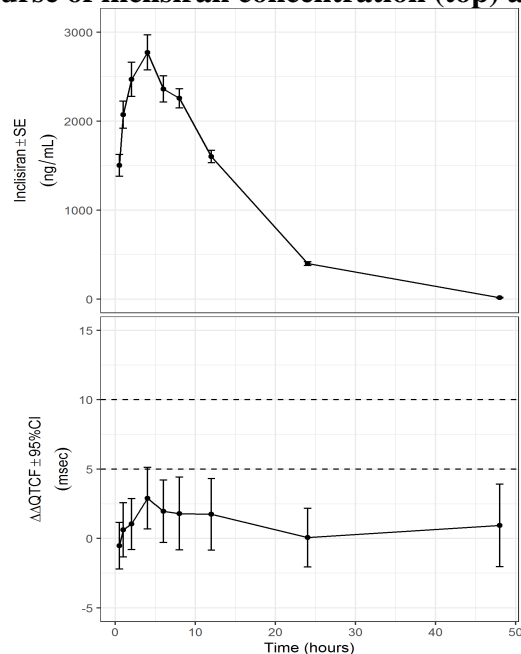
#### 4.5 EXPOSURE-RESPONSE ANALYSIS

The objective of the clinical pharmacology analysis is to assess the relationship between  $\Delta QTcF$  and concentration of inclisiran. Exposure-response analysis was conducted using all subjects with baseline and at a least one post-baseline ECG with time-matched PK.

Prior to evaluating the relationship between concentration of inclisiran and  $QTc$  using a linear model, the three key assumptions of the model were evaluated using exploratory analysis: 1) absence of significant changes in heart rate (more than a 10 bpm increase or decrease in mean HR); 2) delay between concentration of inclisiran and  $\Delta \Delta QTc$  and 3) presence of non-linear relationship.

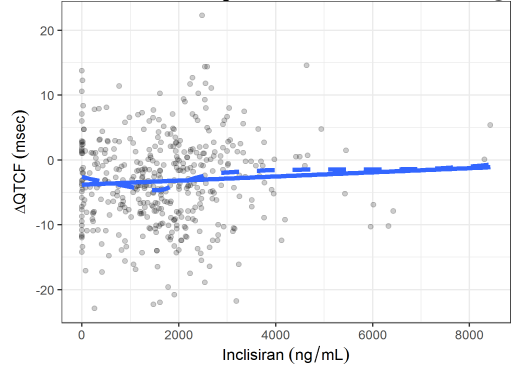
An evaluation of the time-course of inclisiran concentration and changes in  $\Delta \Delta QTcF$  is shown in Figure 5. There was no apparent correlation between the time at maximum effect on  $\Delta \Delta QTcF$  and peak concentrations of inclisiran indicating no significant hysteresis. Figure 2 shows the time-course of  $\Delta \Delta HR$ , which shows an absence of significant  $\Delta \Delta HR$  changes and the maximum change in heart rate is below 10 bpm (sections 4.3.2 and 4.4.2).

**Figure 5: Time course of inclisiran concentration (top) and  $QTcF$  (bottom)**



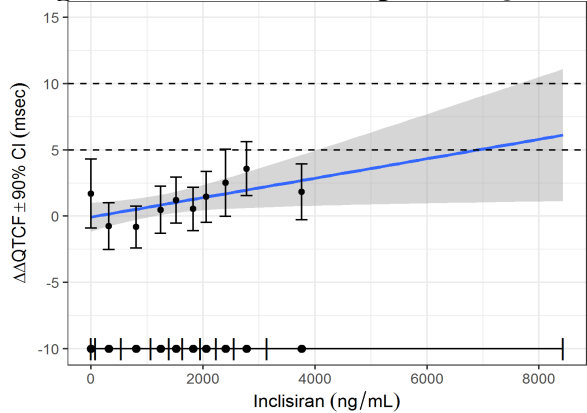
After confirming the absence of significant heart rate changes or delayed  $QTcF$  changes, the relationship between inclisiran concentration and  $\Delta QTcF$  was evaluated to determine if a linear model would be appropriate. Figure 6 shows the relationship between inclisiran concentration and  $\Delta QTcF$  and supports the use of a linear model.

**Figure 6: Assessment of linearity of concentration-QTcF relationship**



Finally, the linear model was applied to the data and the goodness-of-fit plot is shown in Figure 7. Predictions from the concentration-QTc model are provide in Table 7.

**Figure 7: Goodness-of-fit plot for QTcF**



**Table 7: Predictions from concentration-QTc model**

Actual Treatment	Inclisiran (ng/mL)	ΔΔQTcF (msec)	90.0% CI (msec)
Inclisiran 900 mg	2,644.6	1.9	(0.6 to 3.2)

**4.5.1.1 Assay sensitivity**

Assay sensitivity was established using by time analysis. Please see section 4.3 for additional details.



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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\*\*\*

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Date of This Review:	March 12, 2020
Requesting Office or Division:	Division of Metabolism and Endocrinology Products (DMEP)
Application Type and Number:	NDA 214012
Product Name and Strength:	(b) (4) (inclisiran) injection, 284 mg/1.5 mL
Product Type:	Combination Product (Drug-Device)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	The Medicines Company
FDA Received Date:	December 23, 2019
OSE RCM #:	2019-2666
DMEPA Safety Evaluator:	Melina Fanari, R.Ph.
DMEPA Team Leader:	Sevan Kolejian, PharmD, MBA

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## 1 REASON FOR REVIEW

As part of the approval process for (b) (4) (inclisiran) injection, the Division of Metabolism and Endocrinology Products (DMEP) requested that we review the proposed (b) (4) prescribing information (PI), container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

## 2 REGULATORY HISTORY

On April 12, 2019, DMEPA completed a review of the proposed marketing product characteristics, product samples and risk assessment for inclisiran<sup>a</sup>. Based on our review it was concluded that the Applicant did not need to submit the results of a human factors validation study as part of the marketing application.

## 3 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
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

## 4 FINDINGS AND RECOMMENDATIONS

Tables 3 below includes 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.

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<sup>a</sup> Schlick, J. MEMORANDUM for Inclisiran (IND 127589). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 Apr 12. RCM No.: 2019-405.

Table 2. Identified Issues and Recommendations for The Medicines Company (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Carton Labeling and Tray Lid Label			
1.	NDC number denoted by a placeholder.	Facilitate product identification.	Per 21 CFR 207.33, drug products subject to listing with the FDA must have a unique NDC to identify its labeler, product, and package size and type. The NDC number should be updated to reflect the actual numerical NDC number.
2.	Usual dose statement is missing.	Per 21 CFR 201.100 (b)(2).	Add the following statement:  "Recommended Dosage: See prescribing information."
3.	Labeling doesn't include that product should be administered by a healthcare professional.	Improve product usability and prevent use errors by untrained users.	Add the following statement to the principle display panel:  "For administration by a healthcare professional only."
4.	Established name appears small in comparison to proprietary name.	Improve readability.	The established name lacks prominence commensurate with the proprietary name. Increase the prominence of the established name taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10(g)(2).

### 3 CONCLUSION

Our evaluation of the proposed (b) (4) 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 Applicant. We ask that the Division convey Table 2 in its entirety to The Medicines Company so that recommendations are implemented prior to approval of this NDA.

APPEARS THIS WAY ON ORIGINAL

## APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

### APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 3 presents relevant product information for (b) (4) received on December 23, 2019 from The Medicines Company.

Table 3. Relevant Product Information for (b) (4)	
Initial Approval Date	N/A
Active Ingredient	inclisiran
Indication	An adjunct to diet and maximally tolerated statin therapy for the treatment of adults with primary hyperlipidemia (including heterozygous familial hypercholesterolemia) to reduce low-density lipoprotein cholesterol (LDL-C).
Route of Administration	subcutaneous
Dosage Form	injection
Strength	284 mg/1.5 mL
Dose and Frequency	284 mg administered as a single subcutaneous injection by a healthcare professional: initially, again at 3 months, and then every 6 months.
How Supplied	Supplied in a single-use prefilled syringe, filled to deliver 1.5 mL of solution containing 284 mg of inclisiran
Storage	Room temperature: At controlled room temperature (20°C to 25°C [68°F to 77°F] with allowable excursions between 15°C and 30°C [59°F and 86°F]) [see USP, Controlled Room Temperature (CRT)].

## APPENDIX B. PREVIOUS DMEPA REVIEWS

On March 4, 2020, we searched for previous DMEPA reviews relevant to this current review using the terms, inclisiran. Our search identified one previous reviews<sup>b</sup>, and we considered our previous recommendations to see if they are applicable for this current review.

## APPENDIX F. LABELS AND LABELING

### F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,<sup>c</sup> along with postmarket medication error data, we reviewed the following (b) (4) labels and labeling submitted by The Medicines Company.

- Container label received on December 23, 2019
- Tray label received on December 23, 2019
- Carton Labeling received on December 23, 2019
- Prescribing Information (Image not shown) received on December 23, 2019, available from [Application 214012 - Sequence 0001 - Proposed Labeling Text \(Word\)](#)

### F.2 Label and Labeling Images



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<sup>b</sup> Schlick, J. MEMORANDUM for Inclisiran (IND 127589). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 Apr 12. RCM No.: 2019-405.

<sup>c</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.





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