CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

021445Orig1s042

Trade Name:	ZETIA
Generic or Proper Name:	ezetimibe
Sponsor:	Organon LLC
Approval Date:	July 20, 2023
Indication:	• In combination with a statin, or alone when additional low density lipoprotein cholesterol (LDL-C) lowering therapy is not possible, as an adjunct to diet to reduce elevated LDL-C in adults with primary hyperlipidemia, including heterozygous familial hypercholesterolemia (HeFH). • In combination with a statin as an adjunct to diet to reduce elevated LDL-C in pediatric patients 10 years of age and older with HeFH. • In combination with fenofibrate as an adjunct to diet to reduce elevated LDL C in adults with mixed hyperlipidemia. • In combination with a statin, and other LDL-C lowering therapies, to reduce elevated LDL C levels in adults and in pediatric patients 10 years of age and older with homozygous familial hypercholesterolemia (HoFH). • As an adjunct to diet for the reduction of elevated sitosterol and campesterol levels in adults and in pediatric patients 9 years of age and older with homozygous familial sitosterolemia.

CENTER FOR DRUG EVALUATION AND RESEARCH

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APPLICATION NUMBER:

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APPROVAL LETTER

NDA 021445/S-042

SUPPLEMENT APPROVAL

Organon LLC
Attention: Mini Chen
Associate Principal Scientist, Regulatory Liaison
30 Hudson Street, Floor 33
Jersey City, NJ 07302

Dear Ms. Chen:

Please refer to your supplemental new drug application (sNDA) dated and received May 15, 2018, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Zetia (ezetimibe) tablets.

This Prior Approval sNDA provides for updates to the Zetia Prescribing Information:

- Pregnancy and Lactation Labeling Rule (PLLR) conversion as per the guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format*
- Revision to Section 1 – *Indications and Usage,* to clarify that use of ezetimibe as monotherapy in primary hyperlipidemia is appropriate when other additional concomitant LDL-C lowering therapy (i.e., statins, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor therapy) is not possible; clarify the indications for pediatric patients with familial hypercholesterolemia and homozygous sitosterolemia; and removal of the Limitations of Use statement.
- Update to Section 2 – *Dosage and Administration*
- Revision to Section 4 – *Contraindications,* to remove information that was specific to statin therapy
- Revisions to Section 5 – *Warnings and Precautions,* to remove information that was specific to statin or fenofibrate therapy
- Extensive edits made throughout the label to update and modernize with current labeling guidances and practices.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and Patient Package Insert), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

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[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

PATENT LISTING REQUIREMENTS

Pursuant to 21 CFR 314.53(d)(2) and 314.70(f), certain changes to an approved NDA submitted in a supplement require you to submit patent information for listing in the Orange Book upon approval of the supplement. You must submit the patent information required by 21 CFR 314.53(d)(2)(i)(A) through (C) and 314.53(d)(2)(ii)(A) and (C), as applicable, to FDA on Form FDA 3542 within 30 days after the date of approval of the supplement for the patent information to be timely filed (see 21 CFR 314.53(c)(2)(ii)). You also must ensure that any changes to your approved NDA that require the submission of a request to remove patent information from the Orange Book are submitted to FDA at the time of approval of the supplement pursuant to 21 CFR 314.53(d)(2)(ii)(B) and 314.53(f)(2)(iv).

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Martin White, M.S., Regulatory Project Manager, at 240-402-6018.

Sincerely,

{See appended electronic signature page}

John Sharretts, M.D.
Director
Division of Diabetes, Lipid Disorders, and Obesity
Office of Cardiology, Hematology, Endocrinology, and Nephrology
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Patient Package Insert

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JOHN M SHARRETTS
07/20/2023 12:00:15 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021445Orig1s042

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ZETIA safely and effectively. See full prescribing information for ZETIA.

ZETIA® (ezetimibe) tablets, for oral use
Initial U.S. Approval: 2002

----------RECENT MAJOR CHANGES----------

Indications and Usage (1)	7/2023
Dosage and Administration (2)	7/2023
Contraindications (4)	7/2023
Warnings and Precautions (5.1, 5.2, 5.3)	7/2023

----------INDICATIONS AND USAGE----------

ZETIA is indicated (1):

- In combination with a statin, or alone when additional low density lipoprotein cholesterol (LDL-C) lowering therapy is not possible, as an adjunct to diet to reduce elevated LDL-C in adults with primary hyperlipidemia, including heterozygous familial hypercholesterolemia (HeFH).
- In combination with a statin as an adjunct to diet to reduce elevated LDL-C in pediatric patients 10 years of age and older with HeFH.
- In combination with fenofibrate as an adjunct to diet to reduce elevated LDL C in adults with mixed hyperlipidemia.
- In combination with a statin, and other LDL-C lowering therapies, to reduce elevated LDL C levels in adults and in pediatric patients 10 years of age and older with homozygous familial hypercholesterolemia (HoFH).
- As an adjunct to diet for the reduction of elevated sitosterol and campesterol levels in adults and in pediatric patients 9 years of age and older with homozygous familial sitosterolemia.

When ZETIA is used in combination with a statin, fenofibrate, or other LDL-C lowering therapies, refer to the Prescribing Information of these products for information on the safe and effective use (1).

---------- DOSAGE AND ADMINISTRATION ----------

- 10-mg orally once daily, with or without food (2)
- Administer ZETIA either ≥2 hours before or ≥4 hours after administration of a bile acid sequestrant. (2)
- Assess LDL-C when clinically appropriate, as early as 4 weeks after initiating ZETIA. (2)

---------- DOSAGE FORMS AND STRENGTHS ----------

- Tablets: 10 mg (3)

----------CONTRAINDICATIONS----------

- Hypersensitivity to ezetimibe or any excipient of ZETIA. (4)
- When used in combination with a statin, fenofibrate, or other LDL-C lowering therapy, ZETIA is contraindicated in patients for whom a statin, fenofibrate, or other LDL-C lowering therapy are contraindicated. Refer to the Prescribing Information of these products for a list of their contraindications. (4)

---------- WARNINGS AND PRECAUTIONS ----------

- Risks Associated with Combination Treatment with a Statin, Fenofibrate, or Other LDL-C Lowering Therapies: Refer to the Prescribing Information of these products for a description of their risks including, but not limited to, the warnings and precautions. (5.1)
- Liver Enzyme Abnormalities and Monitoring: Increases in serum transaminases have been reported with use of ZETIA. Perform liver enzyme testing as clinically indicated and consider withdrawal of ZETIA if increases in ALT or AST ≥3 X ULN persist. (5.2)
- Skeletal Muscle Effects (e.g., Myopathy and Rhabdomyolysis): ZETIA may cause myopathy and rhabdomyolysis. In post-marketing reports, most patients who developed rhabdomyolysis were taking a statin or other agents known to be associated with an increased risk of rhabdomyolysis, such as fibrates. If myopathy is suspected, discontinue ZETIA and other concomitant medications, as appropriate. (5.3)

---------- ADVERSE REACTIONS ----------

- Common adverse reactions in clinical trials:
  - ZETIA administered alone (incidence ≥2% and greater than placebo): upper respiratory tract infection, diarrhea, arthralgia, sinusitis, pain in extremity, fatigue, and influenza (6.1)
  - ZETIA coadministered with a statin (incidence ≥2% and greater than statin alone): nasopharyngitis, myalgia, upper respiratory tract infection, arthralgia, diarrhea, back pain, influenza, pain in extremity, and fatigue (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Organon LLC, a subsidiary of Organon & Co., at 1-844-674-3200 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Cyclosporine: Combination increases exposure of ZETIA and cyclosporine. Cyclosporine concentrations should be monitored in patients taking ZETIA concomitantly. (7)
- Fibrates: Coadministration of ZETIA with fibrates other than fenofibrate is not recommended until use in patients is adequately studied. If cholelithiasis is suspected in a patient receiving ZETIA and fenofibrate, gallbladder studies are indicated, and alternative lipid-lowering therapy should be considered. (7)
- Bile Acid Sequestrants: Cholestyramine combination decreases exposure of ZETIA. (7)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 7/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ZETIA® is indicated:

- In combination with a statin, or alone when additional low-density lipoprotein cholesterol (LDL-C) lowering therapy is not possible, as an adjunct to diet to reduce elevated LDL-C in adults with primary hyperlipidemia, including heterozygous familial hypercholesterolemia (HeFH).
- In combination with a statin as an adjunct to diet to reduce elevated LDL-C in pediatric patients 10 years of age and older with HeFH.
- In combination with fenofibrate as an adjunct to diet to reduce elevated LDL-C in adults with mixed hyperlipidemia.
- In combination with a statin, and other LDL-C lowering therapies, to reduce elevated LDL-C levels in adults and in pediatric patients 10 years of age and older with homozygous familial hypercholesterolemia (HoFH).
- As an adjunct to diet for the reduction of elevated sitosterol and campesterol levels in adults and in pediatric patients 9 years of age and older with homozygous familial sitosterolemia.

When ZETIA is used in combination with a statin, fenofibrate, or other LDL-C lowering therapies, refer to the Prescribing Information of these products for information on the safe and effective use.

2 DOSAGE AND ADMINISTRATION

- The recommended dose of ZETIA is 10 mg orally once daily, administered with or without food.
- If as dose is missed, take the missed dose as soon as possible. Do not double the next dose.
- Assess LDL-C when clinically appropriate, as early as 4 weeks after initiating ZETIA.
- In patients taking a bile acid sequestrant, administer ZETIA at least 2 hours before or 4 hours after the bile acid sequestrant *[see Drug Interactions (7)]*.

3 DOSAGE FORMS AND STRENGTHS

Tablets: 10-mg white to off-white, capsule-shaped, and debossed with "414" on one side.

4 CONTRAINDICATIONS

ZETIA is contraindicated in patients with a known hypersensitivity to ezetimibe or any of the excipients in ZETIA. Hypersensitivity reactions including anaphylaxis, angioedema, rash, and urticaria have been reported *[see Adverse Reactions (6.2)]*.

When used in combination with a statin, fenofibrate, or other LDL-C lowering therapy, ZETIA is contraindicated in patients for whom a statin, fenofibrate, or other LDL-C lowering therapy are contraindicated. Refer to the Prescribing Information of these products for a list of their contraindications *[see Warnings and Precautions (5.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Risks Associated with Combination Treatment with a Statin, Fenofibrate, or Other LDL-C Lowering Therapies

If ZETIA is administered with a statin, fenofibrate, or other LDL-C lowering therapies, refer to the Prescribing Information of these products for a description of their risks including, but not limited to, the warnings and precautions *[see Contraindications (4)]*.

5.2 Liver Enzymes

Increases in serum transaminases have been reported with use of ZETIA *[see Adverse Reactions (6.1)]*. In controlled clinical combination studies of ZETIA initiated concurrently with a statin, the incidence of

consecutive elevations (≥3 X ULN) in hepatic transaminase levels was 1.3% for patients treated with ZETIA administered with statins and 0.4% for patients treated with statins alone. Perform liver enzyme testing as clinically indicated and consider withdrawal of ZETIA if increases in ALT or AST ≥3 X ULN persist.

5.3 Myopathy/Rhabdomyolysis

ZETIA may cause myopathy [muscle pain, tenderness, or weakness associated with elevated creatine kinase (CK)] and rhabdomyolysis *[see Adverse Reactions (6.1)]*. In post-marketing reports, most patients who developed rhabdomyolysis were taking a statin or other agents known to be associated with an increased risk of rhabdomyolysis, such as fibrates. If myopathy is suspected, discontinue ZETIA and other concomitant medications, as appropriate.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the label:

- Liver enzyme abnormalities *[see Warnings and Precautions (5.2)]*
- Rhabdomyolysis and myopathy *[see Warnings and Precautions (5.3)]*

6.1 Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in clinical practice.

Monotherapy

In 10 double-blind, placebo-controlled clinical trials, 2,396 patients with primary hyperlipidemia (age range 9 to 86 years; 50% female, 90% White, 5% Black or African American, 2% Asian, 3% other races; 3% identified as Hispanic or Latino ethnicity) and elevated LDL-C were treated with ZETIA 10 mg daily for a median treatment duration of 12 weeks (range 0 to 39 weeks).

Adverse reactions reported in ≥2% of patients treated with ZETIA and at an incidence greater than placebo in placebo-controlled studies of ZETIA are shown in Table 1.

TABLE 1: Adverse Reactions Occurring ≥2% and Greater than Placebo in ZETIA-treated Patients

Adverse Reaction	Placebo (%) n = 1,159	ZETIA 10 mg (%) n = 2,396
Upper respiratory tract infection	2.5	4.3
Diarrhea	3.7	4.1
Arthralgia	2.2	3.0
Sinusitis	2.2	2.8
Pain in extremity	2.5	2.7
Fatigue	1.5	2.4
Influenza	1.5	2.0

Combination with a Statin

In 28 double-blind, controlled (placebo or active-controlled) clinical trials, 11,308 patients with primary hyperlipidemia (age range 10 to 93 years, 48% female, 85% White, 7% Black or African American, 3% Asian, 5% other races; 4% identified as Hispanic or Latino ethnicity) and elevated LDL-C were treated with ZETIA 10 mg/day concurrently with or added to on-going statin therapy for a median treatment duration of 8 weeks (range 0 to 112 weeks).

The incidence of consecutive increased transaminases (≥3 X ULN) was higher in patients receiving ZETIA administered with statins (1.3%) than in patients treated with statins alone (0.4%).

Adverse reactions reported in ≥2% of patients treated with ZETIA + statin and at an incidence greater than statin are shown in Table 2.

TABLE 2: Adverse Reactions Occurring ≥2% in ZETIA-treated Patients Coadministered with a Statin and at an Incidence Greater than Statin

Adverse Reaction	All Statins* (%) n = 9,361	ZETIA + All Statins* (%) n = 11,308
Nasopharyngitis	3.3	3.7
Myalgia	2.7	3.2
Upper respiratory tract infection	2.8	2.9
Arthralgia	2.4	2.6
Diarrhea	2.2	2.5
Back pain	2.3	2.4
Influenza	2.1	2.2
Pain in extremity	1.9	2.1
Fatigue	1.6	2.0

* All Statins = all doses of all statins

Combination with Fenofibrate
This clinical trial involving 625 patients with mixed dyslipidemia (age range 20 to 76 years; 44% female, 79% White, 1% Black or African American, 20% other races; 11% identified as Hispanic or Latino ethnicity) treated for up to 12 weeks and 576 patients treated for up to an additional 48 weeks evaluated coadministration of ZETIA and fenofibrate. Incidence rates for clinically important elevations (≥3 X ULN, consecutive) in hepatic transaminase levels were 4.5% and 2.7% for fenofibrate monotherapy (n=188) and ZETIA coadministered with fenofibrate (n=183), respectively, adjusted for treatment exposure. Corresponding incidence rates for cholecystectomy were 0.6% and 1.7% for fenofibrate monotherapy and ZETIA coadministered with fenofibrate, respectively *[see Drug Interactions (7)]*.

6.2 Post-Marketing Experience
Because the reactions below are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

The following additional adverse reactions have been identified during post-approval use of ZETIA:

Blood Disorders: thrombocytopenia

Gastrointestinal Disorders: abdominal pain; pancreatitis; nausea

Hepatobiliary Disorders: elevations in liver transaminases; hepatitis; cholelithiasis; cholecystitis

Immune System Disorders: Hypersensitivity reactions including: anaphylaxis, angioedema, rash, and urticaria

Musculoskeletal Disorders: elevated creatine phosphokinase; myopathy/rhabdomyolysis

Nervous System Disorders: dizziness; paresthesia; depression; headache

Skin and Subcutaneous Tissue Disorders: erythema multiforme

7 DRUG INTERACTIONS

Table 3 includes a list of drugs with clinically important drug interactions when administered concomitantly with ZETIA and instructions for preventing or managing them.

Table 3: Clinically Important Drug Interactions with ZETIA

Cyclosporine	
Clinical Impact:	Concomitant use of ZETIA and cyclosporine increases ezetimibe and cyclosporine concentrations. The degree of increase in ezetimibe exposure may be greater in patients with severe renal insufficiency *[see Clinical Pharmacology (12.3)]*.
Intervention:	Monitor cyclosporine concentrations in patients receiving ZETIA and cyclosporine. In patients treated with cyclosporine, weigh the potential effects of the increased exposure to ezetimibe from concomitant use against the benefits of alterations in lipid levels provided by ZETIA.
Fibrates	
Clinical Impact:	Both fenofibrate and ezetimibe may increase cholesterol excretion into the bile, leading to cholelithiasis. Co-administration of ZETIA with fibrates other than fenofibrate is not recommended *[see Adverse Reactions (6.1)]*.
Intervention:	If cholelithiasis is suspected in a patient receiving ZETIA and fenofibrate, gallbladder studies are indicated, and alternative lipid-lowering therapy should be considered.
Bile Acid Sequestrants	
Clinical Impact:	Concomitant cholestyramine administration decreased the mean exposure of total ezetimibe. This may result in a reduction of efficacy *[see Clinical Pharmacology (12.3)]*.
Intervention:	In patients taking a bile acid sequestrant, administer ZETIA at least 2 hours before or 4 hours after the bile acid sequestrant *[see Dosage and Administration (2)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are insufficient data on ezetimibe use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. In animal reproduction studies, no adverse developmental effects were observed in pregnant rats and rabbits orally administered ezetimibe during the period of organogenesis at doses that resulted in up to 10 and 150 times, respectively, the human exposure at the MRHD, based on AUC *(see Data)*. ZETIA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. When ZETIA is administered with a statin, refer to the Prescribing Information for the statin.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Animal Data

In oral (gavage) embryo-fetal development studies of ezetimibe conducted in rats (gestation days 6-15) and rabbits (gestation days 7-19), there was no evidence of maternal toxicity or embryolethal effects at the doses tested (250, 500, 1,000 mg/kg/day). In rats, increased incidences of common fetal skeletal findings (extra pair of thoracic ribs, unossified cervical vertebral centra, shortened ribs) were observed at 1,000 mg/kg/day (~10 times the human exposure at 10 mg daily based on $AUC_{0\text{-}24hr}$ for total ezetimibe). In rabbits treated with ezetimibe, an increased incidence of extra thoracic ribs was observed at 1,000 mg/kg/day (150 times the human exposure at 10 mg daily based on $AUC_{0\text{-}24hr}$ for total ezetimibe). The animal-to-human exposure multiple for total ezetimibe at the no-observed effect level was 6 times for rat and 134 times for rabbit. Fetal exposure to ezetimibe (conjugated and unconjugated) was confirmed in subsequent placental transfer studies conducted using a maternal dose of 1,000 mg/kg/day. The fetal

maternal plasma exposure ratio (total ezetimibe) was 1.5 for rats on gestation day 20 and 0.03 for rabbits on gestation day 22.

The effect of ezetimibe on prenatal and postnatal development and maternal function was evaluated in pregnant rats at doses of 100, 300 or 1,000 mg/kg/day from gestation day 6 through lactation day 21. No maternal toxicity or adverse developmental outcomes were observed up to and including the highest dose tested (17 times the human exposure at 10 mg daily based on $AUC_{0\text{-}24hr}$ for total ezetimibe).

Multiple-dose studies of ezetimibe given in combination with statins in rats and rabbits during organogenesis resulted in higher ezetimibe and statin exposures. Reproductive findings occurred at lower doses in combination therapy compared to monotherapy.

8.2 Lactation

Risk Summary

There is no information about the presence of ezetimibe in human milk. Ezetimibe is present in rat milk *(see Data)*. When a drug is present in animal milk, it is likely that the drug will be present in human milk. There is no information about the effects of ezetimibe on the breastfed infant or the effects of ezetimibe on milk production. ZETIA should not be used in nursing mothers unless the potential benefit justifies the potential risk to the infant.

Data

Ezetimibe was present in the milk of lactating rats. The pup to maternal plasma ratio for total ezetimibe was 0.5 on lactation day 12.

8.4 Pediatric Use

The safety and effectiveness of ZETIA in combination with a statin as an adjunct to diet to reduce LDL-C have been established in pediatric patients 10 years of age and older with HeFH. Use of ZETIA for this indication is based on a double-blind, placebo-controlled clinical trial in 248 pediatric patients (142 males and 106 postmenarchal females) 10 years of age and older with HeFH *[see Clinical Studies (14)]*. In this limited controlled trial, there was no significant effect on growth or sexual maturation in the adolescent males or females, or on menstrual cycle length in females.

The safety and effectiveness of ZETIA in combination with a statin, and other LDL-C lowering therapies, to reduce LDL-C have been established in pediatric patients 10 years of age and older with HoFH. Use of ZETIA for this indication is based on a 12-week double-blind, placebo-controlled clinical trial followed by an uncontrolled extension period in 7 pediatric patients 11 years of age and older with HoFH *[see Clinical Studies (14)]*.

The safety and effectiveness of ZETIA as an adjunct to diet for the reduction of elevated sitosterol and campesterol levels have been established in adults and pediatric patients 9 years of age and older with homozygous familial sitosterolemia. Use of ZETIA for this indication is based on an 8-week double-blind, placebo-controlled clinical trial in 4 patients 9 years of age and older with homozygous sitosterolemia with elevated plasma sitosterol levels (>5 mg/dL) *[see Clinical Studies (14)]*.

The safety and effectiveness of ZETIA have not been established in pediatric patients younger than 10 years of age with HeFH or HoFH, in pediatric patients younger than 9 years of age with homozygous familial sitosterolemia, or in pediatric patients with other types of hyperlipidemia.

8.5 Geriatric Use

Of the 2,396 patients who received ZETIA in clinical trials, 669 (28%) were 65 years of age and older, and 111 (5%) were 75 years of age and older. Of the 11,308 patients who received ZETIA in combination with a statin in clinical trials, 3587 (32%) were 65 years of age and older, and 924 (8%) were 75 years of age and older *[see Clinical Studies (14)]*. No overall differences in safety or effectiveness of ZETIA have been observed between patients 65 years of age and older and younger patients. No clinically meaningful differences in the pharmacokinetics of ezetimibe were observed in geriatric patients compared to younger adult patients *[see Clinical Pharmacology (12.3)]*.

8.6 Renal Impairment
No dosage adjustment of ZETIA is necessary in patients with renal impairment.

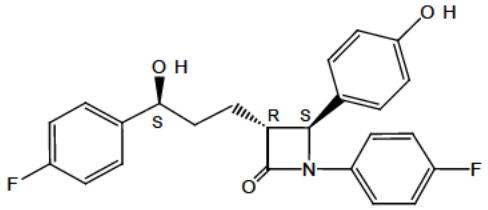
8.7 Hepatic Impairment
ZETIA is not recommended for use in patients with moderate to severe hepatic impairment (Child-Pugh B or C) due to the unknown effects of the increased exposure to ezetimibe *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

In the event of overdose, consider contacting the Poison Help line (1-800-222-1222) or a medical toxicologist for additional overdosage management recommendations.

11 DESCRIPTION

ZETIA (ezetimibe) is a dietary cholesterol absorption inhibitor. The chemical name of ezetimibe is 1-(4-fluorophenyl)-3(R)-[3-(4-fluorophenyl)-3(S)-hydroxypropyl]-4(S)-(4-hydroxyphenyl)-2-azetidinone. The empirical formula is $C_{24}H_{21}F_2NO_3$. Its molecular weight is 409.4 and its structural formula is:



Ezetimibe is a white, crystalline powder that is freely to very soluble in ethanol, methanol, and acetone and practically insoluble in water. Ezetimibe has a melting point of about 163°C and is stable at ambient temperature. ZETIA is available as a tablet for oral use containing 10 mg of ezetimibe and the following inactive ingredients: croscarmellose sodium NF, lactose monohydrate NF, magnesium stearate NF, microcrystalline cellulose NF, povidone USP, and sodium lauryl sulfate NF.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action
Ezetimibe reduces blood cholesterol by inhibiting the absorption of cholesterol by the small intestine.

The molecular target of ezetimibe has been shown to be the sterol transporter, Niemann-Pick C1-Like 1 (NPC1L1), which is involved in the intestinal uptake of cholesterol and phytosterols. Ezetimibe localizes at the brush border of the small intestine and inhibits the absorption of cholesterol, leading to a decrease in the delivery of intestinal cholesterol to the liver. This causes a reduction of hepatic cholesterol stores and an increase in LDL receptors, resulting in clearance of cholesterol from the blood.

12.2 Pharmacodynamics
ZETIA reduces total cholesterol (total-C), LDL-C, apolipoprotein (Apo) B, and non-high-density lipoprotein cholesterol (non-HDL-C) in patients with hyperlipidemia.

In a 2-week clinical trial in 18 hypercholesterolemic patients, ZETIA inhibited intestinal cholesterol absorption by 54%, compared with placebo. ZETIA had no clinically meaningful effect on the plasma concentrations of the fat-soluble vitamins A, D, and E (in a trial of 113 patients) and did not impair adrenocortical steroid hormone production (in a trial of 118 patients).

12.3 Pharmacokinetics
Absorption
After oral administration, ezetimibe is absorbed and extensively conjugated to a pharmacologically active phenolic glucuronide (ezetimibe-glucuronide). After a single 10-mg dose of ZETIA to fasted adults, mean ezetimibe peak plasma concentrations (C_{max}) of 3.4 to 5.5 ng/mL were attained within 4 to 12 hours (T_{max}).

Ezetimibe-glucuronide mean C_{max} values of 45 to 71 ng/mL were achieved between 1 and 2 hours (T_{max}). There was no substantial deviation from dose proportionality between 5 and 20 mg. The absolute bioavailability of ezetimibe cannot be determined, as the compound is virtually insoluble in aqueous media suitable for injection.

Effect of Food
Concomitant food administration (high-fat or non-fat meals) had no effect on the extent of absorption of ezetimibe when administered as ZETIA 10-mg tablets. The C_{max} value of ezetimibe was increased by 38% with consumption of high-fat meals.

Distribution
Ezetimibe and ezetimibe-glucuronide are highly bound (>90%) to human plasma proteins.

Elimination
Metabolism
Ezetimibe is primarily metabolized in the small intestine and liver via glucuronide conjugation (a phase II reaction) with subsequent biliary and renal excretion. Minimal oxidative metabolism (a phase I reaction) has been observed in all species evaluated. In humans, ezetimibe is rapidly metabolized to ezetimibe-glucuronide. Ezetimibe and ezetimibe-glucuronide are the major drug-derived compounds detected in plasma, constituting approximately 10 to 20% and 80 to 90% of the total drug in plasma, respectively.

Both ezetimibe and ezetimibe-glucuronide are eliminated from plasma with a half-life of approximately 22 hours for both ezetimibe and ezetimibe-glucuronide. Plasma concentration-time profiles exhibit multiple peaks, suggesting enterohepatic recycling.

Excretion
Following oral administration of ^{14}C-ezetimibe (20 mg) to human subjects, total ezetimibe (ezetimibe + ezetimibe-glucuronide) accounted for approximately 93% of the total radioactivity in plasma. After 48 hours, there were no detectable levels of radioactivity in the plasma.

Approximately 78% and 11% of the administered radioactivity were recovered in the feces and urine, respectively, over a 10-day collection period. Ezetimibe was the major component in feces and accounted for 69% of the administered dose, while ezetimibe-glucuronide was the major component in urine and accounted for 9% of the administered dose.

Specific Populations
Geriatric Patients
In a multiple-dose trial with ezetimibe given 10 mg once daily for 10 days, plasma concentrations for total ezetimibe were about 2-fold higher in older (≥65 years) healthy subjects compared to younger subjects. However, the difference in plasma concentrations is not clinically meaningful.

Gender
In a multiple-dose trial with ezetimibe given 10 mg once daily for 10 days, plasma concentrations for total ezetimibe were slightly higher (<20%) in females than in males.

Race
Based on a meta-analysis of multiple-dose pharmacokinetic studies, there were no pharmacokinetic differences between Black and White subjects. Studies in Asian subjects indicated that the pharmacokinetics of ezetimibe were similar to those seen in White subjects.

Renal Impairment
After a single 10-mg dose of ezetimibe in patients with severe renal disease (n=8; mean CrCl ≤30 mL/min/1.73 m^2), the mean AUC values for total ezetimibe, ezetimibe-glucuronide, and ezetimibe were increased approximately 1.5-fold, compared to healthy subjects (n=9).

Hepatic Impairment

After a single 10-mg dose of ezetimibe, the mean AUC for total ezetimibe was increased approximately 1.7-fold in patients with mild hepatic impairment (Child-Pugh score 5 to 6), compared to healthy subjects. The mean AUC values for total ezetimibe and ezetimibe were increased approximately 3- to 4-fold and 5- to 6-fold, respectively, in patients with moderate (Child-Pugh score 7 to 9) or severe hepatic impairment (Child-Pugh score 10 to 15). In a 14-day, multiple-dose trial (10 mg daily) in patients with moderate hepatic impairment, the mean AUC values for total ezetimibe and ezetimibe were increased approximately 4-fold on Day 1 and Day 14 compared to healthy subjects *[see Use in Specific Populations (8.7)]*.

Drug Interactions

ZETIA had no significant effect on a series of probe drugs (caffeine, dextromethorphan, tolbutamide, and IV midazolam) known to be metabolized by cytochrome P450 (1A2, 2D6, 2C8/9 and 3A4) in a "cocktail" trial of twelve healthy adult males. This indicates that ezetimibe is neither an inhibitor nor an inducer of these cytochrome P450 isozymes, and it is unlikely that ezetimibe will affect the metabolism of drugs that are metabolized by these enzymes.

TABLE 4: Effect of Coadministered Drugs on Total Ezetimibe

Coadministered Drug and Dosing Regimen	Total Ezetimibe*	
	Change in AUC	Change in C_{max}
Cyclosporine-stable dose required (75-150 mg BID)[†, ‡]	↑240%	↑290%
Fenofibrate, 200 mg QD, 14 days[‡]	↑48%	↑64%
Gemfibrozil, 600 mg BID, 7 days[‡]	↑64%	↑91%
Cholestyramine, 4 g BID, 14 days[‡]	↓55%	↓4%
Aluminum & magnesium hydroxide combination antacid, single dose[§]	↓4%	↓30%
Cimetidine, 400 mg BID, 7 days	↑6%	↑22%
Glipizide, 10 mg, single dose	↑4%	↓8%
Statins		
Lovastatin 20 mg QD, 7 days	↑9%	↑3%
Pravastatin 20 mg QD, 14 days	↑7%	↑23%
Atorvastatin 10 mg QD, 14 days	↓2%	↑12%
Rosuvastatin 10 mg QD, 14 days	↑13%	↑18%
Fluvastatin 20 mg QD, 14 days	↓19%	↑7%

* Based on 10-mg dose of ezetimibe.

† Post-renal transplant patients with mild impaired or normal renal function. In a different trial, a renal transplant patient with severe renal insufficiency (creatinine clearance of 13.2 mL/min/1.73 m^2) who was receiving multiple medications, including cyclosporine, demonstrated a 12-fold greater exposure to total ezetim be compared to healthy subjects.

‡ See Drug Interactions (7).

§ Supralox, 20 mL.

TABLE 5: Effect of Ezetimibe Coadministration on Systemic Exposure to Other Drugs

Coadministered Drug and its Dosage Regimen	Ezetimibe Dosage Regimen	Change in AUC of Coadministered Drug	Change in C_{max} of Coadministered Drug
Warfarin, 25-mg single dose on Day 7	10 mg QD, 11 days	↓2% (R-warfarin) ↓4% (S-warfarin)	↑3% (R-warfarin) ↑1% (S-warfarin)
Digoxin, 0.5-mg single dose	10 mg QD, 8 days	↑2%	↓7%
Gemfibrozil, 600 mg BID, 7 days*	10 mg QD, 7 days	↓1%	↓11%
Ethinyl estradiol & Levonorgestrel, QD, 21 days	10 mg QD, days 8-14 of 21d oral contraceptive cycle	Ethinyl estradiol 0% Levonorgestrel 0%	Ethinyl estradiol ↓9% Levonorgestrel ↓5%
Glipizide, 10 mg on Days 1 and 9	10 mg QD, days 2-9	↓3%	↓5%
Fenofibrate, 200 mg QD, 14 days*	10 mg QD, 14 days	↑11%	↑7%
Cyclosporine, 100-mg single dose Day 7*	20 mg QD, 8 days	↑15%	↑10%

Statins			
Lovastatin 20 mg QD, 7 days	10 mg QD, 7 days	↑19%	↑3%
Pravastatin 20 mg QD, 14 days	10 mg QD, 14 days	↓20%	↓24%
Atorvastatin 10 mg QD, 14 days	10 mg QD, 14 days	↓4%	↑7%
Rosuvastatin 10 mg QD, 14 days	10 mg QD, 14 days	↑19%	↑17%
Fluvastatin 20 mg QD, 14 days	10 mg QD, 14 days	↓39%	↓27%

* See Drug Interactions (7).

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

A 104-week dietary carcinogenicity study with ezetimibe was conducted in rats at doses up to 1,500 mg/kg/day (males) and 500 mg/kg/day (females) (~20 X the human exposure at 10 mg daily based on $AUC_{0\text{-}24hr}$ for total ezetimibe). A 104-week dietary carcinogenicity study with ezetimibe was also conducted in mice at doses up to 500 mg/kg/day (>150 X the human exposure at 10 mg daily based on $AUC_{0\text{-}24hr}$ for total ezetimibe). There were no statistically significant increases in tumor incidences in drug-treated rats or mice.

No evidence of mutagenicity was observed *in vitro* in a microbial mutagenicity (Ames) test with *Salmonella typhimurium* and *Escherichia coli* with or without metabolic activation. No evidence of clastogenicity was observed *in vitro* in a chromosomal aberration assay in human peripheral blood lymphocytes with or without metabolic activation. In addition, there was no evidence of genotoxicity in the *in vivo* mouse micronucleus test.

In oral (gavage) fertility studies of ezetimibe conducted in rats, there was no evidence of reproductive toxicity at doses up to 1,000 mg/kg/day in male or female rats (~7 X the human exposure at 10 mg daily based on $AUC_{0\text{-}24hr}$ for total ezetimibe).

14 CLINICAL STUDIES

Primary Hyperlipidemia in Adults

ZETIA reduces total-C, LDL-C, Apo B, and non-HDL-C in patients with hyperlipidemia. Maximal to near maximal response is generally achieved within 2 weeks and maintained during chronic therapy.

Monotherapy

In two multicenter, double-blind, placebo-controlled, 12-week trials in 1719 patients (age range 18 to 86 years, 52% females; 91% White, 5% Black or African American, 1% Asian, 3% other races mostly identified as Hispanic or Latino ethnicity) with primary hyperlipidemia, ZETIA significantly lowered total-C, LDL-C, Apo B, and non-HDL-C compared to placebo (see **Table 7**). Reduction in LDL-C was consistent across age, sex, and baseline LDL-C.

TABLE 7: Response to ZETIA in Patients with Primary Hyperlipidemia (Mean* % Change from Untreated Baseline†)

	Treatment Group	N	Total-C	LDL-C	Apo B	Non-HDL-C
Trial 1‡	Placebo	205	+1	+1	-1	+1
	Ezetimibe	622	-12	-18	-15	-16
Trial 2‡	Placebo	226	+1	+1	-1	+2
	Ezetimibe	666	-12	-18	-16	-16
Pooled Data‡ (Trials 1 & 2)	Placebo	431	0	+1	-2	+1
	Ezetimibe	1288	-13	-18	-16	-16

† Baseline - on no lipid-lowering drug.
‡ ZETIA significantly reduced total-C, LDL-C, Apo B, and non-HDL-C compared to placebo.

Combination with Statins: ZETIA Added to On-going Statin Therapy
In a multicenter, double-blind, placebo-controlled, 8-week trial, 769 patients (age range 22 to 85 years, 42% females; 90% White, 6% Black or African American, 1% Asian, 3% other races; and 2% identified as Hispanic or Latino ethnicity) with primary hyperlipidemia, known coronary heart disease or multiple cardiovascular risk factors who were already receiving statin monotherapy but who had not met their NCEP ATP II target LDL-C goal, were randomized to receive either ZETIA or placebo in addition to their on-going statin.

ZETIA, added to on-going statin therapy, significantly lowered total-C, LDL-C, Apo B, and non-HDL-C compared with a statin administered alone (see **Table 8**). LDL-C reductions induced by ZETIA were generally consistent across all statins.

TABLE 8: Response to Addition of ZETIA to On-Going Statin Therapy* in Patients with Hyperlipidemia (Mean % Change from Treated Baseline‡)

Treatment (Daily Dose)	N	Total-C	LDL-C	Apo B	Non-HDL-C
On-going Statin + Placebo§	390	-2	-4	-3	-3
On-going Statin + ZETIA§	379	-17	-25	-19	-23

* Patients receiving each statin: 40% atorvastatin, 31% simvastatin, 29% others (pravastatin, fluvastatin, cerivastatin, lovastatin).
‡ Baseline - on a statin alone.
§ ZETIA + statin significantly reduced total-C, LDL-C, Apo B, and non-HDL-C compared to statin alone.

Combination with Statins: ZETIA Initiated Concurrently with a Statin
In four multicenter, double-blind, placebo-controlled, 12-week trials, in 2,382 patients (age range 18 to 87 years, 57% female; 88% White, 5% Black or African American, 2% Asian, 5% other races mostly identified as Hispanic or Latino) with hyperlipidemia, ZETIA or placebo was administered alone or with various doses of atorvastatin, simvastatin, pravastatin, or lovastatin.

When all patients receiving ZETIA with a statin were compared to all those receiving the corresponding statin alone, ZETIA significantly lowered total-C, LDL-C, Apo B, and non-HDL-C compared to the statin administered alone. LDL-C reductions induced by ZETIA were generally consistent across all statins. (See footnote ‡, **Tables 9** to **12**.)

TABLE 9: Response to ZETIA and Atorvastatin Initiated Concurrently in Patients with Primary Hyperlipidemia (Mean % Change from Untreated Baseline†)

Treatment (Daily Dose)	N	Total-C	LDL-C	Apo B	Non-HDL-C
Placebo	60	+4	+4	+3	+4
ZETIA	65	-14	-20	-15	-18
Atorvastatin 10 mg	60	-26	-37	-28	-34
ZETIA + Atorvastatin 10 mg	65	-38	-53	-43	-49
Atorvastatin 20 mg	60	-30	-42	-34	-39
ZETIA + Atorvastatin 20 mg	62	-39	-54	-44	-50
Atorvastatin 40 mg	66	-32	-45	-37	-41
ZETIA + Atorvastatin 40 mg	65	-42	-56	-45	-52
Atorvastatin 80 mg	62	-40	-54	-46	-51
ZETIA + Atorvastatin 80 mg	63	-46	-61	-50	-58
Pooled data (All Atorvastatin Doses)‡	248	-32	-44	-36	-41
Pooled data (All ZETIA + Atorvastatin Doses)‡	255	-41	-56	-45	-52

† Baseline - on no lipid-lowering drug.
‡ ZETIA + all doses of atorvastatin pooled (10-80 mg) significantly reduced total-C, LDL-C, Apo B, and non-HDL-C compared to all doses of atorvastatin pooled (10-80 mg).

TABLE 10: Response to ZETIA and Simvastatin Initiated Concurrently in Patients with Primary Hyperlipidemia (Mean % Change from Untreated Baseline†)

Treatment (Daily Dose)	N	Total-C	LDL-C	Apo B	Non-HDL-C
Placebo	70	-1	-1	0	-1
ZETIA	61	-13	-19	-14	-17
Simvastatin 10 mg	70	-18	-27	-21	-25
ZETIA + Simvastatin 10 mg	67	-32	-46	-35	-42
Simvastatin 20 mg	61	-26	-36	-29	-33
ZETIA + Simvastatin 20 mg	69	-33	-46	-36	-42
Simvastatin 40 mg	65	-27	-38	-32	-35
ZETIA + Simvastatin 40 mg	73	-40	-56	-45	-51
Simvastatin 80 mg	67	-32	-45	-37	-41
ZETIA + Simvastatin 80 mg	65	-41	-58	-47	-53
Pooled data (All Simvastatin Doses)‡	263	-26	-36	-30	-34
Pooled data (All ZETIA + Simvastatin Doses)‡	274	-37	-51	-41	-47

† Baseline - on no lipid-lowering drug.
‡ ZETIA + all doses of simvastatin pooled (10-80 mg) significantly reduced total-C, LDL-C, Apo B, and non-HDL-C compared to all doses of simvastatin pooled (10-80 mg).

TABLE 11: Response to ZETIA and Pravastatin Initiated Concurrently in Patients with Primary Hyperlipidemia (Mean % Change from Untreated Baseline†)

Treatment (Daily Dose)	N	Total-C	LDL-C	Apo B	Non-HDL-C
Placebo	65	0	-1	-2	0
ZETIA	64	-13	-20	-15	-17
Pravastatin 10 mg	66	-15	-21	-16	-20
ZETIA + Pravastatin 10 mg	71	-24	-34	-27	-32
Pravastatin 20 mg	69	-15	-23	-18	-20
ZETIA + Pravastatin 20 mg	66	-27	-40	-31	-36
Pravastatin 40 mg	70	-22	-31	-26	-28
ZETIA + Pravastatin 40 mg	67	-30	-42	-32	-39
Pooled data (All Pravastatin Doses)‡	205	-17	-25	-20	-23
Pooled data (All ZETIA + Pravastatin Doses)‡	204	-27	-39	-30	-36

† Baseline - on no lipid-lowering drug.
‡ ZETIA + all doses of pravastatin pooled (10-40 mg) significantly reduced total-C, LDL-C, Apo B, and non-HDL-C compared to all doses of pravastatin pooled (10-40 mg).

TABLE 12: Response to ZETIA and Lovastatin Initiated Concurrently in Patients with Primary Hyperlipidemia (Mean % Change from Untreated Baseline†)

Treatment (Daily Dose)	N	Total-C	LDL-C	Apo B	Non-HDL-C
Placebo	64	+1	0	+1	+1
ZETIA	72	-13	-19	-14	-16
Lovastatin 10 mg	73	-15	-20	-17	-19
ZETIA + Lovastatin 10 mg	65	-24	-34	-27	-31
Lovastatin 20 mg	74	-19	-26	-21	-24
ZETIA + Lovastatin 20 mg	62	-29	-41	-34	-39
Lovastatin 40 mg	73	-21	-30	-25	-27
ZETIA + Lovastatin 40 mg	65	-33	-46	-38	-43
Pooled data (All Lovastatin Doses)‡	220	-18	-25	-21	-23
Pooled data (All ZETIA + Lovastatin Doses)‡	192	-29	-40	-33	-38

† Baseline - on no lipid-lowering drug.
‡ ZETIA + all doses of lovastatin pooled (10-40 mg) significantly reduced total-C, LDL-C, Apo B, and non-HDL-C compared to all doses of lovastatin pooled (10-40 mg).

Combination with Fenofibrate

In a multicenter, double-blind, placebo-controlled, clinical trial in patients with mixed hyperlipidemia, 625 patients (age range 20 to 76 years, 44% female; 79% White, 1% Black or African American, 20% other races; and 11% identified as Hispanic or Latino ethnicity) were treated for up to 12 weeks and 576 for up to an additional 48 weeks. Patients were randomized to receive placebo, ZETIA alone, 160 mg fenofibrate alone, or ZETIA and 160 mg fenofibrate in the 12-week trial. After completing the 12-week trial, eligible patients were assigned to ZETIA coadministered with fenofibrate or fenofibrate monotherapy for an additional 48 weeks.

ZETIA coadministered with fenofibrate significantly lowered total-C, LDL-C, Apo B, and non-HDL-C compared to fenofibrate administered alone (see **Table 13**).

TABLE 13: Response to ZETIA and Fenofibrate Initiated Concurrently in Patients with Mixed Hyperlipidemia (Mean % Change from Untreated Baseline† at 12 weeks)

Treatment (Daily Dose)	N	Total-C	LDL-C	Apo B	Non-HDL-C
Placebo	63	0	0	-1	0
ZETIA	185	-12	-13	-11	-15
Fenofibrate 160 mg	188	-11	-6	-15	-16
ZETIA + Fenofibrate 160 mg	183	-22	-20	-26	-30

† Baseline - on no lipid-lowering drug.

The changes in lipid endpoints after an additional 48 weeks of treatment with ZETIA coadministered with fenofibrate or with fenofibrate alone were consistent with the 12-week data displayed above.

HeFH in Pediatric Patients

The effects of ZETIA coadministered with simvastatin (n=126) compared to simvastatin monotherapy (n=122) have been evaluated in males and females with HeFH. In a multicenter, double-blind, controlled trial followed by an open-label phase, 142 males and 106 postmenarchal females, 10 to 17 years of age (mean age 14.2 years, 43% females, 82% White, 4% Asian, 2% Black or African American, 13% multi-racial; 14% identified as Hispanic or Latino ethnicity) with HeFH were randomized to receive either ZETIA coadministered with simvastatin or simvastatin monotherapy. Inclusion in the trial required 1) a baseline LDL-C level between 160 and 400 mg/dL and 2) a medical history and clinical presentation consistent with HeFH. The mean baseline LDL-C value was 225 mg/dL (range: 161 to 351 mg/dL) in the ZETIA coadministered with simvastatin group compared to 219 mg/dL (range: 149 to 336 mg/dL) in the simvastatin monotherapy group. The patients received coadministered ZETIA and simvastatin (10 mg, 20 mg, or 40 mg) or simvastatin monotherapy (10 mg, 20 mg, or 40 mg) for 6 weeks, coadministered ZETIA and 40-mg simvastatin or 40-mg simvastatin monotherapy for the next 27 weeks, and open-label coadministered ZETIA and simvastatin (10 mg, 20 mg, or 40 mg) for 20 weeks thereafter.

The results of the trial at Week 6 are summarized in **Table 14**. Results at Week 33 were consistent with those at Week 6.

TABLE 14: Mean Percent Difference at Week 6 Between the Pooled ZETIA Coadministered with Simvastatin Group and the Pooled Simvastatin Monotherapy Group in Adolescent Patients with HeFH

	Total-C	LDL-C	Apo B	Non-HDL-C
Mean percent difference between treatment groups	-12%	-15%	-12%	-14%
95% Confidence Interval	(-15%, -9%)	(-18%, -12%)	(-15%, -9%)	(-17%, -11%)

HoFH in Adults and Pediatric Patients

A trial was conducted to assess the efficacy of ZETIA in the treatment of HoFH. This double-blind, randomized, 12-week trial enrolled 50 patients (age range 11 to 74 years, 58% female; 90% White, 2% Black or African American, 8% other races identified as Hispanic or Latino) with a clinical and/or genotypic diagnosis of HoFH, with or without concomitant LDL apheresis, already receiving atorvastatin or simvastatin (40 mg). Patients were randomized to one of three treatment groups, atorvastatin or simvastatin (80 mg), ZETIA administered with atorvastatin or simvastatin (40 mg), or ZETIA administered with atorvastatin or simvastatin (80 mg). Due to decreased bioavailability of ezetimibe in patients concomitantly receiving cholestyramine *[see Drug Interactions (7)]*, ezetimibe was dosed at least 4 hours before or after administration of resins. Mean baseline LDL-C was 341 mg/dL in those patients randomized to atorvastatin 80 mg or simvastatin 80 mg alone and 316 mg/dL in the group randomized to ZETIA plus atorvastatin 40 or 80 mg or simvastatin 40 or 80 mg. ZETIA, administered with atorvastatin or simvastatin (40- and 80-mg

statin groups, pooled), significantly reduced LDL-C (21%) compared with increasing the dose of simvastatin or atorvastatin monotherapy from 40 to 80 mg (7%). In those treated with ZETIA plus 80-mg atorvastatin or with ZETIA plus 80-mg simvastatin, LDL-C was reduced by 27%.

Homozygous Sitosterolemia (Phytosterolemia) in Adults and Pediatric Patients
A trial was conducted to assess the efficacy of ZETIA in the treatment of homozygous sitosterolemia. In this multicenter, double-blind, placebo-controlled, 8-week trial, 37 patients (age range 9 to 72 years, 65% females; 89% White, 3% Asian, 8% other races identified as Hispanic or Latino) with homozygous sitosterolemia with elevated plasma sitosterol levels (>5 mg/dL) on their current therapeutic regimen (diet, bile-acid-binding resins, statins, ileal bypass surgery and/or LDL apheresis), were randomized to receive ZETIA (n=30) or placebo (n=7). Due to decreased bioavailability of ezetimibe in patients concomitantly receiving cholestyramine *[see Drug Interactions (7)]*, ZETIA was dosed at least 2 hours before or 4 hours after resins were administered. Excluding the one subject receiving LDL apheresis, ZETIA significantly lowered plasma sitosterol and campesterol, by 21% and 24% from baseline, respectively. In contrast, patients who received placebo had increases in sitosterol and campesterol of 4% and 3% from baseline, respectively. For patients treated with ZETIA, mean plasma levels of plant sterols were reduced progressively over the course of the trial. Reductions in sitosterol and campesterol were consistent between patients taking ZETIA concomitantly with bile acid sequestrants (n=8) and patients not on concomitant bile acid sequestrant therapy (n=21).

16 HOW SUPPLIED/STORAGE AND HANDLING

ZETIA 10 mg tablets are white to off-white, capsule-shaped, and debossed with “414” on one side and are supplied as follows:

Package Size	NDC
Bottle of 30 tablets	78206-178-01

Store ZETIA at room temperature between 68ºF to 77ºF (20ºC to 25ºC). Protect from moisture.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-Approved Patient Labeling (Patient Information).

Inform patients that ZETIA may cause liver enzyme elevations *[see Warnings and Precautions (5.2)]*.

Muscle Pain
Advise patients that ZETIA may cause myopathy and rhabdomyolysis. Inform patients that the risk is also increased when taking certain types of medication and they should discuss all medication, both prescription and over the counter, with their healthcare provider. Instruct patients to promptly report any unexplained muscle pain, tenderness or weakness particularly if accompanied by malaise or fever *[see Warnings and Precautions (5.3), and Drug Interactions (7)]*.

Pregnancy
Advise patients to inform their healthcare provider of a known or suspected pregnancy to discuss if ZETIA should be discontinued *[see Use in Specific Populations (8.1)]*.

Breastfeeding
Advise patients who have a lipid disorder and are breastfeeding to discuss the options with their healthcare provider *[see Use in Specific Populations (8.2)]*.

Missed Dose
Instruct patients to take ZETIA only as prescribed. If a dose is missed, it should be taken as soon as possible. Advise patients not to double their next dose.

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For patent information: www.organon.com/our-solutions/patent/

uspi-og0653-t-2307r002

PATIENT INFORMATION
ZETIA [zeh-TEE-uh]
(ezetimibe)
tablets, for oral use

Read this information carefully before you start taking ZETIA® and each time you get more ZETIA. There may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment. If you have any questions about ZETIA, ask your doctor. Only your doctor can determine if ZETIA is right for you.

What is ZETIA?

ZETIA is a medicine used with a cholesterol lowering diet:

- and with other cholesterol medicines called a statin, or alone (when additional cholesterol lowering treatments are not possible), to lower elevated low-density lipoprotein cholesterol (LDL-C) or bad cholesterol in adults with primary hyperlipidemia (too many fats in your blood), including heterozygous familial hypercholesterolemia (HeFH). HeFH is an inherited condition that causes high levels of bad cholesterol.
- and with a statin to lower LDL-C in adults and children 10 years of age and older with HeFH.
- and with a medicine called fenofibrate to lower elevated LDL-C in adults with mixed hyperlipidemia.
- to lower elevated sitosterol and campesterol levels in adults and in children 9 years of age and older with homozygous familial sitosterolemia (a rare inherited condition that prevents the body from getting rid of cholesterol from plants).

ZETIA is also used:

- with a statin and other cholesterol lowering treatments to lower elevated LDL-C levels in adults and patients 10 years of age and older with homozygous familial hypercholesterolemia (HoFH). HoFH is an inherited condition that causes high levels of bad cholesterol.

The safety and effectiveness of ZETIA has not been established in children:

- younger than 10 years of age with HeFH or HoFH.
- younger than 9 years of age with homozygous familial sitosterolemia.
- with other types of hyperlipemia.

Do not take ZETIA:

- if you are allergic to ezetimibe or any of the ingredients in ZETIA. See the end of this Patient Information leaflet for a complete list of ingredients in ZETIA. Stop using ZETIA and get medical help right away if you have symptoms of a serious allergic reaction including:
  - swelling of the face, tongue, or throat
  - difficulty breathing or swallowing
  - fainting or feeling dizzy
  - very fast heartbeat
  - severe skin rash, hives, and itching
  - flu-like symptoms including fever, sore throat, cough, tiredness, and joint pain
- with certain statins, fenofibrate, or other LDL-C lowering medicines if your healthcare provider has told you not to take them.

Before you take ZETIA, tell your healthcare provider about all your medical conditions, including if you:

- have liver problems. ZETIA may not be right for you.
- are pregnant or plan to become pregnant. It is not known if ZETIA will harm your unborn baby. You and your healthcare provider should decide if you will take ZETIA while you are pregnant.
- are breastfeeding. It is not known if ZETIA passes into your breast milk. You and your healthcare provider should decide the best way to feed your baby if you take ZETIA.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Talk to your healthcare provider before you start taking any new medicines.

Taking ZETIA with certain other medicines may affect each other causing side effects. ZETIA may affect the way other medicines work, and other medicines may affect how ZETIA works.

Especially tell your healthcare provider if you take:

- cyclosporine (a medicine for your immune system)
- fibrates (medicine for lowering cholesterol)
- bile acid sequestrants (medicine for lowering LDL-C)

Ask your healthcare provider or pharmacist for a list of medicines if you are not sure. Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How should I take ZETIA?

- Take ZETIA 1-time each day, with or without food. It may be easier to remember to take your dose if you do it at the same time every day, such as with breakfast, dinner, or at bedtime. If you also take another medicine to reduce your cholesterol, ask your healthcare provider if you can take them at the same time.
- If you miss a dose, take it as soon as you remember. If you do not remember until it is time for your next dose, skip the missed dose and go back to your regular schedule. Do not take 2 doses of ZETIA at the same time.
- While taking ZETIA, continue to follow your cholesterol-lowering diet and to exercise as your healthcare provider told you to.
- If you take a medicine called a bile acid sequestrant, take ZETIA at least 2 hours before or 4 hours after you take the bile acid sequestrant.
- Your healthcare provider may do blood tests to check your LDL-C levels as early as 4 weeks after starting treatment with ZETIA.
- In case of an overdose, get medical help or contact a live Poison Center expert right away at 1-800-222-1222. Advice is also available online at poisonhelp.org.

What are the possible side effects of ZETIA?
ZETIA may cause serious side effects including:

- **increased liver enzymes**. An increase in liver enzymes can happen in people taking ZETIA alone or with statins. Your healthcare provider may do blood tests to check your liver before and during treatment. Your healthcare provider may need to change or stop your treatment with ZETIA because of an increase in liver enzymes.
- **muscle pain, tenderness, and weakness (myopathy)**. Muscle problems, including muscle breakdown (rhabdomyolysis) can happen. Tell your healthcare provider right away if:
  - you have unexplained muscle pain, tenderness, weakness, feel more tired than usual, or fever.
  - you have muscle problems that do not go away even after your healthcare provider has advised you to stop taking ZETIA. Your healthcare provider may do further tests to diagnose the cause of your muscle problems.

  Your chances of getting muscle problems are higher if you are also taking statins or fibrates.

The most common side effects of ZETIA taken alone include:

- upper respiratory tract infection
- diarrhea
- joint pain
- inflammation of the sinuses
- pain in arms or legs
- feeling tired
- flu-like symptoms

The most common side effects of ZETIA taken with a statin include:

- runny nose, sore throat
- muscle aches and pains
- upper respiratory tract infection
- joint pain
- diarrhea
- back pain
- flu-like symptoms
- pain in arms or legs
- feeling tired

Tell your healthcare provider if you have any side effect that bothers you or does not go away. These are not all the possible side effects of ZETIA.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store ZETIA?

- Store ZETIA at room temperature between 68ºF to 77ºF (20ºC to 25ºC).
- Protect from moisture.

Keep ZETIA and all medicines out of the reach of children.

General information about safe and effective use of ZETIA.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use ZETIA for a condition for which it was not prescribed. Do not give ZETIA to other people, even if they have the same symptoms you have. It may harm them.

You can ask your pharmacist or healthcare provider for information about ZETIA that is written for health professionals.

What are the ingredients in ZETIA?

Active ingredient: ezetimibe.

Inactive ingredients: croscarmellose sodium NF, lactose monohydrate NF, magnesium stearate NF, microcrystalline cellulose NF, povidone USP, and sodium lauryl sulfate NF.

Manuf. for: Organon LLC, a subsidiary of
ORGANON & Co.,
Jersey City, NJ 07302, USA

For patent information: www.organon.com/our-solutions/patent/

For more information, go to www.organon.com/our-focus/products-list/ or call 1-844-674-3200.

usppi-og0653-t-2307r001

This Patient Informa ion has been approved by the U.S. Food and Drug Administration.

Revised: 7/2023

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021445Orig1s042

CLINICAL REVIEW(S)

Prior Approval Labeling Supplement-Clinical Memo

NDA:	21445/SD1832/S-42
Sponsor:	Organon LLC
Drug name:	Zetia (ezetimibe) tablets
Date of submission:	May 15, 2018 (SD 1832) and multiple updated label submissions up to July 6, 2023 (SD 1860)
Type of submission:	Prior Approval Supplement #42
Review Division:	Diabetes, Lipid Disorders, and Obesity (DDLO)
Clinical Reviewer:	Eileen Craig, MD
Deputy Director for Safety:	Monika Houstoun, Pharm.D., M.P.H
Review Date:	7/10/2023
Project Manager:	Martin White

PRIOR APPROVAL SUPPLEMENT (PAS) 42
Pregnancy and Lactation Labeling Rule (PLLR) Update

This supplemental application proposes changes to the prescribing information for Zetia in accord with the Pregnancy and Lactation Labeling Rule (PLLR) as described in the December 2014 Guidance for Industry.

(b) (4)

They each provide for updating the package insert into PLLR format. DMEP (now DDLO) consulted the Division of Pediatric and Maternal Health (DPMH) on May 30, 2018, to assist with the Pregnancy and Lactation subsections of labeling. The reader is referred to the full Maternal Health review by Jane Liedtka, MD, in DARRTS dated February 28, 2019, Reference ID: 4396340.

Additional background information for this PLLR and general label updates for Zetia includes:

- Section 1 Indications and Usage
  - Use of ezetimibe as monotherapy in primary hyperlipidemia: Primary hyperlipidemia indication was revised to clarify that monotherapy use of ezetimibe is only appropriate when other additional concomitant LDL-C lowering therapy (i.e., statins, PCSK9 inhibitor therapy) is not possible. The goal of this modification is to minimize or de-emphasize the monotherapy indication as 20% LDL reduction achieved with ezetimibe as

monotherapy does not meet minimal LDL-C reduction threshold as per 2018 ACC/AHA guidelines.[1]

- Pediatric patients with HeFH: The HeFH indication was revised to include use of ezetimibe in combination with a statin in pediatric patients 10 years and older. Refer to Vytorin review (NDA 21687 S-23) in DARRTS dated 6/10/2008 and Zetia review (NDA 21445 S-20) in DARRTS dated 6/5/2008. At the time of review in 2008, the Division stated that before this application could be approved, we would need to review ENHANCE and IMPROVE-IT. Review of those trials resolved pending concerns. Trial results for pediatric patients were thus moved from Section 8.4 to Section 14 of the PI.
- Pediatric patients with HoFH: The HoFH indication was revised to clarify use of ezetimibe in combination with a statin in pediatric patients 10 years and older. The previous indication was for subjects with HoFH and did not specify adults vs pediatric patients. From the original NDA in 2002: Treatment experience with Zetia in the pediatric population is limited to 7 patients, ages 11-17 years of age in the HoFH trial. There were 2 subjects < 18 years treated with 40 mg atorvastatin + ezetimibe (EZ); 2 subjects < 18 years treated with 80 mg atorvastatin + EZ; 1 subject < 18 years treated with 40 mg simvastatin + EZ; 2 subjects on atorvastatin 80 mg. After a 12 week in duration randomized, controlled phase, the subjects entered an open-label extension (OLE) phase of ezetimibe+statin therapy. Median exposure was 6 months for the entire group of 50 subjects. There is also safety and efficacy data from a pediatric population with a similar disease (HeFH) to support the indication for 10 years and older.
- Removal of non-LDL-C parameters from the indications described above.
- Pediatric patients with homozygous sitosterolemia: The homozygous sitosterolemia indication was revised to clarify use of ezetimibe in pediatric patients 9 years and older. The previous indication was for subjects with homozygous sitosterolemia and did not specify adults vs pediatric patients. The original review from 2002: 4 patients, ages 9-17 years, in the sitosterolemia study. Duration of exposure in the double-blind trial, 8 weeks. There is also safety data from a pediatric population (10 years and older) with HeFH to support the indication.
- Combination use statement: The combination use statement was broadened from statins or fenofibrate to a statement that includes other LDL-C lowering therapies, such as PCSK9 inhibitor therapies and bempedoic acid. We also included a statement in Sections 1, 4, and 5 referring to the PI of the concomitantly used statin, fenofibrate, or other

[1] Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, Braun LT, de Ferranti S, Faiella-Tommasino J, Forman DE, Goldberg R, Heidenreich PA, Hlatky MA, Jones DW, Lloyd-Jones D, Lopez-Pajares N, Ndumele CE, Orringer CE, Peralta CA, Saseen JJ, Smith SC Jr, Sperling L, Virani SS, Yeboah J. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2019 Jun 25;73(24):3168-3209. doi: 10.1016/j.jacc.2018.11.002. Epub 2018 Nov 10. Erratum in: J Am Coll Cardiol. 2019 Jun 25;73(24):3234-3237. PMID: 30423391.

LDL-C lowering therapy for all of its conditions of use, and removal of statin- or fenofibrate-specific recommendations from the PI.
    - The Limitations of Use statement (The effect of ZETIA on cardiovascular morbidity and mortality has not been determined) was removed as there is no concern that Zetia may increase CV risk, given the results of the IMPROVE-IT trial[2])
- Section 2 Dosage and Administration
    - Removal of information that was specific to concomitant use with a statin or fenofibrate
    - Added in a statement to assess LDL-C when clinically appropriate, as early as 4 weeks after initiating ZETIA. This is consistent with the statin labels. In some statin labels, the recommendation to assess LDL-C as early as 2 to 4 weeks after initiating statin was changed to 4 weeks to simplify and standardized the recommendation across the statin class and to be more consistent with national guideline recommendations for the treatment of hypercholesterolemia.
- Section 4 Contraindications: Removal of information that was specific to concomitant use with a statin
- Section 5 Warnings & Precautions: Removal of information that was specific to concomitant use with a statin or fenofibrate
- Section 6, adverse reactions, was revised to remove duplicative information that was stated in text and in tables. Tables 1 and 2 were revised to reflect organization by preferred terms in descending order (system organ class categories were removed). Post-marketing experience, Section 6.2, was also updated.
- Section 7 Drug Interactions was updated using a tabular format.
- Section 8—extensive revisions were made throughout to update 8.1 Pregnancy, 8.2 Lactation, 8.4 Pediatric Use (to include information on the indications for HoFH, HeFH, and homozygous sitosterolemia), 8.5 Geriatric Use, 8.6 Renal Impairment [information on adverse reactions in the Study of Heart and Renal Protection (SHARP) were removed as this information is in the Vytorin label and does not need to be repeated in the Zetia label], and 8.7 Hepatic Impairment.
- Section 10 Overdosage—information on clinical studies using greater than approved doses of ezetimibe was removed.
- Section 12 Clinical Pharmacology
    - Section 12.1 Mechanism of Action: This section was edited for conciseness and clarity and to align with other recent approvals.
    - Section 12.2 Pharmacodynamics: Edits were made to remove language that is too broad in scope and not focused on the relevant pharmacodynamic aspects specific to Zetia. Relevant lipid parameter changes for Zetia's indication include LDL, TC, non-HDL, and ApoB. Information on TG and HDL was removed.
    - Section 12.3 Pharmacokinetics: Renal impairment information that was in Section 8.5 Geriatric Use was appropriately relocated to Section 12.3.

[2] Cannon CP, Blazing MA, Giugliano RP, et al. Ezetimibe added to statin therapy after acute coronary syndromes. N Engl J Med 2015;372:2387-2397

- Section 13.2 Animal Toxicology and/or Pharmacology was removed as the inclusion of animal data is no longer warranted, based on the availability of sufficient human data to address the clinical relevance of these findings. In addition, the pharmacodynamics/efficacy and drug interactions have been addressed elsewhere in the label.
- Section 14 Clinical Studies:
    - Relevant lipid parameter changes for Zetia's indication include LDL, TC, non-HDL, and ApoB. Information on TG and HDL was removed throughout this section.
    - Clinical trial information for pediatric patients with HeFH was moved from Section 8.4 to Section 14.
    - The HoFH clinical trial information was updated to clarify the pediatric age range.
    - The homozygous sitosterolemia clinical trial information was updated to clarify the pediatric age range.
    - The Limitations of Use statement (The effect of ZETIA on cardiovascular morbidity and mortality has not been determined) was removed as there is no concern that Zetia may increase CV risk, given the results of the IMPROVE-IT trial[2])
- Sections 16 and 17: Edits were made to conform with current labeling guidance.

With this submission dated July 6, 2023, the Applicant accepts all of FDA's most recent recommendations for labeling and submits the with revision marks (WRM) and the clean running text (CRT) of the USPI. One minor change will be requested from the Applicant: changing "Advice" to "Advise" in the Section 17 heading.

APPEARS THIS WAY ON ORIGINAL

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021445Orig1s042

OTHER REVIEW(S)

Division of Regulatory Operations for Cardiology, Hematology, Endocrinology, and Nephrology

REGULATORY PROJECT MANAGER LABELING REVIEW

Application: NDA 021445/S-042

Name of Drug: Zetia (ezetimibe) tablets

Applicant: Organon LLC, a subsidiary of Organon & Co.

Labeling Reviewed

Submission Date: May 15, 2018

Receipt Date: May 15, 2018

Background and Summary Description:
A prior approval supplement (PAS), Supplement-42, was submitted on May 15, 2018, which proposed revisions to the prescribing information (PI) in accordance with the Pregnancy and Lactation Labeling Rule (PLLR).

Review

This project manager compared the PI and Patient Package Insert submitted on July 6, 2023, to the currently approved version, approved with supplement 33 on January 24, 2012, using the MS Word electronic comparison function. A copy of this comparison document is appended to this review.

For a full list of recommendations, please see the following reviews in DARRTS:

- Clinical Review for Supplement 42 dated July 11, 2023, (Eileen Craig, MD, Clinical Reviewer, Team Leader, Monika Houstoun, PharmD, MPH, Deputy Division Director of Safety)
    - Listed below are significant updates:
        - Revision to Section 1- *Indications and Usage* to clarify that use of ezetimibe as monotherapy in primary hyperlipidemia is appropriate when other additional concomitant LDL-C lowering therapy (i.e., statins, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor therapy) is not possible; clarify the indications for pediatric patients with familial hypercholesterolemia and homozygous sitosterolemia; and removal of the Limitations of Use statement.
        - Update to Section 2-*Dosage and Administration*

- Revision to Section 4 – *Contraindications* to remove information that was specific to statin therapy
- Revisions to Section 5 - *Warnings and Precautions* to remove information that was specific to statin or fenofibrate therapy

- Office of Prescription Drug Promotion (OPDP) review dated: May 2, 2023 (Ankur Kalola, PharmD, Regulatory Review Officer (OPDP))

- Division of Medical Policy Programs (DMPP) review dated: May 1, 2023 (Maria T Nguyen, MSHS, BSN, RN, Patient Labeling Reviewer, Division of Medical Policy Programs, (DMPP), Marcia Williams PhD, Team Leader, Patient Labeling Reviewer (DMPP); Ankur Kalola, PharmD, Regulatory Review Officer (OPDP).

- Division of Pediatric and Maternal Health (DPMH), Maternal health review dated February 28, 2019 (Jane Liedtka, MD, Medical Officer, Miriam Dinatale, MD, Team Leader, Lynne Yao, MD, Division Director)

- A drug safety communication, posted 7/20/2021, requesting revisions to the information about use in pregnancy in the PI of the entire class of statin medicines.

https://www.fda.gov/drugs/drug-safety-and-availability/fda-requests-removal-strongest-warning-against-using-cholesterol-lowering-statins-during-pregnancy

Recommendations

The labeling was reviewed and found acceptable. This supplement is ready for approval. The Agency should issue an approval letter for this supplement.

Regulatory Project Manager	Date
Chief, Project Management Staff	Date

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

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

Memorandum

Date: **May 2, 2023**

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

Melinda Wilson, Associate Director for Labeling, DDLO

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

CC: Susannah O'Donnell, Team Leader, OPDP

Subject: OPDP Labeling Comments for ZETIA® (ezetimibe) tablets, for oral use

NDA: 21445, S-42

Background:

In response to DDLO's consult request dated May 30, 2018, OPDP has reviewed the proposed Prescribing Information (PI) and Patient Package Insert (PPI) for Zetia. This supplement provides for changes to the labeling to modernize and comply with the PLLR rule.

PI & PPI

OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on April 25, 2023, and our comments are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed for the proposed PPI, and comments were sent under separate cover on May 1, 2023.

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

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

PATIENT LABELING REVIEW

Date:	April 28, 2023
To:	Martin White, Regulatory Project Manager **Division of Diabetes, Lipid Disorders, and Obesity (DDLO)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Maria Nguyen, MSHS, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Ankur Kalola, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	ZETIA (ezetimibe)
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	NDA 021445
Supplement Number:	042
Applicant:	Organon LLC, a subsidiary of Organon and Company

1 INTRODUCTION

On May 15, 2018, Organon LLC, a subsidiary of Organon and Company, submitted for the Agency's review a Prior Approval Supplement (PAS)-Labeling for their approved New Drug Application (NDA) #021445/S-042 for ZETIA (ezetimibe). This supplemental application proposes to comply with the Pregnancy and Lactation Labeling Rule (PLLR). In addition, the Division of Diabetes, Lipid Disorders, and Obesity (DDLO) is in the process of updating all the statin labels to modernize them and better communicate use and important safety information. As a result of this modernization, the Patient Package Insert (PPI) is also being updated.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Diabetes, Lipid Disorders, and Obesity (DDLO) on April 18, 2023 and May 30, 2018, respectively, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for ZETIA (ezetimibe) tablets, for oral use.

2 MATERIAL REVIEWED

- Draft ZETIA (ezetimibe) PPI received on May 15, 2018, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on April 18, 2023.
- Draft ZETIA (ezetimibe) Prescribing Information (PI) received on May 15, 2018, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on April 18, 2023.
- Approved VYTORIN (ezetimbe and simvastatin) comparator labeling dated September 25, 2020.
- Approved ROSZET (rosuvastatin and ezetimibe) comparator labeling dated March 23, 2021.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level and have a reading ease score of at least 60%.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)

- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI is consistent with the approved labeling where applicable.

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

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

Please let us know if you have any questions.

APPEARS THIS
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MARIA T NGUYEN
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DMPP-OPDP review of ezetimibe (ZETIA) NDA 021445 S-042 PPI

ANKUR S KALOLA
04/29/2023 09:27:14 AM

MARCIA B WILLIAMS
05/01/2023 06:47:53 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
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: February 27, 2019 **Date consulted:** May 30, 2018

From: Jane Liedtka M.D., Medical Officer (MO), Maternal Health
Division of Pediatric and Maternal Health (DPMH)

Through: Miriam Dinatale, DO, Team Leader, Maternal Health
Division of Pediatric and Maternal Health

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

To: Martin White, M.S.
Regulatory Health Project Manager (RPM)
Division of Metabolism & Endocrinology Products (DMEP)

Drug: Zocor (simvastatin)/Zetia (ezetimibe)/ (b) (4)

NDA: 19766 S-099/21445 S-042/ (b) (4)

Applicant: Merck

Subject: Pregnancy and Lactation Labeling [Prior Approval Supplements (PASs), Pregnancy and Lactation Labeling Rule (PLLR) conversions]

Approved Indications:
ZOCOR is an HMG-CoA reductase inhibitor (statin) indicated as an adjunctive therapy to diet to:

- Reduce the risk of total mortality by reducing CHD deaths and reduce the risk of non-fatal myocardial infarction, stroke, and the need for revascularization procedures in patients at high risk of coronary events.

- Reduce elevated total-C, LDL-C, Apo B, TG and increase HDL-C in patients with primary hyperlipidemia (heterozygous familial and non-familial) and mixed dyslipidemia.
- Reduce elevated TG in patients with hypertriglyceridemia and reduce TG and VLDL-C in patients with primary dysbetalipoproteinemia.
- Reduce total-C and LDL-C in adult patients with homozygous familial hypercholesterolemia.
- Reduce elevated total-C, LDL-C, and Apo B in boys and post-menarchal girls, 10 to 17 years of age with heterozygous familial hypercholesterolemia after failing an adequate trial of diet therapy.

Limitations of Use

- ZOCOR has not been studied in Fredrickson Types I and V dyslipidemias. (1.4)

ZETIA is an inhibitor of intestinal cholesterol (and related phytosterol) absorption indicated as an adjunct to diet to:

- Reduce elevated total-C, LDL-C, Apo B, and non-HDL-C in patients with primary hyperlipidemia, alone or in combination with an HMG-CoA reductase inhibitor (statin)
- Reduce elevated total-C, LDL-C, Apo B, and non-HDL-C in patients with mixed hyperlipidemia in combination with fenofibrate
- Reduce elevated total-C and LDL-C in patients with homozygous familial hypercholesterolemia (HoFH), in combination with atorvastatin or simvastatin
- Reduce elevated sitosterol and campesterol in patients with homozygous sitosterolemia (phytosterolemia)

Limitations of Use

- The effect of ZETIA on cardiovascular morbidity and mortality has not been determined.
- ZETIA has not been studied in Fredrickson Type I, III, IV, and V dyslipidemias.

(b) (4)

[redacted]

Materials Reviewed[1]:

- Applicant's submitted background package for ZOCOR, NDA 19766 S-099, 5/15/18
- Applicant's submitted background package for ZETIA, NDA 21445 S-042, 5/15/18

(b) (4)

[redacted]

[1] The three previous DPMH reviews for Altoprev, Zypitamag and Pravachol were a part of the materials reviewed but were not a source relied upon for the labeling recommendations below. Although there is overlap in the labeling proposed for these previous reviews and that being proposed here, the labeling recommendations in this review are based on DPMH's independent analysis of the underlying data.

- DPMH review of Altoprev (lovastatin extended-release), N21316/S-035. Christos Mastroyannis, M.D. 2/8/18. DARRTS Reference ID 4219958[2, 3].
- DPMH review of Zypitamag (pitavastatin), N 208379. Carrie Ceresa, Pharm D., MPH. 6/22/17. DARRTS Reference ID 4115095[4, 5].
- DPMH review of Pravachol (pravastatin sodium), N 208379. Miriam Dinatale, D.O. 10/30/15. DARRTS Reference ID 3841077[6, 7].

INTRODUCTION AND BACKGROUND

(b) (4)

They each provide for updating the package insert into PLLR format. DMEP consulted DPMH on 5/30/18, to assist with the Pregnancy and Lactation subsections of labeling.

DPMH has written multiple consult reviews for HMG-CoA reductase inhibitors (also known as statins)[2, 3, 4]. The reader is referred to the previous DPMH reviews on statins for background information regarding the published studies describing the use of statins, as a class, during pregnancy, lactation and the effect of statins on fertility.

Current State of the Labeling

Proprietary Name	Zocor	Zetia	(b) (4)
Non-Proprietary Name	simvastatin	ezetimibe	
NDA#	21445	19766	
Original approval date	12/23/91	10/25/02	
Date of approval for most recent labeling	2/28/18	2/26/2016	
PLR	Yes (Y)	Y	
PLLR	No (N)	N	
Contraindication to pregnancy	Y	Y (When used with statins)	
Contraindication to lactation	Y	Y (When used with statins)	
Relevant Entries in HPI under "Use in Specific Populations"	N	N	
Relevant Boxed Warnings	N	N	

[2] DPMH review of Altoprev (lovastatin extended-release), N21316/S-035 Christos Mastroyannis, M.D. 2/8/18. DARRTS Reference ID 4219958

[3] The Altoprev review was part of the materials reviewed but was not a source relied upon for the labeling recommendations below.

[4] DPMH review of Zypitamag (pitavastatin), N 208379 Carrie Ceresa, Pharm D., MPH. 6/22/17. DARRTS Reference ID 4115095

[5] The Zypitamag review was part of the materials reviewed but was not a source relied upon for the labeling recommendations below.

[6] DPMH review of Pravachol (pravastatin sodium), N 208379 Miriam Dinatale, D.O. 10/30/15. DARRTS Reference ID 3841077

[7] The Pravachol review was part of the materials reviewed but was not a source relied upon for the labeling recommendations below.

			(b) (4)
Relevant Warnings & Precautions	N	N	
Interactions with contraceptives	N	N	
Pregnancy Category	X	C	

Source: Reviewer's table

Section 8.1 Pregnancy states:

Zocor

Pregnancy Category X [*See Contraindications (4)*].

ZOCOR is contraindicated in women who are or may become pregnant. Lipid lowering drugs offer no benefit during pregnancy, because cholesterol and cholesterol derivatives are needed for normal fetal development. Atherosclerosis is a chronic process, and discontinuation of lipid-lowering drugs during pregnancy should have little impact on long-term outcomes of primary hypercholesterolemia therapy. There are no adequate and well-controlled studies of use with ZOCOR during pregnancy; however, there are rare reports of congenital anomalies in infants exposed to statins *in utero*. Animal reproduction studies of simvastatin in rats and rabbits showed no evidence of teratogenicity. Serum cholesterol and triglycerides increase during normal pregnancy, and cholesterol or cholesterol derivatives are essential for fetal development. Because statins decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, ZOCOR may cause fetal harm when administered to a pregnant woman. If ZOCOR is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

There are rare reports of congenital anomalies following intrauterine exposure to statins. In a review[8] of approximately 100 prospectively followed pregnancies in women exposed to simvastatin or another structurally related statin, the incidences of congenital anomalies, spontaneous abortions, and fetal deaths/stillbirths did not exceed those expected in the general population. However, the study was only able to exclude a 3- to 4-fold increased risk of congenital anomalies over the background rate. In 89% of these cases, drug treatment was initiated prior to pregnancy and was discontinued during the first trimester when pregnancy was identified.

Simvastatin was not teratogenic in rats or rabbits at doses (25, 10 mg/kg/day, respectively) that resulted in 3 times the human exposure based on mg/m^2 surface area. However, in studies with another structurally-related statin, skeletal malformations were observed in rats and mice. Women of childbearing potential, who require treatment with ZOCOR for a lipid disorder, should be advised to use effective contraception. For women trying to conceive, discontinuation of ZOCOR should be considered. If pregnancy occurs, ZOCOR should be immediately discontinued.

Zetia

Pregnancy Category C:

There are no adequate and well-controlled studies of ezetimibe in pregnant women. Ezetimibe should be used during pregnancy only if the potential benefit justifies the risk to the fetus.

[8]Manson JM et al. Post-marketing Surveillance of Lovastatin and Simvastatin Exposure during Pregnancy. Reproductive Toxicology. 1996; Vol. 10, No. 6, pp. 439446.

In oral (gavage) embryo-fetal development studies of ezetimibe conducted in rats and rabbits during organogenesis, there was no evidence of embryolethal effects at the doses tested (250, 500, 1000 mg/kg/day). In rats, increased incidences of common fetal skeletal findings (extra pair of thoracic ribs, unossified cervical vertebral centra, shortened ribs) were observed at 1000 mg/kg/day (~10 × the human exposure at 10 mg daily based on AUC for total ezetimibe). In rabbits treated with ezetimibe, an increased incidence of extra thoracic ribs was observed at 1000 mg/kg/day (150 × the human exposure at 10 mg daily based on AUC for total ezetimibe). Ezetimibe crossed the placenta when pregnant rats and rabbits were given multiple oral doses.

Multiple-dose studies of ezetimibe given in combination with statins in rats and rabbits during organogenesis result in higher ezetimibe and statin exposures. Reproductive findings occur at lower doses in combination therapy compared to monotherapy.

All statins are contraindicated in pregnant and nursing women. When ZETIA is administered with a statin in a woman of childbearing potential, refer to the pregnancy category and product labeling for the statin. [*See Contraindications (4).]*

(b) (4)

Section 8.3 Nursing Mothers states:

Zocor
It is not known whether simvastatin is excreted in human milk. Because a small amount of another drug in this class is excreted in human milk and because of the potential for serious adverse reactions in nursing infants, women taking simvastatin should not nurse their infants. A decision should be made whether to discontinue nursing or discontinue drug, taking into account the importance of the drug to the mother *[see Contraindications (4)]*.

Zetia
It is not known whether ezetimibe is excreted into human breast milk. In rat studies, exposure to total ezetimibe in nursing pups was up to half of that observed in maternal plasma. Because many drugs are excreted in human milk, caution should be exercised when ZETIA is administered to a nursing woman. ZETIA should not be used in nursing mothers unless the potential benefit justifies the potential risk to the infant.

(b) (4)

PREGNANCY

Hypercholesterolemia and Pregnancy[9,10, 11, 12]

Cholesterol is important for embryo-fetal development. During pregnancy, it is normal for total cholesterol (TC), high density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) to increase by 25-50%, while triglycerides (TG) increase two to four times. It is believed that these elevations in lipid levels occur possibly due to the rise in estrogen levels which enhance lipid synthesis in the liver. Increases in TC and LDL-C have been reported in up to 40% of women during pregnancy. Levels of LDL-C begin rising around the 12th week of pregnancy and peak in the second trimester. Levels of HDL-C also begin rising in the first trimester and remain high during the entire gestation. The increase in cholesterol during pregnancy does not lead to endothelial dysfunction.

The term 'maternal hypercholesterolemia' refers to pregnant females with cholesterol levels above that which is to be expected in an already healthy pregnancy. Both TC and TG are transferred to the placenta, metabolized and transported to the fetus. According to Vrijkotte[7] et al., high levels of TC and/or TG are associated with preterm birth (PTB), pregnancy-induced hypertension (HTN), pre-eclampsia and large for gestational age (LGA) infants; however, decreased levels of TC are also associated with PTB and increased risk of small for gestational age (SGA) infants. Additionally, the authors state that there are conflicting publications that show no association with high cholesterol levels and adverse pregnancy outcomes.

Current recommendation is that women who are planning pregnancy or who become pregnant should stop HMG-CoA reductase inhibitor 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. Additionally, 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[8].

When HMG-CoA reductase inhibitors were originally approved in the 1980s, they were given a Category X designation because there were no studies that had been done in pregnant women using HMG-CoA reductase inhibitors and there was positive evidence of fetal abnormalities in animal studies. At the time, there were no indications that warranted the use of a HMG-CoA reductase inhibitor in pregnancy (no benefit to outweigh the risk); there was a theoretical concern

[9] Mukherjee, M, 2014, Dyslipidemia in Pregnancy, American College of Cardiology. http://www.acc.org/latest-incardiology/ articles/2014/07/18/16/08/dyslipidemia-in-pregnancy. Accessed 6/9/17.

[10] Avis, H et al, 2009, Pregnancy in women suffering from familial hypercholesterolemia: a harmful period for both mother and newborn? Curr Opin Lipidol, 20:484-490.

[11] Vrijkotte, T et al., 2012, Maternal Lipid Profile During Early Pregnancy and Pregnancy Complications and Outcomes: The ABCD Study, J Clin Endocrinol Metab, 97(11): 3917-3925.

[12] Thorogood, M et al., 2009, Management of fertility in women with familial hypercholesterolemia: summary of NICE guidance, BJOG, 116:478-479.

for human teratogenicity due to the inhibition of cholesterol synthesis during embryological development in pregnancy.

REVIEW

ZOCOR (simvastatin)

Nonclinical Experience
Simvastatin was not teratogenic in rats or rabbits at doses (25, 10 mg/kg/day, respectively) that resulted in 3 times the human exposure based on mg/m^2 surface area. However, in studies with another structurally-related statin, skeletal malformations were observed in rats and mice.

The reader is referred to the full Pharmacology/Toxicology review by Lee Elmore, PhD.

Review of Pharmacovigilance Database
The applicant reviewed the Global PVDB from 1/1/03 through 12/31/16, which is summarized below. For PVDB reports from approval through 12/31/02, the applicant cited a publication by Pollack[13] PS et al (2005).

> There were 319 prospective reports and 52 retrospective reports of maternal exposure to simvastatin included and based on their analysis, the authors concluded that although the number of reports was relatively small, there was no evidence of a notable increase in congenital anomalies in women exposed to simvastatin versus the general population.

Further review of this publication, by this reviewer, reveals that there were 191 prospective reports with known outcomes in pregnant women exposed to simvastatin:

- 154 (≈80% of known outcomes) live-born infants (LBI), first trimester (TM) exposure in 15
- 46 elective abortions (TAB)
- 17 spontaneous abortions (SAB), ≈ 9% of known outcomes
- Three fetal deaths/stillbirths, (one at 6 months with no additional information available (NAIA), one at 40 weeks with NAIA, one fetus from a twin gestation at 22 weeks with trisomy 18 and multiple CA), ≈ 1.6 % of known outcomes
- Six congenital anomalies (CA), ≈ 3.1 % of known outcomes

According to the authors, this rate of congenital anomalies (6/158; 3.8%; 95% CI, 1.4, 8.2) is similar to that of the overall U.S. population (3.15%) reported by the MACDP of the CDC[14]. The CAs included postaxial polydactyly (reported as skin tag), balanic hypospadias (also exposed to alpidem and fluoxetine), duodenal atresia, cleft lip (also exposed to diltiazem and aspirin), balanced translocation of chromosomes I and II (also exposed to bendroflumethazide) and trisomy 18 and multiple CA (See details above under fetal deaths). Additional CA seen in the retrospective reports include cleft lip, lower limb aplasia, club foot and "features of VATER".

[13] Pollack PS et al. Pregnancy Outcomes after Maternal Exposure to Simvastatin and Lovastatin. Birth Defects Research (Part A). 2005; 73: 888–896.
[14] Honein et al. Evaluation of selected characteristics of pregnancy drug registries. Teratology. 1999; 60:356 –364.

Reviewer comment
Since the two chromosomal abnormalities would not be included as potential drug-induced events by DPMH, our calculated rate of major CA possibly due to simvastatin would be lower than that reported by the authors. It is also unlikely that the "skin tag" would be considered as a "major" anomaly in this rate. There was no discernable pattern to the CAs noted.

PVDB Review from 1/1/03 through 12/31/16

There were 100 reports identified. For one of these, the applicant references Bateman[15] BT et al (2015) which is discussed in the previous DPMH review of Altoprev.[1] Of the remaining 99 reports, three cases reported paternal exposure. Of the total 99 reports, 46 were prospective and 53 were retrospective. Of the 46 prospective reports, there were four LBIs of which one had a CA (discussed later), one TAB, one SAB and 40 reports in which the outcome was unknown. A second CA (unspecified) was reported as unknown outcome. For cases that provided information regarding timing of exposure (70), the majority of patients were exposed during the 1st TM only. Of the total of 99 reports, the following were reported

- Three abortions-type unknown
- Nine TABs
- Nine SABs
- One fetal death
- 35 live births
- Two neonatal deaths
- 40 unknown outcomes

Table 1 below displays the list of CAs seen.

APPEARS THIS WAY
ON ORIGINAL

[15] Bateman BT et al. Statins and congenital malformations: Cohort study. BMJ 2015;350:h1035

Table 1: Congenital Anomalies Reported after Exposure to Simvastatin during Pregnancy

Case Number	Birth Defect	Type*	Country	Maternal Age	Time of exposure relative to LMP	Pregnancy Outcome
0301USA02509	Congenital hypothyroidism	R	United States	34 years	1st trimester	Live birth
0305FRA00028	Urinary tract malformation	P	France	unknown	1st trimester	Live birth
0406DEU00083	Trisomy 21	R	Germany	41 years	1st trimester	Elective termination
0502AUS00041	Cytogenetic abnormality (Trisomy 18)	R	Australia	40 years	1st trimester	Neonatal death
0502GBR00015	Congenital diaphragmatic hernia	R	United Kingdom	34 years	unknown	Live birth
0505USA00195	Foetal malformation	R	Japan	unknown	unknown	Live birth
0506USA03353	Scaphocephaly Anomaly of external ear congenital High arched palate Neck deformity Haemangioma Livedo reticularis Congenital musculoskeletal anomaly Limb hypoplasia congenital Congenital foot malformation Congenital cutis laxa Enlarged clitoris	R	United States	unknown	unknown	Live birth
0704USA02457	Congenital anomaly unspecified	P	United States	22 years	Unknown	Unknown
0710CAN00098	Ventricular septal defect	R	Canada	24 years	1st trimester	Live birth

Case Number	Birth Defect	Type*	Country	Maternal Age	Time of exposure relative to LMP	Pregnancy Outcome
0710CAN00099	Congenital musculoskeletal anomaly	R	Canada	23 years	Between 1 year and 1 month prior to pregnancy	Live birth
0710CAN00100	Atrial septal defect	R	Canada	37 years	Between 1 year and 1 month prior to pregnancy	Live birth
1606DEU012160	Dysmorphism Abnormal palmar/plantar creases Developmental delay	R	Germany	Unknown	1st and 2nd trimester	Live birth
1611SWE013101[3]	Ventricular septal defect	R	Sweden	unknown	unknown	Live birth
1611SWE013104	Ventricular septal defect Atrial septal defect	R	Sweden	unknown	unknown	Live birth
1611SWE013150	Cleft palate	R	Sweden	unknown	unknown	Live birth
1611SWE013273	Atrial septal defect	R	Sweden	unknown	unknown	Live birth
1611SWE013384	Congenital cardiovascular anomaly	R	Sweden	unknown	unknown	Live birth
1611SWE013393	Congenital hydronephrosis	R	Sweden	unknown	unknown	Live birth

*R=retrospective, P=prospective
Source: Applicant's Review and Summary for Simvastatin, pg 4-5.

The applicant's summary noted

> Overall, there was no pattern of events reported. A ventricular septal defect (VSD) was reported in three cases and atrial septal defect (ASD) and cleft lip were reported in two cases each. These events are relatively common CAs.

Reviewer comment
The large proportion of unknown outcomes, and the lack of details for those that were identified, make it difficult to assess these findings in any meaningful way other than to note a "lack of pattern" for the CAs reported.

Applicant's Review of Literature

The applicant provided a review of the published literature regarding simvastatin use in pregnant women. They cited publications by Ofori[16] B et al (2007), Lander[17] C et al (2005), Hedegaard[18] U et al (2016), Davidovits[19] J et al (2012), Edison[20] RJ et al. (2003), Lemoine[21] T et al (2001), Colvin[22] L et al (2010), McGrogan[23] A et al (2009), McGrogan[24] A et al (2017), Taguchi[25] N et al (2008) and Winterfeld[26] U et al (2013).

Publications by Ofori[16] B et al (2007), Davidovits[19] J et al (2012), Edison[20] RJ et al. (2003), Taguchi[25] N et al (2008) and Winterfeld [26]U et al (2013) are discussed in the previous DPMH review of Pravachol.[6] The remaining publications cited by the applicant are summarized from the applicant's supporting information below:

- Lander[17] C et al (2005), in a retrospective report, described a 40-year old female who received simvastatin during the 1st TM of pregnancy. Trisomy 18 was reported. According to the authors, maternal age increases the risk of trisomy 18; therefore, the mother's age may have been a contributing factor. An infant was delivered at week 26 following antepartum hemorrhage due to placental abruption. The neonate expired the same day.
- Hedegaard[18] U et al (2016) reported on information from the Swedish birth registry and described 128 children in the registry whose mothers were exposed to simvastatin during pregnancy. The applicant reported that "Very little information was provided concerning these pregnancies". Results obtained by this reviewer, accessing the article directly, revealed that 42 (21%) of the children were premature, which was more than expected (6.2%). Seven of the children were diagnosed with a defect (compared to four expected). The defects included one child with ASD, three with VSDs, one of whom also had ASD, and three children with, respectively, one unspecified heart defect, hydronephrosis and cleft palate.
- Lemoine[21] T et al (2001), in a prospective report, described a female of unknown age who was exposed to simvastatin during the 1st TM of pregnancy who delivered a male baby in

[16]Ofori B et al. Risk of congenital anomalies in pregnant users of statin drugs. Br J Clin Pharmacol. 2007 Oct; 64(4):496-509.
[17] Lander C et al. Statins contraindicated in pregnancy. Aust Adv Drug Reactions Bull. 2005 Feb; 24(1):4.
[18] Hedegaard U et al. Simvastatin and pregnancy. Manedskrift for almen praksis. 2016; 94(11):836-9.
[19] Davidovits J et al. Exposure to statins during pregnancy: outcomes over a 13 year period [abstract]. J Popul Ther Clin Pharmacol. 2012 Aug 1; 19(2 Suppl):e273. Abstract no. 27.
[20] Edison RJ et al. An update [abstract]. Abstracts of the 16th International conference of the Organization of Teratology Information Services (OTIS), TS/OTIS Joint Platform Session; 2003 July 13; Philadelphia, PA: OTIS; 2003. p. 1.
[21] Lemoine T et al. Follow-up of medications and pregnancy at the Midi-Pyrenees Pharmacovigilance Center. Therapie. 2001 May- Jun; 56(3):287-93. French.
[22] Colvin L et al. Linking a pharmaceutical claims database with a birth defects registry to investigate birth defect rates of suspected teratogens. Pharmacoepidemiol Drug Saf. 2010 Nov; 19(11):1137-50.
[23] McGrogan A et al. Statins and pregnancy outcomes: A cohort study in the GPRD [abstract]. Pharmacoepidemiology and Drug Safety. 2009; 18(1 Suppl):S75-6. Abstract no. 174.
[24] McGrogan A et al. Statins during pregnancy: a cohort study using the General Practice Research Database to investigate pregnancy loss. Pharmacoepidemiol Drug Saf. 2017. Feb 8. [Epub ahead of print].
[25] Taguchi N et al. Prenatal exposure to HMG-CoA reductase inhibitors: effects on fetal and neonatal outcomes. Reprod Toxicol. 2008. Oct; 26(2):175-7.
[26] Winterfeld U et al. Pregnancy outcome following maternal exposure to statins: a multi-centre prospective study. BJOG. 2013 Mar; 120(4):463-71.

good health at week 40. An ultrasound at week 32 after the mother's last menstrual period showed a dilatation of the right renal cavities of the fetus. At birth there was a right urinary tract malformation consisting of a stricture of the right uretero-pelvic junction requiring surveillance only. There was no anomaly of the kidney or the bladder.

- Colvin[22] L et al (2010), linked a pharmaceutical claims database with a birth defects registry to investigate birth defect rates of suspected teratogens (category D or X drugs). 106,074 pregnancies were identified. For simvastatin, there were 18 births identified with <5 CA noted. This yields a birth defect rate of ≈56/1000 births. The odds ratio (95% CI) was 1.2 (0.2-8.9) was not significant with a confidence interval (CI) that included one.
- McGrogan[23]A et al (2009), investigated the use of statins during the first TM of pregnancy and evaluated any associated risk of pregnancy termination (did not differentiate whether TAB or SAB) and premature birth. 192 statin users and 1943 matched reference women were identified. The relative risk-adjusted (RRadj) of recorded pregnancy terminations associated with statin use in the first TM was 2.48 (95% CI 1.65–3.73). There were no premature births amongst the statin exposed pregnancies. CAs were recorded for 3% of statin-exposed and statin unexposed pregnancies.
- McGrogan[24] A et al (2017), in a retrospective cohort study using the General Practice Research Database identified 281 pregnancies potentially exposed to statins and matched to 2643 unexposed pregnancies. There were 149 live births in the statin-exposed group (53.02%) and 1633 live births in the unexposed group (61.79%). 25% of all pregnancies potentially exposed to a statin resulted in a spontaneous loss compared with 21% in those not exposed. Using a time to event analysis with exposure as a time-dependent covariate gave an adjusted hazards ratio of 1.64 (95% CI 1.10 to 2.46) of spontaneous pregnancy loss in the statin exposed group.

  In the unexposed group, 41 major malformations were identified in 40 LBIs and one major malformation each was identified in eight pregnancies that ended in termination (2.8% of live-born deliveries and terminations - numerator 48, denominator 1701). In the group where a statin was received in the 3 months before or during the first TM, seven malformations were identified in five LBIs with no malformations recorded in pregnancies that resulted in a termination (3.2% of live-born deliveries and terminations - numerator 5, denominator 156).

DPMH's Review of Literature

DPMH conducted a search of published literature in PubMed on 8/30/18 using the search terms "simvastatin and pregnancy," "simvastatin and pregnant women," "simvastatin and pregnancy and birth defects," "simvastatin and pregnancy and congenital malformations," "simvastatin and pregnancy and stillbirth," "simvastatin and spontaneous abortion" and "simvastatin and pregnancy and miscarriage." No reports of adequate and well-controlled studies of simvastatin use in pregnant women were found. Table 4 is attached as Appendix A and includes summaries of many of the publications cited by the applicant and in previous DPMH reviews.

In addition to the publications cited by the applicant and those previously discussed in DPMH reviews of Altoprev[2], Pravachol[6] and Zypitamag[4], DPMH identified several additional relevant

publications. Publications by Peterson[27]et al (2008) and Manson[8] et al (1996) are summarized in Table 4 in Appendix A and in the currently approved label for Zocor and will not be discussed further here. The relevant articles not previously discussed are summarized below:

- An editorial by Gibb[28] (2005) disputed the existence of a "pattern of congenital defects consistent with dysfunction of cholesterol biosynthesis, diminished Sonic Hedgehog activity, and Smith-Lemli-Opitz syndrome." suggested by Edison and Muenke[29,30] (2004) after exposure to statins during pregnancy. Gibb goes on to refute the "five cases of CNS anomalies" reported by Edison and Muenke[29] (2004) stating that after discussion with the manufacturer, the "apparent holoprosencephaly" case turned out to be a cardiac VSD and not a cerebral ventricular defect. They also noted that microtia is an abnormality of the pharyngeal arches (not the CNS). They also gave detailed rationale for why they did not agree that the "five cases of limb deficiency' demonstrated a consistent pattern.
- An editorial by Lione[31] (1997) pointed out discrepancies in the numbers presented in a publication by Manson[8] (see summary of Manson[8] in Table 4 in Appendix A) regarding pregnancy outcomes in women treated with statins. A reply by Manson explained the disputed numbers.

Simvastatin is referenced in MicroMedex.[32] The authors note that the drug crosses the placenta and reference the previously discussed publications by Edison and Muenke[29] (2004), Taguchi[25]N et al (2008) and Pollack[13] PS et al (2005).

The "Quick Take" in the Reprotox[32] database states

> Based on experimental animal studies, inadvertent exposure to simvastatin during early pregnancy is not expected to increase the risk of adverse pregnancy outcome. Theoretical considerations concerning the role of cholesterol in embryo development plus the lack of demonstrated benefit of treating hyperlipidemia during gestation are the basis for avoidance of statins during pregnancy.

In *Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk,*[33] the authors quote the current label and state that simvastatin is contraindicated in both pregnancy and lactation. The authors go on to state

> Based on animal data and limited human experience, exposure to simvastatin during early pregnancy does not appear to present a significant risk to the fetus. However, because the interruption of cholesterol-lowering therapy should have no apparent effect on the long-term treatment of hyperlipidemia, simvastatin should

[27] Peterson EE et al. Research Letter Maternal Exposure to Statins and Risk for Birth Defects: A Case-Series Approach. American Journal of Medical Genetics Part A. 2008; 146A:2701–2705.
[28] Gibb H. Statin Drugs and Congenital Anomalies. American Journal of Medical Genetics.2005; 135A:230–231.
[29] Edison RJ, Muenke M. Mechanistic and epidemiologic considerations in the evaluation of adverse birth outcomes following gestational exposure to statins. Am J Med Gen.2004; 131A:287–298.
[30] The article by Edison and Muenke was discussed in the DPMH review of Pravachol.[6]
[31] Lione A . Letter to the Editor. Reproductive Toxicology. 1997; Vol. 11, No. 4, pp. 64-642.
[32] Truven Health Analytics information, http://www.micromedexsolutions.com/. Accessed 6/6/18.
[33] Briggs, GG. Freeman, RK. & Yaffe, SJ. (2015). Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk. Philadelphia, Pa, Lippincott Williams & Wilkins.

> not be used during pregnancy. Women taking this agent before conception should ideally stop the therapy before becoming pregnant and certainly on recognition of pregnancy. Accidental use of the drug during gestation, though, apparently has no known consequences for the fetus.

In the previous DPMH review of Pravachol,[6] the reviewer had the following comments

> Although two studies suggested a potential for an increased risk for CNS, cardiac and limb defects with lipophilic HMG-CoA reductase inhibitors (e.g., simvastatin, atorvastatin), eight studies have not demonstrated an increased risk of fetal malformations with lipophilic or hydrophilic HMG-CoA reductase inhibitors… Current labeling contraindicates statin use during pregnancy, reflecting conclusions based on animal data and the lack of information about the safe use of HMG-CoA reductase inhibitors in pregnant women. DPMH finds that limited published human data regarding statin use in pregnancy does not demonstrate a teratogenic risk from statins and labeling should state that data are insufficient to determine a drug-associated risk of major congenital malformations or miscarriage. Emphasizing a theoretical risk of a drug product taken during pregnancy may result in unnecessary concern, especially in women with inadvertent exposure. Therefore, while DPMH finds the data do not support a pregnancy contraindication for statins, DPMH recommends that a statement regarding a potential for fetal harm based on mechanism of action should be included in statin labeling.

In the previous DPMH review of Zypitamag,[4] the reviewer had the following comments

> Under existing regulations 201.57(c)(5) of the Federal Food, Drug and Cosmetic Act (FD&C Act), a drug should be contraindicated only if there is a "known hazard" and not a "theoretical possibility."[34,35] DPMH recommends DMEP remove the contraindication language for HMG-CoA reductase inhibitors.

DPMH discussed the labeling language regarding a contraindication for use in pregnant woman and the level of warning of potential embryofetal harm with the DMEP Clinical Review Team. DMEP agreed that the class contraindication statement should be removed and replaced with a statement regarding a potential for fetal harm based on mechanism of action. It was decided that "class labeling" for the statins for Section 8 would be developed so that all statin labels could be updated at the same time.

[34] 201.57(c)(5) of the FD&C Act

[35] Guidance for Industry, Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products-Contents and Format. 2011. U.S. Department of Health and Human Services. Food and Drug Administration

ZETIA (ezetimibe)

Nonclinical Experience

In oral (gavage) embryo-fetal development studies of ezetimibe conducted in rats and rabbits during organogenesis, there was no evidence of embryolethal effects at the doses tested (250, 500, 1000 mg/kg/day). In rats, increased incidences of common fetal skeletal findings (extra pair of thoracic ribs, unossified cervical vertebral centra, shortened ribs) were observed at 1000 mg/kg/day (~10 × the human exposure at 10 mg daily based on AUC for total ezetimibe). In rabbits treated with ezetimibe, an increased incidence of extra thoracic ribs was observed at 1000 mg/kg/day (150 × the human exposure at 10 mg daily based on AUC for total ezetimibe). Ezetimibe crossed the placenta when pregnant rats and rabbits were given multiple oral doses.

The reader is referred to the full Pharmacology/Toxicology review by Lee Elmore, PhD.

Review of Pharmacovigilance Database

According to the applicant, the company pharmacovigilance database (PVDB) Merck Adverse Event Reporting and Review System (MARRS) was searched for spontaneous reports for ezetimibe during the cumulative period up to and including 12/31/16 concerning ezetimibe use during pregnancy and lactation.

A total of 47 pregnancy exposures were identified, with a total of 48 outcomes (one report describing a twin gestation). Of these 47 total exposures, 37 were prospective, and 10 were retrospective. A pregnancy outcome was reported in 16 cases, the outcome was pending in 6 cases and unknown in the remaining 25 cases as summarized Table 2 below.

Table 2: Pregnancy Outcomes after Exposure to Ezetimibe

Pregnancy Outcome*	**# of Cases**	**# of Outcomes**
LBIs	13	14
Pending	6	6
SAB	3	3
Unknown	25	25
TAB	0	0
Fetal death/Stillborn	0	0
Grand total	47	48

Note: A single case may have more than one outcome e.g. a twin gestation
Source: Reviewer's Table

Of the 16 cases reporting a pregnancy outcome, one report describes a congenital anomaly, a case of a hemangioma congenital with a fetal outcome of a normal live birth.

Applicant's Review of Literature

The applicant provided a review of the literature. No relevant publications regarding the use of ezetimibe during pregnancy were identified.

DPMH's Review of Literature

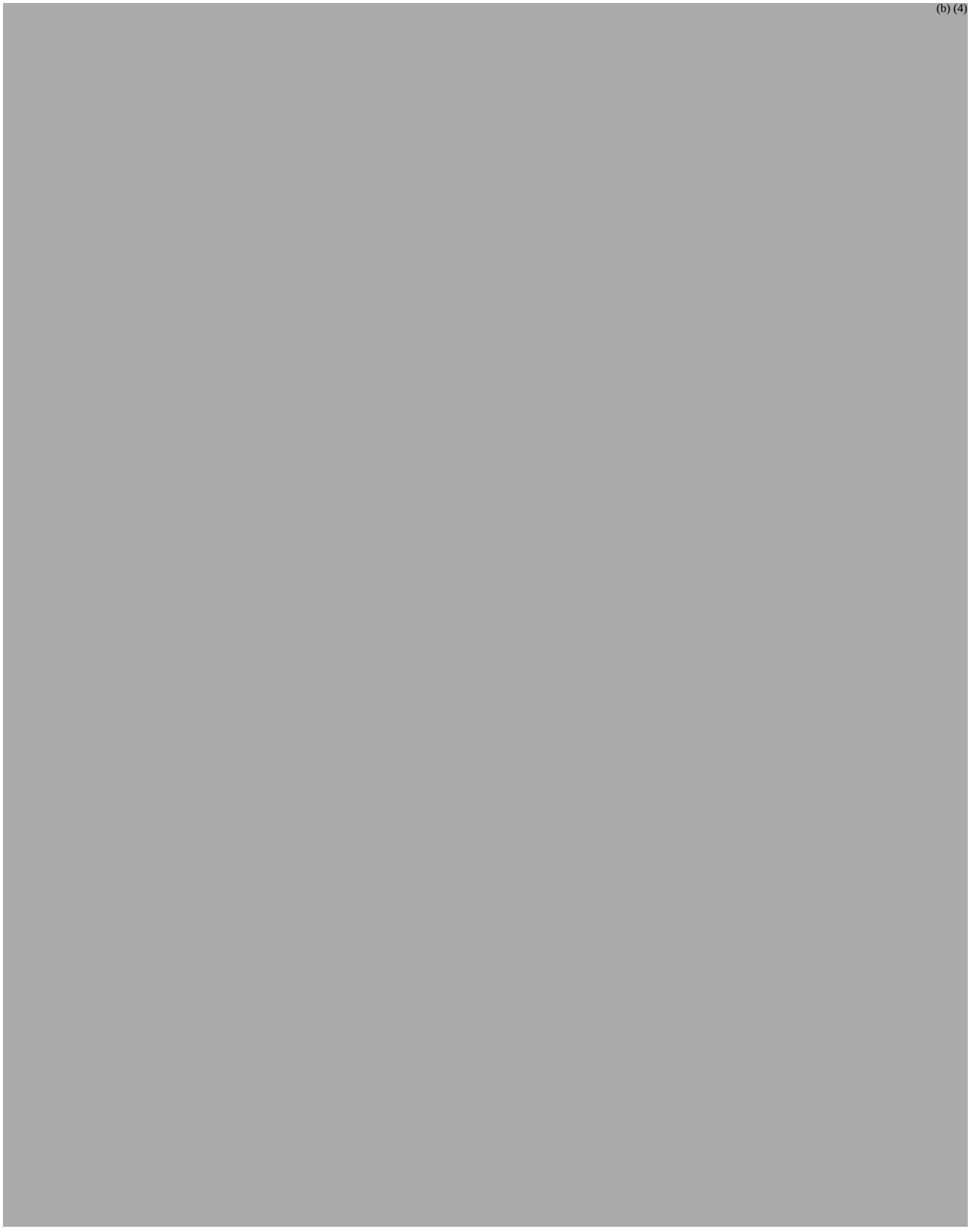
DPMH conducted a search of published literature in PubMed on 8/30/18 using the search terms "ezetimibe and pregnancy," "ezetimibe and pregnant women," "ezetimibe and pregnancy and birth defects," "ezetimibe and pregnancy and congenital malformations," "ezetimibe and pregnancy and stillbirth," "ezetimibe and spontaneous abortion" and "ezetimibe and pregnancy and miscarriage." No reports of adequate and well-controlled studies of ezetimibe use in pregnant women were found. No published case reports involving pregnancy in ezetimibe patients were identified.

Ezetimibe is referenced in MicroMedex.[32] The authors note that "it unknown whether the drug crosses the placenta in humans but does cross the placenta in rats and rabbits".

The "Quick Take" in the Reprotox[32] database states "Based on experimental animal studies reported in the product labeling, ezetimibe therapy is not anticipated to increase the risk of congenital anomalies."

In *Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk,*[33] the authors' Pregnancy recommendation states: "No human data, animal data suggests moderate risk".

(b) (4)


(b) (4)

LACTATION

ZOCOR (simvastatin)

Nonclinical Experience
There are no animal studies of simvastatin during lactation.

Review of Pharmacovigilance Database
The applicant reviewed the Global PVDB from approval cumulatively through 12/31/16; no case reports regarding use of simvastatin during lactation were identified.

Applicant's Review of Literature
The applicant did provide a review of the literature. No publications regarding use of simvastatin during lactation were identified.

DPMH's Review of Literature
DPMH conducted a search of *Medications and Mother's Milk*[36], Micromedex[32], LactMed[37] and of published literature in PubMed using the search terms "simvastatin and lactation" and "simvastatin and breastfeeding." No relevant publications were identified.

The molecular weight of simvastatin is ≈ 419 Daltons and is highly protein bound (≈ 95%). The half-life is < 5 hours. The most common adverse reactions (≥5%) were upper respiratory infection, headache, abdominal pain, constipation, and nausea.

[36] Hale, Thomas (2017) Medications and Mothers' Milk. Amarillo, Texas Hale Publishing.
[37]http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding. Accessed 4/9/18.

The relevant "Summary of Use" information for simvastatin in LactMed[37] states

> No relevant published information exists on the use of simvastatin during breastfeeding. Because of a concern with disruption of infant lipid metabolism, the consensus is that simvastatin should not be used during breastfeeding.

In *Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk,*[33] the authors' state that

> No published reports describing the use of simvastatin during lactation have been located. However, the passage of simvastatin into milk should be expected because at least two other similar agents (fluvastatin and pravastatin) appear in human milk. Because of the potential for adverse effects in the nursing infant, the drug should not be used during lactation.

Hale[38] et al categorizes simvastatin as "probably compatible" with breast feeding but then states

> It is likely that milk levels will be low and oral bioavailability is poor; however, the effect on the infant is unknown and statins could reduce cholesterol synthesis. Cholesterol and other products of cholesterol biosynthesis are essential components for neonatal development; therefore, it is not clear if it would be safe for use in a breastfed infant who needs high levels of cholesterol. Caution is recommended until more data is available.

ZETIA (ezetimibe)

Nonclinical Experience

In rat studies, exposure to ezetimibe in nursing pups was up to half of that observed in maternal plasma.

The reader is referred to the full Pharmacology/Toxicology review by Lee Elmore, PhD.

Review of Pharmacovigilance Database

The applicant reviewed the Global PVDB from approval cumulatively through 12/31/16, a total of three case reports regarding use of ezetimibe during lactation were identified and are summarized below:

- A Spanish female patient of unknown age with hypercholesterolemia was reported. On an unknown date, the patient started therapy with ezetimibe 10 mg. She interrupted ezetimibe while she was pregnant and had restarted it on an unknown date, during her "lactancy" period. Follow up information received from a physician reported the baby was "fine".
- A Japanese female patient of unknown age started therapy with ezetimibe (dose, therapy dates, indication not reported). On an unknown date, the patient was taking ezetimibe and breast feeding. The outcome of the event was not reported.

- Another Japanese female patient of unknown age started therapy with ezetimibe (dose, therapy dates, indication not reported). On an unknown date, the patient experienced drug administration during lactation. The outcome of breast feeding was unknown.

Applicant's Review of Literature
No publications regarding use of ezetimibe during lactation were identified.

DPMH's Review of Literature
DPMH conducted a search of *Medications and Mother's Milk*[36], Micromedex[32], LactMed[37] and of published literature in PubMed using the search terms "ezetimibe and lactation" and "ezetimibe and breastfeeding." No relevant publications were identified.

The molecular weight of ezetimibe is ≈ 409 Daltons and is highly protein bound (> 90%). The half-life is ≈ 22 hours. Common adverse reactions (≥2%) were upper respiratory tract infection, diarrhea, arthralgia, sinusitis, and pain in extremity. When administered with a statin, common adverse reactions (≥2%) were nasopharyngitis, myalgia, upper respiratory tract infection, arthralgia, and diarrhea.

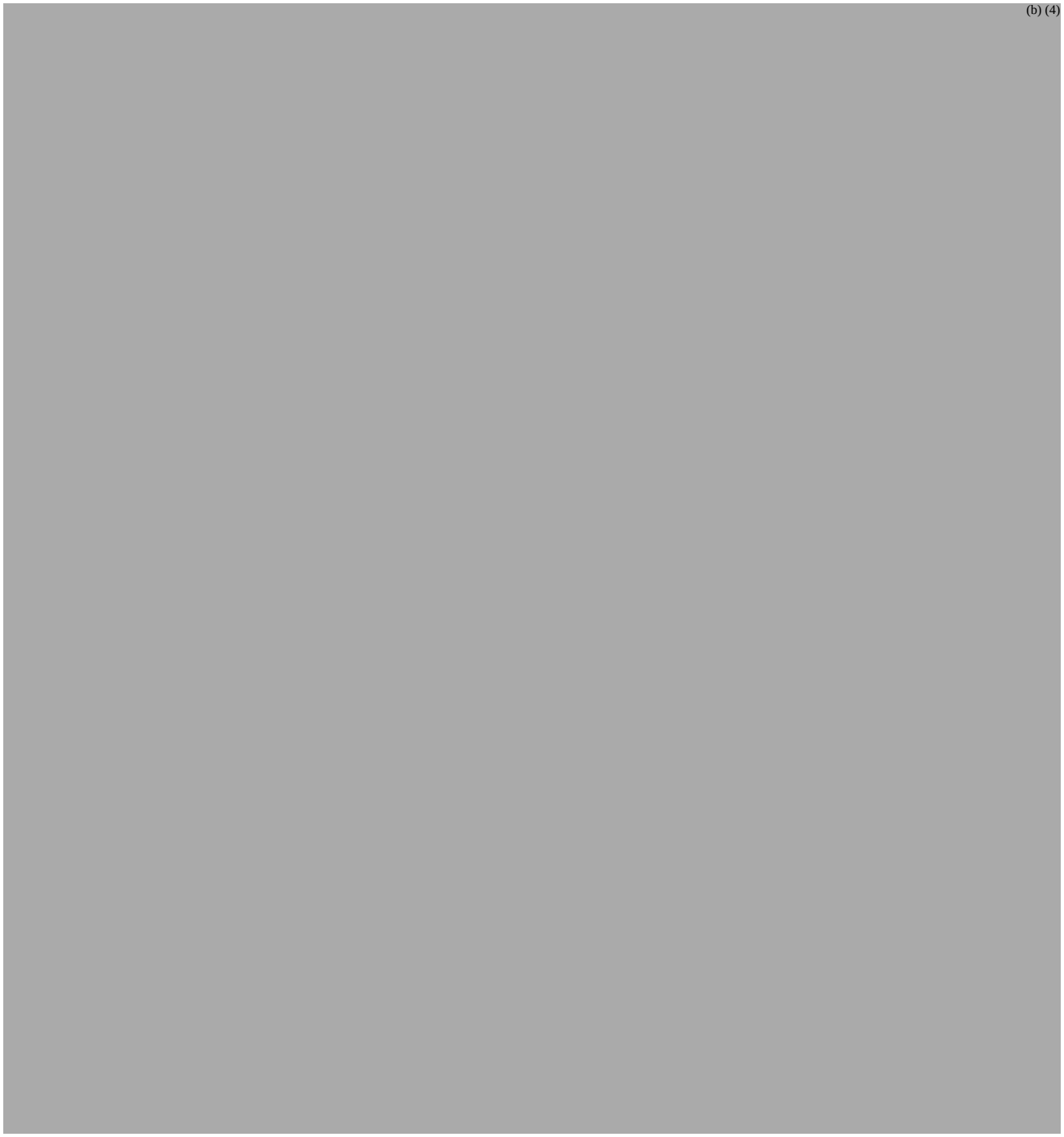
The relevant "Summary of Use" information for ezetimibe in LactMed[37] states

> No relevant published information exists on the use of ezetimibe during breastfeeding. Because of a concern with disruption of infant lipid metabolism, ezetimibe is best avoided during breastfeeding. An alternate drug is preferred, especially while nursing a newborn or preterm infant. Ezetimibe treatment in combination with a statin (e.g., atorvastatin, simvastatin) should be avoided in nursing mothers.

In *Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk*,[33] the authors' state that

> No reports describing the use of ezetimibe during human lactation have been located. The molecular weight (≈ 409 for the parent compound) and the prolonged elimination half-life (about 22 hours) for both ezetimibe and its active metabolite suggest that the drug and/or its metabolite will be excreted into breast milk. However, the high plasma protein binding (>90%) should limit the amount excreted. The effect on a nursing infant from this exposure is unknown. If ezetimibe is taken during lactation, the nursing infant should be closely observed for adverse effects that are commonly seen in adults (e.g., headache, diarrhea, pharyngitis, sinusitis and arthralgia).

(b) (4)


(b) (4)


(b) (4)

(b) (4)

(b) (4)

The Applicant proposes (b) (4) DPMH recommends removal of the contraindication to pregnancy and to lactation, there does not appear to be a need (b) (4)

(b) (4)

(b) (4) See DPMH proposed labeling for details.

DISCUSSION AND CONCLUSIONS

Pregnancy

With regard to statins, in this case, simvastatin (Zocor (b) (4) based on limited human experience and lack of adverse developmental outcomes in animal studies, inadvertent exposure during early pregnancy does not appear to significantly increase the risk of adverse pregnancy outcomes such as congenital abnormalities. Theoretical considerations concerning the role of cholesterol in embryo development plus the lack of demonstrated benefit of treating hyperlipidemia during gestation are the reasons for avoidance of statins during pregnancy. DPMH recommends the removal of the contraindication for pregnancy, in favor of replacing it with a discussion in subsection 8.1 of the potential embryofetal toxicity due to the mechanism of action. If an inadvertent early pregnancy exposure occurs, the medication should be stopped when the diagnosis of pregnancy occurs.

With regard to ezetimibe, there are no human data available beyond a small number of exposures in the applicant's PVDB, many of which had unknown outcomes. In nonclinical studies there were "common fetal skeletal findings" observed in rats at 10-times MHD and "an increased incidence of extra thoracic ribs" in rabbits at 150-times the usual HD. Given the lack of information and the lack of evidence of benefit to be gained from treatment of hypercholesterolemia during pregnancy, DPMH recommends avoiding use of ezetimibe during pregnancy. If an inadvertent early pregnancy exposure occurs, the medication should be stopped when the diagnosis of pregnancy occurs.

(b) (4) DPMH recommends changing the contraindication to a discussion in subsection 8.1 of the potential embryofetal toxicity due to the mechanism of action. See DPMH Proposed Labeling for details.

Lactation

With regard to simvastatin, there are no data regarding the presence in human or animal milk. However, closely related members of the statin class are found in human milk. Given the concern for potential effects on the nursing infant, and the likely lack of harm from a temporary interruption in therapy for elevated lipids, DPMH recommends not breastfeeding during treatment.

With regard to ezetimibe, there are very limited human data available (three cases in the PVDB with few details). Ezetimibe is found in rat milk, but there are no data regarding its presence in human milk. Pharmacokinetic parameters would suggest that ezetimibe is likely to be found in human milk, though in low amounts due to high protein binding. Given the lack of information and the likely lack of harm from a temporary interruption in therapy for elevated lipids, DPMH recommends not breastfeeding during treatment.

LABELING RECOMMENDATIONS

DPMH revised the HPI, sections 4, 8.1, 8.2, (b) (4) and 17 of labeling for compliance with the PLLR (see below). DPMH discussed our labeling recommendations with the Division on October 18, 2018. DPMH recommendations are below and reflect the discussions with DMEP. DPMH refers to the final NDA action for final labeling.

APPEARS THIS WAY ON ORIGINAL

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

Appendix A

Table 4: Summary of Reports on Outcomes of Statin-Exposed Pregnancies

Table 1. Summary of Reports on Outcomes of Statin-Exposed Pregnancies[a]

Reference	Defects (n)/Statin Exposures (N)	Statin Exposure Period	Outcomes	Potential Cofounders	Limitations
Case series					
Petersen (2007)[15]	Atorvastatin: 12/NS; cerivastatin: 1/NS; simvastatin: 6/NS; pravastatin: 3/NS Total: 22/NS	First trimester (19); first-second trimester (1); second-third trimester (1); NS (1)	Heart defects (12), cleft lip (4), neural tube defects (2), isolated defects (8), trisomy 21 (1)	12/22 women with diabetes mellitus; 18/22 women overweight or obese; 2-27 additional medications used but no known teratogens	Relied on maternal recall for exposure period; defects in spontaneously aborted fetuses not reported
Edison (2004)[16]	Atorvastatin: 4/NS; cerivastatin: 1/NS; lovastatin: 7/NS; simvastatin: 10/NS; fluvastatin: 0/NS; pravastatin: 0/NS Total: 22/NS	First trimester	CNS malformations (5), limb deficiencies (5 [2 VACTERL]), isolated defects (12) Other: IUGR (4), IUFD (5)	Nonsignificant differences in type 1 diabetes mellitus and FH between statins; additional drug use, if any, included: promegestone, aspirin, codeine, acetaminophen, dextropropoxyphene, diltiazem, cephalexin, fluoxetine, alpidem, dextroamphetamine	1 VACTERL reclassified as cardiac malformation, background prevalence rates estimated with possible bias, exclusion criteria eliminated 2/3 of reported cases
Systematic reviews					
Manson (1996)[20]	Lovastatin: 4 (R)/76; simvastatin: 5 (P + R)/187 Total: 9 (P + R)/263	First trimester	1 each: septal defect and cerebral dysfunction, VATER, spina bifida, holoprosencephaly, polydactyly, cleft lip, hypospadia, trisomy 18, club foot Other: stillbirths (2), spontaneous abortion (16), miscellaneous adverse outcomes (4)	1 woman with hypertension taking antihypertensive medications, 1 woman also taking dextroamphetamine, no other information	Power to rule out only 3- to 4-fold increase in frequency of birth defects; included unknown and pending outcomes in calculation of defect rate
Pollack (2005)[22]	Lovastatin: 0 (P)/30; simvastatin: 6 (P)/128; total (P): 6/158 Lovastatin: 7 (R)/NS; simvastatin: 6 (R)/NS; total (R): 13/NS Total: 19 (P + R)/NS	First trimester	6 prospective reports: chromosomal (2), hypospadias (1), postaxial polydactyly (1), cleft lip (1), duodenal atresia (1) 13 retrospective reports: minimal information (3), isolated anomalies (5), multiple anomalies (5)	2/19 women with hypertension; 8/19 also exposed to 1 or more of alpidem, fluoxetine, cephalexin, diltiazem, aspirin, bendroflumethazide, caffeine, pseudoephedrine, acetaminophen, ethinyl estradiol/ethynodiol, codeine, dextropropoxyphene, indapamide, dextroamphetamine	Reporting bias with retrospective reports
Registry-based studies					
Toleikyte (2011)[23]	Total: NS/16	NS	Nonsignificant differences in birth weights of exposed vs unexposed infants and in the frequency of congenital malformations before vs after statin introduction (1987)	All 2184 births (16 with concurrent statin exposure) involved women with FH, no data on omega-3 supplements or other concurrent medication use	Population limited to white women with FH; only frequency of outcomes compared
Ofori (2007)[24]	Atorvastatin: 1/33; fluvastatin: 0/3; lovastatin: 1/2; simvastatin: 1/11; pravastatin: 0/12 Total: 3/64	First trimester	Cardiac anomalies (3): unspecified (1), ventricular septal defect and unspecified defect of septal closure (1), ostium secundum type atrial septal defect and other specified heart anomaly (1)	33/64 women used >2 additional medications(NS), 13/64 with diabetes mellitus, 15/64 with hypertension, 8/64 with hypothyroidism[b]	Data from non-live births not reported, small sample size that lacked power to detect small increases in overall risk
Prospective observational cohort					
Taguchi (2008)[25]	Atorvastatin: NS/46; simvastatin NS/9; pravastatin NS/6; rosuvastatin NS/3 Total: 1/64[c]	First trimester only (61); first-second (3)	Cervical soft tissue mass (1/46 live births); gestational age at birth and birth weight significantly lower than controls	Maternal prepregnancy weight and diabetes mellitus status significantly higher in statin-exposed group, 33% had other chronic medical conditions; no exposure to other teratogens	Powered to detect 5-fold increased risk over general population

CNS = central nervous system; FH = familial hypercholesterolemia; IUFD = intrauterine fetal demise; IUGR = intrauterine growth retardation; NS = not specified; P = prospective; R = retrospective; VACTERL = vertebral, anal, cardiac, tracheal, esophageal, renal, and limb association; VATER = vertebral anomalies, anal atresia, trachea-esophageal fistula with esophageal atresia.

[a]Single case reports not included.

[b]Data based on n = 64 women, only 55 of whom continued statin use into first trimester (differentiation in characteristics not specified).

[c]Statin associated with single birth defect in statin group not reported.

Source: Godfrey[41] et al (2012)

[41] Godfrey LM et al. Teratogenic Risk of Statins in Pregnancy. Ann Pharmacother. 2012; 46:1419-24.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JANE E LIEDTKA
02/27/2019 08:26:22 AM

MIRIAM C DINATALE
02/28/2019 11:00:41 AM

LYNNE P YAO
02/28/2019 11:10:02 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021445Orig1s042

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

From: White, Martin
Sent: Mon, 26 Jun 2023 17:53:27 +0000
To: CHEN, MINI
Subject: RE: [EXTERNAL] RE: NDA 21445_S-042_Zetia_Labeling
Attachments: NDA 21445 S-042 zetia PPI to firm on 6.26.2023.docx, NDA 21445 S-042 zetia PI to firm on 6.26.2023.docx

Mini,

The team has accepted all changes in the PI and PPI. Please review. If there are no changes, please submit the final agreed upon label to me via email by July 6, 2023. Use the SRPI checklist to ensure that the label conforms with format items in regulations and guidances.

Acknowledge receipt of this email and let me know if you have any questions.

Regards,
Martin

Martin White, M.S.
Phone 240.402.6018
Martin.White@fda.hhs.gov

From: CHEN, MINI <mini.chen@organon.com>
Sent: Wednesday, May 10, 2023 11:12 AM
To: White, Martin <Martin.White@fda.hhs.gov>
Subject: RE: [EXTERNAL] RE: NDA 21445_S-042_Zetia_Labeling

[Organon] Proprietary

Hi Martin,

Thank you so much!

Kind Regards,
Mini

Mini Chen, PharmD
Associate Principal Scientist, Regulatory Liaison
Phone: (551) 430-6291

From: White, Martin <Martin.White@fda.hhs.gov>
Sent: Tuesday, May 9, 2023 9:12 PM

To: CHEN, MINI <mini.chen@organon.com>
Subject: RE: [EXTERNAL] RE: NDA 21445_S-042_Zetia_Labeling

Yes, you may send the label back in by May 31, 2023.

Martin White, M.S.
Phone 240.402.6018
Martin.White@fda.hhs.gov

From: CHEN, MINI <mini.chen@organon.com>
Sent: Monday, May 8, 2023 1:43 PM
To: White, Martin <Martin.White@fda.hhs.gov>
Subject: RE: [EXTERNAL] RE: NDA 21445_S-042_Zetia_Labeling

[Organon] Proprietary

Hi Martin,

Thank you for much for the comments; Organon acknowledges receipt of this email. Would we be able to request an extension until May 31, 2023?

Kind Regards,
Mini

Mini Chen, PharmD
Associate Principal Scientist, Regulatory Liaison
Phone: (551) 430-6291

From: White, Martin <Martin.White@fda.hhs.gov>
Sent: Friday, May 5, 2023 2:26 PM
To: CHEN, MINI <mini.chen@organon.com>
Subject: [WARNING: UNSCANNABLE EXTRACTION FAILED]RE: [EXTERNAL] RE: NDA 21445_S-042_Zetia_Labeling

Mini,

FDA has compiled the attached comments for your draft labeling submitted for NDA 021445, supplement-42, submitted on November 15, 2018. We request that you accept all proposed changes that you agree with, make additional revisions as requested, and return a revised labeling no later than COB **May 24, 2023**.

If there are no changes, please submit the final agreed upon label to me via email.

Acknowledge receipt of this email and let me know if you have any questions.

Thanks
Martin

Martin White, M.S.
Phone 240.402.6018
Martin.White@fda.hhs.gov

From: CHEN, MINI <mini.chen@organon.com>
Sent: Tuesday, April 18, 2023 1:12 PM
To: White, Martin <Martin.White@fda.hhs.gov>
Subject: RE: [EXTERNAL] RE: NDA 21445_S-042_Zetia_Labeling

[Organon] Proprietary

Hi Martin,

Thank you for the confirmation!

Kind Regards,
Mini

Mini Chen, PharmD
Associate Principal Scientist, Regulatory Liaison
Phone: (551) 430-6291

From: White, Martin <Martin.White@fda.hhs.gov>
Sent: Monday, April 17, 2023 5:55 PM
To: CHEN, MINI <mini.chen@organon.com>
Subject: RE: [EXTERNAL] RE: NDA 21445_S-042_Zetia_Labeling

this message looks suspicious, click the “Report Suspicious Email” button on the Outlook toolbar or forward to “Report Spam”.

Mini,

We will provide comments to the USPPI once we receive your revised PI.

Thanks
Martin

Martin White, M.S.
Phone 240.402.6018
Martin.White@fda.hhs.gov

From: CHEN, MINI <mini.chen@organon.com>
Sent: Monday, April 17, 2023 5:34 PM
To: White, Martin <Martin.White@fda.hhs.gov>
Subject: RE: [EXTERNAL] RE: NDA 21445_S-042_Zetia_Labeling

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[Organon] Proprietary

Dear Martin,

Hope you are doing well. I am following up on the below, Supplement 042, that was submitted to the FDA on March 22, 2023. In the submission, Organon included labeling updates to the USPPI & USPI, however as per the below email chain, the FDA has provided feedback on only the USPI included in S-042. Therefore, Organon plans to respond back to the FDA comments on the USPI as agreed upon in the below deadline and wanted to confirm if the FDA will be providing comments on the USPPI as well included in S-042?

Thank you!

Kind Regards,
Mini

Mini Chen, PharmD
Associate Principal Scientist, Regulatory Liaison
Phone: (551) 430-6291

From: White, Martin <Martin.White@fda.hhs.gov>
Sent: Wednesday, March 29, 2023 7:53 PM
To: CHEN, MINI <mini.chen@organon.com>
Subject: RE: [EXTERNAL] RE: NDA 21445_S-042_Zetia_Labeling

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Mini,

April 21, 2023 is acceptable.

Martin

Martin White, M.S.
Phone 240.402.6018
Martin.White@fda.hhs.gov

From: CHEN, MINI <mini.chen@organon.com>
Sent: Wednesday, March 29, 2023 2:52 PM
To: White, Martin <Martin.White@fda.hhs.gov>
Subject: RE: [EXTERNAL] RE: NDA 21445_S-042_Zetia_Labeling

CAUTION: This email originated from outside of the organization. Do not click links or open attachments unless you recognize the sender and know the content is safe.

[Organon] Proprietary

Hi Martin,

Thank you for your email. Organon acknowledges receipt. In addition, would it be possible to request an extension until April 21, 2023?

Kind Regards,
Mini

Mini Chen, PharmD
Associate Principal Scientist, Regulatory Liaison
Phone: (551) 430-6291

From: White, Martin <Martin.White@fda.hhs.gov>
Sent: Tuesday, March 28, 2023 2:09 PM
To: CHEN, MINI <mini.chen@organon.com>
Subject: RE: [EXTERNAL] RE: NDA 21445_S-042_Zetia_Labeling

EXTERNAL EMAIL WARNING: The sender of this email originated from outside of Organon. Do not click links, open attachments, or reply with personal information unless you recognize the sender and know the content is safe. If this message looks suspicious, click the "Report Suspicious Email" button on the Outlook toolbar or forward to "Report Spam".

Mini,

FDA has compiled the attached comments for your draft labeling submitted for NDA 021445, supplement-42, submitted on November 15, 2018. We request that you accept all proposed changes that you agree with, make additional revisions as requested, and return a revised labeling no later than COB **April 11, 2023**.

If there are no changes, please submit the final agreed upon label to me via email.

Acknowledge receipt of this email and let me know if you have any questions.

Thanks
Martin

Martin White, M.S.
Phone 240.402.6018
Martin.White@fda.hhs.gov

From: CHEN, MINI <mini.chen@organon.com>
Sent: Thursday, February 2, 2023 1:27 PM
To: White, Martin <Martin.White@fda.hhs.gov>
Subject: RE: [EXTERNAL] RE: NDA 21445_S-042_Zetia_Labeling

[Organon] Proprietary

Great, thank you!

Mini Chen, PharmD
Associate Principal Scientist, Regulatory Liaison
Phone: (551) 430-6291

From: White, Martin <Martin.White@fda.hhs.gov>
Sent: Thursday, February 2, 2023 11:11 AM
To: CHEN, MINI <mini.chen@organon.com>
Subject: RE: [EXTERNAL] RE: NDA 21445_S-042_Zetia_Labeling

Mini,

March 22, 2023 works for the team.

Martin

Martin White, M.S.
Phone 240.402.6018
Martin.White@fda.hhs.gov

From: CHEN, MINI <mini.chen@organon.com>
Sent: Thursday, February 2, 2023 10:52 AM
To: White, Martin <Martin.White@fda.hhs.gov>
Subject: [EXTERNAL] RE: NDA 21445_S-042_Zetia_Labeling

[Organon] Proprietary

Dear Martin,

Thank you, I acknowledge receipt of the email. Would it be possible to have an extension to March 22, 2023? The changes are quite extensive, therefore, Organon requires more time to review and address them.

Kind Regards,
Mini

Mini Chen, PharmD
Associate Principal Scientist, Regulatory Liaison
Phone: (551) 430-6291

From: White, Martin <Martin.White@fda.hhs.gov>
Sent: Monday, January 30, 2023 7:02 PM
To: CHEN, MINI <mini.chen@organon.com>
Subject: NDA 21445_S-042_Zetia_Labeling

Mini,

FDA has compiled the attached comments for your draft labeling submitted for NDA 021445, supplement-42, submitted on November 15, 2018. We request that you accept all proposed changes that you agree with, make additional revisions as requested, and return a revised labeling no later than COB **February 28, 2023**.

If there are no changes, please submit the final agreed upon label to me via email.

Acknowledge receipt of this email and let me know if you have any questions.

Thanks
Martin

Martin White, MS
Regulatory Project Manager
Diabetes, Lipid Disorders, and Obesity
Division of Regulatory Operations for Cardiology, Hematology, Endocrinology, and Nephrology
Office of Regulatory Operations
Center for Drug Evaluation and Research
WO22 - Room 3389
10903 New Hampshire Avenue
Silver Spring, MD 20903
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Martin.White@fda.hhs.gov

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MARTIN L WHITE
06/27/2023 07:39:30 PM

From: CHEN, MINI <mini.chen@organon.com>
Sent: Mon, 8 May 2023 17:43:18 +0000
To: White, Martin
Subject: RE: [EXTERNAL] RE: NDA 21445_S-042_Zetia_Labeling

[Organon] Proprietary

Hi Martin,

Thank you for much for the comments; Organon acknowledges receipt of this email. Would we be able to request an extension until May 31, 2023?

Kind Regards,
Mini

Mini Chen, PharmD
Associate Principal Scientist, Regulatory Liaison
Phone: (551) 430-6291

From: White, Martin <Martin.White@fda.hhs.gov>
Sent: Friday, May 5, 2023 2:26 PM
To: CHEN, MINI <mini.chen@organon.com>
Subject: [WARNING: UNSCANNABLE EXTRACTION FAILED]RE: [EXTERNAL] RE: NDA 21445_S-042_Zetia_Labeling

Mini,

FDA has compiled the attached comments for your draft labeling submitted for NDA 021445, supplement-42, submitted on November 15, 2018. We request that you accept all proposed changes that you agree with, make additional revisions as requested, and return a revised labeling no later than COB **May 24, 2023**.

If there are no changes, please submit the final agreed upon label to me via email.

Acknowledge receipt of this email and let me know if you have any questions.

Thanks
Martin

Martin White, M.S.
Phone 240.402.6018
Martin.White@fda.hhs.gov

From: CHEN, MINI <mini.chen@organon.com>
Sent: Tuesday, April 18, 2023 1:12 PM
To: White, Martin <Martin.White@fda.hhs.gov>
Subject: RE: [EXTERNAL] RE: NDA 21445_S-042_Zetia_Labeling

[Organon] Proprietary

Hi Martin,

Thank you for the confirmation!

Kind Regards,
Mini

Mini Chen, PharmD
Associate Principal Scientist, Regulatory Liaison
Phone: (551) 430-6291

From: White, Martin <Martin.White@fda.hhs.gov>
Sent: Monday, April 17, 2023 5:55 PM
To: CHEN, MINI <mini.chen@organon.com>
Subject: RE: [EXTERNAL] RE: NDA 21445_S-042_Zetia_Labeling

Mini,

We will provide comments to the USPPI once we receive your revised PI.

Thanks
Martin

Martin White, M.S.
Phone 240.402.6018
Martin.White@fda.hhs.gov

From: CHEN, MINI <mini.chen@organon.com>
Sent: Monday, April 17, 2023 5:34 PM
To: White, Martin <Martin.White@fda.hhs.gov>
Subject: RE: [EXTERNAL] RE: NDA 21445_S-042_Zetia_Labeling

[Organon] Proprietary

Dear Martin,

Hope you are doing well. I am following up on the below, Supplement 042, that was submitted to the FDA on March 22, 2023. In the submission, Organon included labeling updates to the USPPI & USPI, however as per the below email chain, the FDA has provided feedback on only the USPI included in S-042. Therefore, Organon plans to respond back to the FDA comments on the USPI as agreed upon in the below deadline and wanted to confirm if the FDA will be providing comments on the USPPI as well included in S-042?

Thank you!

Kind Regards,
Mini

Mini Chen, PharmD
Associate Principal Scientist, Regulatory Liaison
Phone: (551) 430-6291

From: White, Martin <Martin.White@fda.hhs.gov>
Sent: Wednesday, March 29, 2023 7:53 PM
To: CHEN, MINI <mini.chen@organon.com>
Subject: RE: [EXTERNAL] RE: NDA 21445_S-042_Zetia_Labeling

Mini,

April 21, 2023 is acceptable.

Martin

Martin White, M.S.
Phone 240.402.6018
Martin.White@fda.hhs.gov

From: CHEN, MINI <mini.chen@organon.com>
Sent: Wednesday, March 29, 2023 2:52 PM
To: White, Martin <Martin.White@fda.hhs.gov>
Subject: RE: [EXTERNAL] RE: NDA 21445_S-042_Zetia_Labeling

[Organon] Proprietary

Hi Martin,

Thank you for your email. Organon acknowledges receipt. In addition, would it be possible to request an extension until April 21, 2023?

Kind Regards,
Mini

Mini Chen, PharmD
Associate Principal Scientist, Regulatory Liaison
Phone: (551) 430-6291

From: White, Martin <Martin.White@fda.hhs.gov>
Sent: Tuesday, March 28, 2023 2:09 PM
To: CHEN, MINI <mini.chen@organon.com>
Subject: RE: [EXTERNAL] RE: NDA 21445_S-042_Zetia_Labeling

Mini,

FDA has compiled the attached comments for your draft labeling submitted for NDA 021445, supplement-42, submitted on November 15, 2018. We request that you accept all proposed changes that you agree with, make additional revisions as requested, and return a revised labeling no later than COB **April 11, 2023**.

If there are no changes, please submit the final agreed upon label to me via email.

Acknowledge receipt of this email and let me know if you have any questions.

Thanks
Martin

Martin White, M.S.
Phone 240.402.6018
Martin.White@fda.hhs.gov

From: CHEN, MINI <mini.chen@organon.com>
Sent: Thursday, February 2, 2023 1:27 PM
To: White, Martin <Martin.White@fda.hhs.gov>
Subject: RE: [EXTERNAL] RE: NDA 21445_S-042_Zetia_Labeling

[Organon] Proprietary

Great, thank you!

Mini Chen, PharmD
Associate Principal Scientist, Regulatory Liaison
Phone: (551) 430-6291

From: White, Martin <Martin.White@fda.hhs.gov>
Sent: Thursday, February 2, 2023 11:11 AM
To: CHEN, MINI <mini.chen@organon.com>
Subject: RE: [EXTERNAL] RE: NDA 21445_S-042_Zetia_Labeling

Mini,

March 22, 2023 works for the team.

Martin

Martin White, M.S.
Phone 240.402.6018
Martin.White@fda.hhs.gov

From: CHEN, MINI <mini.chen@organon.com>
Sent: Thursday, February 2, 2023 10:52 AM

To: White, Martin <Martin.White@fda.hhs.gov>
Subject: [EXTERNAL] RE: NDA 21445_S-042_Zetia_Labeling

[Organon] Proprietary

Dear Martin,

Thank you, I acknowledge receipt of the email. Would it be possible to have an extension to March 22, 2023? The changes are quite extensive, therefore, Organon requires more time to review and address them.

Kind Regards,
Mini

Mini Chen, PharmD
Associate Principal Scientist, Regulatory Liaison
Phone: (551) 430-6291

From: White, Martin <Martin.White@fda.hhs.gov>
Sent: Monday, January 30, 2023 7:02 PM
To: CHEN, MINI <mini.chen@organon.com>
Subject: NDA 21445_S-042_Zetia_Labeling

Mini,

FDA has compiled the attached comments for your draft labeling submitted for NDA 021445, supplement-42, submitted on November 15, 2018. We request that you accept all proposed changes that you agree with, make additional revisions as requested, and return a revised labeling no later than COB **February 28, 2023**.

If there are no changes, please submit the final agreed upon label to me via email.

Acknowledge receipt of this email and let me know if you have any questions.

Thanks
Martin

Martin White, MS

Regulatory Project Manager
Diabetes, Lipid Disorders, and Obesity
Division of Regulatory Operations for Cardiology, Hematology, Endocrinology, and Nephrology
Office of Regulatory Operations
Center for Drug Evaluation and Research
WO22 - Room 3389
10903 New Hampshire Avenue
Silver Spring, MD 20903
Phone 240.402.6018
Fax 301.595.2123
Martin.White@fda.hhs.gov

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APPEARS THIS WAY ON ORIGINAL

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/s/

MARTIN L WHITE
05/09/2023 09:18:12 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR PATIENT LABELING REVIEW CONSULTATION

TO: **CDER-DMPP-PatientLabelingTeam**	FROM: (Name/Title, Office/Division/Phone number of requestor) Martin White 240-402-6018

REQUEST DATE:	NDA/BLA NO.	TYPE OF DOCUMENTS: (PLEASE CHECK OFF BELOW)
4.18.2023	21445	

NAME OF DRUG:	PRIORITY CONSIDERATION:	CLASSIFICATION OF DRUG:	DESIRED COMPLETION DATE (Generally 2 Weeks after receiving substantially complete labeling)
Zetia	Priority	Statin	May 15, 2023

SPONSOR:	
Merck	PDUFA Date: November 15, 2018 (Action date is May 31, 2018)

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:
(Check all that apply)
☒ PATIENT PACKAGE INSERT (PPI)
☐ MEDICATION GUIDE
☐ INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION
☐ ORIGINAL NDA/BLA/ANDA
☐ EFFICACY SUPPLEMENT
☐ SAFETY SUPPLEMENT
☒ LABELING SUPPLEMENT
☐ MANUFACTURING (CMC) SUPPLEMENT
☐ PLR CONVERSION

REASON FOR LABELING CONSULT
☐ INITIAL PROPOSED LABELING
☒ LABELING REVISION

EDR link to submission: **\\CDSESUB1\evsprod\NDA021445\0071**

Please Note: DMPP uses substantially complete labeling, which has already been marked up by the CDER Review Team, when reviewing MedGuides, IFUs, and PPIs. Once the substantially complete labeling is received, DMPP will complete its review within 14 calendar days. Please provide a copy of the sponsor's proposed patient labeling in Word format.

COMMENTS/SPECIAL INSTRUCTIONS: The purpose of this supplement is to update the Zetia Prescribing Information to comply with the Pregnancy and Lactation Labeling Rule (PLLR). In addition, DDLO is in the process of updating all the statin labels to modernize them and better communicate use and important safety information, so it is our priority to work through these labels as soon as possible. As a result of this modernization, the PPI is also being updated.

The Division plans to take action on the supplement around May 31, 2023.

The reviewer is Eileen Craig

SIGNATURE OF REQUESTER

SIGNATURE OF RECEIVER

Version: 06/06/2016

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/s/

MARTIN L WHITE
04/18/2023 12:12:12 PM

From: White, Martin
Sent: Tue, 28 Mar 2023 18:08:54 +0000
To: CHEN, MINI
Subject: RE: [EXTERNAL] RE: NDA 21445_S-042_Zetia_Labeling
Attachments: NDA 21445 S-042 tracked PI to firm on 3.28.2023.docx

Mini,

FDA has compiled the attached comments for your draft labeling submitted for NDA 021445, supplement-42, submitted on November 15, 2018. We request that you accept all proposed changes that you agree with, make additional revisions as requested, and return a revised labeling no later than COB **April 11, 2023**.

If there are no changes, please submit the final agreed upon label to me via email.

Acknowledge receipt of this email and let me know if you have any questions.

Thanks
Martin

Martin White, M.S.
Phone 240.402.6018
Martin.White@fda.hhs.gov

From: CHEN, MINI <mini.chen@organon.com>
Sent: Thursday, February 2, 2023 1:27 PM
To: White, Martin <Martin.White@fda.hhs.gov>
Subject: RE: [EXTERNAL] RE: NDA 21445_S-042_Zetia_Labeling

[Organon] Proprietary

Great, thank you!

Mini Chen, PharmD
Associate Principal Scientist, Regulatory Liaison
Phone: (551) 430-6291

From: White, Martin <Martin.White@fda.hhs.gov>
Sent: Thursday, February 2, 2023 11:11 AM
To: CHEN, MINI <mini.chen@organon.com>
Subject: RE: [EXTERNAL] RE: NDA 21445_S-042_Zetia_Labeling

EXTERNAL EMAIL WARNING: The sender of this email originated from outside of Organon. Do not click links, open attachments, or reply with personal information unless you recognize the sender and know the content is safe. If this message looks suspicious, click the "Report Suspicious Email" button on the Outlook toolbar or forward to "Report Spam".

Mini,

March 22, 2023 works for the team.

Martin

Martin White, M.S.
Phone 240.402.6018
Martin.White@fda.hhs.gov

From: CHEN, MINI <mini.chen@organon.com>
Sent: Thursday, February 2, 2023 10:52 AM
To: White, Martin <Martin.White@fda.hhs.gov>
Subject: [EXTERNAL] RE: NDA 21445_S-042_Zetia_Labeling

CAUTION: This email originated from outside of the organization. Do not click links or open attachments unless you recognize the sender and know the content is safe.

[Organon] Proprietary

Dear Martin,

Thank you, I acknowledge receipt of the email. Would it be possible to have an extension to March 22, 2023? The changes are quite extensive, therefore, Organon requires more time to review and address them.

Kind Regards,
Mini

Mini Chen, PharmD
Associate Principal Scientist, Regulatory Liaison
Phone: (551) 430-6291

From: White, Martin <Martin.White@fda.hhs.gov>
Sent: Monday, January 30, 2023 7:02 PM
To: CHEN, MINI <mini.chen@organon.com>
Subject: NDA 21445_S-042_Zetia_Labeling

EXTERNAL EMAIL WARNING: The sender of this email originated from outside of Organon. Do not click links, open attachments, or reply with personal information unless you recognize the sender and know the content is safe. If this message looks suspicious, click the "Report Suspicious Email" button on the Outlook toolbar or forward to "Report Spam".

Mini,

FDA has compiled the attached comments for your draft labeling submitted for NDA 021445, supplement-42, submitted on November 15, 2018. We request that you accept all proposed changes that you agree with, make additional revisions as requested, and return a revised labeling no later than COB **February 28, 2023**.

If there are no changes, please submit the final agreed upon label to me via email.

Acknowledge receipt of this email and let me know if you have any questions.

Thanks
Martin

Martin White, MS
Regulatory Project Manager
Diabetes, Lipid Disorders, and Obesity
Division of Regulatory Operations for Cardiology, Hematology, Endocrinology, and Nephrology
Office of Regulatory Operations
Center for Drug Evaluation and Research
WO22 - Room 3389
10903 New Hampshire Avenue
Silver Spring, MD 20903
Phone 240.402.6018
Fax 301.595.2123
Martin.White@fda.hhs.gov

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/s/

MARTIN L WHITE
03/29/2023 07:55:00 PM

From: White, Martin
Sent: Tue, 31 Jan 2023 00:02:09 +0000
To: CHEN, MINI
Subject: NDA 21445_S-042_Zetia_Labeling
Attachments: NDA 21445 S-042 tracked to firm on 1.30.2023.docx

Mini,

FDA has compiled the attached comments for your draft labeling submitted for NDA 021445, supplement-42, submitted on November 15, 2018. We request that you accept all proposed changes that you agree with, make additional revisions as requested, and return a revised labeling no later than COB **February 28, 2023**.

If there are no changes, please submit the final agreed upon label to me via email.

Acknowledge receipt of this email and let me know if you have any questions.

Thanks
Martin

Martin White, MS
Regulatory Project Manager
Diabetes, Lipid Disorders, and Obesity
Division of Regulatory Operations for Cardiology, Hematology, Endocrinology, and Nephrology
Office of Regulatory Operations
Center for Drug Evaluation and Research
WO22 - Room 3389
10903 New Hampshire Avenue
Silver Spring, MD 20903
Phone 240.402.6018
Fax 301.595.2123
Martin.White@fda.hhs.gov

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/s/

MARTIN L WHITE
01/31/2023 07:41:44 AM

From: Ulmer, Marisa
To: White, Martin
Cc: Gallagher, Deborah L.
Subject: RE: NDAs 19766, 21445, (b) (4) Information Requests
Date: Wednesday, October 31, 2018 5:07:23 PM

Dear Martin,
I confirm receipt of the information request.

We will get the tracked changes versions of 1.11.3 submitted through the gateway this week.

Kind regards,
Marisa

From: White, Martin [mailto:Martin.White@fda.hhs.gov]
Sent: Wednesday, October 31, 2018 10:16 AM
To: Ulmer, Marisa
Subject: NDAs 19766, 21445, (b) (4) Information Requests

EXTERNAL EMAIL – Use caution with any links or file attachments.
Marisa,

We refer to your submissions dated October 29, 2018 for the above referenced NDAs. Please provide the track changes version of the supporting documentation for each supplement.

Please confirm receipt.

Regards,
Martin

Martin White, M.S.
Regulatory Project Manager
FDA/Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
WO22 - Room 3389
10903 New Hampshire Avenue
Silver Spring, MD 20903
Phone 240.402.6018
Fax 301.796.9712
Martin.White@fda.hhs.gov

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/s/

MARTIN L WHITE
10/31/2018

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR OPDP (previously DDMAC) LABELING REVIEW CONSULTATION

****Please send immediately following the Filing/Planning meeting****

TO:

CDER-OPDP-RPM

FROM: (Name/Title, Office/Division/Phone number of requestor)

Martin White, M.S.
Regulatory Health Project Manager
Division of Metabolism & Endocrinology Products (DMEP)
Center for Drug Evaluation and Research
Martin.white@fda hhs.gov
240-402-6018

REQUEST DATE:	IND NO.	NDA/BLA NO.	TYPE OF DOCUMENTS
5/30/2018	N/A	21445	(PLEASE CHECK OFF BELOW) Prescribing Information

NAME OF DRUG:	PRIORITY CONSIDERATION:	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting)
Zetia	no		October 10, 2018

NAME OF FIRM:
Merck

PDUFA Date: November 15, 2018

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:
(Check all that apply)
☐ PACKAGE INSERT (PI)
☐ PATIENT PACKAGE INSERT (PPI)
☐ CARTON/CONTAINER LABELING
☐ MEDICATION GUIDE
☐ INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION
☐ ORIGINAL NDA/BLA
☐ IND
☐ EFFICACY SUPPLEMENT
☐ SAFETY SUPPLEMENT
☐ LABELING SUPPLEMENT
☐ PLR CONVERSION

REASON FOR LABELING CONSULT
☐ INITIAL PROPOSED LABELING
☒ LABELING REVISION

For OSE USE ONLY
☐ REMS

EDR link to submission:
EDR Location: \\CDSESUB1\evsprod\NDA021445\0071

Please Note: There is no need to send labeling at this time. OPDP reviews substantially complete labeling, which has already been marked up by the CDER Review Team. After the disciplines have completed their sections of the labeling, a full review team labeling meeting can be held to go over all of the revisions. Within a week after this meeting, "substantially complete" labeling should be sent to OPDP. Once the substantially complete labeling is received, OPDP will complete its review within 14 calendar days.

OSE/DRISK ONLY: For REMS consults to OPDP, send a word copy of all REMS materials and the most recent labeling to CDER DDMAC RPM. List out all materials included in the consult, broken down by audience (consumer vs provider), in the comments section below.

COMMENTS/SPECIAL INSTRUCTIONS:

This supplemental application proposes to update the Zetia Prescribing Information to comply with the Pregnancy and Lactation Labeling Rule (PLLR).

Review team:
Project Manager: Martin White
Clinical reviewer & Team Leader: Eileen Craig
Pharmacology/Toxicology reviewer & Team Leader: Lee Elmore

No Meetings

SIGNATURE OF REQUESTER	
SIGNATURE OF RECEIVER	METHOD OF DELIVERY (Check one) ☐ eMAIL ☐ HAND

APPEARS THIS WAY ON ORIGINAL

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/s/

MARTIN L WHITE
05/30/2018

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			**DIVISION OF PEDIATRIC AND MATERNAL HEALTH REQUEST FOR CONSULTATION**	
TO: CDER Division of Pediatric and Maternal Health *(please check appropriate box(es))* ☐ Pediatric Team ☒ Maternal Health Team			FROM *(Name, Office/Division, and Phone Number of Requestor)*: Martin White, M.S. Regulatory Health Project Manager Division of Metabolism & Endocrinology Products (DMEP) Center for Drug Evaluation and Research Martin.white@fda.hhs.gov 240-402-6018	
DATE OF CONSULT 5/30/2018	IND NO. N/A	NDA/BLA/ANDA NO. 21445	TYPE OF SUBMISSION supplement	DATE OF SUBMISSION 5/15/2018
NAME OF DRUG Zetia	NAME OF FIRM Merck		DRUG CLASS	INDICATION(S) see below
PDUFA/BsUFA Goal Date 11/15/2018	**DPMH will work with you to establish a suitable due date for the completed consult. Please check one of the three boxes.**			
	☐ Urgent* (< 14 days)		☐ Priority (14-29 days)	☒ Routine (1 – 10 months)

*Note: Any consult requests with a desired completion date of < 14 days from receipt must receive prior approval from DPMH team leaders.

REASON FOR REQUEST (check all that apply)

Pediatrics:	Maternal Health Team:
☐ Labeling Review – non-PLLR ☐ Safety Labeling Supplement ☐ 505(b)(2)/ANDA Pediatric Labeling ☐ Industry Meeting Attendance (PDUFA or BSUFA) ☐ Other Industry Meeting Attendance ☐ BPCA-Related Questions or Documents for Review ☐ PREA-Related Questions or Documents for Review ☐ PeRC Preparation Assistance/iPSP Review ☐ SPA ☐ 30-day IND Review ☐ Other Protocol Review ☐ Tracked Safety Issue ☐ Advisory Committee Preparation ☐ Assistance with Guidance development ☐ Assistance with Citizen Petition Response ☐ Medical Necessity Determination ☐ Off-Patent BPCA/409i Related Questions ☐ Other (please explain):	☒ Labeling Review – PLLR ☐ Labeling Review – non-PLLR ☐ Industry Meeting Attendance ☐ Pregnancy Exposure Registry (protocol or report) ☐ 30-day IND Review ☐ Evaluation of possible safety signal ☐ Risk Management – Pregnancy Prevention and Planning ☐ Clinical Lactation Study (protocol or report) ☐ Pregnancy PK (protocol or report) ☐ Guidance development ☐ Advisory Committee Preparation ☐ Citizen Petition ☐ Other (please explain):
Link to electronic submission (if available): EDR Location: \\CDSESUB1\evsprod\NDA021445\0071	Materials to be reviewed: Prescribing Information

1. Please briefly describe the submission:
This supplemental application proposes to update the Zetia Prescribing Information to comply with the Pregnancy and Lactation Labeling Rule (PLLR).

2. Describe the reason for your consult. Include specific questions:
Please confirm PLLR format is acceptable

3. Meeting dates requiring DPMH presence:
N/A

4. Please list any prior Pediatric or Maternal Health consults for this product by date within the last 3 years that may be relevant to this consult (DARRTS Reference ID # if known):

Version: 10/01/2017

Indication:
ZETIA is an inhibitor of intestinal cholesterol (and related phytosterol) absorption indicated as an adjunct to diet to:

- Reduce elevated total-C, LDL-C, Apo B, and non-HDL-C in patients with primary hyperlipidemia, alone or in combination with an HMG-CoA reductase inhibitor (statin) (1.1)
- Reduce elevated total-C, LDL-C, Apo B, and non-HDL-C in patients with mixed hyperlipidemia in combination with fenofibrate (1.1)
- Reduce elevated total-C and LDL-C in patients with homozygous familial hypercholesterolemia (HoFH), in combination with atorvastatin or simvastatin (1.2)
- Reduce elevated sitosterol and campesterol in patients with homozygous sitosterolemia (phytosterolemia) (1.3)

Limitations of Use (1.4)

- The effect of ZETIA on cardiovascular morbidity and mortality has not been determined.
- ZETIA has not been studied in Fredrickson Type I, III, IV, and V dyslipidemias.

Review team:
Project Manager: Martin White
Clinical reviewer & Team Leader: Eileen Craig
Pharmacology/Toxicology reviewer & Team Leader: Lee Elmore
Clinical Pharmacology reviewer & Team Leader: N/A
Other:

PRINTED NAME or SIGNATURE OF REQUESTOR:
Martin White

APPEARS THIS WAY ON ORIGINAL

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/s/

MARTIN L WHITE
05/30/2018

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 021445/S-042

ACKNOWLEDGMENT --
PRIOR APPROVAL SUPPLEMENT

Merck Sharp & Dohme Corp.
US Agent for MSD International GmbH
Attention: Marisa Ulmer
Principal Scientist, Global Regulatory Affairs
351 North Sumneytown Pike, P.O. Box 1000
North Wales, PA 19454

Dear Ms. Ulmer:

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

NDA NUMBER: 021445

SUPPLEMENT NUMBER: 042

PRODUCT NAME: Zetia (ezetimibe)

DATE OF SUBMISSION: MAY 15, 2018

DATE OF RECEIPT: MAY 15, 2018

This supplemental application proposes to update the Zetia Prescribing Information to comply with the Pregnancy and Lactation Labeling Rule (PLLR).

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on July 14, 2018, in accordance with 21 CFR 314.101(a).

If the application is filed, the goal date will be November 15, 2018.

If you have questions, call me at (240) 402-6018.

Sincerely,

{See appended electronic signature page}

Martin White, M.S.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

MARTIN L WHITE
05/25/2018