

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

210895Orig1s000

OTHER REVIEW(S)

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

Date of This Memorandum: March 27, 2019

Requesting Office or Division: Division of Metabolism and Endocrinology Products (DMEP)

Application Type and Number: NDA 210895

Product Name and Strength: Welchol (colesevelam hydrochloride) chewable bars, 3.75 g

Applicant/Sponsor Name: Daiichi Sankyo, Inc.

FDA Received Date: March 22, 2019

OSE RCM #: 2017-2285-2

DMEPA Safety Evaluator: Madhuri R. Patel, PharmD

DMEPA Team Leader: Sevan Kolejian, PharmD, MBA

1 PURPOSE OF MEMORANDUM

Division of Metabolism and Endocrinology Products (DMEP) requested that we review the revised container labels and carton labeling for Welchol (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

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

^a Patel, M. Label and Labeling Review Memo for WELCHOL (colesevelam) chewable bar (NDA 210895). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 MAR 13. RCM No.: 2017-2285-1.

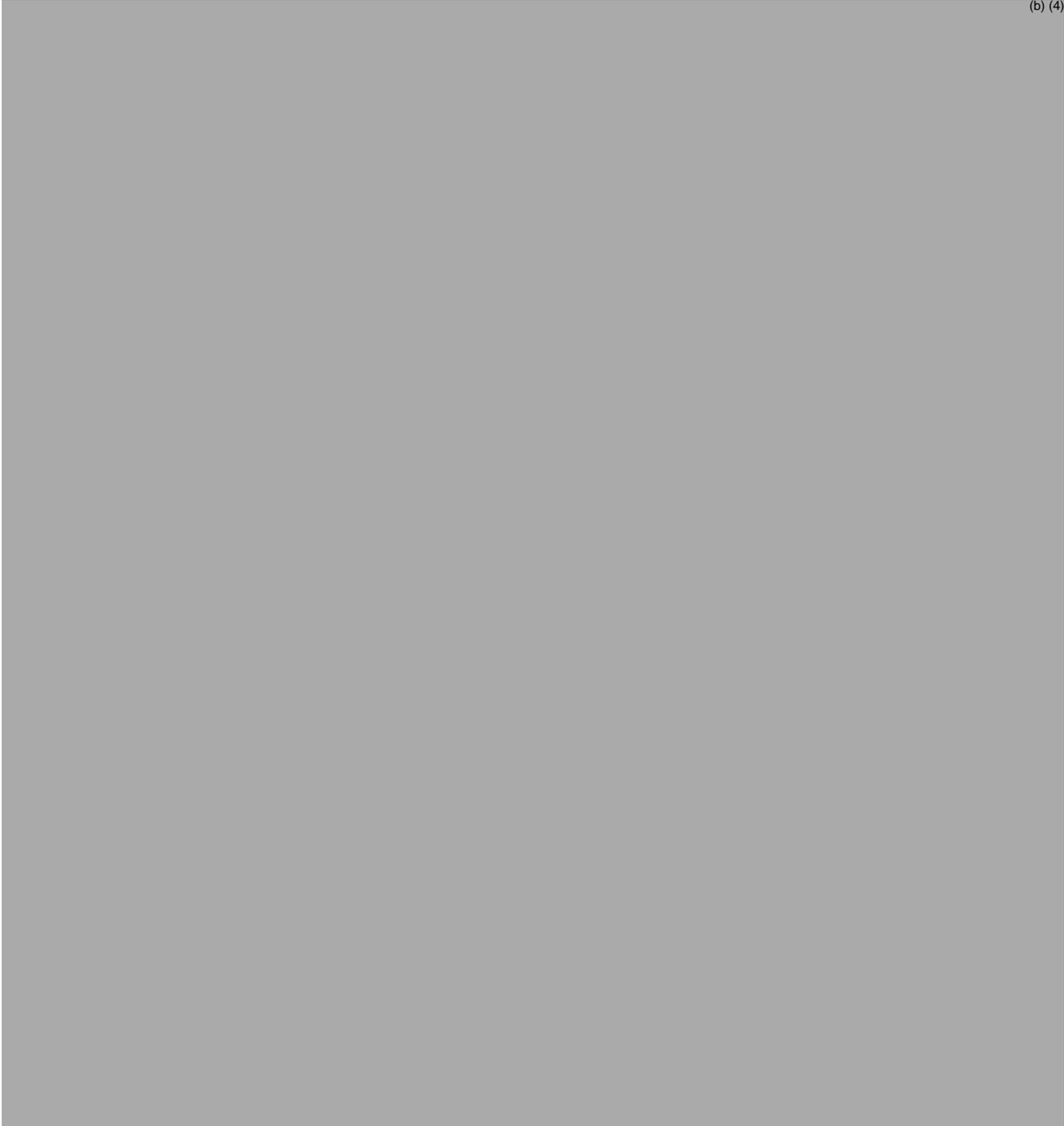
APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON MARCH 22, 2019

Container labels and carton labeling available in EDR:

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Container labels

(b) (4)



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/s/

MADHURI R PATEL
03/27/2019 11:31:37 AM

SEVAN H KOLEJIAN
03/27/2019 12:21:30 PM

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

Date of This Memorandum: March 13, 2019

Requesting Office or Division: Division of Metabolism and Endocrinology Products (DMEP)

Application Type and Number: NDA 210895

Product Name and Strength: Welchol (colesevelam hydrochloride) chewable bars, 3.75 g

Applicant/Sponsor Name: Daiichi Sankyo, Inc.

FDA Received Date: February 28, 2019

OSE RCM #: 2017-2285-1

DMEPA Safety Evaluator: Madhuri R. Patel, PharmD

DMEPA Team Leader: Sevan Kolejian, PharmD, MBA

1 PURPOSE OF MEMORANDUM

Division of Metabolism and Endocrinology Products (DMEP) requested that we review the revised container labels, carton labeling, and Prescribing Information (PI) for Welchol (Appendix A) to determine if it is acceptable from a medication error perspective. NDA 210895 received a Complete Response (CR) on August 24, 2018 for facility deficiencies. A Complete Response resubmission was then submitted on October 3, 2018 and the revised labels and labeling on February 28, 2019. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

The revised Prescribing Information (PI) is acceptable from a medication error perspective. However, the revised container labels and carton labeling are unacceptable from a medication error perspective. The labels and labeling can be improved to provide clarity in the dosage form, aid in product identification, and prevent deteriorated drug errors.

^a Rimmel, S. Label and Labeling Review for WELCHOL (colesevelam) chewable bar (NDA 210895). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 May 16. RCM No.: 2017-2285.

3 RECOMMENDATIONS FOR DAIICHI SANKYO, INC.

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

- A. General Comments (Container Labels, Carton Labeling, Professional Sample Container Labels, and Professional Sample Carton Labeling)
 - a. Revise the dosage form statement ('chewable bar' for container label and 'chewable bars' for the carton labeling) to appear on the same line as the established name or on the next line below the established name, as per Draft Guidance: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013.

- B. Carton Labeling (Trade)
 - a. As currently presented, the NDC number for the container labels is the same as the NDC number for the carton labeling. Because the carton contains 30 units of the product, then the carton labeling should have a different NDC package code (last 2 digits of the NDC) than the containers within the carton. Revise the NDC numbers so that the carton labeling and wrapper labels use a different NDC package code.
 - b. In September 2018, FDA released draft guidance on product identifiers required under the Drug Supply Chain Security Act.^b The Act requires manufacturers and repackagers, respectively, to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce beginning November 27, 2017, and November 27, 2018, respectively. We recommend that you review the draft guidance for the format and content outlined in the guidance for the human-readable portion of identification as well as mentions of the GTIN. We continue to recommend moving the GTIN number away from the lot and expiration date to minimize the risk of confusion due to close proximity to the lot and expiration date.

- C. Carton Labeling (Professional Sample 3 chewable bars for the assorted flavors (NDC (b) (4))).
 - a. We note there is no placeholder for the lot and expiration date on the carton labeling. Please ensure the lot and expiration date are included on the sample carton labeling in accordance with 21 CFR 201.17.

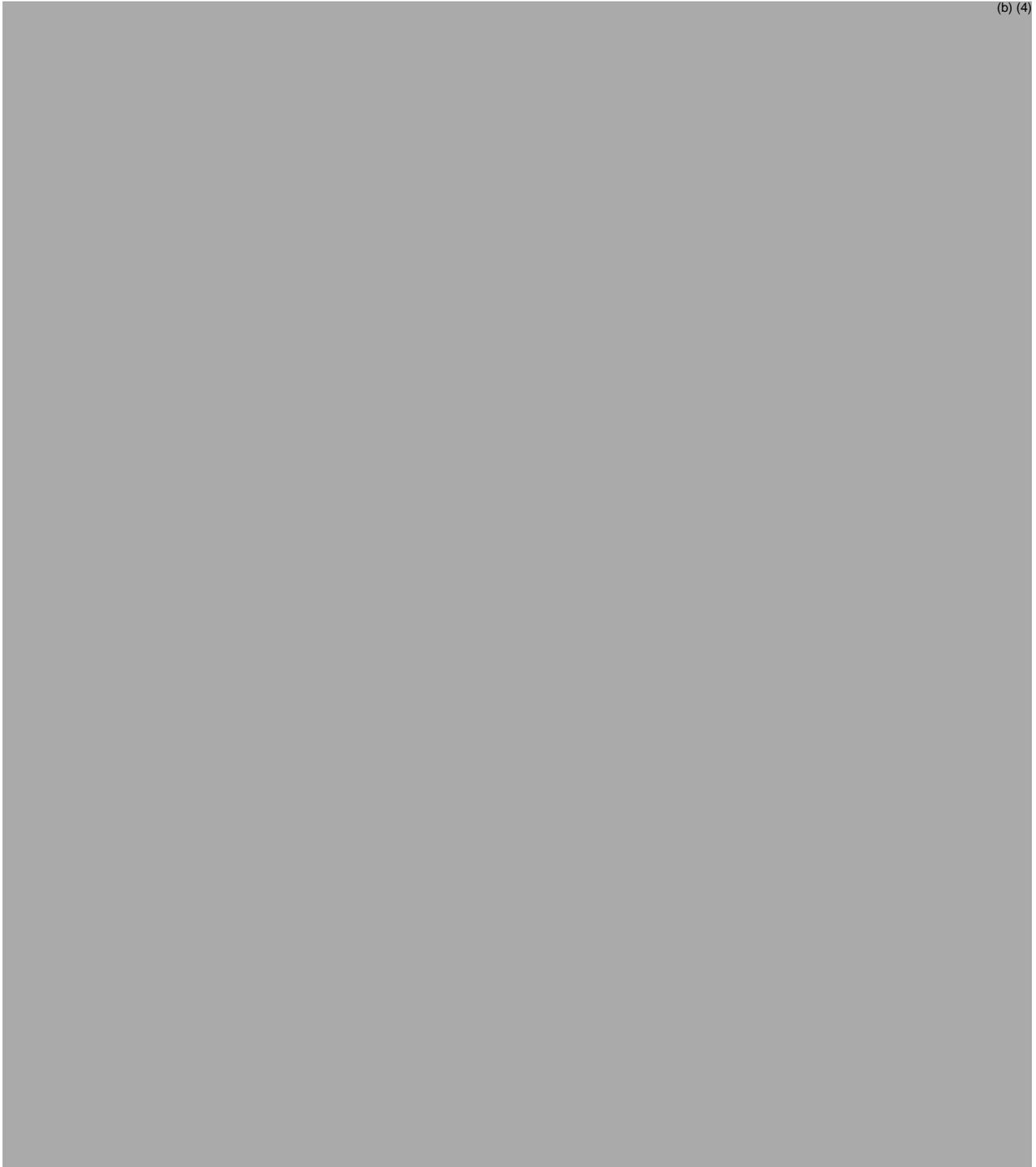
^b The draft guidance is available from: <https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf>

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON FEBRUARY 28, 2019

Container labels and carton labeling available in EDR:

<\\CDSESUB1\evsprod\NDA210895\0023\m1\us\114-labeling\draft\carton-and-container>

Container labels



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/s/

MADHURI R PATEL
03/13/2019 10:51:16 AM

SEVAN H KOLEJIAN
03/13/2019 10:55:27 AM



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 Memorandum

Date: June 26, 2018 **Date consulted:** December 26, 2017

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

Through: Tamara Johnson, M.D., MS, Team Leader, Maternal Health, DPMH
Lynne P. Yao, MD, OND, Division Director, DPMH

To: Division of Metabolism and Endocrinology Products (DMEP)

Drug: Welchol (colesevelam hydrochloride), Chewable

Drug Class: Bile acid Sequestrant, Hypolipidemic Agent

NDA: 210895/00

Applicant: Daiichi Sankyo, Inc.

Subject: Pregnancy and Lactation Labeling Rule (PLLR)

Indication: As an adjunct to diet and exercise to:

1. Reduce elevated low density lipoprotein cholesterol (LDL-C) in patients with primary hypercholesterolemia as monotherapy or in combination with an hydroxy-methylglutaryl-coenzyme A (HMG CoA) reductase inhibitor.
2. Improve glycemic control in adults with type 2 diabetes mellitus.

Materials Reviewed:

- DPMH consult request dated December 26, 2017 in DARRTS (Reference ID:4200515)
- Applicant's submission for NDA 210895 dated October 30, 2017 and the latest Prescribing Information (PI) for Welchol Chewable of October 30 and Welchol Tablets and Oral Suspension labelings dated January 22, 2014 in Physician Labeling Rule (PLR,) hybrid format
- Applicant's response to information request of January 3, 2018, dated February 9,

2018.

Consult Question:

DMEP requests DPMH assistance with reviewing the applicant's Pregnancy and Lactation labeling subsections to comply with PLLR format.

INTRODUCTION

The Division of Metabolism and Endocrinology Products (DMEP) consulted the Division of Pediatric and Maternal Health (DPMH) on December 26, 2017, to provide input and recommendations related to the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections in labeling to provide clinically relevant information for prescribing decisions and to comply with current PLLR regulatory requirements.

Colesevelam hydrochloride is currently marketed by Daiichi Sankyo Inc. as Welchol Tablets under NDA 21176 and as an Oral Suspension under NDA 22362. A new NDA 210895 was submitted under 505(b)(1) pathway on October 30, 2017 for a chewable bar formulation. As per the applicant, colesevelam, a bile acid sequestrant, has been marketed in the US since 2000. Colesevelam, is not hydrolyzed by digestive enzymes, and is not absorbed systemically. Welchol is indicated as an adjunct to diet and exercise to:

- reduce elevated low-density lipoprotein cholesterol (LDL-C) in adults with primary hyperlipidemia as monotherapy or in combination with a hydroxymethyl-glutaryl-coenzyme A (HMG CoA) reductase inhibitor (statin).
- reduce LDL-C levels in boys and postmenarchal girls, 10 to 17 years of age, with heterozygous familial hypercholesterolemia as monotherapy or in combination with a statin after failing an adequate trial of diet therapy.
- improve glycemic control in adults with type 2 diabetes mellitus

In addition, the warnings address precautions regarding fat-soluble vitamin deficiencies and recommend that patients take such vitamins 4 hours before using colesevelam.

BACKGROUND

Welchol Drug Characteristics¹

- Welchol is a bile acid sequestrant and impedes the bile acid reabsorption
- it is not bound to plasma proteins because it is not systemically absorbed
- half-life is unknown
- molecular weight is 618.25 gr/mol

Hypercholesterolemia and Pregnancy^{2,3}

Cholesterol is important for embryofetal development. The conceptus derives a substantial proportion (at least 80%) of its cholesterol needs from endogenous synthesis rather than via the maternal circulation.⁴ Across multiple species including humans, the rates of cholesterol synthesis in the fetus are much greater than in the adult.⁵ Whether mediated by dietary

¹ Welchol existing labeling of January 22, 2014

² Dukic, *et. al.* Hyperlipidemia and Pregnancy. Med Pregl. 2009; 62 Suppl 3: 80-84

³ Ofori, *et. al.* Risk of congenital anomalies in pregnant users of statin drugs. British Journal of Clinical Pharmacology. 2007; 64(4):496-509.

⁴ Bartels A and O'Donoghue K. Cholesterol in pregnancy: a review of knowns and unknowns. Obstetric Med. 2011; 4:147-151.

⁵ Dietschy JM, Turley SD, and Spady DK. Role of liver in the maintenance of cholesterol and low density lipoprotein homeostasis in different animal species, including humans. 1993; J Lipid Res. 34:1637-1659

intervention or by genetic mutations resulting in 50% reduction in maternal serum LDL-C, no negative effects on embryo-fetal development have been observed in children born to mothers with low cholesterol throughout pregnancy.⁶ High synthetic rate in the conceptus and/or the placenta provides sufficient cholesterol to maintain sterol-independence from maternal sources.⁷ This finding may indicate that low cholesterol is a low risk for fetal harm in humans. During pregnancy, it is normal for total cholesterol, high density lipoprotein (HDL-C) and low density lipoprotein (LDL) to increase by 25 to 50% in the pregnant woman. Triglycerides may increase up to 2 to 4 times during the same period.

Cholesterol is recognized as a major cause of macrovascular disease and is associated with impaired endothelium-dependent vasodilation. The increase of cholesterol in women during pregnancy does not lead to endothelial dysfunction.⁸ Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on long-term outcomes of primary hyperlipidemia therapy.⁹ Therefore, there are no justifications to warrant the use of cholesterol reducing agents in pregnancy (no benefit to outweigh the risk).

Current Labeling

The current labelings for Welchol (NDA 021176) of January 22, 2014 is in Physician Labeling Rule format (PLR), and has not yet complied with PLLR and still has letter category (Pregnancy Category B). It states:¹⁰

FULL PRESCRIBING INFORMATION: CONTENTS

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.3 Nursing Mothers

FULL PRESCRIBING INFORMATION

8.1 Pregnancy

Pregnancy Category B

There are no adequate and well-controlled studies of colesevelam use in pregnant women. Animal reproduction studies in rats and rabbits revealed no evidence of fetal harm.

Requirements for vitamins and other nutrients are increased in pregnancy. However, the effect of colesevelam on the absorption of fat-soluble vitamins has not been studied in pregnant women. This drug should be used during pregnancy only if clearly needed.

In animal reproduction studies, colesevelam revealed no evidence of fetal harm when administered to rats and rabbits at doses 50 and 17 times the maximum human dose, respectively. Because animal reproduction studies are not always predictive of human response, this drug should be used in pregnancy only if clearly needed.

8.3 Nursing Mothers

Colesevelam hydrochloride is not expected to be excreted in human milk because colesevelam

⁶ Hormanics GE, Smith TJ, Zhang SH, *et al.* Targeted modification of the apolipoprotein B gene results in hypobetalipoproteinemia and developmental abnormalities in mice. *Proc. Natl. Acad. Sci. USA.* 1992; 90:2389-2393

⁷ Woollett LA. Maternal cholesterol in fetal development: transport of cholesterol from the maternal to the fetal circulation. *Am J Clin Nutr.* 2005;82:1155-1161

⁸ Multiple Risk Factor Intervention Trial Group. Multiple Risk Factor Intervention Trial: risk factor changes and mortality results. *JAMA.* 1982;248:1465-1477

⁹ Crestor labeling, last revised on August 4, 2017

¹⁰ Welchol labeling of January 22, 2014

hydrochloride is not absorbed systemically from the gastrointestinal tract.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: A 104-week carcinogenicity study with colesevelam hydrochloride was conducted in CD-1 mice, at oral dietary doses up to 3 g/kg/day. This dose was approximately 50 times the maximum recommended human dose of 4.5 g/day, based on body weight, mg/kg. There were no significant drug-induced tumor findings in male or female mice. In a 104-week carcinogenicity study with colesevelam hydrochloride in Harlan Sprague-Dawley rats, a statistically significant increase in the incidence of pancreatic acinar cell adenoma was seen in male rats at doses >1.2 g/kg/day (approximately 20 times the maximum human dose, based on body weight, mg/kg) (trend test only). A statistically significant increase in thyroid C-cell adenoma was seen in female rats at 2.4 g/kg/day (approximately 40 times the maximum human dose, based on body weight, mg/kg).

Mutagenesis: Colesevelam hydrochloride and 4 degradants present in the drug substance have been evaluated for mutagenicity in the Ames test and a mammalian chromosomal aberration test. The 4 degradants and an extract of the parent compound did not exhibit genetic toxicity in an *in vitro* bacterial mutagenesis assay in *S. typhimurium* and *E. coli* (Ames assay) with or without rat liver metabolic activation. An extract of the parent compound was positive in the Chinese Hamster Ovary (CHO) cell chromosomal aberration assay in the presence of metabolic activation and negative in the absence of metabolic activation. The results of the CHO cell chromosomal aberration assay with 2 of the 4 degradants, decylamine HCl and aminohexyltrimethyl ammonium chloride HCl, were equivocal in the absence of metabolic activation and negative in the presence of metabolic activation. The other 2 degradants, didecylamine HCl and 6-decylamino-hexyltrimethyl ammonium chloride HCl, were negative in the presence and absence of metabolic activation.

Impairment of Fertility: Colesevelam hydrochloride did not impair fertility in rats at doses up to 3 g/kg/day (approximately 50 times the maximum human dose, based on body weight, mg/kg).

13.2 Animal Toxicology and/or Pharmacology

Reproductive Toxicology Studies

Reproduction studies have been performed in rats and rabbits at doses up to 3 g/kg/day and 1 g/kg/day, respectively (approximately 50 and 17 times the maximum human dose, based on body weight, mg/kg) and have revealed no evidence of harm to the fetus due to colesevelam hydrochloride.

REVIEW

PREGNANCY

Animal Data

No new additional information exists. The existing labeling states that embryo-fetal development studies in rats and rabbits at doses approximately 50 and 17 times the maximum human dose, respectively, have revealed no evidence of harm to the fetus due to colesevelam hydrochloride.

Review of Literature

Applicant's Review

The databases searched included OVID:

- BIOSIS Previews 1980 to 2018, Embase 1980 to January 12, 2018,

- Ovid MEDLINE(R) 1996 to Present with Daily Update,
- Ovid MEDLINE(R) Epub Ahead of Print January 12, 2018,
- Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations January 12, 2018

The literature review revealed only one publication reporting on a small case series (5 cases) report from Emory University of pregnant women with familial hypercholesterolemia.¹¹ Their healthcare providers discontinued statin therapy with pregnancy and started all 5 on colesevelam 625 mg twice daily. Three women completed colesevelam use throughout pregnancy and experienced no maternal or fetal adverse events. Two stopped after 1 month secondary to GI upset and fear of harm to the unborn child. The authors reported 2 spontaneous abortions, a preterm labor and a cesarean section. They considered that these adverse events were not related to colesevelam.

DPMH Review

In addition to the search by the applicant, DPMH also conducted a literature search in PubMed, Embase and the TERIS and ReproTox databases for colesevelam and use in pregnancy. Drugs in Pregnancy and Lactation by Briggs GG and Freeman RK, was also searched. No additional case reports or any trials/studies were identified.

Applicant's Review of Pharmacovigilance Database

The applicant conducted an analysis of adverse events in the safety database related to colesevelam and fat soluble vitamin deficiency. There were only two non-serious cases, neither of which involving pregnant women. In addition, a review of all colesevelam pregnancy cases failed to associate any adverse effects with vitamin A, D, E or K deficiency. The depletion of fat soluble vitamins during pregnancy is a concern. The applicant states that colesevelam use is not recommended during pregnancy and the USPI already warns that patients should take fat soluble vitamins 4 hours prior to Welchol.

Daiichi Sankyo, the applicant, searched its global safety database that contains all spontaneous post-marketing adverse event reports, all literature reports of adverse events and all serious adverse events from clinical trials. MedDRA version 20.1 was used. The database was searched from first colesevelam case received through December 31, 2017 for:

Pregnancy:

- SOC: Pregnancy, Puerperium & Perinatal Conditions
- HLT: Exposures, Chemical Injuries & Poisoning (includes fetal exposure during pregnancy and other relevant PTs)
- SMQ: Pregnancy, Labor & Delivery Complications (broad)

Fat Soluble Vitamin Deficiencies:

- HLT: Fat Soluble Vitamin Deficiencies & Disorders
- Review of events in pregnancy search results above for signs/symptoms of vitamin A, D, E, K deficiencies such as visual disorders, fractures, gait disturbances and hemorrhages respectively.

There were 17 cases reported, out of which only 4 were serious. Reason for use of the drug included Diabetes mellitus (6), Dyslipidemia (5), Diarrhea (2), bile acid malabsorption (1), Unknown (3). Six cases reported an adverse event (AEs are not referenced).

Table 1: Relevant Pregnancy Cases Reported in Pharmacovigilance Database

¹¹ Eapen DJ, Valiani K, Reedy S, Sperling L, et al. Management of familial hypercholesterolemia during pregnancy: Case series and discussion. *Journal of Clinical Lipidology*. 2012;6:88-91.

Cases#	Age y/o	Time starting treatment	Treatment duration in pregnancy	Pregnancy outcome
1	26	2 years before pregnancy	Throughout pregnancy	Healthy male by cesarean section
2	22	1 month before pregnancy	At unspecified time, she stopped medication	Miscarriage 3 months later Concomitant meds: atorvastatin, ezetimibe
3	15	She took the drug for 7 months, when she found she was pregnant.		Preterm delivery at 22 weeks with non-viable infant
4	17	She took the drug for 10 months, when she found she was pregnant		Miscarriage at 3 months

From applicant's response to IR, dated February 9, 2018 PP 8-9

Fat soluble vitamins

Review of Literature

A literature review by the applicant and DPMH did not identify any publications on the effects of colesevelam on fat soluble vitamins.

Applicant's Review of Pharmacovigilance Database

A review of adverse events for all 23 cases retrieved during the pregnancy search did not indicate any concerns for vitamin A, D, E or K. The applicant states that this review focused on possible adverse events such as vision disorder, fractures, gait disturbances and hemorrhaging.

Summary

Embryofetal development studies in rats and rabbits at high multiples to the maximum human dose, based on body weight, (mg/kg), have revealed no evidence of harm to the fetus due to colesevelam hydrochloride.

No studies with colesevelam in pregnant women were identified. Only 5 case reports have been identified in the literature and 4 reports through the applicant's pharmacovigilance program. No clinical evidence was identified of the drug associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes, but the data are extremely limited and no definitive conclusions can be made.

LACTATION

Animal Data

Because the drug is not systemically absorbed, it is not expected to be in breast milk. No animal studies were conducted.

Applicant's Review of Literature

- The applicant searched BIOSIS Previews 1980 to 2018, Embase 1980 to January 12, 2018
 - Ovid MEDLINE(R) 1996 to Present with Daily Update,
 - Ovid MEDLINE(R) Epub Ahead of Print January 12, 2018,
- No publications were identified. Because the drug is not systemically absorbed, it is not expected to be in breast milk

Applicant's Review of Pharmacovigilance Database

The applicant does not present any pharmacovigilance reports.

Summary

Colesevelam, as a bile acid sequestrant, is not systemically absorbed and as such is not expected to be present in breast milk. Therefore, subsection 8.2 will contain the required language per the PLLR for products not systemically absorbed.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Animal Data

Reproduction studies have been performed in rats and rabbits at doses approximately 50 and 17 times the maximum human dose, respectively, and have revealed no evidence of harm to the fetus due to colesevelam hydrochloride.

Review of Literature

A literature review by the applicant and DPMH did not identify any publications on the effects of colesevelam on female and male fertility.

Applicant's Review of Pharmacovigilance Database

The most common adverse event in 6 of the 11 cases was sexual dysfunction or erectile dysfunction in male patients. Most were confounded by underlying disease (including diabetes mellitus and cardiac disease) or a pre-existing history of sexual dysfunction.

Interaction with Oral Contraceptives: When Welchol is taken together with oral contraceptives, it decreases their effect. The labeling recommends that drugs with a known interaction with colesevelam should be administered at least 4 hours prior to Welchol.

Summary

No clinical data exists which suggests that therapeutic doses of colesevelam have any effect on fertility. Colesevelam is not genotoxic or mutagenic. There is no information to be conveyed regarding pregnancy testing or fertility, however, drug-contraceptive interaction should be mentioned in labeling subsection 8.3.

CONCLUSIONS

Welchol labeling has been updated to comply with the PLLR. The drug is not systemically absorbed and the available data are not sufficient to identify an association between colesevelam use during pregnancy and adverse developmental outcomes.

DPMH revised subsections 8.1, 8.2, and 8.3 and section 17 of labeling for compliance with the PLLR (see below). DPMH refers to the final NDA action for final labeling.

The *Pregnancy* and *Lactation* subsections of Welchol labeling were structured to be consistent with the PLLR as follows:

- **Pregnancy, Subsection 8.1**
 - The “Pregnancy” subsection of Welchol labeling was formatted in the PLLR format to include: “Risk Summary” and “Data” headings.
- **Lactation, Subsection 8.2**
- **Females and Males of Reproductive Potential, Subsection 8.3**
The proposed Females and Males of Reproductive Potential subsection of Welchol labeling was formatted in the PLLR format to include the “Contraception” heading [*see Drug Interactions (7)*]

RECOMMENDATIONS

DPMH has the following recommendations for Welchol 17 PATIENT COUNSELING INFORMATION

Females of Reproductive Potential

Advise females of reproductive potential that WELCHOL may reduce the effectiveness of oral contraceptives, and to take oral contraceptives at least 4 hours before taking WELCHOL [*see Drug Interactions (7.x) and Use in Specific Populations (8.3)*] labeling.

FULL PRESCRIBING INFORMATION: CONTENTS

USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.2 Lactation
- 8.3 Females and Males of Reproductive Potential**

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

WELCHOL is not absorbed systemically [*see Clinical Pharmacology (12.3)*] following oral administration, and maternal use is not expected to result in fetal exposure to the drug. However, WELCHOL may decrease the absorption of fat-soluble vitamins [*see Warnings and Precautions (5.3)*]. There are no data available on the effect of colessevelam on the absorption of fat-soluble vitamins in pregnant women. Animal studies in rats and rabbits with colessevelam hydrochloride administered during organogenesis at doses up to approximately 50 and 17 times the maximum human dose, based on body weight, (mg/kg) have revealed no evidence of harm to the offspring due to colessevelam hydrochloride (*see Data*).

If the patient becomes pregnant while taking WELCHOL, the patient should be advised of the lack of known clinical benefit with continued use during pregnancy.

The estimated background risk of major birth defects and miscarriage for the indicated population are unknown. All pregnancies have a background risk of birth defect, loss or other adverse outcomes. In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

In animal reproduction studies, colesevelam revealed no evidence of fetal harm when administered to rats and rabbits during organogenesis at doses 50 and 17 times the maximum human dose, respectively.

8.2 Lactation

WELCHOL is not absorbed systemically [*see Clinical Pharmacology (12.3)*] by the mother following oral administration, and breastfeeding is not expected to result in exposure of the infant to WELCHOL

8.3 Females and Males of Reproductive Potential

Contraception

Use of WELCHOL may reduce the efficacy of oral contraceptives. Advise patients to take oral contraceptives at least 4 hours prior to taking WELCHOL [*see Drug Interactions (7)*].

17 PATIENT COUNSELING INFORMATION

Females of Reproductive Potential

Advise females of reproductive potential that WELCHOL may reduce the effectiveness of oral contraceptives, and to take oral contraceptives at least 4 hours before taking WELCHOL [*see Drug Interactions (7) and Use in Specific Populations (8.3)*].

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/s/

CHRISTOS MASTROYANNIS
06/27/2018

TAMARA N JOHNSON
07/02/2018

LYNNE P YAO
07/02/2018

MEMORANDUM

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

DATE: June 22, 2018

TO: William Chong, M.D.
Director (Acting)
Division of Metabolism and Endocrinology Products
(DMEP)
Office of Drug Evaluation II (ODE II)
Office of New Drugs

FROM: Mohsen Rajabi Abhari, Ph.D.
Pharmacologist
Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Arindam Dasgupta, Ph.D.
Deputy Director
Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: Surveillance inspection of [REDACTED] (b) (4)
[REDACTED]

Inspection Summary

The Office of Study Integrity and Surveillance (OSIS) conducted an inspection of studies 062319-06-03 (M12601, M13400) and 062319-06-02 (M12602, M4176) conducted at [REDACTED] (b) (4)
[REDACTED]

Form FDA 483 was issued at the inspection close-out. The final inspection classification is Voluntary Action Indicated (VAI).

Although objectionable conditions were observed during this inspection, the findings did not impact the reliability of the data from the audited studies. Thus, I recommend that the data from studies 062319-06-03 (M12601, M13400) and 062319-06-02 (M12602, M4176) and other studies using similar methods be accepted for further Agency review.

Inspected Studies:

NDA 210895

Study Number: 062319-06-03 (M12601, M13400)

Study Title: "Analysis Report for the Equilibrium Bioequivalency Comparison Study for the Binding of Bile Acids in Welchol Tablets and Soft Chews."

Dates of conduct: 8/10/2016 - 9/19/2016

Study Number: 062319-06-02 (M12602, M4176)

Study Title: "Analysis Report for the Kinetic Bioequivalency Comparison for the Binding of Bile Acids in Welchol Tablets and Welchol Soft Chews."

Dates of conduct: 5/19/2016 - 9/10/2016

Analytical site: [REDACTED] (b) (4)

OSIS scientist Mohsen Rajabi Abhari, Pharmacologist and ORA investigator Jonathan Campos, CSO audited the above in vitro studies at [REDACTED] (b) (4)

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

At the conclusion of the inspection, we observed one objectionable condition and Form FDA 483 was issued to the analytical site. In addition, one discussion item was also discussed with the firm during close out. The Form FDA 483 observation (**Attachment 2**), the firm's response dated 6/5/2018 (**Attachment 3**), and my evaluation is presented below.

[REDACTED] (b) (4)

Conclusion:

Some objectionable conditions were observed during this inspection and Form FDA 483 was issued. The final inspection classification is Voluntary Action Indicated (VAI).

After reviewing the inspectional findings and the firm's response to Form FDA 483, the objectionable conditions did not impact the reliability of the data from the audited studies. In addition, the overall performance of the site was adequate and is unlikely to impact the integrity of the data from other studies using similar methods.

I recommend that the data from studies 062319-06-03 (M12601, M13400) and 062319-06-02 (M12602, M4176) and the data from studies submitted to pending applications (**Attachment 1**) be accepted for further Agency review. In addition, studies using similar methods conducted between the previous inspection ([REDACTED] (b) (4)) and the end of the current surveillance interval

should also be accepted for review by the Agency without an inspection.

Mohsen Rajabi Abhari, Ph.D.
Pharmacologist

Final Classification:

VAI

(b) (4)

cc:

OTS/OSIS/Kassim/Choe/Mitchell/Fenty-Stewart/Nkah
OTS/OSIS/DNDBE/Bonapace/Dasgupta/Ayala/Biswas/Rajabi
OTS/OSIS/DGDBE/Cho/Jang/Choi/Skelly/Au

Draft: 6/16/2018, 6/21/2018

Edit: GB 6/19/2018, 6/21/2018; AD 6/22/2018

ECMS: Cabinets/CDER_OC/OSI/OSIS--Office of Study Integrity and Surveillance/INSPECTIONS/BE Program/ANALYTICAL SITES/[REDACTED] (b) (4)
[REDACTED] (b) (4)/NDA 210895_Welchol® colesevelam hydrochloride Chewable Bar 3.75 g equivalent to 6 x 625 mg tablets

OSIS File #: [REDACTED] (b) (4)

FACTS: [REDACTED] (b) (4)

Attachment 1
Studies in support of Pending Applications

Application #	Study #	Study Type (in vitro)	Drug Name	Dates of conduct
NDA 210895	062319-06-03 (M12601, M13400)	In Vitro	colesevelam hydrochloride	[REDACTED] (b) (4)
NDA 210895	062319-06-02 (M12602, M4176)	In Vitro	colesevelam hydrochloride	

Attachment 2

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/s/

MOHSEN RAJABI ABHARI
06/22/2018

GOPA BISWAS
06/22/2018

ARINDAM DASGUPTA
06/22/2018

LABEL AND LABELING REVIEW

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

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

Date of This Review:	May 16, 2018
Requesting Office or Division:	Division of Metabolism and Endocrinology Products
Application Type and Number:	NDA 210895
Product Name and Strength:	Welchol (colesevelam hydrochloride) chewable bar, 3.75 g
Product Type:	Single Ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Daiichi Sankyo, Inc.
FDA Received Date:	October 30, 2017
OSE RCM #:	2017-2285
DMEPA Safety Evaluator:	Susan Rimmel, PharmD
DMEPA Team Leader:	Hina Mehta, PharmD

1 REASON FOR REVIEW

The Division of Metabolism and Endocrinology Products (DMEP) consulted DMEPA to evaluate the Prescribing Information (PI), container labels (trade and professional sample), and carton labeling (trade and professional sample) for Welchol (colesevelam hydrochloride) chewable bar, 3.75 g submitted by Daiichi Sankyo, Inc. on October 30, 2017, under NDA 210895, utilizing the 505(b)(1) regulatory pathway. The original NDA is seeking approval for three flavors (chocolate, strawberry, and caramel) of the new oral dosage form, chewable bar. The application relies in part on safety and efficacy information, with relevant cross-reference to required Clinical, Nonclinical Pharmacology and Toxicology, and Clinical Pharmacology elements in the approved NDAs for Welchol tablet and Welchol for oral suspension.

1.1 REGULATORY HISTORY

Welchol (colesevelam hydrochloride) tablet, 625 mg (NDA 021176) and capsule, 375 mg (NDA 021141) were approved on May 26, 2000. However, the 375 mg capsule has never been marketed. In addition, Welchol for oral suspension, 1.875 g and 3.75 g single-dose packets (NDA 022362) was approved on October 2, 2009. We note the submission on October 30, 2017, proposes to remove all references to the 1.875 g for oral suspension strength in the PI. The Applicant proposes a single PI based on the currently approved tablet and for oral suspension labeling, with appropriate sections modified to incorporate the chewable bar dosage form.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

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

N/A=not applicable for this review

*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We performed a risk assessment of the revised PI, container labels (trade and professional sample), and carton labeling (trade and professional sample) to identify deficiencies that may lead to medication errors and other areas of improvement. We identified areas of the proposed PI, container labels, and carton labeling that could be improved to promote the safe use of the product.

For the Division, we provide revisions for Section 3 and Section 16 to clarify and remove redundancy of the available flavors for better readability. In addition, we note the Applicant uses the term [REDACTED] (b) (4) in Section 16 but does not describe the chewable bar in the same manner in Section 3, the container labels, or carton labeling. Therefore, we defer to CMC regarding use of the term [REDACTED] (b) (4) and recommend revising language, where appropriate, throughout the PI, container labels, and carton labeling for consistency.

For the Applicant, we recommend replacing the NDC displayed underneath the linear barcode with the NDC displayed on the respective Principal Display Panel (PDP) and increasing the prominence of the strength statement on all container labels and carton labeling for all three flavors. For the container labels, we recommend the dosage form (chewable bar) appear on the same line as the established name or on the next line below the established name. In addition, we note there is no placeholder for the lot and expiration date (including for the professional sample carton labeling), and recommend revising language regarding folding along the dotted line to mitigate any confusion. For the carton labeling, we recommend replacing the drawn images on the inner flap with more realistic pictures of the container label to more accurately depict the foil pouch during each step to open the wrapper. In addition, we note that the panel with the perforated flap to open the carton is not represented as the PDP and provide recommendations to ensure important information is not overlooked, including a discrepancy we noted in the 6 count professional product samples (does not include the warning statement, "THIS CONTAINER IS NOT CHILD RESISTANT") we received for our review. Furthermore, we provide recommendations regarding the expiration date format to minimize confusion and reduce the risk for deteriorated drug medication errors.

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the revised Prescribing Information, container labels (trade and professional sample), and carton labeling (trade and professional sample) can be improved to increase the readability and prominence of important information, and promote the safe use of the product and mitigate any confusion.

4.1 RECOMMENDATIONS FOR THE DIVISION

- A. Highlights of Prescribing Information
 - 1. Dosage Forms and Strengths
 - a. For clarity, we recommend revising "Chewable Bar: 3.75 gram per bar" to "Chewable Bar: 3.75 gram per bar (available in chocolate, strawberry, or caramel)."

B. Prescribing Information (PI)

1. Section 3 Dosage Forms and Strengths

a. For clarity and to mitigate any confusion, we recommend revising the following:

i. [redacted] (b) (4)
[redacted] to “Oral Suspension: 3.75 gram [redacted] (b) (4)
packet containing a white to pale yellow powder containing
yellow granules”

ii. [redacted] (b) (4)
[redacted] to

Chewable Bar:

- 3.75 gram brown, rectangular, chocolate flavored bar
- 3.75 gram pink, rectangular, strawberry flavored bar
- 3.75 gram tan, rectangular, caramel flavored bar

2. Section 16 How Supplied/Storage and Handling

a. We note the Applicant uses the term [redacted] (b) (4) in this section but does not describe the chewable bar in the same manner in Section 3 Dosage Forms and Strengths. We defer to CMC regarding use of the term [redacted] (b) (4) and recommend revising language, where appropriate, throughout the PI, container labels, and carton labeling for consistency.

b. For better readability and less redundancy, we recommend removing the statement, [redacted] (b) (4)

[redacted] and revising the statements and table that follows, such as:

[redacted] (b) (4)

Package Size	Flavor	NDC
Cartons of 30 chewable bars	Chocolate (brown)	65597-209-30
Cartons of 30 chewable bars	Strawberry (pink)	65597-210-30
Cartons of 30 chewable bars	Caramel (tan)	65597-208-30

4.2 RECOMMENDATIONS FOR DAIICHI SANKYO, INC.

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

- A. General Comments (Container Labels, Carton Labeling, Professional Sample Container Labels, and Professional Sample Carton Labeling)

1. We note the NDC on the Principal Display Panel (PDP) is different from the NDC displayed underneath the linear barcode. Replace the NDC displayed underneath the linear barcode with the NDC displayed on the respective PDP.
 2. We recommend increasing the prominence of the strength statement in accordance with 21 CFR 201.15(a)(6).
- B. Container Labels (Trade and Professional Sample)
1. We recommend the dosage form (chewable bar) appear on the same line as the established name or on the next line below the established name per *Draft Guidance: Container and Carton, April 2013 (lines 336-338)*.
 2. We note there is no placeholder for the lot and expiration date. Please ensure the lot and expiration date are included on the container label in accordance with 21 CFR 201.10(i)(1).
 3. For clarity and to mitigate any confusion, we recommend revising [REDACTED] (b) (4) [REDACTED] to “Fold along dotted line, then tear at arrow.”
- C. Carton Labeling (Trade and Professional Sample)
1. We note the instructions on the inner perforated flap depicts images that are drawn, which may be confusing for users unfamiliar with this product and the packaging. Therefore, we recommend replacing the drawn images with more realistic pictures of the container label to more accurately depict the foil pouch during each step to open the wrapper.
 2. We note that the panel with the perforated flap to open the carton is not represented as the PDP. To ensure important information is not overlooked, we recommend:
 - a. Trade and Professional Sample
 - i. adding the strength (3.75 g) to the area within the perforated flap.
 - b. Trade
 - i. moving the statement, “**NOTE TO PHARMACISTS: DO NOT BREAK BOX. DISPENSE AS 1 BOX.**” to the PDP and adding the statement to the panel of the perforated side.
 - c. Professional Sample
 - i. adding the flavor (chocolate, caramel, or strawberry flavor) to the panel of the perforated side (top and front panels), similar to the trade carton labeling.
 - ii. adding the statement, “CONTAINS MEDICATION,” “KEEP OUT OF REACH OF CHILDREN” to the area within the perforated flap, similar to the trade carton labeling.
 - iii. increasing the prominence of the statement, “PROFESSIONAL SAMPLE NOT FOR SALE,” such as moving the statement to the top portion of the PDP.

D. Carton Labeling (Trade)

1. We note the expiration date format is defined as “XX/XX” on the side panel. To minimize confusion and reduce the risk for deteriorated drug medication errors, we recommend using a format such as:

DDMMYYYY (e.g., 31JAN2013)

MMYYYY (e.g., JAN2013)

YYYY-MMM-DD (e.g., 2013-JAN-31)

YYYY-MM-DD (e.g., 2013-01-31)

In addition, we recommend moving the SN and GTIN numbers away from the lot and expiration date to minimize the risk of confusion due to close proximity to the lot and expiration date.

E. Carton Labeling (Professional Sample)

1. We note there is no placeholder for the lot and expiration date. Please ensure the lot and expiration date are included on the sample carton labeling in accordance with 21 CFR 201.17.
2. We note that the statement, “THIS CONTAINER IS NOT CHILD RESISTANT” is not displayed on the 6 count product samples we received for our review. Please ensure this important warning statement is included on the final intend-to-market 6 count professional sample, as depicted in the images of your submission.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Welchol received on October 30, 2017, from Daiichi Sankyo, Inc. and the listed drug (LD).

Table 2. Relevant Product Information for Welchol [chewable bar] and the Listed Drug				
Product Name	Welchol (NDA 210895)	Welchol (NDA 021176)	Welchol (NDA 021141)	Welchol (NDA 022362)
Initial Approval Date	N/A – proposed	May 26, 2000		October 2, 2009
Active Ingredient	colesevelam hydrochloride			
Indication	Adjunct to diet and exercise to: <ul style="list-style-type: none"> • reduce elevated low-density lipoprotein cholesterol (LDL-C) in adults with primary hyperlipidemia as monotherapy or in combination with a hydroxymethyl-glutaryl-coenzyme A (HMG CoA) reductase inhibitor (statin) • reduce LDL-C levels in boys and postmenarchal girls, 10 to 17 years of age, with heterozygous familial hypercholesterolemia as monotherapy or in combination with a statin after failing an adequate trial of diet therapy • improve glycemic control in adults with type 2 diabetes mellitus 			
Route of Administration	oral			
Dosage Form	Chewable bar	Tablet	Capsule	For oral suspension
Strength	3.75 g (available in a chocolate flavor, strawberry flavor, and caramel flavor)	625 mg	375 mg	3.75 g
Dose and Frequency	1 bar once daily with a meal	6 tablets once daily or 3 tablets twice	10 capsules once daily or 5 capsules twice	1 single-dose 3.75 g packet once daily mixed with ½ to 1

Table 2. Relevant Product Information for Welchol [chewable bar] and the Listed Drug				
Product Name	Welchol (NDA 210895)	Welchol (NDA 021176)	Welchol (NDA 021141)	Welchol (NDA 022362)
		daily with a meal and liquid	daily with a meal and liquid	cup (4 to 8 ounces) of water, fruit juice, or diet soft drinks; take with a meal
How supplied	Carton containing 30 (b) (4) chewable bars in a foil packet	180 count bottles	N/A (never marketed)	Carton containing 30 single-dose 3.75 g powder containing granules in a packet
Storage	25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature] Protect from moisture.	25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature] Brief exposure to 40°C (104°F) does not adversely affect the product. Protect from moisture.	Unknown	25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature] Protect from moisture.
Container Closure	Foil packet	Bottle	N/A (never marketed)	Packet

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^a along with postmarket medication error data, we reviewed the following Welchol labels and labeling submitted by Daiichi Sankyo, Inc.

- Container Labels received on October 30, 2017
- Carton Labeling received on October 30, 2017
- Professional Sample Container Labels received on October 30, 2017
- Professional Sample Carton Labeling received on October 30, 2017
- Prescribing Information (image not shown) received on October 30, 2017

G.2 Label and Labeling Images

Container Labels/Professional Sample Container Labels

(b) (4)



^a Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI: 2004.

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/s/

SUSAN RIMMEL
05/16/2018

HINA S MEHTA
05/16/2018