

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

210895Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

| | |
|--|--|
| Date | April 1, 2019 |
| From | John Sharretts, MD |
| Subject | Cross-Discipline Team Leader Review |
| NDA/BLA # and Supplement# | NDA 210895 |
| Applicant | Daiichi Sankyo |
| Date of Submission | October 3, 2018 |
| PDUFA Goal Date | April 3, 2019 |
| Proprietary Name | Welchol |
| Established or Proper Name | colesevelam hydrochloride |
| Dosage Form(s) | Chewable bars (3.75 g) |
| Applicant Proposed Indication(s)/Population(s) | <p>Adjunct to diet and exercise to:</p> <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 |
| Applicant Proposed Dosing Regimen(s) | One bar once daily |
| Recommendation on Regulatory Action | Approval |
| Recommended Indication(s)/Population(s) (if applicable) | <p><i>Adjunct to diet and exercise to:</i></p> <ul style="list-style-type: none"> • <i>Reduce elevated low-density lipoprotein cholesterol (LDL-C) in adults with primary hyperlipidemia</i> • <i>Reduce LDL-C levels in boys and postmenarchal girls, 10 to 17 years of age, with heterozygous familial hypercholesterolemia (HeFH) who are unable to reach LDL-C target levels despite an adequate trial of dietary therapy and lifestyle modification</i> • <i>Improve glycemic control in adults with type 2 diabetes mellitus</i> |
| Recommended Dosing Regimen(s) (if applicable) | <i>One bar once daily</i> |

1. Benefit-Risk Assessment

This new drug application (NDA) proposes a new presentation for Welchol (colesevelam hydrochloride). The proposed new presentation is as a flavored chewable bar, and the NDA previously received a Complete Response due to manufacturing facility deficiencies (see Dr. James Smith's August 23, 2018 Summary Review and the Complete Response letter issued on August 24, 2018 for details).

To support this NDA, the applicant provided *in vitro* data to demonstrate that the Welchol chewable bars formulation has similar bile acid binding properties when compared to the currently approved Welchol tablets. While there was concern that the additional caloric content in the chewable bar formulation may attenuate the effectiveness of the proposed drug product, any effect of increased caloric intake associated with this formulation can be addressed adequately with labeling.

The applicant's re-submission adequately addressed the CMC deficiencies identified in the original review cycle, and the facility reviewer now recommends approval. I concur with the Product Quality review team's assessment that the applicant's responses to the deficiencies are acceptable. The applicant provided sufficient data to conclude that the safety and effectiveness of this formulation is consistent with that of other colesevelam formulations, and thus the previous conclusion of favorable benefit-risk applies. As there are no other outstanding review issues, I recommend approval of Welchol (colesevelam hydrochloride) chewable bars.

2. Background

Colesevelam hydrochloride is a non-absorbed polymer intended for oral administration that binds bile acids in the intestine, impeding their reabsorption. Bile acid sequestration in the intestine results in increased conversion of cholesterol to bile acids in the liver, which leads to increased transcription and activity of HMG-CoA reductase and increased number of hepatic LDL receptors, with the net effect of increased clearance of LDL cholesterol (LDL-C) from the blood and thus decreased LDL-C levels. Colesevelam also improves glycemic control in patients with type 2 diabetes via unknown mechanisms.

Welchol (colesevelam hydrochloride) capsules was originally approved for marketing in 2000 (NDA 021141). It is currently marketed in two other formulations, Welchol tablets (NDA 021176, approved in 2000) and Welchol powder for oral suspension (NDA 022362, approved in 2009). Welchol is indicated as an adjunct to diet and exercise to reduce elevated LDL-C: (1) in adults with primary hyperlipidemia, and (2) in boys and postmenarchal girls, 10 to 17 years of age, with heterozygous familial hypercholesterolemia, who have failed an adequate trial of diet therapy. Welchol is also indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Welchol formulations have been approved previously on the basis of demonstrating similar binding properties using *in vitro* assays as described in the draft guidance on colesevelam HCl for the development of a generic drug product. In written responses dated December 15, 2015, the Division agreed that a similar approach appeared acceptable for the development of the

Welchol chewable bars formulation, but the Division advised the applicant to evaluate the impact of chewing on in vivo performance. Furthermore, in a pre-NDA teleconference on July 24, 2017, the Division recommended to the applicant to justify that the process of chewing would not adversely affect the efficacy of the product.

The applicant, Daiichi Sankyo, submitted NDA 210895 for Welchol (colesevelam hydrochloride) chewable bars under the 505(b)(1) pathway on October 30, 2017. The applicant proposed to manufacture three flavors of chewable bars (chocolate, strawberry, and caramel). The final formulation is a 30-gram bar in child-resistant packaging containing 3.75 grams of colesevelam hydrochloride. The applicant sought approval of this alternative dosage form by relying on previous studies with other colesevelam formulations for which they have right of reference.

During the original NDA review cycle, the Office of Pharmaceutical Quality facilities reviewer identified deficiencies at a drug product manufacturing facility, and recommended a complete response action, requiring satisfactory resolution of the deficiencies prior to approval. The remainder of the review team concluded that the data otherwise supported approval. Based on the manufacturing facility deficiency, the Division issued a Complete Response Letter on August 23, 2018.

Refer to the individual discipline reviews and the Division Director's review dated August 23, 2018, for details.

3. Product Quality

In the initial review cycle, the Division issued a Complete Response action, citing facility deficiencies.

The Complete Response letter cited the following Product Quality deficiency:

“During a recent inspection of the [REDACTED] (b) (4) drug product manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.”

Noting that this was not an approvability issue, the Complete Response letter also included a request for 24-month stability data for the six registration batches and all available stability data for the six demonstration batches. The applicant submitted stability data for the commercial lots with the resubmission.

Following a re-inspection in [REDACTED] (b) (4), the facility reviewer concluded that the firm's investigation into the root cause of microbial contamination in the product and their subsequent controls were acceptable. The reviewer recommended approval.

The Product Quality Assessment concluded that the stability data supports an 18-month expiry at 25°C/60% R/H conditions for all flavors (chocolate, caramel, and strawberry) in the (b) (4) wrapper.

Refer to the Product Quality assessment dated March 12, 2019 for details.

4. Nonclinical Pharmacology/Toxicology

The applicant did not submit any new nonclinical data during this review cycle. Refer to the nonclinical review by Dr. Dongyu Guo from the initial review cycle dated May 31, 2018, for information that supported the recommendation for approval.

5. Clinical Pharmacology

The applicant did not submit any new clinical pharmacology data in this review cycle. Refer to the clinical pharmacology review by Dr. Mohammad Absar dated June 12, 2018 from the initial review cycle for details of the clinical pharmacology program that supported the recommendation for approval.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

The applicant did not submit any new clinical data during this review cycle. Refer to the clinical review by Dr. Ovi Galescu from the original review cycle dated August 23, 2018 for details of the clinical information that supported the recommendation for approval.

The applicant provided substantial evidence of effectiveness by successfully bridging the bile acid binding capacity of the Welchol chewable bar formulation to the reference product, Welchol tablets. The applicant submitted additional data to evaluate the effect of chewing on performance of the chewable bar formulation. During the review, Dr. Galescu identified a concern regarding potential effects on efficacy and safety due to excipients in the chewable bar formulation, including maltitol, maltodextrin, palm oil, and cocoa powder. Issues included potential effects on glycemia due to additional carbohydrate load, potential effects on lipids due to increased carbohydrate and fat calories and potential gastrointestinal adverse reactions. The applicant provided additional data, and Dr. Galescu conducted a literature review. He concluded that it was unlikely that the excipients in the chewable bar formulation would attenuate the efficacy or safety of the product, but that the caloric content should be communicated in the label. In summary, the data provided by the applicant during the initial review cycle supported approval.

8. Safety

The applicant did not submit any new safety data in this review cycle. In the original review cycle, Dr. Galescu, concluded that the quantity of certain excipients (especially maltitol) in the chewable bar formulation could lead to increased gastrointestinal adverse reactions, but that this could be adequately addressed in labeling. Refer to the clinical review from the initial review cycle for details.

9. Pediatrics

Welchol chewable bars is a new dosage form and is therefore subject to Pediatric Research Equity Act (PREA) requirements for assessment of efficacy and safety in pediatric patients. The Pediatric Research Committee (PeRC) considered the application during the original review cycle on February 21, 2018. PeRC determined that because the sponsor is relying on bioequivalence data for this product compared to the approved tablet formulation, bioequivalence could be considered the assessment for 10 to 17 years. PeRC agreed that partial waiver could be granted less than 10 years for the two cholesterol-lowering indications.

Because there are ongoing pediatric studies for the powder for oral suspension formulation, PeRC recommended to defer studies for 10 to 17 years for the chewable bars and require the sponsor to conduct these studies under PREA. If the sponsor conducts adequate studies for the oral suspension, the Division could consider releasing the sponsor from the PMR, but if the studies are conducted poorly, the Division would retain the authority to require the sponsor to conduct more studies under this PMR. PeRC agreed with a partial waiver for less than 10 years for type 2 diabetes. Refer to the PeRC minutes dated March 19, 2018.

10. Other Relevant Regulatory Issues

None.

11. Labeling

Prescribing Information

The major changes to the label fall into three categories: (1) changes to the prescribing information specific to the new dosage form, including Division edits to the applicant's proposed labeling, (2) changes to format and content throughout the Prescribing Information recommended by the Division to update the label for consistency with current labeling practices, and (3) updates to Section 8 – Special Population to conform with the Pregnancy and Lactation Labeling Rule (PLLR), including Division edits to the Sponsor's proposed language.

- INDICATIONS AND USAGE:
 - Removed of Frederickson classification for primary hyperlipidemia consistent with other approved products
 - Removed wording regarding use alone or in combination with statins; the revised language no longer specifies this condition of use; in general, current practice for

treatment of patients with established cardiovascular disease or at high risk for cardiovascular disease who require additional lipid lowering would be to add additional lipid lowering agents to maximally tolerated statin therapy with or without ezetimibe or a PCSK9 inhibitor, but Welchol was not studied under these conditions of use

- Edited conditions of use for pediatric patients with HeFH who are unable to reach LDL-L target, to be more consistent with current clinical practice guidelines
- Removed language regarding treatment goals in hyperlipidemia that are not consistent with current clinical practice
- Added Limitation of Use stating that the effect of Welchol on cardiovascular outcomes has not been determined, and replacing similar language previously in Warnings and Precautions (see WARNINGS AND PRECAUTIONS below)
- **DOSAGE AND ADMINISTRATION:**
 - Added testing procedures (lipid parameters) prior to initiation of Welchol, because Welchol is contraindicated in patients with TG levels > 500 mg/dL, and closer monitoring is recommended for patients with TG > 300 mg/dL
 - Separated dosing (Section 2.2) from Administration Instructions (2.4)
 - Added lipid monitoring recommendations consistent with Warnings and Precautions information regarding the risk and mitigation of severe hypertriglyceridemia and pancreatitis
 - Dosage form name changed to Welchol chewable bars for consistency with other formulations (i.e. tablets, capsules)
 - Added caloric content of chewable bars to Administration Instructions (2.4)
- **Safety information in the BOXED WARNING, CONTRAINDICATIONS, or WARNINGS AND PRECAUTIONS:**
 - Rearranged CONTRAINDICATIONS to emphasize the risk of severe hypertriglyceridemia and pancreatitis
 - Removed statement regarding the undetermined effect on cardiovascular outcomes from WARNINGS AND PRECAUTIONS; moved this information to Limitations of Use consistent with current labeling practices (see INDICATIONS AND USAGE above)
 - Updated language in WARNINGS AND PRECAUTIONS regarding the risks of Hypertriglyceridemia and Pancreatitis, Gastrointestinal Obstruction, Vitamin K or Fat-Soluble Vitamin deficiencies, and Risks in Patients with Phenylketonuria for consistency with current labeling practices
 - Removed [REDACTED] (b) (4) from WARNINGS AND PRECAUTIONS
 - Updated tables and language in ADVERSE REACTIONS
- **CLINICAL STUDIES section:**

Removed data regarding the use of colesevlam in patients with mixed hyperlipidemia, as Welchol is not indicated in this population

Other Labeling

- Updated DRUG INTERACTIONS (Section 7), including table

- Updated Section 8 – USE IN SPECIAL POPULATIONS to comply with PLLR; the applicant submitted draft labeling during the initial review cycle; refer to the DPMH consult review by Dr. Christos Mastroyannis dated July 2, 2018 for details of the recommended changes
- Edited STORAGE AND HANDLING information (Section 16) and PATIENT COUNSELING (Section 17) information, both previous content and format, and new information proposed by the applicant regarding the new dosage form

12. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)

Not applicable

Postmarketing Requirements (PMRs) and Commitments (PMCs)

I recommend the following PMR:

A deferred, 1-year, pediatric efficacy and safety study under PREA for the treatment of type 2 diabetes in pediatric patients ages 10 to 17 years.

13. Recommended Comments to the Applicant

None

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
04/01/2019 04:22:53 PM

WILLIAM H CHONG
04/01/2019 04:54:55 PM
I agree with Dr. Sharretts' assessment and recommendation.

Summary Review for Regulatory Action

| | |
|--|--|
| Date | See <i>electronic stamp</i> |
| From | James P. Smith, MD, MS |
| Subject | Summary Review for Regulatory Action |
| NDA# | 210895 |
| Applicant | Daiichi Sankyo, Inc. |
| Date of Submission | 30 Oct 2017 |
| PDUFA Goal Date | 30 Aug 2018 |
| Proprietary Name / Established (USAN) names | Welchol (colesevelam hydrochloride) |
| Dosage forms / Strength | Chewable bar, 3.75 g |
| Proposed Indication | <p>Adjunct to diet and exercise to:</p> <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 |
| Recommended: | Complete Response |

| Material Reviewed/Consulted & Primary Reviewer(s) | | |
|---|-------------|---|
| Clinical Pharmacology Review | 12 Jun 2018 | Mohammad (Abir) Absar, PhD |
| Pharmacology/Toxicology Review | 31 May 2018 | Dongyu Guo, PhD |
| OPQ Multidisciplinary Review | 17 May 2018 | Su Tran, PhD (Application Technical Lead) |
| OSIS Memo | 22 Jun 2018 | Mohsen Rajabi Abhari, PhD |
| OSE/DMEPA Label & Labeling Review | 16 May 2018 | Susan Rimmel, PharmD |
| OSE/DMEPA Proprietary Name Review | 09 Apr 2018 | Susan Rimmel, PharmD |
| DPMH Memo (PLLR consult) | 02 Jul 2018 | Christos Mastroyannis, MD |
| Medical Officer Review | 22 Aug 2018 | Ovi Galescu, MD |

OPQ: Office of Pharmaceutical Quality; OSIS: Office of Study Integrity and Surveillance; OSE: Office of Surveillance and Epidemiology; DMEPA: Division of Medication Error Prevention and Analysis; DPMH: Division of Pediatrics and Maternal Health; PLLR: Pregnancy and Lactation Labeling Rule

1. INTRODUCTION

Daiichi Sankyo submitted original NDA 210895 for Welchol (colesevelam hydrochloride [HCl]) chewable bar under the 505(b)(1) pathway. The applicant is seeking approval of this alternative dosage form of the same drug for which they have other approved formulations: Welchol capsules (NDA 21141, approved in 2000), Welchol tablets (NDA 21176, approved in 2000), and Welchol powder for suspension (NDA 22362, approved in 2009). The applicant proposes to manufacture three flavors of

this chewable bar (chocolate, strawberry, and caramel). The final formulation is in the form of a 30-g bar in child-resistant packaging.¹

All disciplines have recommended approval except for OPQ, which has recommended a complete response based on deficiencies at the manufacturing facility.

2. BACKGROUND

Welchol is a bile acid sequestrant that is indicated as an adjunct to diet and exercise to (1) reduce elevated LDL-C in adults with primary hyperlipidemia as monotherapy or in combination with an HMG CoA reductase inhibitor (statin); (2) reduce LDL-C 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; and (3) improve glycemic control in adults with type 2 diabetes mellitus.

Colesevelam is a non-absorbed polymer that acts in the GI tract by binding the salts of bile acids, impeding their reabsorption, leading to a depletion of hepatic cholesterol as it is converted to bile acids; in turn, this has downstream effects of upregulating hepatic LDL receptors, resulting in increased clearance of LDL-C from the blood.

Welchol formulations have been previously approved on the basis of demonstrating similar binding properties using *in vitro* assays as described, for example, in the draft guidance on colesevelam HCl that provides recommendations for the development of a generic drug product. In written responses dated 15 December 2015, the Agency opined that a similar approach appeared acceptable for the development of the currently proposed Welchol formulation. Because of the novelty of the dosage form (“chewable bar”), the applicant was advised to address whether there is any impact of chewing on *in vivo* performance. Furthermore, in a pre-NDA teleconference on 24 July 2017, the Division recommended that the applicant would need to provide justification that the process of chewing, bolus formation, etc. would not be expected to adversely affect the efficacy of the product as it reaches its site of action in the GI tract.

3. CMC/DEVICE

CMC

See the multidisciplinary OPQ review for details.

Drug Substance

The drug substance colesevelam HCl is a non-absorbed, water-insoluble polymer. Reference is made to an adequate DMF for all CMC information on the drug substance. The DMF holder is the drug substance manufacturer of the applicant’s approved referenced NDAs. The applicant confirmed that the drug substance is the same for this NDA and their approved NDAs.

¹ The Division consulted with CDER Product Jurisdiction to query whether this product would be considered a “drug/food” combination product given the nature of several of the. In a 07 March 2018 e-mail from Cherryn Chang, PhD (Product Jurisdiction Officer) to Kati Johnson, it was conveyed that “[t]here is no question that colesevelam is a drug. The ingredients (e.g., maltitol, palm oil, cocoa powder, etc.) are intended for use as drug components and therefore meet the drug definition..., regardless of whether they can also be a food.” She cited Section 201(g) of the FD&C Act (21 USC 321(g)), which includes the clause “(D) articles intended for use as a component of any articles specified in clause (A), (B), or (C)...”

Drug Product

The drug product is a “chewable bar” containing 3.75g colesevelam HCl, formulated with food ingredients, and packaged in a child-resistant foil laminate pouch. According to the OPQ review, the food excipients have adequate quality information and all are confirmed to be well-known food ingredients. Notably, excipients include maltitol (b) (4) palm oil (b) (4) as discussed in the Clinical section of this memo.

Facilities Review/Inspection

The chewable bars are manufactured, wrapped, and labeled a (b) (4) a contract manufacturer specializing in nutraceuticals. ORA conducted a pre-approval inspection of (b) (4) on (b) (4). A “Withhold” was recommended based on an inadequate FDA-483 response provided by the firm that did not provide a completed investigation or a root cause into microbial contamination found on manufacturing equipment used for the exhibit batches and for the proposed commercial batches (*Enterobacteriaceae*).

I concur with the conclusions reached by the OPQ reviewers that the objectionable conditions observed at the drug product manufacturing facility preclude approval of this application at this time.

4. NONCLINICAL PHARMACOLOGY/TOXICOLOGY

Dr. Dongyu Guo reviewed this application from the pharm/tox perspective. No new nonclinical studies were conducted to support this NDA. The applicant provided safety information from publicly available literature to support the safety of the excipients that are considered non-compendial or are present at higher concentrations than those listed in the FDA’s Inactive Ingredient Database based on amounts in previously approved products. He concluded that there are no toxicological concerns for the use of maltitol syrup, palm oil, alkalized cocoa powder, or rosemary extract at the proposed levels in the Welchol chewable bar; however, he recommends that labeling should indicate that the maltitol may induce laxative effects² and that Welchol chewable bars are a significant source of additional calories.

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval.

5. CLINICAL PHARMACOLOGY

Dr. Mohammad Absar reviewed this NDA from the clinical pharmacology perspective. The applicant submitted comparative in vitro binding data (equilibrium and kinetic binding) that compared the chewable bar (test) with Welchol tablet (reference). In addition, an in vitro study to address the effect of chewing was submitted. At mid-cycle of this review, several deficiencies were noted by the clinical pharmacology reviewers, leading to a Discipline Review letter (19 March 2018); in response, the applicant addressed a deficiency in bioanalytical methods and also conducted a “clinical” chewing study. These additional data were submitted to the NDA on 31 May 2018.

There were two pivotal studies to support approval of this NDA:

² See the labeling for Phoslyra (calcium acetate oral solution), which warns, “PHOSLYRA contains maltitol (1 g per 5 mL) and may induce a laxative effect, especially if taken with other products containing maltitol.”

1. An in vitro equilibrium binding study was conducted according to the recommendations outlined in the product-specific draft guidance for Colesevelam HCl (revised Jan 2016). The 90% CI for the test/reference ratio was calculated for the capacity constant (k_2) for each flavor of the chewable bar both with and without acid pretreatment. Under both conditions, each flavor of the Welchol chewable bar was sufficiently similar to Welchol tablets with respect to total bile acid salt binding. See Dr. Absar's review for details (e.g., Tables 13 and 23).
2. Kinetic testing was performed following the recommendations in the same product-specific draft guidance. Binding was rapid under conditions of 0.3 mM and 3.0 mM bile acid salts; almost no bile acid salts were left after the first few minutes of the study. The kinetic binding of each bile salt for both dosage forms were similar. See Dr. Absar's review for details (Tables 24-25).

In both studies, the registration stability lots of Welchol chewable bars were used.

OSIS inspected the facility that conducted these studies and recommended that the data be accepted for Agency review.

To address the Agency's concern regarding the impact of chewing on the in vivo performance of this product, the applicant attempted to simulate "chewing" by manually cutting a sample of the chewable bar into various sizes and conducted an analysis of the amount of unbound bile acid and bile acid capacity for each size and extraction time. Dr. Absar notes that the data show that the bile acid binding of the two bile acids tested (GC and GCDC) was essentially the same across sizes of the pieces and extraction time.

Since the review team was concerned that manually cutting a bar into different sizes may not represent the in vivo process of bolus formation and digestion, the applicant had 12 healthy volunteers take 6 bite-sized pieces, chew for 45 seconds or until there was an urge to swallow, and then expectorate the bolus into a sample tube (1 per subject). After addition of simulated gastric fluid, a disintegration test was conducted. They found that the mean (SD) time to complete disintegration of the bolus (in 10 evaluable subjects) was 24.0 (13.7) minutes, with a range of 5 to 45 minutes. Dr. Absar concluded that given the reported normal gastric emptying times, the chewed mass is likely to be disintegrated in the stomach prior to reaching the intestine; therefore, it is not expected that physical elements related to chewing and swallowing this product should impact its therapeutic performance.

Dr. Absar recommends approval from the clinical pharmacology perspective. I concur that there are no outstanding clinical pharmacology issues that preclude approval.

6. CLINICAL MICROBIOLOGY

See concern regarding microbial contamination at the drug product manufacturing facility.

7. CLINICAL – EFFICACY/SAFETY

The basis for efficacy of the Welchol chewable bar relies upon bridging to the approved Welchol tablets using in vitro assays as described in Section 5, above.

The clinical reviewer, Dr. Ovi Galescu, considered whether the excipients maltodextrin, palm oil, and/or maltitol may be expected to modify the efficacy of colesevelam with respect to its effects on LDL-C reduction and/or glycemic control. Dr. Galescu reviewed the literature as well as references provided by the applicant and concluded that "it is unlikely that the excipients in the Welchol chewable bar will attenuate the efficacy of the product on lipids or glycemic control." He does note, however, that the excipients in this product (especially maltitol) have a potential to cause increased GI

adverse effects (e.g., flatulence, abdominal discomfort, diarrhea), and that this should be addressed in labeling. See Dr. Galescu's review for further details.

I concur with Dr. Galescu that there are no outstanding clinical deficiencies that would preclude approval of this application.

8. ADVISORY COMMITTEE MEETING

An advisory committee meeting was not necessary for this application.

9. PEDIATRICS

This NDA was discussed with PeRC on 21 February 2018. The PeRC opined that since the applicant is relying on bioequivalence data for this product to the approved tablet, bioequivalence could be considered the assessment for 10-17 years (HeFH) and a partial waiver could be granted for less than 10 years for hypercholesterolemia. Since there are ongoing studies due at the end of the year for the type 2 diabetes indication, it was recommended to defer studies (for 10-17 years) and require the sponsor conduct these studies under PREA. If the ongoing studies are conducted well but fail to establish safety/effectiveness for type 2 diabetes, the Division could consider releasing the sponsor from the PMR. However, if the studies are conducted poorly, the Division could compel the sponsor to conduct more studies under this NDA. The PeRC agreed with a partial waiver for less than 10 years for the type 2 diabetes indication.

10. OTHER RELEVANT REGULATORY ISSUES

There are no other outstanding regulatory issues.

11. LABELING

Proprietary Name Review

DMEPA concluded that the proposed proprietary name, Welchol, is acceptable.

Labeling

Labeling was not negotiated during this review cycle given the complete response action. Future labeling considerations should include the potential for maltitol to induce laxative effects as well as information regarding caloric content of the bar. The review team discussed the latter with the Labeling Development Team, who were unable to find examples for labeling regarding caloric content other than in a limited number of drugs indicated as a source of calories/nutrition (e.g., Clinimix). One possibility for future consideration was to model a warning after those recommended for drugs that contain phenylalanine, which could be harmful to patients with PKU. For example, "The Welchol chewable bar provides (b) (4) calories. Before prescribing the Welchol chewable bar for patients seeking to limit caloric intake, consider the daily caloric intake of the patient from all sources, including the Welchol chewable bar."³

PLLR recommendations were provided by Dr. Christos Mastroyannis.

³ I note that in an 18 May 2018 response to an FDA information request, the applicant states that there are approximately 80 calories in a Welchol chewable bar. If this NDA is resubmitted, the review team should clarify the caloric content for labeling consideration.

12. DECISION/ACTION/RISK BENEFIT ASSESSMENT

Risk/Benefit Assessment

The applicant has provided sufficient data to demonstrate similar bile acid binding properties between the Welchol chewable bar with their reference product, Welchol tablets, in two pivotal biopharmaceutic studies. Although it seems somewhat counterintuitive to administer a drug to treat either hypercholesterolemia or type 2 diabetes in the form of a product with non-negligible caloric content (especially given the quite modest effect of colesevelam on LDL-C and glycemic control), I note that Welchol labeling specifies that the approved formulations should be taken with meals; therefore, if patients are aware of the caloric content of this product, they could make appropriate adjustments to their diet. With proper labeling, therefore, this formulation should be considered for approval once the deficiencies at the manufacturing facility are resolved.

Recommended Regulatory Action

Complete response because of deficiencies at the drug product manufacturing facility.

Recommendations for Risk Evaluation and Mitigation Strategies

None.

Recommendations for Post-marketing Requirements and Commitments

None anticipated.

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/

JAMES P SMITH
08/23/2018