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)	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
Applicant Proposed Dosing Regimen(s)	One bar once daily
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	*Adjunct to diet and exercise to:* • *Reduce elevated low-density lipoprotein cholesterol (LDL-C) in adults with primary hyperlipidemia* • *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* • *Improve glycemic control in adults with type 2 diabetes mellitus*
Recommended Dosing Regimen(s) (if applicable)	*One bar once daily*

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 (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 (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 (b) (4) from WARNINGS AND PRECAUTIONS
    - Updated tables and language in ADVERSE REACTIONS

- CLINICAL STUDIES section:
  Removed data regarding the use of colesevelam 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.