CLINICAL REVIEW

Application Type	NDA 505(b)(1)
Application Number(s)	210895
Priority or Standard	Standard
Submit Date(s)	October 30, 2017
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PDUFA Goal Date	August 30, 2018
Division/Office	DMEP/OND
Reviewer Name(s)	Ovidiu A. Galescu
Review Completion Date	August 8, 2018
Established/Proper Name	colesevelam hydrochloride
(Proposed) Trade Name	Welchol Chewable Bar
Applicant	Daiichi Sankyo, Inc.
Dosage Form(s)	Chewable Bar
Applicant Proposed Dosing Regimen(s)	1 chewable bar (3.75 grams colesevelam hydrochloride) / day
Applicant Proposed Indication(s)/Population(s)	Primary Hyperlipidemia and Type 2 Diabetes Mellitus
Recommendation on Regulatory Action	Complete Response due to facilities deficiency. No clinical issues identified.
Recommended Indication(s)/Population(s)	Reduce elevated low-density lipoprotein cholesterol in adults and children ages 10-17 years Improve glycemic control in adults with type 2 diabetes mellitus

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Glossary

AC	advisory committee
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity

OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

WELCHOL® (colesevelam hydrochloride) is a commercially available bile acid sequestrant and is indicated 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 hydroxymethylglutarylcoenzyme A (HMG CoA) reductase inhibitor
2. 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
3. Improve glycemic control in adults with type 2 diabetes mellitus.

WELCHOL® is currently available as Tablets, 625 mg and Powder for Oral Suspension, 3.75g. The daily dose of WELCHOL® is 3.75 g either as six tablets or in the form of the oral suspension (one 3.75 g package). Daiichi Sankyo proposes a new formulation which provides 3.75 grams of colesevelam hydrochloride (equivalent to six 625 mg WELCHOL® Tablets), in a chewable bar unit dose. The active ingredient, colesevelam hydrochloride, in the proposed Welchol® Chewable Bar dosage form is provided by the same manufacturer for the active ingredient in the currently marketed Welchol (colesevelam hydrochloride) Tablets and Welchol (colesevelam hydrochloride) Powder for Oral Suspension, approved in NDA 021176 and NDA 022362, respectively. The active ingredient was also approved in NDA 021141 for a non-marketed capsule formulation of colesevelam hydrochloride.

WELCHOL® (colesevelam hydrochloride) Chewable Bar is being developed for the same indications as WELCHOL® Tablets and WELCHOL® for Oral Suspension which have been approved by the FDA.

This submission relies on bridging safety and efficacy to Welchol tablets by establishing bioequivalence with the newly proposed formulation. The Sponsor conducted and submitted in vitro bioequivalent (BE) studies, i.e., in vitro equilibrium binding study and in vitro kinetic binding study, between each flavored colesevelam HCl chewable bar and the commercial Welchol tablets.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Sponsor relies on bridging Efficacy to the Welchol tablets. The in-vitro studies submitted as part of this application sufficiently establish bioequivalence of all 3 flavors of Welchol chewable bar to the reference product Welchol tablets (please see Clinical Pharmacology review by Mohammad (Abir) Absar, Ph.D for additional details). From a clinical

perspective, we considered the possibility that the excipients (i.e. palm oil, maltitol) might impact the efficacy or tolerability of this formulation. Following our review of relevant literature, we concluded that potential effects on tolerability are meaningful and should be addressed in labeling, whereas the potential of excipients to attenuate efficacy is minimal and would not preclude approval. Nonetheless, the label should address the added caloric content of the chewable bar.

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

Both hyperlipidemia and diabetes are highly prevalent diseases in the U.S. and around the world with significant associated morbidity and mortality and a large socio-economic impact. Both conditions have been linked with an increased risk of cardiovascular disease and treating these conditions is a staple in the prevention of CVD.

There are currently many FDA approved therapies for LDL-C lowering as well as glycemic control.

Welchol belongs to the bile acid sequestrant class of drugs and is currently being commercialized in the US in tablet and suspension form. The Sponsor proposes the new formulation of chewable bars as an alternative treatment form to increase adherence to therapy. This new formulation is designed to be palatable and easy to administer, however it has added calories (b) (4) kcal/bar) from both fats (i.e. palm oil) and carbohydrates (i.e. maltodextrin). The chewable bars also contain Maltitol (b) (4) which in large quantities may cause osmotic diarrhea (usually above 30g).

There are no major clinical concerns regarding Welchol Chewable Bar. This product is bioequivalent to the FDA approved Welchol formulations and may be approved from the clinical standpoint, however in its Integrated Quality Review, the Office of Pharmaceutical Quality (OPQ) recommended a Complete Response due to inadequate responses to the facilities inspection related to microbial contamination.

This unique dosage form may change the tolerability of the drug due to the added GI impact of the excipients. The potential increase in AE and the added caloric load should be included in the labeling. We also considered whether the additional carbohydrates in the chewable bar formulation might affect efficacy. Following our review of the literature, we concluded that any potential impact of the excipients on efficacy would be negligible.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Hyperlipidemia: • Clinical dyslipidemia includes, but is not limited to, patients with abnormal levels of low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol, triglycerides, or lipoprotein(a) • Hyperlipidemia is defined as total cholesterol or LDL-C levels above the 90th percentile for the general population • The prevalence of one or more abnormal lipid fractions varies with the population being studied. It is highest in populations of patients with premature coronary heart disease (CHD), which can be defined as occurring before 55 to 60 years of age in men and before 65 years in women. In this setting, the prevalence of dyslipidemia is as high as 75 to 85 percent compared with approximately 40 to 48 percent in age-matched controls without CHD • Most hyperlipidemia is caused by genetic polymorphism in the context of dietary and other lifestyle factors. • Having hyperlipidemia increases the risk of developing CHD which is the leading cause of death in the U.S. Type 2 Diabetes Mellitus T2DM: • T2DM is a condition characterized by high blood glucose levels caused by either a lack of insulin or the body's inability to use insulin efficiently. Type 2 diabetes develops most often in middle-aged and older adults but can appear in children, teens, and young people. • There are an estimated of more than 3 million new cases/year in the U.S. • Type 2 diabetes can develop gradually over several years without any noticeable symptoms. Symptoms of hyperglycemia may include: extreme thirst, frequent urination, tiredness and listlessness, nausea, dizziness. Extremely high blood sugar levels may lead to patients feeling confused and drowsy or even lose consciousness	• Both hyperlipidemia and type 2 diabetes mellitus are highly prevalent conditions in the U.S. adult population and carry an extremely high burden of morbidity and mortality. • Both conditions are related to an increased risk of atherosclerotic cardiovascular disease which is recognized as the number 1 cause of mortality in the U.S. • Aggressive therapy aimed at lowering LDL-C, especially in at-risk populations, has been associated with decreased morbidity and mortality in these patients. • Improved glycemic control is associated with a reduction in microvascular disease in patients with Type 2 diabetes.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	(diabetic coma). • People who have type 2 diabetes are also at greater risk of developing cardiovascular conditions such as a heart attack, stroke or problems with the circulation in their legs and feet (peripheral artery disease, PAD). • Uncontrolled T2DM may lead to microvascular disease such as retinopathy, neuropathy, and nephropathy.	
Current Treatment Options	• The cornerstone of therapy of hyperlipidemia is focusing on reduction of ASCVD risk See Figure 1[1]. • In order to determine which patients should make an attempt to lower their LDL-C, their risk for the development of cardiovascular disease (CVD) events needs to be assessed using risk evaluation tools that take into account more than the baseline LDL-C. Cardiovascular risk should be calculated using validated risk models/calculators. • The American College of Cardiology ACC identified the following groups that benefit from LDL-C lowering therapy despite associated risks: adult patients ≥21 years of age with clinical atherosclerotic cardiovascular disease ASCVD; adults ≥21 years of age with LDL-C ≥190 mg/dL (not due to secondary modifiable causes); adults aged 40 to 75 years without ASCVD, but with diabetes and with LDL-C 70 to 189 mg/dL; and adults ages 40 to 75 years without ASCVD or diabetes, with LDL-C 70 to 189 mg/dL, and an estimated 10-year risk	• Bile acid sequestrants such as colesevelam hydrochloride are not first line agents in the management of either hypercholesterolemia or type 2 diabetes mellitus. • Colesevelam has demonstrated therapeutic effect on plasma LDL cholesterol (LDL-C) levels, resulting typically in a decrease in levels in the range of 15% to 20% when added to a statin. • An additional effect of colesevelam is glucose lowering, with standard doses lowering glycated hemoglobin (A1C) by an average of 0.5%

[1] Stone, N. J., J. G. Robinson, A. H. Lichtenstein, D. C. Goff, Jr., D. M. Lloyd-Jones, S. C. Smith, Jr., C. Blum and J. S. Schwartz (2014). "Treatment of blood cholesterol to reduce atherosclerotic cardiovascular disease risk in adults: synopsis of the 2013 American College of Cardiology/American Heart Association cholesterol guideline." Ann Intern Med **160**(5): 339-343.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	for ASCVD of ≥7.5% as determined by the Pooled Cohort Equations[2]. • For patients identified at risk the first step in management is lifestyle modification with dietary intervention and increased exercise. • The initial pharmacological intervention is statin therapy • Clinicians treating high-risk patients who have a less than-anticipated response to statins, who are unable to tolerate a less-than-recommended intensity of a statin, or who are completely statin intolerant, may consider the addition of a non-statin cholesterol lowering therapy. High-risk individuals include those with ASCVD, those with LDL-C ≥190 mg/dL, and those with diabetes 40 to 75 years of age. In this situation, this guideline recommends clinicians preferentially prescribe drugs that have been shown in RCTs to provide ASCVD risk-reduction benefits that outweigh the potential for adverse effects and drug–drug interactions, and consider patient preferences[3] • Ezetimibe has been reported to improve the lipid profile and exert anti-atherogenic, antioxidant, and anti-inflammatory properties, thus further reducing CV risk[4]. • Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors are a class of lipid-lowering drugs administered subcutaneously every two	

[2] Goff, D. C., Jr., D. M. Lloyd-Jones, G. Bennett, S. Coady, R. B. D'Agostino, Sr., R. Gibbons, P. Greenland, D. T. Lackland, D. Levy, C. J. O'Donnell, J. G. Robinson, J. S. Schwartz, S. T. Shero, S. C. Smith, Jr., P. Sorlie, N. J. Stone and P. W. Wilson (2014). "2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines." J Am Coll Cardiol **63**(25 Pt B): 2935-2959.

[3] Stone, N. J., J. G. Robinson, A. H. Lichtenstein, C. N. Bairey Merz, C. B. Blum, R. H. Eckel, A. C. Goldberg, D. Gordon, D. Levy, D. M. Lloyd-Jones, P. McBride, J. S. Schwartz, S. T. Shero, S. C. Smith, Jr., K. Watson and P. W. Wilson (2014). "2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines." J Am Coll Cardiol **63**(25 Pt B): 2889-2934.

[4] Katsiki, N., E. Theocharidou, A. Karagiannis, V. G. Athyros and D. P. Mikhailidis (2013). "Ezetimibe therapy for dyslipidemia: an update." Curr Pharm Des **19**(17): 3107-3114.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	weeks or once a month. These drugs have been reported to significantly reduce LDL-C up to 73% when co-administered with a statin ± ezetimibe as well as improve other lipid parameters including lipoprotein(a)[5]. FDA has approved Repatha (evolocumab) to reduce the risk of myocardial infarction (MI), stroke, and coronary revascularization in adults with established cardiovascular disease (CVD)[6] • Fibrates are useful drugs to treat mixed (atherogenic) dyslipidemia as they target not only TG metabolism but also increase HDL-C and decrease small dense LDL particles [7]. • Treatment of T2DM includes diet, exercise, medication, and insulin therapy[8]. • Approved anti-diabetic medications include metformin, glucagon-like peptide-1 (GLP-1) receptor agonists, dipeptidylpeptidase-4 (DPP-4) inhibitors, sodium-glucose co-transporter-2 (SGLT-2) inhibitors, sulfonylureas, meglitinides, alpha glucosidase inhibitors, pramlintide, colesevelam, and bromocriptine. • Bile acid sequestrants (BASs) constitute a class of drugs that have been used for cholesterol-lowering treatment for decades. • The BASs comprise first-generation cholestyramine and colestipol and second-generation colesevelam hydrochloride and colestimide. BASs form a nonabsorbable complex with bile acids in the intestine, which prevents reabsorption and increases fecal excretion of bile	

[5] Ferdinand, K. C. and S. A. Nasser (2015). "PCSK9 Inhibition: Discovery, Current Evidence, and Potential Effects on LDL-C and Lp(a)." Cardiovasc Drugs Ther **29**(3): 295-308.
[6] https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/125522s014lbl.pdf
[7] Katsiki, N., D. Nikolic, G. Montalto, M. Banach, D. P. Mikhailidis and M. Rizzo (2013). "The role of fibrate treatment in dyslipidemia: an overview." Curr Pharm Des **19**(17): 3124-3131.
[8] https://www.mayoclinic.org/diseases-conditions/type-2-diabetes/

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	acids.	
Benefit	• Welchol™ (colesevelam hydrochloride) Tablets, 625 mg are a commercially available bile acid sequestrant that lowers cholesterol levels. Six tablets is the prescribed daily dose. The efficacy of colesevelam hydrochloride has been demonstrated in clinical studies. These studies are documented in the approved NDAs for capsule and tablet formulations of colesevelam hydrochloride (NDA 21-141 and NDA 21-176, respectively) and the labeling for these products. • Welchol™ (colesevelam hydrochloride) for Oral Suspension (3.75 g package) was approved following a 505(b)(2) application in 2009	• The Sponsor proposes an alternate dosage form (30 g flavored chewable bars) for the previously approved indications for Welchol tablets and Welchol oral suspension. • The WELCHOL® Chewable Bar drug product is being developed in three flavors; chocolate, strawberry and caramel. The final formulation is in the form of a 30 gram bar provided in child resistant (b) (4) wrap packaging. • The proposed advantage of the new form is improved palatability ease of administration which may lead to improved treatment compliance. • The applicant demonstrated bioequivalence between Welchol chewable bar and the approved tablet formulation of colesevelam.
Risk and Risk Management	• The newly proposed formulation has the same active ingredient as currently approved Welchol formulations, however the excipients used may present additional risks to the intended treatment population. • The Welchol chewable bars have a caloric load of approximately (b) (4)	• The risk of added caloric intake is small, but should be addressed in labeling.. • The added excipients may adversely impact the GI adverse event profile of Welchol Chewable Bars particularly by increasing

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	kcal/bar. In our review, we considered whether the added calories might impact the intended population (hyperlipidemic and diabetic). • Each Welchol chewable bar contains (b) (4) of Maltitol which may lead to GI upset and **abdominal distension**. • [9] . Because maltitol is a low-glycemic-index carbohydrate, and the quantity is relatively small, the added carbohydrate load due to maltitol should have a minimal adverse impact on glycemic control in patients with diabetes using the product[10]. Welchol may cause bowel obstruction (in patients with a history of bowel obstruction or resection), dysphagia or esophageal obstruction (occasionally requiring medical intervention), fecal impaction, pancreatitis, **abdominal distension**, exacerbation of hemorrhoids, and increased transaminases.	incidence of abdominal distension (due to partial fermentation of Maltitol). This AE may be labeled accordingly.

[9] Sharafetdinov, K. K., O. A. Plotnikova, A. M. Churicheva, V. V. Pilipenko, R. I. Alekseeva, T. B. Sentsova, G. Y. Maltsev, A. A. Kochetkova, V. M. Vorobyova and I. S. Vorobyova (2016). "Assessment of efficacy of specialized food products with modified carbohydrate profile in patients with type 2 diabetes." Vopr Pitan **85**(6): 103-109.

[10] Secchi, A., A. E. Pontiroli, L. Cammelli, A. Bizzi, M. Cini and G. Pozza (1986). "Effects of oral administration of maltitol on plasma glucose, plasma sorbitol, and serum insulin levels in man." Klin Wochenschr **64**(6): 265-269.

1.4. Patient Experience Data

Patient experience data was not submitted as part of this application.

1.5 Recommendation on Regulatory Action

The Office of Pharmaceutical Quality (OPQ) recommended a Complete Response. The OPQ facilities reviewer identified persistent bacterial contamination at a manufacturing site, and concluded that the site's responses to the deficiencies was inadequate..

The application is approvable from the clinical perspective. The applicant demonstrated bioequivalence between the Welchol chewable bar and the approved tablet formulation of cholesevelam.

Reviewer comment: The proposed novel formulation raises unique issues. Taken individually, each ingredient is safe in the proposed quantities. However the combination of active drug with the proposed "excepients" may result in more GI adverse events. The added caloric load should be described in labeling.

2. Therapeutic Context

2.1. Analysis of Condition

Dyslipidemias are disorders of lipoprotein metabolism that include abnormal levels oflow density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), triglycerides, or lipoprotein(a). In adults, dyslipidemia is an established risk factor for cardiovascular disease (CVD), and correcting dyslipidemia reduces the risk of CVD. Dyslipidemia begins as early as childhood or adolescence.

In the United States, coronary heart disease (CHD) is the leading cause of death, killing about half a million men and women annually. In addition, some 12 million adults in the United States live with CHD, including angina, heart attacks and other forms of the disease[11].

[11] Younus, A., E. C. Aneni, E. S. Spatz, C. U. Osondu, L. Roberson, O. Ogunmoroti, R. Malik, S. S. Ali, M. Aziz, T. Feldman, S. S. Virani, W. Maziak, A. S. Agatston, E. Veledar and K. Nasir (2016). "A Systematic Review of the Prevalence and Outcomes of Ideal Cardiovascular Health in US and Non-US Populations." Mayo Clin Proc **91**(5):

Increased blood cholesterol levels, or, more specifically, increased levels of low density lipoprotein (LDL)-cholesterol, are causally related to an increased risk of coronary heart disease (CHD)[12].

The prevalence of one or more abnormal lipid fractions varies with the population being studied. It is highest in populations of patients with premature coronary heart disease (CHD), which can be defined as occurring before 55 to 60 years of age in men and before 65 years in women. In this setting, the prevalence of dyslipidemia is as high as 75 to 85 percent compared with approximately 40 to 48 percent in age-matched controls without CHD[1314]. In one study, for example, 54 percent of all patients with premature CHD (and 70 percent of those with a lipid abnormality) had a familial disorder[13]. In the great majority of patients, inheritance is polygenic and the expression of dyslipidemia is strongly influenced by factors such as obesity (particularly central obesity) and the saturated fat and cholesterol content of the diet.

Hyperlipidemia is defined as total cholesterol or LDL-C levels above the 90th percentile for the general population. Elevation of LDL-C is common in the general population. Most of these individuals have one or more genetic abnormalities rather than a secondary cause (such as liver or kidney disease. For individuals with LDL-C above 190 mg/dL, the genetic defects that lead to familial hypercholesterolemia (FH) are the most common underlying cause.

Most hyperlipidemia is caused by genetic polymorphism in the context of dietary and other lifestyle factors. Identifiable familial forms account for only a fraction of all hyperlipidemia yet carry the highest cardiovascular risk.

Familial hypercholesterolemia (FH) is the most common autosomal dominant genetic disease. It affects up to 0.2% of the United States population; is the most common cause of marked hypercholesterolemia in children and in adolescents and is associated with early onset of CHD[15]. The clinical syndrome (phenotype) is characterized by extremely elevated levels of low density lipoprotein cholesterol (LDL-C) and a propensity to early onset atherosclerotic cardiovascular disease. In general, homozygotes manifest the disease at a much earlier age than heterozygotes and the disease is more severe. Intense low density lipoprotein cholesterol (LDL-C) lowering in individuals with heterozygous or homozygous familialhypercholesterolemia (FH) decreases progression of angiographically demonstrated coronary artery disease, and reduces cardiovascular disease events (myocardial infarction), coronary heart disease

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649-670.

[12] (2002). "Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report." Circulation **106**(25): 3143-3421.

[13] Genest, J. J., Jr., S. S. Martin-Munley, J. R. McNamara, J. M. Ordovas, J. Jenner, R. H. Myers, S. R. Silberman, P. W. Wilson, D. N. Salem and E. J. Schaefer (1992). "Familial lipoprotein disorders in patients with premature coronary artery disease." Ibid. **85**(6): 2025-2033.

[14] Roncaglioni, M. C., L. Santoro, B. D'Avanzo, E. Negri, A. Nobili, A. Ledda, F. Pietropaolo, M. G. Franzosi, C. La Vecchia, G. A. Feruglio and et al. Ibid."Role of family history in patients with myocardial infarction. An Italian case-control study. GISSI-EFRIM Investigators." 2065-2072.

[15] Liyanage, K. E., J. R. Burnett, A. J. Hooper and F. M. van Bockxmeer (2011). "Familial hypercholesterolemia: epidemiology, Neolithic origins and modern geographic distribution." Crit Rev Clin Lab Sci **48**(1): 1-18.

mortality, and all-cause mortality[16][17][18][19]. For homozygous familial hypercholesterolemia (FH) patients, who often have untreated low density lipoprotein cholesterol (LDL-C) of >500 mg/dL (>13 mmol/L) there is no agreement on LDL-C goal. Generally intensive LDL-C lowering, with a minimal target of <150 mg/dL (3.9 mmol/L) is accepted across guidelines and practices. The vast majority of adult patients with familial hypercholesterolemia (FH) encountered in clinical practice will be heterozygotes and will usually have an untreated low density lipoprotein cholesterol (LDL-C) ≥190 mg/dL.

Familial combined hyperlipidemia (FCHL) is a relatively common lipid disorder. It occurs in 1 to 2 percent of the general population and accounts for one-third to one-half of familial causes of coronary heart disease (CHD)[20] and 10 percent of cases of premature CHD[21]. In affected families, some individuals will have hypertriglyceridemia, some hypercholesterolemia, some both, and some neither.

The clinical manifestations of hyperlipidemia include premature CHD (particularly in patients with concurrent hypertriglyceridemia), xanthelasma (in 10 percent of cases), and obesity. Coexisting diabetes mellitus or impaired glucose tolerance is more common in patients who also have hypertriglyceridemia.

Most people will have no symptoms, but having hyperlipidemia increases the risk of developing CHD which is the leading cause of death in the U.S. In familial, or inherited, hyperlipidemia, there may be yellowish fatty growths (called xanthomas) around the eyes or the joints.

Multiple meta-analyses of randomized clinical trials (RCT)of LDL-C lowering therapy in patients with and without manifest CVD found strong evidence of reductions in CVD events

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[16] Kane, J. P., M. J. Malloy, T. A. Ports, N. R. Phillips, J. C. Diehl and R. J. Havel (1990). "Regression of coronary atherosclerosis during treatment of familial hypercholesterolemia with combined drug regimens." JAMA **264**(23): 3007-3012.

[17] Versmissen, J., D. M. Oosterveer, M. Yazdanpanah, J. C. Defesche, D. C. Basart, A. H. Liem, J. Heeringa, J. C. Witteman, P. J. Lansberg, J. J. Kastelein and E. J. Sijbrands (2008). "Efficacy of statins in familial hypercholesterolaemia: a long term cohort study." BMJ **337**: a2423.

[18] Neil, A., J. Cooper, J. Betteridge, N. Capps, I. McDowell, P. Durrington, M. Seed and S. E. Humphries (2008). "Reductions in all-cause, cancer, and coronary mortality in statin-treated patients with heterozygous familial hypercholesterolaemia: a prospective registry study." Eur Heart J **29**(21): 2625-2633.

[19] Raal, F. J., G. J. Pilcher, V. R. Panz, H. E. van Deventer, B. C. Brice, D. J. Blom and A. D. Marais (2011). "Reduction in mortality in subjects with homozygous familial hypercholesterolemia associated with advances in lipid-lowering therapy." Circulation **124**(20): 2202-2207.

[20] Williams, R. R., P. N. Hopkins, S. C. Hunt, L. L. Wu, S. J. Hasstedt, J. M. Lalouel, K. O. Ash, B. M. Stults and H. Kuida (1990). "Population-based frequency of dyslipidemia syndromes in coronary-prone families in Utah." Arch Intern Med **150**(3): 582-588.

[21] Goldstein, J. L., H. G. Schrott, W. R. Hazzard, E. L. Bierman and A. G. Motulsky (1973). "Hyperlipidemia in coronary heart disease. II. Genetic analysis of lipid levels in 176 families and delineation of a new inherited disorder, combined hyperlipidemia." J Clin Invest **52**(7): 1544-1568.

and CVD mortality[22][23][24]. Other meta-analyses have also found a reduction in the risk of all-cause mortality. In terms of individual components, all have found important reductions in myocardial infarction and in CHD mortality; reductions in stroke are somewhat smaller in magnitude but also clinically important[25].

In 2016

Type 2 Diabetes Mellitus (T2D) is a condition characterized by high blood glucose levels caused by either a lack of insulin or the body's inability to use insulin efficiently. Type 2 diabetes develops most often in middle-aged and older adults but can appear in children, teens, and young people.

Worldwide in 2014, 8.5% of adults aged 18 years and older had diabetes. In 2015, diabetes was the direct cause of 1.6 million deaths and in 2012 high blood glucose was the cause of another 2.2 million deaths[26].

More than 30 million Americans have diabetes (about 1 in 10), and 90% to 95% of them have type 2 diabetes[27]. There are an estimated of more than 3 million new cases/year.

Despite the relatively large increase in cases over the last 20 years, T2D in youth remains comparatively rare, unlike T2D in adults. The National Institutes of Health (NIH) and National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) estimate that there are 40,000–50,000 youth with T2D in the USA, a number far less than the more than 18 million adults with T2D[28].

If type 2 diabetes goes untreated, blood sugar levels stay high all the time. This isn't always noticeable at first. Type 2 diabetes can develop gradually over several years without any noticeable symptoms. Symptoms of hyperglycemia may include: extreme thirst, frequent urination, tiredness and listlessness, nausea, dizziness. Extremely high blood sugar levels may lead to patients feeling confused and drowsy or even lose consciousness (diabetic coma).

People who have type 2 diabetes are also at greater risk of developing cardiovascular conditions such as a heart attack, stroke or problems with the circulation in their legs and feet (peripheral artery disease, PAD). The risk of macrovascular complications of diabetes is especially high in people who also have high blood pressure.

Uncontrolled T2DM may lead to microvascular disease such as retinopathy, neuropathy, and

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[22] Mihaylova, B., J. Emberson, L. Blackwell, A. Keech, J. Simes, E. H. Barnes, M. Voysey, A. Gray, R. Collins and C. Baigent (2012). "The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials." Lancet **380**(9841): 581-590.

[23] Ray, K. K., S. R. Seshasai, S. Erqou, P. Sever, J. W. Jukema, I. Ford and N. Sattar (2010). "Statins and all-cause mortality in high-risk primary prevention: a meta-analysis of 11 randomized controlled trials involving 65,229 participants." Arch Intern Med **170**(12): 1024-1031.

[24] Taylor, F., M. D. Huffman, A. F. Macedo, T. H. Moore, M. Burke, G. Davey Smith, K. Ward and S. Ebrahim (2013). "Statins for the primary prevention of cardiovascular disease." Cochrane Database Syst Rev(1): CD004816.

[25] Chou, R., T. Dana, I. Blazina, M. Daeges and T. L. Jeanne (2016). "Statins for Prevention of Cardiovascular Disease in Adults: Evidence Report and Systematic Review for the US Preventive Services Task Force." JAMA **316**(19): 2008-2024.

[26] http://www.who.int/mediacentre/factsheets/fs312/en/

[27] https://www.cdc.gov/diabetes/basics/type2.html

[28] https://www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.pdf

2.2. Analysis of Current Treatment Options

The treatment for both hyperlipidemia as well as glycemic control is complex. The desired outcome when addressing both conditions is to reduce the risk of cardiovascular disease. Lifestyle modifications that include weight management, increased physical activity and diet control, are the cornerstone of clinical care for patients with hyperlipidemia and/or T2D. Per the current AHA/ACC/TOS guidelines lifestyle changes that produce even modest, sustained weight loss of 3%–5% produce clinically meaningful health benefits, and greater weight losses produce greater benefits. Sustained weight loss of 3%–5% is likely to result in clinically meaningful reductions in triglycerides, blood glucose, hemoglobin A1c, and the risk of developing type 2 diabetes. Greater amounts of weight loss will reduce BP, improve LDL–C and HDL–C, and reduce the need for medications to control BP, blood glucose, and lipids as well as further reduce triglycerides and blood glucose[29].

For LDL-C lowering regardless of weight status the AHA/ACC guidelines recommend consuming a dietary pattern that emphasizes intake of vegetables, fruits, and whole grains; including low-fat dairy products, poultry, fish, legumes, nontropical vegetable oils, and nuts; and limiting intake of sweets, sugar-sweetened beverages, and red meats. This dietary pattern should be adapted to appropriate calorie requirements, personal and cultural food preferences, and nutrition therapy for other medical conditions (including diabetes. Patients can achieve this pattern by following plans such as the DASH dietary pattern, the USDA Food Pattern, or the AHA Diet. Patients should aim for a dietary pattern that achieves 5%–6% of calories from saturated fat and reduce percent of calories from saturated fat as well as reduce percent of calories from trans fat [30].

In 2016 The American College of Cardiology ACC identified the following groups that benefit from LDL-C lowering therapy despite associated risks: adult patients ≥21 years of age with clinical atherosclerotic cardiovascular disease ASCVD; adults ≥21 years of age with LDL-C ≥190 mg/dL (not due to secondary modifiable causes); adults aged 40 to 75 years without ASCVD, but with diabetes and with LDL-C 70 to 189 mg/dL; and adults ages 40 to 75 years without ASCVD or diabetes, with LDL-C 70 to 189 mg/dL, and an estimated 10-year risk for ASCVD of ≥7.5% as determined by the Pooled Cohort Equations[31].

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[29] http://www.onlinejacc.org/content/accj/63/25_Part_B/2985.full.pdf?_ga=2.29815420.215041164.1509638786-2003018969.1472140967

[30]http://www.onlinejacc.org/content/accj/63/25_Part_B/2960.full.pdf?_ga=2.134080011.486408902.1510851575-2003018969.1472140967

[31] Goff, D. C., Jr., D. M. Lloyd-Jones, G. Bennett, S. Coady, R. B. D'Agostino, Sr., R. Gibbons, P. Greenland, D. T. Lackland, D. Levy, C. J. O'Donnell, J. G. Robinson, J. S. Schwartz, S. T. Shero, S. C. Smith, Jr., P. Sorlie, N. J. Stone and P. W. Wilson (2014). "2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American

Based on their 2017 assessment the U.S. Preventive Services Task Force (USPSTF) recommends that adults without a history of cardiovascular disease (CVD) (i.e., symptomatic coronary artery disease or ischemic stroke) use a low- to moderate-dose statin for the prevention of CVD events and mortality when all of the following criteria are met: (1) they are aged 40 to 75 years; (2) they have 1 or more CVD risk factors (i.e., dyslipidemia, diabetes, hypertension, or smoking); and (3) they have a calculated 10-year risk of a cardiovascular event of 10% or greater[32].

Multiple meta-analyses of randomized clinical trials (RCT) of LDL-C lowering therapy (statins) in patients with and without manifest CVD found strong evidence of reductions in CVD events and CVD mortality[333435]. Other meta-analyses have also found a reduction in the risk of all-cause mortality. In terms of individual components, all have found important reductions in myocardial infarction and in CHD mortality; reductions in stroke are somewhat smaller in magnitude but also clinically important[36].

For T2D the current recommendations emphasize individualization of glycemic goals and suggest that for most patients, an HbA1c of <7% is a reasonable target to reduce future risk of microvascular disease events (AHA/ACC Class IIb, Level of Evidence: A; ADA Level of Evidence: B)[37]. Based on improved primary prevention of macrovascular disease in a subset of patients (n = 342) from the UKPDS trial, metformin is generally considered to be first-line therapy for glycemic control [38]. Recent trials have suggested other pharmacological strategies may also reduce vascular risk for patients with diabetes. A sodium glucose cotransporter-2 (SGLT2) inhibitor (empagliflozin) and glucagon-like peptide (GLP)-1 analogues (liraglutide and

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College of Cardiology/American Heart Association Task Force on Practice Guidelines." J Am Coll Cardiol **63**(25 Pt B): 2935-2959.

[32] https://www.aafp.org/afp/2017/0115/od1.pdf

[33] Mihaylova, B., J. Emberson, L. Blackwell, A. Keech, J. Simes, E. H. Barnes, M. Voysey, A. Gray, R. Collins and C. Baigent (2012). "The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials." Lancet **380**(9841): 581-590.

[34] Ray, K. K., S. R. Seshasai, S. Erqou, P. Sever, J. W. Jukema, I. Ford and N. Sattar (2010). "Statins and all-cause mortality in high-risk primary prevention: a meta-analysis of 11 randomized controlled trials involving 65,229 participants." Arch Intern Med **170**(12): 1024-1031.

[35] Taylor, F., M. D. Huffman, A. F. Macedo, T. H. Moore, M. Burke, G. Davey Smith, K. Ward and S. Ebrahim (2013). "Statins for the primary prevention of cardiovascular disease." Cochrane Database Syst Rev(1): CD004816.

[36] Chou, R., T. Dana, I. Blazina, M. Daeges and T. L. Jeanne (2016). "Statins for Prevention of Cardiovascular Disease in Adults: Evidence Report and Systematic Review for the US Preventive Services Task Force." JAMA **316**(19): 2008-2024.

[37] American Diabetes Association Standards of Medical Care in Diabetes–2016 Diabetes Care, 39 (Suppl 1) (2016), pp. S1-S93

[38] UK Prospective Diabetes Study (UKPDS) Group Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34)

semaglutide), have recently demonstrated a reduction in mortality and CVD events among patients with diabetes and pre-existing CVD or multiple CVD risk factors[39] [40] [41].

Alternative therapies have been suggested in CVD prevention although not directly linked to LDL-c lowering and/or glycemic control. For example in 2017 the AHA released a scientific statement regarding the impact of meditation on CVD in which after reviewing >400 trials they found a possible, though not definitively established, benefit of meditation on cardiovascular risk reduction[42].

The following drugs are currently approved for patients with primary hyperlipidemia or mixed dyslipidemia:

- atorvastatin, simvastatin, pitavastatin, lovastatin, fluvastatin, pravastatin, niacin extended-release, fenofibrate (to reduce elevated TC, LDL-C, Apo B, and TG and to increase HDL-C).
- rosuvastatin, atorvastatin/ezetimibe and simvastatin/ezetimibe (to reduce elevated TC, LDL-C, Apo B, TG and non-HDL-C and to increase HDL-C.
- Praluent (Alirocumab) is indicated as adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease, who require additional lowering of LDL-C
- Repatha (evolocumab) was approved to treat patients with heterozygous familial hypercholesterolemia (HeFH) and patients with the rarer homozygous (HoFH) form of the disease.
- Other lipid lowering therapies available are listed in Table 1

While many oral and injectable anti-diabetic medications have been developed and are now available to treat adults with T2D, only metformin and insulin have been approved in the USA and EU for use in children.

Table 1 FDA Approved Drugs for Treatment of Hyperlipidemia

Product Name	Class	Year of Approval	Route and Frequency of Administration	Important Safety and Tolerability Issues
Atorvastatin	HMG-CoA reductase Inhibitors	June 15, 2015	10 to 80 mg/day	Headache; nausea; sleep disturbance; elevations in hepatocellular enzymes and alkaline phosphatase. Myositis and rhabdomyolysis,
Fluvastatin		May 8,	IR: 20 to 80	

[39] B. Zinman, C. Wanner, J.M. Lachin, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes N Engl J Med, 373 (2015), pp. 2117-2128
[40] S.P. Marso, G.H. Daniels, K. Brown-Frandsen, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes N Engl J Med, 375 (2016), pp. 311-322
[41] S.P. Marso, S.C. Bain, A. Consoli, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes N Engl J Med, 375 (2016), pp. 1834-1844
[42] https://doi.org/10.1161/JAHA.117.002218 Journal of the American Heart Association. 2017;6:e002218

		1999	mg/day XR: 80 mg/day	primarily when given with gemfibrozil or cyclosporine; myositis is also seen with severe renal insufficiency (CrCl <30 mL/min). Lovastatin, atorvastatin, rosuvastatin, and simvastatin potentiate effect of warfarin; this interaction is not seen with pravastatin, fluvastatin, or pitavastatin. Most statins can also affect digoxin metabolism and levels.
Lovastatin		Septemb er, 1987	IR: 20 to 80 mg/day XR: 20 to 60 mg/day	
Pitavastatin		August 3, 2009	1 to 4 mg/day	
Pravastatin		February 10, 2000	10 to 80 mg/day	
Rosuvastatin		August 13, 2003	5 to 40 mg/day	
Simvastatin		July 10, 1998	5 to 40 mg/day	
Alirocumab	PCSK9 Inhibitors	July 24, 2015	75 to 150 mg every two weeks SQ	Injection site reactions
Evolocumab		August 27, 2015	140 mg every two weeks or 420 mg every month SQ Homozygous familial hypercholesterolemia: 420 mg every month to 420 mg every two weeks SQ	
Fenofibrate	Fibric acid derivatives	Septemb er 4, 2001	Nanocrystal 145 mg/day Micronized 160 to 200 mg/day	skin rash, gastrointestinal (nausea, bloating, cramping) myalgia; lowers blood cyclosporine levels; potentially nephrotoxic in cyclosporine treated patients. Avoid in patients with CrCl <30 mL/min.
Gemfibozil		Novembe r 20, 1986	600 mg twice per day	Potentiates warfarin action. Absorption of gemfibrozil diminished by bile acid sequestrants.
Niacin	Nicotinic acid	July 28, 1997	IR: 1 to 6 g/day XR (Niaspan): 0.5 to 2 g/day	Prostaglandin-mediated cutaneous flushing, headache, warm sensation, and pruritus; hyperpigmentation (particularly in intertriginous regions); acanthosis nigricans; dry skin; nausea; vomiting; diarrhea; and myositis
Cholestyram ine	Bile acid sequestran ts	August 3, 1973	4 to 24 g/day PO	Nausea, bloating, cramping, and constipation; elevations in hepatic transaminases and alkaline phosphatase. Impaired absorption of fat soluble vitamins and coadministered medications including: Amiodarone, digoxin, warfarin, thiazides, beta blockers, levothyroxine, others; interaction can be minimized by taking other medications at least one hour before or four hours after bile acid sequestrant.
Colestipol		April 4, 1977	5 to 30 g/day PO	
Colesevelam		May 26, 2000	3.75 g/day PO	

Ezetimibe	Cholesterol absorption inhibitors	October 25, 2002	10 mg/day	Increased transaminases in combination with statins

Table 2 FDA Approved Drugs for Treatment of Glycemic Control in Type 2Diabetes Mellitus

Product Name	Class	Year of Approval	Route and Frequency of Administration	Important Safety and Tolerability Issues
Acarbose	Alpha-Glucosidase Inhibitors	August 16, 1999	25-100 mg q8h PO	Abdominal pain, diarrhea, elevated serum transaminases, flatulence. Fulminant hepatitis with fatal outcome, ileus/subileus, jaundice and/or hepatitis and associated liver damage Hypersensitive skin reactions: rash, erythema, exanthema and urticaria. Edema , thrombocytopenia, pneumatosis cystoides intestinalis
Miglitol		August 16, 1999	25-100 mg q8h PO	Flatulence, diarrhea, abdominal pain, rash, low serum iron. Contraindicated in diabetic ketoacidosis, inflammatory bowel disease, colonic ulceration, partial intestinal obstruction, severe renal impairment
Pramlintide	Amylin Mimetics	March 16, 2005	60-120 mcg SC	Nausea, headache, vomiting, anorexia, severe hypoglycemia. Black Box Warnings: increased risk of insulin-induced severe hypoglycemia.
Metformin	Biguanides	December 30, 1994	500 to 2550 mg/day PO	Nausea, vomiting, diarrhea, abdominal pain, flatulence, hypoglycemia, lactic acidosis. Asthenia, chills, flu like syndrome. Myalgia, rhinitis.
Colesevelam	Bile Acid Sequestrants	May 26, 2000	3.75 g/day PO	Nausea, bloating, cramping, and constipation; elevations in hepatic transaminases and alkaline phosphatase.
Bromocriptine (Cycloset)	Dopamine-2 Agonists	May 5, 2009	1.5-4.8 mg/day PO	Nausea, rhinitis, headache, astenia, dizziness, constipation.
Alogliptin	DPP-4 Inhibitors	January 25, 2013	25 mg/day PO	Hypoglycemia, nasopharyngitis, headache. Postmarketing reports of severe and disabling arthralgia, bullous pemphigoid.
Linagliptin		May 2, 2011	5mg/day PO	Nasopharyngitis, hyperlipidemia, cough, Hypertriglyceridemia, weight gain, hypoglycemia. Acute pancreatitis, including fatal pancreatitis, Rash, Mouth ulceration, stomatitis, Hypersensitivity reactions including anaphylaxis, angioedema, and exfoliative skin conditions, Severe disabling arthralgia
Saxagliptin		July 31, 2009	2.5-5 mg/day PO	UTI, headache, hypersensitivity events, peripheral edema, URI, gastroenteritis, hypoglycemia. Severe and disabling arthralgia. Bullous pemphigoid
Sitagliptin		February 15, 2006	100 mg/day PO	Nasopharyngitis, Diarrhea, Headache, Constipation, Peripheral edema, Nausea,

				Pharyngitis, Osteoarthritis, URI, Pruritus, Bullous pemphigoid, Mouth ulceration; stomatitis
Albiglutide	GLP-1 Receptor Agonists	April 15, 2014	30-50 mg SC/ week	Upper respiratory tract infection, diarrhea, nausea, injection site reaction, pancreatitis. GLP-1 receptor agonists may increase the risk of thyroid C-cell tumors and are contraindicated in patients with family history of MTC and/or MEN2.
Dulaglutide		Septemb er 18, 2014	0.75-1.5 mg SC/week	Nausea, diarrhea, vomiting, abdominal pain, decrease appetite, dyspepsia, fatigue. Pancreatitis, hypoglycemia and severe gastrointestinal and renal disease may occur.
Exenatide		April 28, 2005	5-10 mcg BID SC	Nausea, vomiting, upset stomach, diarrhea, constipation, weight loss, loss of appetite, heartburn, dizziness, headache. Post-marketing reports of dysgeusia, somnolence, altered renal function and alopecia.
Exenatide LAR		January 27, 2012	2mg SC/week	
Liraglutide		January 25, 2010	0.6-1.8mg SC/day	Headache, dizziness, nausea, vomiting, upset stomach, indigestion, loss of appetite, diarrhea, constipation, cold symptoms (stuffy nose, sneezing, sinus pain, sore throat), back pain, tired feeling, skin rash, upper respiratory tract infection, injection site reactions.
Semaglutide		Decembe r 5, 2017	0.25-1mg SC/week	Nausea, vomiting, diarrhea, abdominal pain and constipation, injection site reactions. Increases in Amylase and Lipase, cholelithiasis, fatigue, dysgeusia and dizziness.
Insulin Degludec	Insulins and Insulin Analogues	Septemb er 25, 2015	SQ administration. Starting dose of 10Units/day (or 0.1-0.2 Units/kg)	Hypoglycemia, hypokalemia, allergic reactions, injection site reactions, body fat redistribution (lipodystrophy), itching, rash, swelling, peripheral edema, weight gain, runny or stuffy nose, upper respiratory tract infection, headache, sinusitis, upset stomach or stomach pain, and diarrhea. Intensification or rapid improvement in glucose control has been associated with a transitory, reversible ophthalmologic refraction disorder, worsening of diabetic retinopathy, and acute painful peripheral neuropathy. However, long-term glycemic control decreases the risk of diabetic retinopathy and neuropathy.
Insulin Detemir		June 16, 2005		
Insulin Glargine		April 20, 2000		
Insulin Isophane		Septemb er 28, 1982		
Insulin Lispro (Admelog)		Decembe r 11, 2017		
Insulin Lispro (Humalog)		June 1996		
Insulin Regular		Decembe r 5, 1979		
Insulin Aspart		June 7, 2000		
Insulin Glulisine		April 16, 2004		
Insulin human (Afrezza)		June 27, 2014	Inhaled insulin	Acute bronchospasm has been observed in patients with asthma and COPD. AFREZZA should

				not be used in patients with active lung cancer. In patients with a history of lung cancer or at risk for lung cancer, the benefit of AFREZZA use should outweigh this potential risk.
Nateglinide	Meglitinides	December 22, 2000	120 mg PO TID	Upper Respiratory Infection, back pain, flu symptoms, dizziness, arthropathy, diarrhea, accidental trauma, bronchitis, coughing, hypoglycemia, increase in uric acid, jaundice, cholestatic hepatitis, and elevated liver enzymes.
Repaglinide		April 24, 2015	0.5-4mg PO before meals up to 16mg/day	Upper respiratory infection, headache, sinusitis, arthralgia, nausea, diarrhea, back pain, rhinitis, constipation, vomiting, paresthesia, chest pain, bronchitis, dyspepsia, urinary tract infection, tooth disorder, allergy. Post marketing reports of alopecia, hemolytic anemia, pancreatitis, Stevens-Johnson syndrome, jaundice, hepatitis.
Canagliflozin	SGLT2 Inhibitors	March 29, 2013	100-300mg PO daily	UTI, increased urination, thirst, constipation, nausea, fatigue, weakness, skin sensitivity to sunlight, hypersensitivity reactions, female genital mycotic infections, vulvovaginal pruritus, male genital mycotic infections. Hypotension, acute kidney injury, hyperkalemia, bone fractures.
Dapagliflozin		January 8, 2014	5-10mg PO daily	Hypotension, ketoacidosis, acute kidney injury, impaired renal function, urosepsis and pyelonephritis, hypoglycemia, genital mycotic infections, increased LDL-C, bladder cancer. Nasopharyngitis, back pain, nausea, influenza, constipation, pain in extremity.
Empagliflozin		August 1, 2014	10-25mg PO daily	Dehydration, dizziness, lightheadedness, weakness, yeast infection, hypoglycemia, nausea, upper respiratory tract infection, high cholesterol, joint pain, increased urination, urinary tract infection, thirst, hypotension, genital mycotic infections.
Ertugloflozin		December 22, 2017	5-15mg PO daily	Genital mycotic infections, upper respiratory tract infection, urinary tract infections (UTIs), vaginal itching, increased urination, back pain,
Chlorpropamide	Sulfonylureas	September 28, 1958	starting dose 250mg PO daily	Hypoglycemia, headache, nausea, dizziness, weakness, weight gain, allergic reactions, such as pruritus, erythema, urticaria, and morbilliform or maculopapular eruptions, anaphylaxis, angioedema, and Stevens-Johnson Syndrome. Elevated ALT, hemolytic anemia in patients with and without G6PD deficiency, cholestasis, jaundice, hepatitis. Porphyria cutanea tarda, photosensitivity reactions and allergic vasculitis, leukopenia, agranulocytosis, aplastic anemia, pancytopenia, thrombocytopenia, hyponatremia, dysgeusia, alopecia.
Glimepiride		February 24, 1999	1-2 mg PO daily	
Glipizide		May 8, 1984	5-40 mg PO	
Glyburide		March 4, 1992	1.25-20 mg PO daily	
Tolazamide		September 3, 1984	100-250 mg PO daily. Dose can be titrated to max of	

			1000mg/day	
Tolbutamide		July 10, 1974	0.25-3mg PO daily	
Pioglitazone	Thiazolidinediones	July 15, 1999	15-45 mg PO daily	Hypoglycemia, URI, headache, sinusitis, myalgia, pharyngitis, edema, weight gain, UTI, congesitive heart failure, fractures.
Rosiglitazone		May 25, 1999	4-8mg PO daily	Hypoglycemia, URI, headache, back pain, hyperglyceamia, fatigue, sinusitis, diarrhea, hypertension, cardiac failure, edema, weight gain, fractures.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Colesevelam hydrochloride has been previously approved in the U.S. as Welchol™ Tablets, 625 mg (initial U.S. approval May 26, 2000) and Welchol™ Capsules, 625mg (not marketed) under NDA 21141 and NDA21176 respectively as well as Welchol™ for Oral Suspension 3.75 gram packet (approved on October 2, 2009) under NDA 22362.

The initial approval in 2000 indicated Welchol as an adjunct to diet and exercise to reduce LDL in adults with primary hyperlipidemia alone or in combination with statins. Welchol® was subsequently approved in 2009 to 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[43]. A waiver of the requirement to study Welchol® in subjects 0-9 years was granted by FDA in 2009 because necessary studies are impossible or highly impracticable due to the limited population of hypercholesterolemia in this age group.

Welchol® was approved as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus in 2008. Upon the approval of Welchol® Oral Suspension as an alternative formulation in 2009, Daiichi Sankyo initiated a 1-year efficacy and safety study for the treatment of type 2 diabetes in pediatric patients ages 10 to 17 years under PREA. Per Sponsor as of December 2017 the Welchol pediatric T2D study (WELKid DM) has randomized approximately 90% of planned subjects and is on track to complete the study enrollment in 2018 and complete study treatment in 2019.

A waiver of the requirement to study Welchol® in subjects 0-9 years was granted in 2009 because the low prevalence of the disease in children below 10 years of age makes the conduct of pediatric studies in this age group highly impracticable.

[43] https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/022362lbl.pdf

Welchol Tablets: The recommended dose is 6 tablets once daily or 3 tablets twice daily. Welchol Tablets should be taken with a meal and liquid.

Welchol for Oral Suspension: The recommended dose is one 3.75 gram packet once daily or one 1.875 gram packet twice daily. To prepare, empty the entire contents of one packet into a glass or cup. Add ½ to 1 cup (4 to8 ounces) of water. Stir well and drink. Welchol for Oral Suspension should be taken with meals. To avoid esophageal distress. Welchol for Oral Suspension should not be taken in its dry form.

Daiichi Sankyo is seeking approval of the chewable bar as an alternate dosage form to the marketed WELCHOL® Tablets, and Oral Suspension, and are proposing a single WELCHOL® package insert based on the currently approved tablet and oral suspension labeling with appropriate sections modified to incorporate the chewable bar dosage form.

3.2. Summary of Presubmission/Submission Regulatory Activity

Pre-NDA:

The pre-NDA meeting between Daiichi Sankyo Inc and DMEP on July 24, 2017 discussed the Sponsor's intention to develop a new chewable bar formulation in collaboration with (b) (4) Prior to this teleconference preliminary comments were sent to the Sponsor on July 20, 2017 regarding their overall development program.

Briefly during this telecon the FDA and the Sponsor discussed the overall submission strategy and requirements. The FDA agreed that the Sponsor's proposal to cross-reference the drug substance DMF was acceptable. The agency reminded Daiichi that any excipient that has not been approved by FDA in a drug is considered a novel excipient, and complete CMC information on the material should be provided in the NDA or a referenced DMF.

Regarding the pediatric studies requirements, following internal discussions with the Pediatric Review Committee (PeRC), the firm was instructed to include an initial Pediatric Study Plan (iPSP) in the NDA to be reviewed as part of the application.

The Sponsor was instructed to submit an updated Environmental Assessment (EA) in the new NDA because colesevelam HCl is an insoluble polymer that is expected to partition to wastewater treatment plant biosolids.

The proposal for demonstrating bioequivalence between the commercial Welchol Tablets and the Welchol Chewable Bar appeared to be reasonable at that time. The Agency instructed the Sponsor to justify the use of 4.75 g of the chewable bar (equivalent to 600 mg of colesevelam) in the in vitro kinetic binding study as well as to submit details of the analytical method and the validation report for the in vitro BE studies. The Agency agreed that the primary determination of bioequivalence may be based on the total bile salt binding, but comparisons with respect to individual bile salt binding should be provided as supportive data

In response to a September 30, 2015 inquiry from the Sponsor, the FDA commented that Daiichi should address whether there is any impact of chewing on in vivo performance of the proposed formulation, e.g., alteration of bile acid binding. In response to this request, Daiichi Sankyo completed a study to evaluate the impact of chewing on bile acid binding by reducing the typical bite size of the chewable bar drug product to a size suitable for swallowing and then determining the bile acid binding capacity on various sample sizes. In this study, small, medium and large samples were evaluated to simulate different sizes of chewable bar pieces chewed and swallowed by the patients. Despite the Sponsor's statement that there is no commercially available standard equipment to perform a chewing study for a chewable bar product, the Agency suggested that a clinical trial would adequately assess the effects of mastication on the drug's in vivo performance. No clinical trial was required at this time for filing.

Other issues such as specific labeling questions, REMS requirements as well as CMC submission details were deferred as review issues post submission.

NDA Review Cycle:

Daiichi Sankyo submitted this new NDA on October 30, 2017 with a PDUFA date of August 30, 2018.

On December 22, 2017 the following filing review issues were presented to the Sponsor from Clinical Pharmacology: "You are proposing to evaluate safety and efficacy through demonstration of an in vitro bioequivalence assessment between the approved tablet formulation and the proposed chewable dosage form. At the July 24, 2017, pre-NDA telecon, we voiced our concern that chewing and digestion are complex processes and that the Agency will review whether the in vitro assessments are sufficient to conclude that an ingested chewable bar would have similar safety and effectiveness as the listed product. If this conclusion cannot be reached after our review of the submitted data, a clinical trial may be required to directly assess the effects of the product when consumed.

On March 19, 2018 the Agency communicated with the Sponsor several identified deficiencies found during the Clinical Pharmacology review: see **4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety**

Additionally, the Agency expressed concern whether in vitro assessments are sufficient to conclude that an ingested chewable bar would have similar safety and effectiveness as the approved product. The Sponsor's study simulates a condition where a patient may simply bite off small chunks of the chewable bar and swallow with minimal or no chewing. As we had previously pointed out during the pre-NDA telecon, in a clinical scenario, the patient may chew the bar in a way that can form a bolus which will then be swallowed. However, there is no evidence that the swallowed bolus would disintegrate in the same manner as the small piece of intact bar used in the chewing study. The Agency requested that the Sponsor provide

justification that swallowed bolus will disintegrate in the same manner as small pieces. We also previously recommended that the Sponsor conduct in vitro equilibrium binding study to assess the effect of chewing on the product performance. We noted that the Sponsor used (b) (4) method for bile acid binding (M12600) which, is used for release and stability testing. The Agency requested that the Sponsor justify the sensitivity of this method in detecting differences in bile salts binding to assess impact of chewing. Alternatively, we recommended that the chewing study be repeated using in vitro equilibrium binding study.

On February 21, 2018 the PeRC committee recommended a partial waiver less than 10 years and deferral for 10-17 years for glycemic control in Type 2 Diabetes and partial waiver less than 10 years and assessment 10-17 years for hypercholesterolemia.

On April 25, 2018, an Information request was sent to the Sponsor from the Clinical Team. The team was concerned of a potential adverse effect of maltodextrin and palm oil (in addition to other excipients present in lower quantities) on LDL-C and glucose levels in patients who would be using this product to reduce LDL C or improve glycemic control. The Sponsor was asked to submit their justification that the "excipients" in the proposed product would not attenuate its efficacy.

On May 18, 2018 the Sponsor replied stating that these excipients (i.e. maltitol, maltodextrin, palm oil) are generally regarded as safe (GRAS) and are commonly used in drug formulations or as food additives. The Sponsor further stated that although it is generally accepted that excessive caloric intake or diet high in saturated or trans-fat, or high in carbohydrates are associated with adverse metabolic and cardiovascular health. However, the impact of small alternations in dietary carbohydrate has been much more difficult to ascertain. Carbohydrates with a low glycemic index break down slowly during digestion, are slowly assimilated and have a slower impact on blood glucose levels and insulin response. Although the effects on long term cardiovascular outcomes benefits remain unresolved, carbohydrates with low glycemic index are thought to offer improved metabolic impact compared to carbohydrates with high glycemic index, especially for patients with type 2 diabetes.

The Sponsor concluded that taken together, the total caloric content in the added excipients is unlikely to cause clinically significant attenuation in the efficacy of WCB, given a small addition of (b) (4) to the daily caloric intake and the nature of low glycemic index for maltitol, the principal caloric contributor.

The Division's second concern sent to the Sponsor in the same communication as above was related to the product contents of Maltitol. A literature review at that time had identified levels of maltitol as low as 15g to induce osmotic diarrhea. Since the formulation has (b) (4) Maltitol we requested that the Sponsor provide justification addressing whether the effect of maltitol will have an impact on the overall safety and efficacy of the product.

The Sponsor's reply stated that Maltitol has been used as a sweetener and food additive. In the GI tract, maltitol is subject to bacterial fermentation but is poorly absorbed. Like other polyols, maltitol can have a laxative effect due to the osmotic effects of unabsorbed polyols reaching the colon. As a food additive, maltitol has been extensively evaluated since the 1980s for its digestive tolerance profile at doses up to more than 100g per day. The threshold dose reported to induce laxative effects is above 30g per day. The Sponsor noted that the observed discrepancy between the literature cited by the Division[44] (threshold for osmotic diarrhea at 15mg vs 30 mg Maltitol) may arise from the patient population of the study (young college females with relatively lower body masses) as well as the formulation used (liquid solution of maltitol, not maltitol blended in food).

The Sponsor also referenced the FDA approval of NDA 22-581 for the calcium acetate oral solution, Phoslyra. In the pharmacology/toxicology NDA review of Phoslyra, FDA concluded that the maximal recommended daily dose of Phoslyra containing 18g of maltitol was approvable and indicated that this is less than the threshold level of 30g reported to induce laxative effects.

3.3. Foreign Regulatory Actions and Marketing History

Not applicable

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

Not applicable

4.2. Product Quality

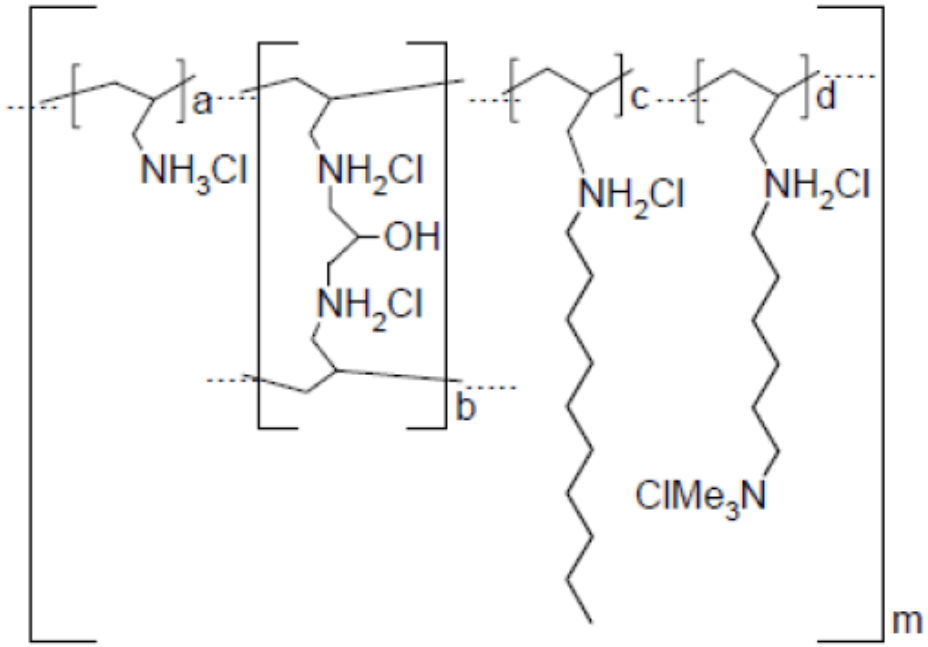
The active ingredient, colesevelam hydrochloride, in the proposed Welchol® Chewable Bar dosage form is provided by the same manufacturer for the active ingredient in the currently marketed Welchol™ (colesevelam hydrochloride) Tablets and Welchol™ (colesevelam hydrochloride) Powder for Oral Suspension, approved in NDA 021176 and NDA 022362, respectively. The active ingredient was also approved in NDA 021141 for a non-marketed capsule formulation of colesevelam hydrochloride.

[44] Oku, T., R. Hongo, and S. Nakamura, Suppressive effect of cellulose on osmotic diarrhea caused by maltitol in healthy female subjects. J Nutr Sci Vitaminol (Tokyo), 2008. 54(4): p. 309-14.

Chemical Abstracts Services (CAS):

1-Hexanaminium, N,N,N-trimethyl-6-(2-propenylamine)-, chloride, polymer with (chloromethyl)oxirane, 2-propen-1-amine and N-2-propenyl-1-decanamine, hydrochloride

Figure 1 Structure



Where:
a: number of primary amine groups (a = 0.14)
b: number of cross-linked amine groups (b = 0.12)
c: decylbromide alkylated amine groups (d = 0.40)
d: monoquat alkylated amine groups (c = 0.34)
m: > 100 to indicate extended polymer network

All aspects of the synthesis of colesevelam hydrochloride are conducted by (b) (4) under DMF (b) (4). (b) (4) of colesevelam hydrochloride, particle size testing, and bulk packaging is conducted by (b) (4)

The Welchol® (colesevelam hydrochloride) Chewable Bars are available in three flavors, chocolate, strawberry and caramel, containing 3.75 g of colesevelam hydrochloride (b) (4) as the active ingredient in a 30 g bar.

Figure 2 Description of Welchol® Chewable Bars

Item	Chocolate Bar	Strawberry Bar	Caramel Bar
Description (Appearance)	Brown, Oblong, rectangular	Pink Oblong, rectangular	Tan Oblong, rectangular
Dosage Form	Chewable bar	Chewable bar	Chewable bar
Picture			
Weight	30 g	30 g	30 g

Each Welchol® Chewable Bar is individually packaged in child-resistant (as certified by the Sponsor) white foil laminate (b) (4) wrappers.

Table 2 Welchol® (colesevelam hydrochloride) Chewable Bars Composition

Ingredient	Grade	Function	Amount					
			Chocolate		Strawberry		Caramel	
			mg/bar	% w/w	mg/bar	% w/w	mg/bar	% w/w
Colesevelam Hydrochloride[a]	DMF	Active						(b) (4)
Maltitol (b) (4) (D) (4)	NF							(D) (4)
(b) (4)	NF							
Maltodextrin	NF							
(b) (4)	In-house/GRAS							
Palm Oil	In-house/GRAS							
Glycerin	USP							
Lecithin	NF							
Sucralose	NF							
(b) (4) Rosemary Extract Flavor	21 CFR 182.20							
(b) (4) Vanilla (b) (4) Flavor (b) (4)	DMF							
Alkalized Cocoa	21 CFR 163.5							

Ingredient	Grade	Function	Amount					
			Chocolate		Strawberry		Caramel	
			mg/bar	% w/w	mg/bar	% w/w	mg/bar	% w/w
(b) (4)	DMF							(b) (4)
Chocolate Flavor (b) (4)								
(b) (4)	DMF							
Strawberry Cheesecake (b) (4) Flavor (b) (4) (b) (4)								
Acacia	NF							
FD&C (b) (4) No. 40	21 CFR 74.1340							
(b) (4) Citric Acid	USP							
(b) (4) Caramel (b) (4) Flavor (b) (4)	DMF							
Caramel Color	21 CFR 73.85							
(b) (4)	USP							
		TOTAL	30,000	100	30,000	100	30,000	100

(b) (4)

The strawberry and caramel flavor registration batches exhibited a change in color for the appearance test when stored under accelerated storage conditions. (b) (4)

Figure 3 Welchol® Chewable Bar Stability Samples Stored under Long-Term, Intermediate and Accelerated Conditions for 6 Months

	Caramel	Strawberry	Chocolate
Long-Term:	(b) (4)		
Intermediate:			
Accelerated			

Clinically relevant studies submitted in support of the product include an in vitro bioequivalence study with Welchol Tablets and a study of the effects of chewing and digestion on bile acid capacity (reference is made to the Clinical Pharmacology review). The biobatches are also primary stability batches (chocolate 125.6034R3A, strawberry 126.6039R1A, and caramel 127.6032R1A). They were manufactured at the commercial site (b) (4) at pilot scale (b) (4)

No drug substance manufacturing, container closure or drug stability issues have been identified during the OPQ Review.

Facilities: One PAI was conducted in support of this application at (b) (4) . A "Withhold" is recommended based on the 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.

The final OPQ recommendation is for Complete Response, including the overall manufacturing inspection recommendation.

Summary of Complete Response issue:
(b) (4) is the proposed commercial drug product manufacturing site. Prior to this NDA, this site was known to FDA as a dietary supplement manufacturer and did not have any inspectional history for human drug manufacture. After the NDA-specific pre-approval inspection of the site (conducted from (b) (4) FDA issued inspection observations. Responses by the site to FDA's observations were found inadequate by FDA. The major issue that has not been resolved involves persistent microbial contamination at the site.

In the resubmission, the Sponsor should provide 24-month stability data for the six registration batches (b) (4) and all available stability data for the six demonstration batches (b) (4)

4.3. Clinical Microbiology

Not applicable

4.4. Nonclinical Pharmacology/Toxicology

The safety profile for colesevelam hydrochloride has been defined in nonclinical studies. These studies are documented in the approved NDAs for tablet and oral suspension formulations of colesevelam hydrochloride (NDA 21-176 and NDA 22-362, respectively) and the labeling for these products.

The Applicant provided safety information from publically available literature to support the safety of maltitol syrup, palm oil, alkalized cocoa powder, and rosemary extract, which are considered non-compendial or are present at higher concentrations than those listed in the FDA's Inactive Ingredient Database (IID) based on amounts in previously approved products.

There are no additional safety concerns related to the colesevelam drug substance administered as chewable bars compared to the tablet and oral suspension formulations. Welchol® is not absorbed, the risk of systemic toxicity is low. Safety concerns for colesevelam are well known and are primarily related to processes that depend on bile acid action in the gut, which includes the absorption of fat-soluble vitamins A, D, E, and K.

Per Pharm/Tox review by Dongyu Guo, Ph.D. maltitol syrup, palm oil, alkalized cocoa powder, and rosemary extract are allowable as excipients at the proposed levels in the Welchol® chewable bar formulation.

The maximum amount of maltitol in the Welchol® chewable bars is (b) (4) mg/bar. While not listed in adequate amounts for any product in the IID, the safety of maltitol as a crystalline powder (>98%) or as liquid syrup was identified as having been evaluated previously to support approval of NDA 022581 (Phoslyra®, approved in 2011, which is indicated for the reduction of serum phosphorus in patients with end stage renal disease). The maximum daily dose of Phoslyra® contains 18 grams of maltitol. Therefore, the levels of maltitol in Welchol® chewable bar are supported by prior clinical use in a U.S.-approved drug for chronic once-daily oral administration.

Welchol® chewable bar contains (b) (4) mg/bar palm oil. Palm oil is a common human dietary component with a long history of use; palm oil is the most consumed oil in the world. No apparent association of palm oil consumption with cardiovascular disease was noted based on available epidemiology data (Ismail et al., 2018). Additionally, palm oil (10-20%) was

administered in the diet to rats in a series of subchronic toxicity studies, and no adverse effects were observed. The no-observed-adverse-effect-level (NOAEL) based on a conservative analysis was (b) (4) g/kg, which is (b) (4)-times higher than the clinical exposure to (b) (4) mg/day palm oil contained in the Welchol® chewable bar, based on body surface area. Therefore, since palm oil is a common human food and no significant safety concerns have been identified, oral administration of (b) (4) mg/day palm oil is acceptable from a nonclinical perspective.

Welchol chewable bar (chocolate flavor) contains (b) (4) mg/bar alkalized cocoa powder. Cocoa powder is a common human dietary component with a long history of use. Cocoa powder may contain heavy metals and/or caffeine; acceptable levels are specified for drug product release testing. Cocoa powder was not genotoxic in a series of in *vitro* genotoxicity assays including Ames Test, mouse lymphoma assay, chromosomal aberration assay, sister-chromatid exchange assay, and an in *vitro* cell transformation assay in mouse Balb/c-3T3 cells. No treatment-related teratogenicity/embryotoxicity was detected in pregnant New Zealand rabbits given cocoa powder at up to 7.5% of the diet (~ 2,678 mg/kg) during gestation days 6-29. A 104-week chronicle/carcinogenicity study was conducted using Sprague-Dawley rats fed cocoa powder in diet at levels of 0.0, 1.5, 3.5, or 5.0%. In male rats fed 5.0% cocoa powder, there was an increased incidence of bilateral diffuse testicular atrophy and a concomitant decrease in spermatogenesis compared with controls. The NOAEL was the mid-dose of 3.5% (1.5 g/kg/day based on the more conservative daily intake), which was (b) (4)-times the human exposure of (b) (4) mg/bar cocoa powder, based on body surface area. Therefore, cocoa powder at up to (b) (4) mg is acceptable from a nonclinical perspective.

Rosemary extract was not genotoxic in prokaryotic (Ames Test) and eukaryotic (human lymphocyte, thymidine kinase and hgprt loci of human lymphoblastoid cells) *in vitro* test systems and *in vivo* micronucleus test. Subchronic toxicity studies (14-90 days) were conducted in rats given rosemary extract in diet. The NOAELs in these studies were the highest doses tested ranging from 180 to 400 mg/kg/day, which represents ≥ (b) (4)-times the human exposure of (b) (4) mg/bar roseamy extract. Rosemary extract is generally recognized as safe (GRAS) by the FDA as an essential oil, oleoresin (solvent-free), and natural extractive (including distillates) for human consumption (21 CFR182.20) for its intended use (b) (4) and therefore oral administration of up to (b) (4) mg/day rosemary extract is acceptable from a nonclinical point of view.

4.5. Clinical Pharmacology

The sponsor conducted two pivotal biopharmaceutic studies – in vitro equilibrium binding study and in vitro kinetic binding study. The in vitro equilibrium binding study (test method M12601 and M13400 for the chewable bars and tablets, respectively) were conducted to determine the equilibrium binding of three bile acids, glycocholic acid (GC),

glycochenodeoxycholic acid (GCDC) and taurodeoxycholic acid (TDC) in each of the two dosage forms tested. The equilibrium test procedure with and without acid pretreatment was performed on twelve replicates for the Welchol chewable bars (of each flavor) and the Welchol tablets.

The results of the comparison using Langmuir isotherms without acid pre-treatment were used as the pivotal parameter of bioequivalence. The results indicate that the binding capacities (k2) are comparable (±20%) for all three flavors of WelcholTM chewable bars relative to the commercial WelcholTM tablets as the reference formulation (See Appendix).

To address the Agency's concern regarding the impact of chewing on the in vivo performance of colesevelam HCl, the sponsor conducted an in vitro study to evaluate the bile acid binding capacity for three different sizes of WelcholTM chewable bar pieces using the caramel flavored bar as a representative drug product for all three flavors. The bile acid binding capacity was not impacted by size of the pieces of the chewable bar. Further, the sponsor conducted an open-label one-treatment study in healthy volunteers to assess the effect of chewing on the in vitro disintegration of WelcholTM chewable bar (Study WEL-AU120). The mean (SD) time to complete disintegration of the bolus (chewed lump) was 24.0 (13.7) min, which is shorter than the reported half gastric emptying time.

The final review from Clinical Pharmacology recommends approval of NDA 210895

4.6. Devices and Companion Diagnostic Issues

Not Applicable

4.7. Consumer Study Reviews

Not Applicable

5. Sources of Clinical Data and Review Strategy

No clinical trials were conducted as part of this application.

5.1. Review Strategy

Efficacy and Safety of the newly proposed formulation (Welchol chewable bar) are extrapolated from the FDA approved Welchol tablets and Welchol for suspension and will be labeled as such provided evidence of bioequivalence. No additional clinical trials were conducted to support safety and/or efficacy of this new formulation.

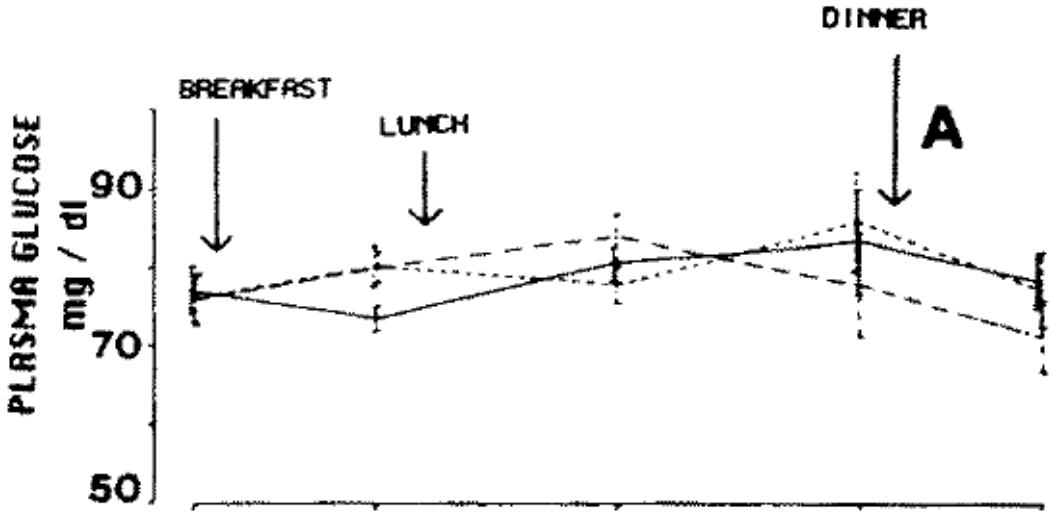
A review of the current label for Welchol and the existing supporting data for safety and efficacy of colesevelam hydrochloride as monotherapy or combined therapy (i.e with statins,

metformin, sulfonylurea and insulin) for hyperlipidemia and glycemic control was conducted. These data are considered largely applicable to the new formulation should the Sponsor adequately demonstrate bioequivalence.

A review of the available literature as well as the supporting literature submitted by the Sponsor on the safety of the excipients with a focus on palm oil, maltitol, maltodextrin and cocoa powder was conducted.

Maltitol was a specific point of interest for this review, since it brings a carbohydrate load in to the patient's daily intake. Maltitol has a low glycemic index (GI) of 35-53% compared to glucose (GI of 100)[45] [46]. Intake of low glycemic intake carbohydrates instead of glucose or other sugars may have a beneficial impact on the glycemic and metabolic parameters in patients with type 2 diabetes[47] . However, we wanted to explore any potential adverse metabolic effects of the added carbohydrates to the diet.

In an article by Secchi et al., the chronic administration of maltitol (10 grams 3 times daily for 5 days) induced no variations of glycemia (Figure 1) or insulinemia[48] in non-diabetic adults.



[45] Livesey, G. (2003). "Health potential of polyols as sugar replacers, with emphasis on low glycaemic properties." Nutr Res Rev **16**(2): 163-191.
[46] Pelletier, X., B. Hanesse, F. Bornet and G. Debry (1994). "Glycaemic and insulinaemic responses in healthy volunteers upon ingestion of maltitol and hydrogenated glucose syrups." Diabete Metab **20**(3): 291-296.
[47] Sharafetdinov, K. K., O. A. Plotnikova, A. M. Churicheva, V. V. Pilipenko, R. I. Alekseeva, T. B. Sentsova, G. Y. Maltsev, A. A. Kochetkova, V. M. Vorobyova and I. S. Vorobyova (2016). "Assessment of efficacy of specialized food products with modified carbohydrate profile in patients with type 2 diabetes." Vopr Pitan **85**(6): 103-109.
[48] Secchi, A., A. E. Pontiroli, L. Cammelli, A. Bizzi, M. Cini and G. Pozza (1986). "Effects of oral administration of maltitol on plasma glucose, plasma sorbitol, and serum insulin levels in man." Klin Wochenschr **64**(6): 265-269.

Figure 1. The 24-h plasma glucose profile (mg/dl) after 5 days of isocaloric diet (…), isocaloric diet plus maltitol 10 g 3 × daily (--) or isocaloric diet plus sucrose (- - -) 10 g 3 x daily.

The low impact on serum glucose and insulin with maltitol observed in this study suggests that the chronic low dose use of maltitol containing products most likely will have little or no adverse impact the glycemic control.

The same study showed that with the dosage of 10 g 3 x daily, five subjects complained of flatulence and increased bowel movements. This may represent a limiting AE for this new formulation since cholesevelam itself can cause abdominal distension. There may be an additive effect which may result in more instances of abdominal distension, flatulence and discomfort.

In an article by Oku et al.[49], levels of maltitol as low as 15g have induced osmotic diarrhea; the new Welchol formulation contains ~(b) (4) maltitol. We asked the Sponsor to provide an insight whether the effect of maltitol will have an impact on the overall safety and efficacy of the product.

The Sponsor responded, pointing out that maltitol has been used as a sweetener and food additive. In the GI tract, maltitol is subject to bacterial fermentation but is poorly absorbed. Like other polyols, maltitol can have a laxative effect due to the osmotic effects of unabsorbed polyols reaching the colon. As a food additive, maltitol has been extensively evaluated since the 1980s for its digestive tolerance profile at doses up to more than 100g per day. The threshold dose reported to induce laxative effects is above 30g per day.

In a double-blind, controlled, crossover study in 59 healthy male and female subjects, Koutsou et al evaluated the GI tolerance of 40g of lactitol, isomal, maltitol or sucrose, or 10g of sucrose plus 30g of lactitol, isomalt or maltitol, administered as milk chocolate.[50] Authors concluded that consumption of 30g of maltitol resulted in no significant increase in reported symptoms except for mild flatulence, compared to consumption of sucrose. Consumption of 40g maltitol resulted in an increase in borborygmus, colic and flatus, all ranked as mild. Loose stool was uncommon and the incidence of loose stool with either 30g or 40g maltitol per day was not significantly higher than after consumption of 40g of sucrose.

Several other digestive tolerance studies also supported the safe use of maltitol:

- Respondek 2014: Administered maltitol from 17.5 to 35g to adult subjects in muffins. The stool frequency was slightly higher and stools were a bit softer with all the desserts containing the different mixtures of maltitol alone and maltitol with short-chain fructo-oligosaccharides than with the control one. However, the consistency was still within the range of 'normal' consistency as it was scored between 3 and 4 out of 7 on the

[49] Oku, T., R. Hongo, and S. Nakamura, Suppressive effect of cellulose on osmotic diarrhea caused by maltitol in healthy female subjects. J Nutr Sci Vitaminol (Tokyo), 2008. 54(4): p. 309-14.
[50] Koutsou GA, Storey DM, Lee A, et al. Dose-related gastrointestinal response to the ingestion of either isomalt, lactitol or maltitol in milk chocolate. 1996: Eur J Clin Nutr. 50:17-21.

Bristol scale, and average stool frequency remained below the diarrhea threshold of three bowel movements per day[51].

- Ruskone 2003: In this single- and repeat-dose study of maltitol in healthy volunteers, a threshold dose of maltitol that led to diarrhea or severe GI symptoms was evaluated with escalating doses of maltitol at 10 g increments. It was reported that the mean threshold dose of maltitol that led to diarrhea was 69 g and that for severe GI symptom was as high as 93 g in 12 HV[52].
- Thabuis et al 2010: In this study of healthy children ages 8-10, the authors reported mild GI symptoms of abdominal bloating, rumbling, pain and flatulence, but without diarrhea at a dose of 15 g per day[53].

In response to our query the Sponsor noted that in the report referenced by the FDA, Oku et al (2008) described a study in young college females in which the minimal doses with any report of loose stool or diarrhea was at doses of 20g/d or higher (but not at 15g). These threshold doses were lower than the threshold doses reported from other investigators. The administration of liquid solution of maltitol, not maltitol blended in food, in the fasted state may have led to these observations.

The concern of the added GI effects of cholesevelam and maltitol remains, however there may be different sites of action of the two. Maltitol escapes from digestion and absorption in the small intestine and is fermented in the large intestine by intestinal bacteria,[54] whereas the primary site of action of cholesevelam is the small intestine, where it binds bile acids forming non-absorbable complexes that are excreted in the feces[55,56].

Additionally, a literature review of the impact of added calories on lipid profile was conducted. No substantial evidence of safety concerns was identified.

In the same IR dated April 25, 2018 as previously, we asked the Sponsor to comment on potential adverse effect of maltodextrin and palm oil (in addition to other excipients present in lower quantities) on LDL-C and glucose levels in patients who would be using this product to

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[51] Respondek F, Hilpipre C, Chauveau P, et al. Digestive tolerance and postprandial glycaemic and insulinaemic responses after consumption of dairy desserts containing maltitol and fructo-oligosaccharides in adults. 2014: Eur J Clin Nutr. 68:575-80.

[52] Ruskone-Fourmestraux A, Attar A, Chassard D, et al. A digestive tolerance study of maltitol after occasional and regular consumption in healthy humans. 2003: Eur J Clin Nutr. 57:26-30.

[53] Thabius C, Cazaubiel M, Pichelin M, et al. Short-term digestive tolerance of chocolate formulated with maltitol in children. 2010: Int J Food Sci Nutr. 61:728-38.

[54] Oku, T., M. Akiba, M. H. Lee, S. J. Moon and N. Hosoya (1991). "Metabolic fate of ingested [14C]-maltitol in man." J Nutr Sci Vitaminol (Tokyo) **37**(5): 529-544.

[55] Donovan JM, Von BK, Setchell KD, et al. Effects of colesevelam HC1 on sterol and bile acid excretion in patients with type IIa hypercholesterolemia. Dig Dis Sci 2005; 50: 1232-8.

[56] Grundy SM, Ahrens EH, Jr., Salen G. Interruption of the enterohepatic circulation of bile acids in man: comparative effects of cholestyramine and ileal exclusion on cholesterol metabolism. J Lab Clin Med 1971; 78: 94-121.

The Sponsor's response noted that the Welchol Chewable Bar will contain approximately (b) (4) of maltitol as (b) (4) maltodextrin, and (b) (4) (b) (4) palm oils. The contributions to total calories consumed from fat, carbohydrate, and protein on a given day are estimated to be 34%, 47%, and 16% for men and 34%, 49%, and 16% for women, unchanged since the NHANES survey of 1999-2000[57]. Based on a simplified daily consumption of 2,000 calories from 34% fat, 50% carbohydrate and 16%, a 30g Welchol Chewable Bar contributes (b) (4) % in the total daily calories, mostly (b) (4) %) from the carbohydrates maltitol and maltodextrin.

Although small alterations in dietary changes are difficult to ascertain, the Sponsor believes that the total caloric content in the added excipients is unlikely to cause clinically significant attenuation in the efficacy of Welchol Chewable Bar, given a small addition of (b) (4) % to the daily caloric intake and the nature of low glycemic index for maltitol, the principal caloric contributor.

In summary, it is unlikely that the excipients in the Welchol chewable bar will attenuate the efficacy of the product on lipids or glycemic control. Although maltitol may induce osmotic diarrhea at high doses, there is no evidence that this would affect bile acid binding in the small intestine. Consumption of less than 10 grams of maltitol is expected to have minimal, if any, effect on glycemic control.

Excipients in the Welchol chewable bar may, however, affect the overall safety profile. There is a potential for increased gastrointestinal adverse effects, including flatulence, abdominal discomfort, abdominal discomfort, increased bowel movements, diarrhea, or loose stools. The increased potential for adverse events should be addressed in labeling.

[57] CDC NCHS Data Brief, No. 49, November 2010, https://www.cdc.gov/nchs/data/databriefs/db49.pdf

6. Labeling Recommendations

6.1. Prescription Drug Labeling

Final labeling recommendations discussions are premature, but several items related to the applicant's proposed labeling would need to be addressed if the applicant submits a complete response to the action letter, and the resubmitted data support approval.

The sponsor's proposed labeling (See Apendices 9.1) relies on the current labeling for the approved Welchol formulation with added information for the chewable bar. The submitted labeling also 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.

Information regarding the composition of the chewable bars including calories/bar appear in Section 11 (Description). Each Welchol® chewable bar contains (b) (4) of maltitol which should be reflected in the labeling. Additionally, since the maltitol in Welchol® chewable bar may induce laxative effects (usually at levels >30g/day) relevant language should be added to section 5.4. Language about maltitol overdoing should be added to Section 10.
Welchol® chewable bars have ~80 calories. This should be included in Section 5.1 with language that reflects that it is not a no-calorie formulation.

Per recommendations from DMEPA consult completed by Susan Rimmel, PharmD on May 16, 2018 I recommend making the following edits to the proposed labeling:

A. Highlights of Prescribing Information
    1. Dosage Forms and Strengths
        a. For clarity, we recommend revising (b) (4) 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. (b) (4) to "Oral Suspension: 3.75 gram single-dose packet containing a white to pale yellow powder containing yellow granules"
            ii. (b) (4) 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) and revising the statements and table that follows, such as:

WELCHOL [redacted] (b) (4) 3.75 grams [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

7. Risk Evaluation and Mitigation Strategies (REMS)

Not applicable

8. Postmarketing Requirements and Commitments

Not applicable

9. Appendices

9.1. Tables and Figures

Clinical Review
Ovidiu A. Galescu, MD
NDA 210895
Welchol (colesevelam hydrochloride)

Table 1. **Major Recommendations for the Treatment of Blood Cholesterol to Reduce ASCVD Risk in Adults*†**

Healthy lifestyle habits should be encouraged for all persons.

The appropriate intensity of statin therapy should be initiated or continued:

1. Clinical ASCVD‡
   a. Persons aged ≤75 y with no safety concerns: high-intensity statin (class I, level A)
   b. Persons aged >75 y or with safety concerns: moderate-intensity statin (class I, level A)
2. Primary prevention: primary LDL-C level ≥190 mg/dL
   a. Rule out secondary causes of hypercholesterolemia
   b. Persons aged ≥21 y: high-intensity statin (class I, level B)
   c. Achieve ≥50% reduction in LDL-C level (class IIa, level B)
   d. May consider LDL-C–lowering nonstatin therapy to further reduce LDL-C levels (class IIb, level C)
3. Primary prevention: persons with diabetes aged 40–75 y with an LDL-C level of 70–189 mg/dL
   a. Moderate-intensity statin (class I, level A)
   b. Consider high-intensity statin when 10-y ASCVD risk is ≥7.5% (class IIa, level B)
4. Primary prevention: persons aged 40–75 y without diabetes with an LDL-C level of 70–189 mg/dL
   a. Estimate 10-y ASCVD risk (risk calculator based on Pooled Cohort Equations recommended)§ in those not receiving a statin; estimate risk every 4–6 y (class I, level B)
   b. To determine whether to initiate a statin, engage in clinician–patient discussion of potential for ASCVD risk reduction, adverse effects, drug–drug interactions, and patient preferences (class IIa, level C). Reemphasize healthy lifestyle habits and address other risk factors. If statin therapy is chosen:
      i. Persons with ≥7.5% 10-y ASCVD risk: moderate- or high-intensity statin (class I, level A)
      ii. Persons with 5% to <7.5% 10-y ASCVD risk: consider moderate-intensity statin (class IIa, level B)
      iii. Other factors may be considered‖: LDL-C level ≥160 mg/dL, family history of premature ASCVD, lifetime ASCVD risk, high-sensitivity C-reactive protein level of ≥2.0 mg/L, coronary artery calcification score ≥300 Agatston units, or ankle–brachial index <0.9 (class IIb, level C)
5. Primary prevention when LDL-C level is <190 mg/dL and person is aged <40 y or >75 y or has <5% 10-y ASCVD risk
   a. Statin therapy may be considered in selected persons‖ (class IIb, level C)
6. Statin initiation is not routinely recommended for persons with NYHA class II–IV heart failure or those who are receiving maintenance hemodialysis.

Regularly monitor adherence to lifestyle and drug therapy with lipid and safety assessments. Nonstatin therapy can be considered in selected persons.

Assess adherence, response to therapy, and adverse effects within 4–12 wk after statin initiation or change in therapy (class I, level A)

   a. Measure fasting lipid panel (class I, level A)
   b. Do not routinely monitor hepatic function with ALT levels or muscle injury with CK levels unless patient is symptomatic (class IIa, level C).
   c. Screen and treat type 2 diabetes mellitus according to current practice guidelines. Healthy lifestyle habits should be encouraged to prevent progression to diabetes (class I, level B).
   d. Anticipated therapeutic response: approximately ≥50% reduction in LDL-C level from baseline for high-intensity statin and 30% to <50% for moderate-intensity statin (class IIa, level B)
      i. Insufficient evidence from RCTs for LDL-C or non–HDL-C treatment goals
      ii. For guidance in persons with unknown baseline LDL-C level, a level of <100 mg/dL was observed in RCTs about high-intensity statin therapy.
   e. Less-than-anticipated therapeutic response:
      i. Reinforce improved adherence to lifestyle and drug therapy (class I, level A)
      ii. Evaluate for secondary causes of hypercholesterolemia if indicated¶ (class I, level A)
      iii. Increase statin intensity, or if patient is receiving maximally tolerated statin intensity, consider addition of nonstatin therapy shown in RCT to reduce ASCVD events in selected high-risk persons** (class IIb, level C)
   f. Regularly monitor adherence to lifestyle and drug therapy every 3–12 mo once statin adherence has been established. Continue to assess adherence for optimum ASCVD risk reduction and safety (class I, level A)

In persons unable to tolerate the recommended intensity of statin therapy, use the maximally tolerated intensity of statin.

If there are muscle or other symptoms, establish their relationship to statin therapy (class IIa, level B)

   a. Obtain a history of muscle symptoms before initiating statin therapy.
   b. If muscle or other symptoms develop during statin therapy, discontinue the statin.
   c. Once mild to moderate muscle or other symptoms resolve, rechallenge with the same dose of statin or lower; if muscle symptoms recur, discontinue statin and rechallenge with progressively lower doses of the same or a different statin.
   d. If muscle symptoms persist >2 mo after statin discontinuation, consider other conditions that may increase the risk for muscle symptoms††

ALT = alanine aminotransferase; ASCVD = atherosclerotic cardiovascular disease; CK = creatine kinase; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; NYHA = New York Heart Association; RCT = randomized, controlled trial.
* Adapted from reference 2. Reprinted with permission.
† For information about class and level, please see **Table 3** of the **Supplement**.
‡ Clinical ASCVD is defined as acute coronary syndromes or a history of myocardial infarction, stable angina, coronary or other arterial revascularization, stroke, transient ischemic attack, or peripheral arterial disease presumed to be of atherosclerotic origin.
§ Estimated 10-y "hard" ASCVD risk includes first occurrence of nonfatal myocardial infarction, death from coronary heart disease, and nonfatal and fatal stroke as used in the Pooled Cohort Equations on the basis of age, sex, smoking status, total cholesterol level, HDL-C level, systolic blood pressure, and the use of antihypertensive therapy.
‖ Other factors that may influence ASCVD risk include primary LDL-C level ≥160 mg/dL or other evidence of genetic hyperlipidemias; family history of premature ASCVD with onset before age 55 y in a first-degree male relative or before age 65 y in a first-degree female relative; high-sensitivity C-reactive protein level of ≥2 mg/L; coronary artery calcification score ≥300 Agatston units or ≥75th percentile for age, sex, and ethnicity (for additional information, see www.mesa-nhlbi.org/CACReference.aspx.); or ankle–brachial index <0.9 or lifetime ASCVD.
¶ Common secondary causes of hypercholesterolemia include diet (saturated or trans fats, weight gain, or anorexia), drugs (diuretics, cyclosporine, glucocorticoids, or amiodarone), diseases (biliary obstruction or nephrotic syndrome), and altered metabolism (hypothyroidism, obesity, or pregnancy).
** High-risk persons include those with clinical ASCVD; those with an untreated LDL-C level ≥190 mg/dL, suggesting genetic hypercholesterolemia; or those aged 40–75 y with diabetes.
†† Common causes of muscle ache, pain, or fatigue include hypothyroidism, reduced renal or hepatic function, rheumatologic disorders (especially polymyalgia rheumatica), steroid myopathy, vitamin D deficiency, or primary muscle diseases.

Supplemental Table 2: Statistical analysis for the total bile acid binding (GC+GCDC+TDC) without acid pretreatment
(n=12)

Parameter	Without Acid Pre-Treatment				
Capacity Constant (k_2)	Type of Chewable Bar	Dosage Form		Chewable Bars/ Tablet	90% CI for Ratio (%)
		Chewable Bars Estimate	Tablets Estimate		
	Chocolate	5.405	6.152	0.879	84.9 – 91.0
	Caramel	5.549		0.902	86.6 – 93.9
	Strawberry	6.469		1.051	101.1 – 109.3

Source: NDA 210895, Module 5.3.1.2. In-vitro Bioequivalence Study Report

Supplemental Table 3: Statistical analysis for the total bile acid binding (GC+GCDC+TDC) with acid pre-treatment (n=12)

Parameter	With Acid Pre-Treatment				
Capacity Constant (k_2)	Type of Chewable Bar	Dosage Form		Chewable Bars/ Tablet	90% CI for Ratio (%)
		Chewable Bars Estimate	Tablets Estimate		
	Chocolate	5.768	5.791	0.996	94.1 – 105.2
	Caramel	5.614		0.969	92.5 – 101.4
	Strawberry	6.099		1.053	100.3 – 110.5

Source: NDA 210895, Module 5.3.1.2. In-vitro Bioequivalence Study Report

9.2. Label

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9.3. References

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JAMES P SMITH
08/23/2018
Concur with regulatory recommendation.