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APPLICATION NUMBER:

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NON-CLINICAL REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	210895
Supporting document/s:	FDA SDN: 1 Applicant Serial number: 0001
Applicant's letter date:	10/20/2017
CDER stamp date:	10/30/2017
Product:	Colesevelam hydrochloride (Welchol® chewable bar)
Indication:	An adjunct to diet and exercise for the reduction of elevated low density lipoprotein cholesterol (LDL-C) in patients with primary hypercholesterolemia
Applicant:	Daiichi Sankyo Inc.
Review Division:	Division of Metabolism and Endocrinology Products
Reviewer:	Dongyu Guo, Ph.D.
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1 Executive Summary

1.1 Introduction

Welchol® (colesevelam hydrochloride) is a bile acid sequestrant approved in the U.S. as an adjunct to diet and exercise for the management of elevated LDL-C in patients with primary hyperlipidemia when used alone or in combination with an hydroxy-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitior (a statin). Colesevelam hydrochloride is currently marketed by Daiichi Sankyo Inc. as Welchol® Tablets under NDA 021176 and as Welchol® Oral Suspension under NDA 022362. The current NDA is for Welchol® chewable bar, also by Daiichi Sankyo (the Applicant), which is proposed as an alternate dosage form to the currently marketed tablet and oral suspension products.

1.2 Brief Discussion of Nonclinical Findings

No nonclinical studies were conducted to support this 505(b)(2) NDA. Instead, the Applicant proposes reliance on the nonclinical studies conducted to support NDAs 021176 and 022362. 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.

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-(b) (4)erse-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 CFR182.2 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.

1.3 Recommendations

1.3.1 Approvability

Colesevelam hydrochloride, which is already approved as Welchol® Tablets under NDA 021176 and as an Oral Suspension under NDA 022362, is approvable under this NDA for the chewable bar formulation. Maltitol syrup, palm oil, alkalized cocoa powder, and rosemary extract are allowable as excipients at the proposed levels in the Welchol® chewable bar formulation.

1.3.2 Additional Non Clinical Recommendations

None.

1.3.3 Labeling

Nonclinical labeling for the marketed colesevelam tablet and oral suspension formulation is applicable to the proposed chewable bar formulation. Regarding excipients, maltitol at above 30-50 g per day induces laxative effects in humans due to the osmotic effects of unabsorbed maltitol reaching the colon. In addition, each Welchol® chewable bar contains approximately (b) (4) Calories. Therefore, the labeling for Welchol® chewable bar should indicate that maltitol in Welchol® chewable bar may induce laxative effects and Welchol® chewable bars may be a source of significant additional Calories.

2 Drug Information

2.1 Drug

CAS Registry Number
182815-44-7

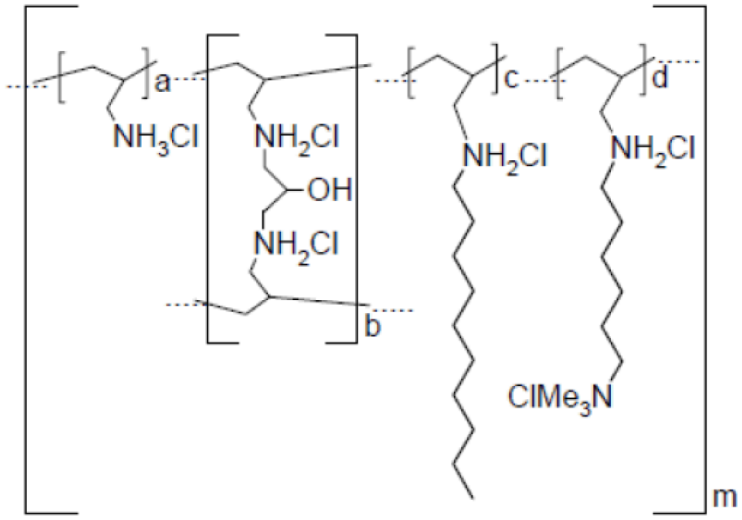
Generic Name
Colesevelam hydrochloride

Trade Name
Welchol®

Chemical Name
Allylamine polymer with 1-chloro-2,3-epoxypropane, [6-(allylamino)-hexyl]trimethylammonium chloride and N-allyldecylamine, hydrochloride (IUPAC)

Molecular Formula/Molecular Weight
$(C_3H_8NCl)_2(C_9H_{20}N_2OCl_2)_1(C_{13}H_{28}NCl)_7(C_{12}H_{28}N_2Cl_2)_6$ / 212 g/mole (one polymer subunit)

Structure or Biochemical Description



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

Pharmacologic Class
Bile acid sequestrant

2.2 Relevant INDs, NDAs, BLAs and DMFs

Welchol® chewable bar is a new dosage form of colesevelam hydrochloride, a product already approved as two formulations: Welchol® Tablets (NDA 021176, approved in 2000) and Welchol® Oral Suspension (NDA 022362, approved in 2009).

2.3 Drug Formulation

Welchol® chewable bars are available in three flavors: chocolate, strawberry, and caramel. The quantitative component compositions of the three Welchol® chewable bars are listed in Table 1.

Table 1: 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						
Maltitol Syrup	NF							
Maltodextrin	NF							
Palm Oil	In-house/GRAS							
Glycerin	USP							
Lecithin	NF							
Sucralose	NF							
Rosemary Extract Flavor	21 CFR 182.20							
Vanilla Flavor	DMF							
Alkalized Cocoa	21 CFR 163.5							
Chocolate Flavor	DMF							
Strawberry Cheesecake Flavor	DMF							
Acacia	NF							
FD&C No. 40	21 CFR 74.1340							
Citric Acid	USP							
Caramel Flavor	DMF							
Caramel Color	21 CFR 73.85							
	USP							
		TOTAL	30,000	100	30,000	100	30,000	100

(b) (4)

2.4 Comments on Novel Excipients

Four excipients in the Welchol® chewable bar formulations are noncompendial or present at higher concentrations than those listed in the IID. The safety evaluation of these excipients is summarized below.

2.4.1 Maltitol Syrup (CAS No. 585-88-6): (b) (4) g / chewable bar

Maltitol syrup is a hydrogenated starch hydrolysate, consisting mainly of maltitol (50-90%) with lesser amounts of sorbitol and hydrogenated oligo- and/or polysaccharides. (b) (4) The maximum amount of maltitol in the Welchol® chewable bars is (b) (4) mg/bar.

Table 2 : Maltitol Syrup Composition in Welchol® (colesevelam hydrochloride) Chewable Bars

Ingredient	Amount					
	Chocolate		Strawberry		Caramel	
	mg/bar	% w/w	mg/bar	% w/w	mg/bar	% w/w
Maltitol Syrup	(b) (4)					

The safety of maltitol as a crystalline powder (>98%) or as liquid syrup was evaluated in the approved NDA 022581 (Phoslyra®, approved in 2011) (https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/022581Orig1s000PharmR.pdf). The maximum daily dose of Phoslyra® contains 18 grams of maltitol. It was concluded that "*The use of maltitol is approvable as an excipient in the liquid formulation of Phoslyra® calcium acetate oral solution*". No new toxicological data of maltitol was found in public literature as well as the documents provided by the sponsor. There are no safety concerns for the usage of (b) (4) mg/bar of maltitol in the Welchol® chewable bars.

2.4.2 Palm Oil (CAS No. 8002-75-3): (b) (4) mg/chewable bar
Palm oil is rich in saturated palmitic acid (~ 50% w/w), monounsaturated oleic acid (~ 40% w/w), and polyunsaturated linoleic acid (10% w/w). Global consumption of palm oil rose from 14.6 million tons in 1995 to 61.1 million tons in 2015, making it the most consumed oil in the world (European Palm Oil Alliance, https://www.palmoilandfood.eu/en/palm-oil-consumption).
Toxicological studies of palm oil in rats are summarized in Table 3.

Table 3. Toxicological studies of palm oil

Species	Route	Duration	Observations	Reference
Wistar albino rats (5/sex/group)	10% crude palm oil with 10% casein protein in diet	28 days	No adverse effects were observed	Manorama and Rukmini 1991
Wistar albino rats (15/sex/group)	10% crude palm oil in diet	90 days	No adverse effects were observed with respect to the following parameters: growth rate, feed-efficiency ration, protein-efficiency ratio, net protein utilization, digestibility, fat absorption, nitrogen balance, phosphorus and calcium retention, serum enzymes, and blood hematology.	Manorama and Rukmini 1991
15 to 16 weanling	20% palm oil in diet	57-67	No significant	Sylvester

Sprague-Dawley rats		days	differences in average body weights, estrous cycle regularity, serum prolactin concentraions, LH, and basal or surge concentrations of LH or estradiol were observed.	et al. 1986
32 weanling Sprague-Dawley rats	20% palm oil in diet prior to and during tumor initiation by 7,12-dimethylbenz(a)anthracene	19 weeks	Using diets hight in vegetable oil, neither polyunsaturated (corn oil) nor saturated (palm oil) fatty acids had an effect on mammary tumorigenesis.	Sylvester et al. 1986
Wistar/NIN inbred wanling albino rats (12/sex/group)	10% crude palm oil in 20% protein diet	Three generation reproductive toxicity study	No adverse effects on reproductive parameters were observed.	Manorama et al. 1993

Palm oil (10 – 20%) in diet was administered to Wistar albino rats or Sprague-Dawley rats in the subchronic toxicity studies. The food comsumption and weight gain of the rats fed diet containing palm oil was similar to that of the controls in the studies. Sprague-Dawley rats consumed 17 – 29 g standard diet daily and weigh from 142 to 617 g in a typical 26 week toxicity study (Matsuzawa et al., 2000). Winstar albino rats have similar daily food intake as Sprague-Dawley rats and weigh less than Sprague-Dawley rats. A conservative estimate of daily intake of palm oil in the subchronic toxicity studies was 2.8 g /kg (17g x 10% / 617g x 1000), based on the study with Sprague-Dawley rats. The estimated dose level of 2.8 g/kg palm oil was (b) (4) the human exposure (based on body surface area) of (b) (4) mg in one Welchol® chewable bar. No chronic toxicity study data were identified for palm oil. However, palm oil is a common cooking oil and is also frequently found in foods historically consumed by humans. While palm oil is rich in saturated fat, there is no clear evidence demonstrating an association of palm oil consumption with cardiovascular disease risk and cardiovascular disease-specific mortality (Ismail et al., 2018). Based on available animal toxicological data and common use of palm oil in foods, (b) (4) mg/bar is acceptable.

2.4.3 Alkalized Cocoa Power (CAS No. 95009-22-6): (b) (4) mg/chewable bar
The genotoxicity of cocoa power (CP) was evaluated in a series of assays including the Ames test (0.5 µg to 5000 µg), the mouse lymphoma assay in mouse lymphoma L5178Y cells (0.625 mg/mL to 6.0 mg/mL), the chromosomal aberration assay (10 µg to 1000 µg), the sister-chromatid exchange assay (39 µg to 2,500 µg), and an *in vitro* cell transformation assay in mouse Balb/c-3T3 cells (0.01 µg/mL to 250 µg/mL). All the test results were negative, indicating that CP was not genotoxic (Brusick et al, 1986).

The teratogenic potential of CP was studied in New Zealand rabbits. CP was given at 2.5, 5.0 or 7.5% of the diet (approximately 925, 1,865 or 2,678 mg CP/kg body weight/day) to a minimum of 14 pregnant rabbits/group during gestation days 6-29. No treatment-related teratogenicity/embryotoxicity was detected in the study (Tarka et al. 1986).

CP was not carcinogenic in a multigenerational chronicle toxicity/carcinogenicity study (Tarka et al., 1991). Sprague Dawley CD rats (90 animals/sex/group) from the F_{3b} generation of a multigeneration study using the same CP diet were fed CP in diet at levels of 0.0 (control), 1.5, 3.5, or 5.0% for 104 weeks. The dietary levels provided initial (week 1) CP intakes of 1.6, 4.1, or 5.8 g/kg/day in males and 1.7, 4.2, or 6.2 g/kg/day in females. Daily CP intakes decreased steadily until approcimately week 26. At week 104, CP intakes were 0.6, 1.5, or 2.0 g/kg/day in males and 0.6, 1.7, or 2.4 g/kg/day in females. There was no early mortality and no treatment-related effects on clinical signs, body weight, food consumption, ophthalmic exams or hematology and urinalysis. In male rats fed 5.0% CP, there was an increased incidence of bilateral diffuse testicular atrophy and a concomitant decrease in spermatogenesis compared with controls. A reduction in testes weight was also noted at the dose of 5.0% CP. The NOAEL was the mid-dose of 3.5% in the 104 week study in rats, based on toxicological findings in male rats fed 5.0% CP. Based on the more conservative daily intake of 1.5 g/kg/day at Week 104, the human equivalent dose (HED) is 243 mg/kg/day, based on body surface area, which represents approximately (b) (4)-fold times the daily amount of CP in a Welchol® chewable bar (based on a 60 kg patient). Based on the calculated margin of safety, use of CP at the proposed level in Welchol® chewable bar does not represent a safety concern.

2.4.4 Rosemary Extract (CAS No. 84604-14-8): (b) (4) mg/chewable bar
Rosemary extract, a complex mixture of a varied chemical nature, is derived from *Rosmaryinus officinalis* L.. Two major phenolic diterpenes – carnosic acid and carnosol are major contributors to the apparent antioxidant activity of rosemary extract. Several other antioxidants in rosemary extract belong to the classes of phenolic acids, flavonoids, diterpenoids and triterpenes. In addition, rosemary extract contains volatiles, tannins, polyphenols, polysaccharides and lipophilic substances. The safety assessment of rosemary extract has been done in a range of studies on acute toxicity, short-term toxicity and genotoxicity. No chronic toxicity studies with rosemary extract were identified.

The genotoxicty potential of rosemary extract was assessed in vitro in an Ames Test at concentrations ≤ 6 mg/plate) and in mammalian cells (human lymphocytes) at concentrations ≤ 100 mg/mL, thymidine kinase and hgprt loci of human lymphoblastoid cells at concentrations ≤ 50 µg/mL and in an in *vivo* mouse micronucleus test. All the results were negative (European Food Safety Authority, 2008).

An acute safety study of rosemary extracts was conducted in Wistar rats at a single oral gavage dosage of 2,000 mg/kg body weight. No abnormal signs, behavioral changes, body weight changes, or change in food and water consumption occurred. There were

no changes in hematological and serum chemistry values, organ weights, or gross or histological characteristics. The oral lethal doses (LD_{50}) for rats were >2,000 mg/kg (Anadón et al., 2008).

Subchronic toxicity studies (14-90 days) of rosemary extracts administered in diet were conducted in rats. The dose levels ranged between 26 and 400 mg/kg/day. An increase in relative liver weight in treated animals was observed, which was associated with centrilobular hypertrophy, cytoplasmic characteristics of increased glycogen storage and increases in smooth endoplasmic reticulum. No changes in clinical chemistry or any morphological features of liver damage were noted in the same studies. The observed hepatic changes are consistent with a common adaptive response of rodent livers and are not adverse (JECFA, 2016). The NOAELs in these studies were the highest dose tested ranging from 180 to 400 mg/kg/day.

JECFA/WHO established a temporary ADI of 0-0.3 mg/kg bw/day for rosemary extract in 2016 (JECFA, 2016). The temporary ADI will be withdrawn if the required developmental and reproductive toxicity studies are not provided by the end of 2018. *Rosmarinus officinalis* L. is GRAS as spice and other natural seasoning and flavoring for human consumption (21 CFR182.10). It is also GRAS as an essential oil, oleoresin (solvent-free), and natural extractive (including distillates) for human consumption (21 CFR182.20). Based on the NOAELs in subchronic toxicity studies in rats, the safety of margin is ≥ (b) (4) at the proposed dose level of (b) (4) mg/bar (calculation based on body surface area). FDA generally accepts GRAS status specific to the intended use as adequate to support for inclusion in an orally administered drug product in the absence of any additional safety concerns.

2.5 Comments on Impurities/Degradants of Concern

No impurities or degradants of concern were identified.

2.6 Proposed Clinical Population and Dosing Regimen

Adults with primary hyperlipidemia, adults with type 2 diabetes mellitus, or boys and girls at age 10 to 17 years with familial hypercholesterolemia will take one bar containing 3.75 grams of colesevelam hydrochlorides once daily.

2.7 Regulatory Background

Welchol® chewable bar is a new alternate dosage form of colesevelam hydrochloride which is already approved as Welchol® Tablets under NDA 021176 (approved in 2000) and as an Oral Suspension under NDA 022362 (approved in 2009).

3 Studies Submitted

No nonclinical studies of the drug substance, colesevelam hydrochloride, were submitted in NDA 210895. The Applicant referred to the nonclinical studies in NDA 021176 and NDA 022362. The Applicant submitted safety information resulting from literature reviews for maltitol syrup, palm oil, alkalized cocoa powder, and rosemary

extract which are noncompendial or present at higher concentrations than those listed in the IID.

4 Integrated Summary and Safety Evaluation

Welchol® (colesevelam hydrochloride) is a bile acid sequestrant currently marketed by Daiichi Sankyo Inc. as Welchol® Tablets under NDA 021176 and as an Oral Suspension under NDA 022362. This NDA is for Welchol® chewable bar as an alternate dosage form to the marketed products.

Safety information resulting from literature reviews for maltitol syrup, palm oil, alkalized cocoa powder, and rosemary extract was submitted in NDA 210895. No nonclinical study of the drug substance, colesevelam hydrochloride, was included in the submission. The sponsor referred to the nonclinical studies in the approved NDAs 021176 and NDA 022362. There are no additional safety concerns related to the colesevelam drug substance administered as chewable bars compared to the tablet and oral suspension formulations. Reproduction studies were performed in rats and rabbits at doses up to 3 g/kg/day and 1 g/kg/day, respectively and revealed no evidence of harm of fetus due to colesevelam. There were no significant drug-induced tumor findings in male or female CD-1 mice at oral dietary doses up to 3 g/kg/day. In a 104 week carcninogenicity study with colesevelam. In a 104-week carcinogenicity study in Sprague-Dawley rats, a statistically significant increase in the incidence of pancreatic acinar cell adenoma was seen in male rats at doses > 1.2 g/kg/day. A statistically significant increase in thyroid C-cell adenoma was seen in female rats at 2.4 g/kg/day.

Up to 18 g/day maltitol as an excipient was approved in the drug Phoslyra® (NDA 022581). The safety of maltitol as a crystalline powder (>98%) or as liquid syrup was evaluated in the NDA 022581. Maltitol at above 30-50 g per day induces laxative effects in humans. A Welchol® chewable bar contains up to (b) (4) mg maltitol. Maltitol is used in many food products and nutritional supplements. Therefore, the labeling for Welchol® chewable bar should indicate that the bar contains maltitol, which may induce laxative effects.

The toxicity of palm oil was evaluated in subchronic toxicity studies in rats administered 10-20% palm oil in diet. No adverse effects were observed in the studies. A conservative estimate of daily intake of palm oil in the subchronic toxicity studies was 2.8 g/kg, which was (b) (4) the human exposure of (b) (4) mg palm oil in a Welchol® chewable bar, based on body surface area. Although there is no chronic toxicity data available, palm oil has been consumed by humans for a very long period of time. No association of palm oil consumption and cardiovascular disease is established epidemiologically. (b) (4) mg/bar palm oil as an excipient in the chewable bar is acceptable.

Alkalized cocoa powder (CP) 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 CP up to 7.5% of the diet (~ 2678 mg/kg) during gestation days 6-29. A 104-week chronicle/carcinogenicity study was conducted using Sprague-Dawley rats fed CP in diet at levels of 0.0, 1.5, 3.5, or 5.0%. In male rats fed 5.0% CP, 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) human exposure of (b) (4) mg/bar CP, based on body surface area.

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. The oral LD_{50} of rosemary extract for rats was >2000 mg/kg. Subchronic toxicity studies (14-90 days) were conducted in rats given rosemary extract in diet. The NOAELs in these studies were the highest dose tested ranging from 180 to 400 mg/kg/day, which were ≥ (b) (4) human exposure of (b) (4) mg/bar rosemary extract. JECFA/WHO established a temporary ADI of 0-0.3 mg/kg bw/day for rosemary extract in 2016 (JECFA, 2016). The temporary ADI will be withdrawn if the required developmental and reproductive toxicity studies are not provided by the end of 2018. *Rosmarinus officinalis* L. is GRAS as spice and other natural seasoning and flavoring for human consumption (21 CFR182.10). It is also GRAS as an essential oil, oleoresin (solvent-free), and natural extractive (including distillates) for human consumption (21 CFR182.20).

In conclusion, there are no toxicological concerns for the use of maltitol syrup, palm oil, alkalized cocoa powder, and rosemary extract as excipients at the proposed levels in the Welchol® chewable bar. However, maltitol has a laxative effect due to the osmotic effects of unabsorbed maltitol reaching the colon and each Welchol® chewable bar contains approximately (b) (4) calories. The labeling for Welchol® chewable bar should indicate that maltitol in Welchol® chewable bar may induce laxative effects and Welchol® chewable bars are a significant source of additional Calories.
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5 Appendix/Attachments

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/s/

DONGYU GUO
05/31/2018

CALVIN L ELMORE
05/31/2018
I concur.