HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use WELCHOL safely and effectively. See full prescribing information for WELCHOL.

WELCHOL (colesevelam hydrochloride)
Initial U.S. Approval: 2000

RECENT MAJOR CHANGES

Dosage and Administration (2.1, 2.2) 01/2019

INDICATIONS AND USAGE

WELCHOL is a bile acid sequestrant indicated as an adjunct to diet and exercise to

- reduce elevated low-density lipoprotein cholesterol (LDL-C) in adults with primary hyperlipidemia as monotherapy or in combination with a hydroxymethyl-glutaryl-coenzyme A (HMG CoA) reductase inhibitor (statin) (1.1).
- reduce LDL-C levels in boys and postmenarchal girls, 10 to 17 years of age, with heterozygous familial hypercholesterolemia as monotherapy or in combination with a statin after failing an adequate trial of diet therapy.
- improve glycemic control in adults with type 2 diabetes mellitus (1.2).

Important Limitations of Use (1.3):

- Do not use for glycemic control in type 1 diabetes or for treating diabetic ketoacidosis.
- WELCHOL has not been studied in type 2 diabetes in combination with a dipeptidyl peptidase 4 inhibitor .
- WELCHOL has not been studied in Fredrickson Type I, III, IV, and V dyslipidemias.

WELCHOL has not been studied in children younger than 10 years of age or in pre-menarchal girls

DOSAGE AND ADMINISTRATION

- 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 (2.1, 2.2).
- WELCHOL for Oral Suspension: The recommended dose is one 3.75 gram packet once daily. To prepare, empty the entire contents of one packet into a glass or cup. Add 1 cup (8 ounces) of water, fruit juice, or diet soft drinks. 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 (2.1, 2.2).

DOSAGE FORMS AND STRENGTHS

- Tablets: 625 mg (3)
- Oral suspension: 3.75 gram packet (3)

CONTRAINDICATIONS

- Do not use in patients with a history of bowel obstruction (4)
- Do not use in patients with serum triglyceride (TG) concentrations >500 mg/dL (4)
- Do not use in patients with a history of hypertriglyceridemia-induced pancreatitis (4)

WARNINGS AND PRECAUTIONS

- The effect of WELCHOL on cardiovascular morbidity and mortality has not been determined (5.1).
- WELCHOL can increase TG, particularly when used with insulin or sulfonylureas. Marked hypertriglyceridemia can cause acute pancreatitis. The effect of hypertriglyceridemia on the risk of coronary artery disease is uncertain. Monitor lipids, including TG and non-high density lipoprotein cholesterol (non-HDL-C) (5.2).
- Bile acid sequestrants may decrease absorption of fat-soluble vitamins. Use caution in patients susceptible to fat-soluble vitamin deficiencies (5.3).
- Because of its constipating effects, WELCHOL is not recommended in patients at risk of bowel obstruction (e.g., patients with gastroparesis, other gastrointestinal motility disorders or a history of major gastrointestinal surgery) (5.4).
- WELCHOL reduces gastrointestinal absorption of some drugs. Administer drugs with a known interaction with colesevelam at least 4 hours prior to WELCHOL. Drugs that have not been tested for interaction with colesevelam, especially those with a narrow therapeutic index, should also be administered at least 4 hours prior to WELCHOL. Alternatively, monitor drug levels of the co-administered drug (5.5, 7, 12.3).
- WELCHOL for Oral Suspension contains 27 mg phenylalanine per 3.75 gram packet (5.6, 11).

ADVERSE REACTIONS

In clinical trials, the most common (incidence ≥2% and greater than placebo) adverse reactions with WELCHOL included constipation, dyspepsia, and nausea.

Postmarketing reports with concomitant WELCHOL administration include:

- Increased seizure activity or decreased phenytoin levels in patients receiving phenytoin. Administer phenytoin 4 hours prior to WELCHOL.
- Reduced International Normalized Ratio (INR) in patients receiving warfarin. Monitor INR.
- Elevated thyroid-stimulating hormone (TSH) in patients receiving thyroid hormone replacement therapy. Administer thyroid hormones 4 hours prior to WELCHOL.

Other postmarketing reports include bowel obstruction, dysphagia, esophageal obstruction, fecal impaction, hypertriglyceridemia, pancreatitis, and increased transaminases (5.5, 6.2, 7, 12.3).

To report SUSPECTED ADVERSE REACTIONS, contact Daiichi Sankyo, Inc. at 1-877-437-7763 or FDA at 1-800-332-1088 or *www.fda.gov/medwatch*.

DRUG INTERACTIONS

In drug interaction studies, WELCHOL reduced levels of cyclosporine, glimepiride, glipizide, glyburide, levothyroxine, olmesartan medoxomil, and oral contraceptives containing ethinyl estradiol and norethindrone. WELCHOL increased levels of metformin when coadministered with metformin extended release. There have been postmarketing reports of decreases in phenytoin levels in patients receiving phenytoin concomitantly with WELCHOL and decreases in INR in patients receiving warfarin concomitantly with WELCHOL (5.5, 7, 12.3).

See 17 for PATIENT COUNSELING INFORMATION

Revised: 01/2019

FULL PRESCRIBING INFORMATION: CONTENTS*

***Sections or subsections omitted from the full prescribing information are not listed.**

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Primary Hyperlipidemia

WELCHOL is indicated as an adjunct to diet and exercise to reduce elevated low-density lipoprotein cholesterol (LDL-C) in adults with primary hyperlipidemia (Fredrickson Type IIa) as monotherapy or in combination with a hydroxymethyl-glutaryl-coenzyme A (HMG CoA) reductase inhibitor (statin).

WELCHOL is indicated as monotherapy or in combination with a statin to reduce LDL-C levels in boys and postmenarchal girls, 10 to 17 years of age, with heterozygous familial hypercholesterolemia if after an adequate trial of diet therapy the following findings are present:
a. LDL-C remains ≥ 190 mg/dL or
b. LDL-C remains ≥ 160 mg/dL and

- there is a positive family history of premature cardiovascular disease or
- two or more other CVD risk factors are present in the pediatric patient.

Lipid-altering agents should be used in addition to a diet restricted in saturated fat and cholesterol when response to diet and non-pharmacological interventions alone has been inadequate *[See Clinical Studies (14.1)]*.

In patients with coronary heart disease (CHD) or CHD risk equivalents such as diabetes mellitus, LDL-C treatment goals are < 100 mg/dL. An LDL-C goal of < 70 mg/dL is a therapeutic option on the basis of recent trial evidence. If LDL-C is at goal but the serum triglyceride (TG) value is > 200 mg/dL, then non-HDL cholesterol (non-HDL-C) (total cholesterol [TC] minus high density lipoprotein cholesterol [HDL-C]) becomes a secondary target of therapy. The goal for non-HDL-C in persons with high serum TG is set at 30 mg/dL higher than that for LDL-C.

1.2 Type 2 Diabetes Mellitus

WELCHOL is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus *[See Clinical Studies (14.2)]*.

Diabetes mellitus is considered a CHD risk equivalent. In addition to glycemic control, intensive lipid control is warranted *[See Indications and Usage (1.1) and Warnings and Precautions (5.2)]*.

1.3 Important Limitations of Use

- WELCHOL should not be used for the treatment of type 1 diabetes or for the treatment of diabetic ketoacidosis.
- WELCHOL has not been studied in type 2 diabetes in combination with a dipeptidyl peptidase 4 inhibitor.
- WELCHOL has not been studied in pediatric patients with type 2 diabetes.
- WELCHOL has not been studied in Fredrickson Type I, III, IV, and V dyslipidemias.
- WELCHOL has not been studied in children younger than 10 years of age or in pre-menarchal girls.

2 DOSAGE AND ADMINISTRATION

2.1 Primary Hyperlipidemia

The recommended dose of WELCHOL Tablets in adults, whether used as monotherapy or in combination with a statin, is 6 tablets once daily or 3 tablets twice daily. WELCHOL Tablets should be taken with a meal and liquid.

The recommended dose of WELCHOL for Oral Suspension, in adults and children 10 to 17 years of age, is one 3.75 gram packet once daily. To prepare, empty the entire contents of one packet into a glass or cup. Add 1 cup (8 ounces) of water, fruit juice, or diet soft drinks. 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. Due to tablet size, it is recommended that any patient who has difficulty swallowing tablets use WELCHOL for Oral Suspension.WELCHOL can be dosed at the same time as a statin or the two drugs can be dosed apart *[See Clinical Studies (14.1)]*.

After initiation of WELCHOL, lipid levels should be analyzed within 4 to 6 weeks.

2.2 Type 2 Diabetes Mellitus

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

The recommended dose of WELCHOL for Oral Suspension is one 3.75 gram packet once daily. To prepare, empty the entire contents of one packet into a glass or cup. Add 1 cup (8 ounces) of water, fruit juice, or diet soft drinks. 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.

3 DOSAGE FORMS AND STRENGTHS

- Tablets: 625 mg tablets are off-white, oval, film-coated and imprinted with “Sankyo” and “C01” on one side.
- Oral Suspension: a white to pale yellow powder containing yellow granules packaged in single-dose packets: 3.75 gram single-dose packet.

4 CONTRAINDICATIONS

WELCHOL is contraindicated in patients with

- A history of bowel obstruction *[See Warnings and Precautions (5.4)]*
- Serum TG concentrations >500 mg/dL *[See Warnings and Precautions (5.2)]*
- A history of hypertriglyceridemia-induced pancreatitis *[See Warnings and Precautions (5.2)]*

5 WARNINGS AND PRECAUTIONS

5.1 General

The effect of WELCHOL on cardiovascular morbidity and mortality has not been determined.

5.2 Serum Triglycerides

WELCHOL, like other bile acid sequestrants, can increase serum TG concentrations.

WELCHOL had small effects on serum TG (median increase 5% compared to placebo) in trials of patients with primary hyperlipidemia *[See Adverse Reactions (6.1) and Clinical Studies (14.1)]*.

In clinical trials in patients with type 2 diabetes, greater increases in TG levels occurred when WELCHOL was used as monotherapy (median increase 9.7% compared to placebo) and when WELCHOL was used in combination with pioglitazone (median increase 11% compared to placebo in combination with pioglitazone), sulfonylureas (median increase 18% compared to placebo in combination with sulfonylureas), and insulin (median increase 22% compared to placebo in combination with insulin) *[See Adverse Reactions (6.1) and Clinical Studies (14.2)]*. Hypertriglyceridemia of sufficient severity can cause acute pancreatitis. The long-term effect of hypertriglyceridemia on the risk of coronary artery disease is uncertain. In patients with type 2 diabetes, the effect of WELCHOL on LDL-C levels may be attenuated by WELCHOL's effects on TG levels and a smaller reduction in non-HDL-C compared to the reduction in LDL-C. Caution should be exercised when treating patients with TG levels greater than 300 mg/dL. Because most patients in the WELCHOL clinical trials had baseline TG <300 mg/dL, it is unknown whether patients with more uncontrolled baseline hypertriglyceridemia would have greater increases in serum TG levels with WELCHOL. In addition, the use of WELCHOL is contraindicated in patients with TG levels >500 mg/dL *[See Contraindications (4)]*. Lipid parameters, including TG levels and non-HDL-C, should be obtained before starting WELCHOL and periodically thereafter. WELCHOL should be discontinued if TG levels exceed 500 mg/dL or if the patient develops hypertriglyceridemia-induced pancreatitis *[See Adverse Reactions (6.1)]*.

5.3 Vitamin K or Fat-Soluble Vitamin Deficiencies Precautions

Bile acid sequestrants may decrease the absorption of fat-soluble vitamins A, D, E, and K. No specific clinical studies have been conducted to evaluate the effects of WELCHOL on the absorption of co-administered dietary or supplemental vitamin therapy. In non-clinical safety studies, rats administered colesevelam hydrochloride at doses greater than 30-fold the projected human clinical dose experienced hemorrhage from vitamin K deficiency. Patients on oral vitamin supplementation should take their vitamins at least 4 hours prior to WELCHOL. Caution should be exercised when treating patients with a susceptibility to deficiencies of vitamin K (e.g., patients on warfarin, patients with malabsorption syndromes) or other fat-soluble vitamins.

5.4 Gastrointestinal Disorders

Because of its constipating effects, WELCHOL is not recommended in patients with gastroparesis, other gastrointestinal motility disorders, and in those who have had major gastrointestinal tract surgery and who may be at risk for bowel obstruction. Because of the tablet size, WELCHOL Tablets can cause dysphagia or esophageal obstruction and should be used with

caution in patients with dysphagia or swallowing disorders. To avoid esophageal distress, WELCHOL for Oral Suspension should not be taken in its dry form. Always mix WELCHOL for Oral Suspension with water, fruit juice, or diet soft drinks before ingesting.

5.5 Drug Interactions

WELCHOL reduces gastrointestinal absorption of some drugs. Drugs with a known interaction with colesevelam should be administered at least 4 hours prior to WELCHOL. Drugs that have not been tested for interaction with colesevelam, especially those with a narrow therapeutic index, should also be administered at least 4 hours prior to WELCHOL. Alternatively, the physician should monitor drug levels of the co-administered drug *[See Drug Interactions (7) and Clinical Pharmacology (12.3)]*.

5.6 Phenylketonurics

WELCHOL for Oral Suspension contains 27 mg phenylalanine per 3.75 gram packet *[See Description (11)]*.

5.7 Macrovascular Outcomes

There have been no clinical studies establishing conclusive evidence of macrovascular disease risk reduction with WELCHOL or any other antidiabetic drugs.

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in clinical studies of another drug and may not reflect the rates observed in practice.

Primary Hyperlipidemia: In 7 double-blind, placebo-controlled, clinical trials, 807 patients with primary hyperlipidemia (age range 18-86 years, 50% women, 90% Caucasians, 7% Blacks, 2% Hispanics, 1% Asians) and elevated LDL-C were treated with WELCHOL 1.5 g/day to 4.5 g/day from 4 to 24 weeks (total exposure 199 patient-years).

In clinical trials for the reduction of LDL-C, 68% of patients receiving WELCHOL vs. 64% of patients receiving placebo reported an adverse reaction.

Table 1
Placebo-Controlled Clinical Studies of WELCHOL for Primary Hyperlipidemia: Adverse Reactions Reported in ≥ 2% of Patients and More Commonly than in Patients Given Placebo, Regardless of Investigator Assessment of Causality

	Number of Patients (%)	
	WELCHOL N = 807	**Placebo N = 258**
Constipation	89 (11.0)	18 (7.0)
Dyspepsia	67 (8.3)	9 (3.5)
Nausea	34 (4.2)	10 (3.9)
Accidental injury	30 (3.7)	7 (2.7)
Asthenia	29 (3.6)	5 (1.9)
Pharyngitis	26 (3.2)	5 (1.9)
Flu syndrome	26 (3.2)	8 (3.1)
Rhinitis	26 (3.2)	8 (3.1)
Myalgia	17 (2.1)	1 (0.4)

Pediatric Patients 10 to 17 Years of Age: In an 8-week double-blind, placebo-controlled study boys and post-menarchal girls, 10 to 17 years of age, with heterozygous familial hypercholesterolemia (heFH) (n=192), were treated with WELCHOL tablets (1.9-3.8 g, daily) or placebo tablets *[See Clinical Studies (14.1)]*.

Table 2
Placebo-Controlled Clinical Study of WELCHOL for Primary Hyperlipidemia in heFH Pediatric Patients: Adverse Reactions Reported in ≥2% of Patients and More Commonly than in Patients Given Placebo, Regardless of Investigator Assessment of Causality

	Number of Patients (%)	
	WELCHOL N = 129	**Placebo N = 65**
Nasopharyngitis	8 (6.2)	3 (4.6)
Headache	5 (3.9)	2 (3.1)
Fatigue	5 (3.9)	1 (1.5)
Creatine Phosphokinase Increase	3 (2.3)	0 (0.0)
Rhinitis	3 (2.3)	0 (0.0)
Vomiting	3 (2.3)	1 (1.5)

The reported adverse reactions during the additional 18-week open-label treatment period with WELCHOL 3.8 g per day were similar to those during the double-blind period and included headache (7.6%), nasopharyngitis (5.4%), upper respiratory tract infection (4.9%), influenza (3.8%), and nausea (3.8%) *[See Clinical Studies (14.1)]*.

Type 2 Diabetes Mellitus: The safety of WELCHOL in patients with type 2 diabetes mellitus was evaluated in 5 add-on combination and 1 monotherapy double-blind, 12-26 week, placebo-controlled clinical trials *[see Clinical Studies (14.2)]*. In these studies 1022 patients were exposed to WELCHOL. The mean exposure duration was 20 weeks (total exposure 393 patient-years). Patients were to receive 3.8 grams of WELCHOL per day. The mean age of patients exposed to WELCHOL was 55.7 years, 52.8 percent of the population was male and 61.9% were Caucasian, 4.8% were Asian, and 15.9% were Black or African American. At baseline the population had a mean HbA1C of 8.2% and 26% had past medical history suggestive of microvascular complications of diabetes. Baseline characteristics in the placebo group were comparable.

In clinical trials of type 2 diabetes, 57% of patients receiving WELCHOL vs. 52% of patients receiving placebo reported an adverse reaction.

Table 3 shows common adverse reactions associated with the use of WELCHOL in the 1015 patients with type 2 diabetes. These adverse reactions were not present at baseline, occurred more commonly on WELCHOL than on placebo, and occurred in at least 2% of patients treated with WELCHOL.

Table 3
Placebo-Controlled Clinical Studies of WELCHOL for Type 2 Diabetes: Adverse Reactions Reported in ≥ 2% of Patients and More Commonly than in Patients Given Placebo, Regardless of Investigator Assessment of Causality

	Number of Patients (%)	
	WELCHOL N = 1015	**Placebo N = 1010**
Constipation	66 (6.5)	22 (2.2)
Hypoglycemia	35 (3.4)	31 (3.1)
Dyspepsia	28 (2.8)	10 (1.0)
Nausea	26 (2.6)	16 (1.6)
Hypertension	26 (2.6)	19 (1.9)
Back Pain	23 (2.3)	13 (1.3)

A total of 5.3% of WELCHOL-treated patients and 3.6% of placebo-treated patients were discontinued from the diabetes trials due to adverse reactions. This difference was driven mostly by gastrointestinal adverse reactions such as abdominal pain and constipation.

One patient in the add-on to sulfonylurea trial discontinued due to body rash and mouth blistering that occurred on the first day of dosing of WELCHOL, which may represent a hypersensitivity reaction to WELCHOL.

Hypertriglyceridemia: Patients with fasting serum TG levels above 500 mg/dL were excluded from the diabetes clinical trials. In the diabetes trials, 1292 (67.7%) patients had baseline fasting serum TG levels less than 200 mg/dL, 426 (22.3%) had baseline fasting serum TG levels between 200 and less than 300 mg/dL, 175 (9.2%) had baseline fasting serum TG levels between 300 and 500 mg/dL, and 16 (0.8%) had fasting serum TG levels greater than or

equal to 500 mg/dL. The median baseline fasting TG concentration for the study population was 160 mg/dL; the median post-treatment fasting TG was 180 mg/dL in the WELCHOL group and 162 mg/dL in the placebo group. WELCHOL therapy resulted in a median placebo-corrected increase in serum TG of 9.7% (p=0.03) in the monotherapy study and of 5% (p=0.22), 11% (p<0.001), 18% (p<0.001), and 22% (p<0.001), when added to metformin, pioglitazone, sulfonylureas, and insulin, respectively *[See Warnings and Precautions (5.2) and Clinical Studies (14.2)]*. In comparison, WELCHOL resulted in a median increase in serum TG of 5% compared to placebo (p=0.42) in a 24-week monotherapy lipid-lowering trial *[See Clinical Studies (14.1)]*.

Treatment-emergent fasting TG concentrations ≥500 mg/dL occurred in 0.9% of WELCHOL-treated patients compared to 0.7% of placebo-treated patients in the diabetes trials. Among these patients, the TG concentrations with WELCHOL (median 606 mg/dL; interquartile range 570-794 mg/dL) were similar to that observed with placebo (median 663 mg/dL; interquartile range 542-984 mg/dL). Five (0.6%) patients on WELCHOL and 3 (0.3%) patients on placebo developed TG elevations ≥1000 mg/dL. In all WELCHOL clinical trials, including studies in patients with type 2 diabetes and patients with primary hyperlipidemia, there were no reported cases of acute pancreatitis associated with hypertriglyceridemia. It is unknown whether patients with more uncontrolled, baseline hypertriglyceridemia would have greater increases in serum TG levels with WELCHOL *[See Contraindications (4) and Warnings and Precautions (5.2)]*.

Cardiovascular adverse events: During the diabetes clinical trials, the incidence of patients with treatment-emergent serious adverse events involving the cardiovascular system was 2.2% (22/1015)) in the WELCHOL group and 1% (10/1010) in the placebo group. These overall rates included disparate events (e.g., myocardial infarction, aortic stenosis, and bradycardia); therefore, the significance of this imbalance is unknown.

6.2 Post-marketing Experience

The following additional adverse reactions have been identified during post-approval use of WELCHOL. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Drug Interactions with concomitant WELCHOL administration include:

- Increased seizure activity or decreased phenytoin levels in patients receiving phenytoin. Phenytoin should be administered 4 hours prior to WELCHOL.
- Reduced International Normalized Ratio (INR) in patients receiving warfarin therapy. In warfarin-treated patients, INR should be monitored frequently during WELCHOL initiation then periodically thereafter.
- Elevated thyroid-stimulating hormone (TSH) in patients receiving thyroid hormone replacement therapy. Thyroid hormone replacement should be administered 4 hours prior to WELCHOL *[See Drug Interactions (7)]*.

Gastrointestinal Adverse Reactions

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.

Laboratory Abnormalities
Hypertriglyceridemia

7 DRUG INTERACTIONS

Table 4 lists the drugs that have been tested in *in vitro* binding, *in vivo* drug interaction studies with colesevelam and/or drugs with postmarketing reports consistent with potential drug-drug interactions. Orally administered drugs that have not been tested for interaction with colesevelam, especially those with a narrow therapeutic index, should also be administered at least 4 hours prior to WELCHOL. Alternatively, the physician should monitor drug levels of the co-administered drug.

Table 4
Drugs Tested in *In Vitro* Binding or *In Vivo* Drug Interaction Testing or With Post-Marketing Reports

Drugs with a known interaction with colesevelam: Decrease in exposure of coadministered drug	cyclosporine[c], glimepiride[a], glipizide[a], glyburide[a], levothyroxine[a], olmesartan medoxomil[a], and oral contraceptives containing ethinyl estradiol and norethindrone[a]
Drugs with a known interaction with colesevelam: Increase in exposure of coadministered drug	metformin extended release (ER)[d]
Drug(s) with postmarketing reports consistent with potential drug-drug interactions when coadministered with WELCHOL	phenytoin[a], warfarin[b]
Drugs that do not interact with colesevelam based on *in vitro* or *in vivo* testing	aspirin, atenolol, cephalexin, ciprofloxacin, digoxin, enalapril, fenofibrate, lovastatin, metformin, metoprolol, phenytoin[a], pioglitazone, rosiglitazone, quinidine, repaglinide, sitagliptin, valproic acid, verapamil, warfarin[b]

[a] Should be administered at least 4 hours prior to WELCHOL
[b] No significant alteration of warfarin drug levels with warfarin and WELCHOL coadministration in an *in vivo* study which did not evaluate warfarin pharmacodynamics (INR). *[See Adverse Reactions (6.2)]*
[c] Cyclosporine levels should be monitored and, based on theoretical grounds, cyclosporine should be administered at least 4 hours prior to WELCHOL.
[d] Patients receiving concomitant metformin ER and colesevelam should be monitored for clinical response as is usual for the use of anti-diabetes drugs.

In an *in vivo* drug interaction study, WELCHOL and warfarin coadministration had no effect on warfarin drug levels. This study did not assess the effect of WELCHOL and warfarin coadministration on INR. In post-marketing reports, concomitant use of WELCHOL and warfarin has been associated with reduced INR. Therefore, in patients on warfarin therapy, the INR should be monitored before initiating WELCHOL and frequently enough during early WELCHOL therapy to ensure that no significant alteration in INR occurs. Once the INR is stable, continue to monitor the INR at intervals usually recommended for patients on warfarin *[See Adverse Reactions (6.2)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

WELCHOL is not absorbed systemically following oral administration, and maternal use is not expected to result in fetal exposure to the drug. Limited available data on the use of WELCHOL are insufficient to determine a drug-associated risk of major congenital malformations or miscarriage. In animal reproduction studies, no evidence of either maternal or fetal toxicity was found in rats or rabbits exposed to colesevelam hydrochloride during the period of fetal organogenesis at 8 and 5 times, respectively, the maximum recommended human dose (MRHD) of 3.75 g/day, based on body surface area (mg/m^2). No adverse effects on offspring survival and development were observed in rats administered 3 times the MRHD *(see Data).* WELCHOL may decrease the absorption of fat-soluble vitamins *[see Warnings and Precautions (5.3)]*. There are no data available on the effect of colesevelam hydrochloride on the absorption of fat-soluble vitamins in pregnant women. If the patient becomes pregnant while taking WELCHOL, the patient should be advised of the lack of known clinical benefit with continued use during pregnancy.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20% respectively.

Data

Human Data

There are no adequate and well-controlled studies of colesevelam hydrochloride use in pregnant women.

In the post-marketing setting there have been infrequent reports of pregnancy with use of WELCHOL and a causal association with congenital anomalies has not been established.

Animal Data

In pregnant rats given dietary doses of 0.3, 1.0, 3.0 g/kg/day colesevelam hydrochloride from gestation days 7 through 17, no teratogenic effects were observed. Exposures at 3.0 g/kg/day were 8 times the human exposure at 3.75 g/day MRHD, based on body surface area (mg/m^2).

In pregnant rabbits given oral gavage doses of 0.1, 0.5, 1.0 g/kg/day colesevelam hydrochloride from gestation days 6 through 18, no teratogenic effects were observed. Exposures at 1.0 g/kg/day were 5 times the human exposure at 3.75 g/day MRHD, based on body surface area (mg/m^2).

In pregnant rats given oral gavage doses of 0.1, 0.3, 1.0 g/kg/day colesevelam hydrochloride from gestation day 6 through lactation day 21 (weaning), no adverse effects on survival and development were observed. Exposures at 1.0 g/kg/day were 3 times the human exposure at 3.75 g/day MRHD, based on body surface area (mg/m^2).

8.2 Lactation

Risk Summary

WELCHOL is not absorbed systemically by the mother following oral administration, and breastfeeding is not expected to result in exposure of the child to WELCHOL.

8.3 Females and Males of Reproductive Potential

Contraception

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

8.4 Pediatric Use

The safety and effectiveness of WELCHOL as monotherapy or in combination with a statin were evaluated in children, 10 to 17 years of age with heFH *[See Clinical Studies (14.1)]*. The adverse reaction profile was similar to that of patients treated with placebo. In this limited controlled study, there were no significant effects on growth, sexual maturation, fat-soluble vitamin levels or clotting factors in the adolescent boys or girls relative to placebo *[See Adverse Reactions (6.1)]*.

Due to tablet size, WELCHOL for Oral Suspension is recommended for use in the pediatric population. Dose adjustments are not required when WELCHOL is administered to children 10 to 17 years of age.

WELCHOL has not been studied in children younger than 10 years of age or in pre-menarchal girls.

8.5 Geriatric Use

Primary Hyperlipidemia: Of the 1350 patients enrolled in the hyperlipidemia clinical studies, 349 (26%) were ≥65 years old, and 58 (4%) were ≥75 years old. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Type 2 Diabetes Mellitus: Of the 2048 patients enrolled in the six diabetes studies, 397 (19%) were ≥65 years old, and 36 (2%) were ≥75 years old. In these trials, WELCHOL 3.8 g/day or placebo was added onto background anti-diabetic therapy. No overall differences in safety or effectiveness were observed between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Hepatic Impairment

No special considerations or dosage adjustments are recommended when WELCHOL is administered to patients with hepatic impairment.

8.7 Renal Impairment

Type 2 Diabetes Mellitus: Of the 2048 patients enrolled in the six diabetes studies, 807 (39%) had mild renal insufficiency (creatinine clearance [CrCl] 50-<80 mL/min), 61 (3%) had moderate renal insufficiency (CrCl 30-<50 mL/min), and none had severe renal insufficiency (CrCl <30 mL/min), as estimated from baseline serum creatinine using the Modification of Diet in Renal Disease (MDRD) equation. No overall differences in safety or effectiveness were

observed between patients with CrCl <50 mL/min (n=53) and those with a CrCl ≥50 mL/min (n=1075) in the add-on to metformin, sulfonylureas, and insulin diabetes studies. In the monotherapy study and add-on to pioglitazone study only 3 and 5 patients respectively had moderate renal insufficiency

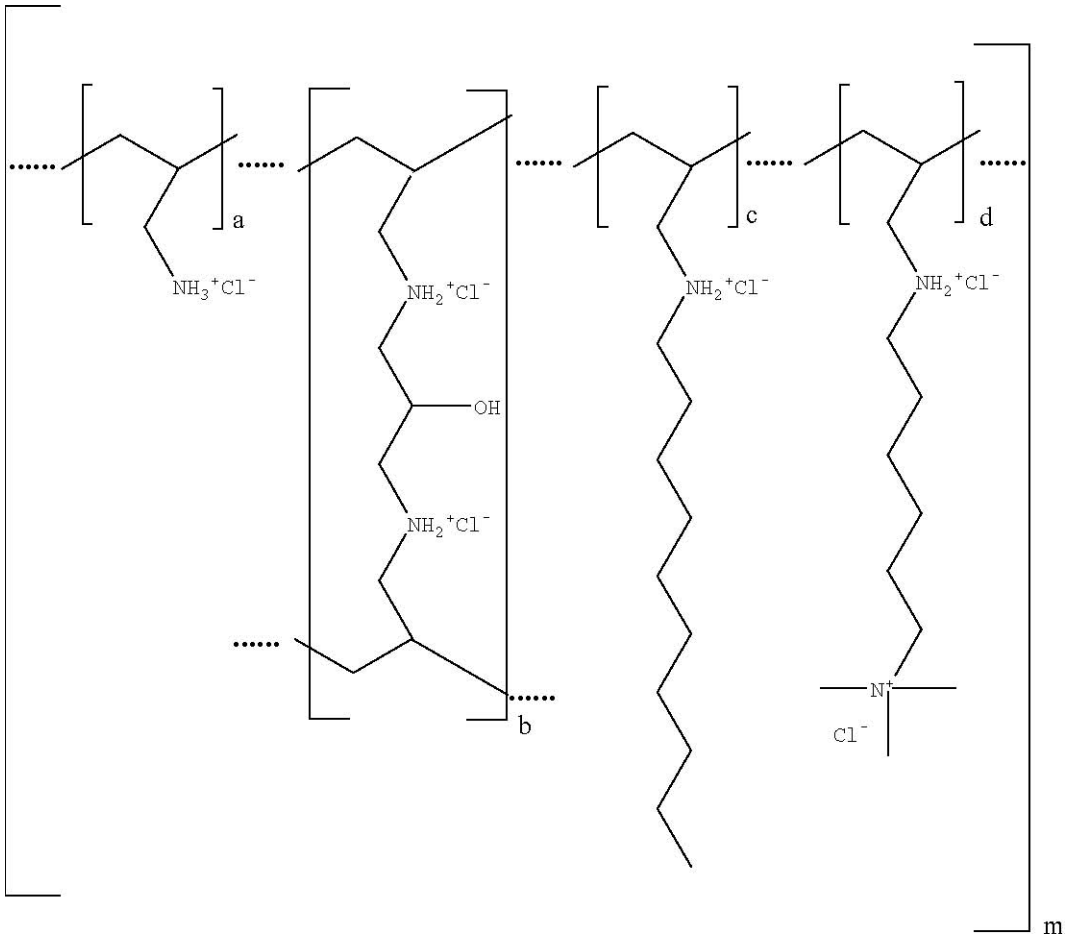
10 OVERDOSAGE

Doses of WELCHOL in excess of 4.5 g/day have not been tested. Because WELCHOL is not absorbed, the risk of systemic toxicity is low. However, excessive doses of WELCHOL may cause more severe local gastrointestinal effects (e.g., constipation) than recommended doses.

11 DESCRIPTION

WELCHOL (colesevelam hydrochloride) is a non-absorbed, polymeric, lipid-lowering and glucose-lowering agent intended for oral administration. Colesevelam hydrochloride is a high-capacity bile acid-binding molecule.

Colesevelam hydrochloride is poly(allylamine hydrochloride) cross-linked with epichlorohydrin and alkylated with 1-bromodecane and (6-bromohexyl)-trimethylammonium bromide. The chemical name (IUPAC) of colesevelam hydrochloride is allylamine polymer with 1-chloro-2,3-epoxypropane, [6-(allylamino)-hexyl]trimethylammonium chloride and N-allyldecylamine, hydrochloride. The chemical structure of colesevelam hydrochloride is represented by the following formula:



wherein (a) represents allyl amine monomer units that have not been alkylated by either of the 1-bromodecane or (6-bromohexyl)-trimethylammonium bromide alkylating agents or cross-linked by epichlorohydrin; (b) represents allyl amine units that have undergone cross-linking with epichlorohydrin; (c) represents allyl amine units that have been alkylated with a decyl group; (d) represents allyl amine units that have been alkylated with a (6-trimethylammonium) hexyl group, and m represents a number ≥ 100 to indicate an extended polymer network. A small amount of the amines are dialkylated, and are not depicted in the formula above. No regular order of the groups is implied by the structure; cross-linking and alkylation are expected to occur randomly along the polymer chains. A large amount of the amines are protonated. The polymer is depicted in the hydrochloride form; a small amount of the halides are bromide. Colesevelam hydrochloride is hydrophilic and insoluble in water.

WELCHOL Tablets are an off-white, oval, film-coated, solid tablet containing 625 mg colesevelam hydrochloride. In addition, each tablet contains the following inactive ingredients: magnesium stearate, microcrystalline cellulose, silicon dioxide, HPMC (hydroxypropyl methylcellulose), and acetylated monoglyceride. The tablets are imprinted using a water-soluble black ink.

WELCHOL for Oral Suspension is a citrus-flavored, white to pale yellow powder containing yellow granules packaged in a single-dose packet containing 3.75 gram colesevelam hydrochloride. In addition, each packet contains the following inactive ingredients: lemon flavor,

orange flavor, propylene glycol alginate, simethicone, aspartame, citric acid, medium chain triglycerides, and magnesium trisilicate.

PHENYLKETONURICS: WELCHOL for Oral Suspension contains 27 mg phenylalanine per 3.75 gram dose.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Primary Hyperlipidemia: Colesevelam hydrochloride, the active pharmaceutical ingredient in WELCHOL, is a non-absorbed, lipid-lowering polymer that binds bile acids in the intestine, impeding their reabsorption. As the bile acid pool becomes depleted, the hepatic enzyme, cholesterol 7-α-hydroxylase, is upregulated, which increases the conversion of cholesterol to bile acids. This causes an increased demand for cholesterol in the liver cells, resulting in the dual effect of increasing transcription and activity of the cholesterol biosynthetic enzyme, HMG-CoA reductase, and increasing the number of hepatic LDL receptors. These compensatory effects result in increased clearance of LDL-C from the blood, resulting in decreased serum LDL-C levels. Serum TG levels may increase or remain unchanged.

Type 2 Diabetes Mellitus: The mechanism by which WELCHOL improves glycemic control is unknown.

12.2 Pharmacodynamics

A maximum therapeutic response to the lipid-lowering effects of WELCHOL was achieved within 2 weeks and was maintained during long-term therapy. In the diabetes clinical studies, a therapeutic response to WELCHOL, as reflected by a reduction in hemoglobin A1C (A1C), was initially noted following 4-6 weeks of treatment and reached maximal or near-maximal effect after 12-18 weeks of treatment.

12.3 Pharmacokinetics

Absorption: Colesevelam hydrochloride is a hydrophilic, water-insoluble polymer that is not hydrolyzed by digestive enzymes and is not absorbed.

Distribution: Colesevelam hydrochloride is not absorbed, and therefore, its distribution is limited to the gastrointestinal tract.

Metabolism: Colesevelam hydrochloride is not metabolized systemically and does not interfere with systemic drug-metabolizing enzymes such as cytochrome P-450.

Excretion: In 16 healthy volunteers, an average of 0.05% of administered radioactivity from a single ^{14}C-labeled colesevelam hydrochloride dose was excreted in the urine.

Drug Interactions: Drug interactions between colesevelam and concomitantly administered drugs were screened through *in vitro* studies and confirmed in *in vivo* studies. *In vitro* studies demonstrated that cephalexin, metformin, and ciprofloxacin had negligible binding to colesevelam hydrochloride. Therefore, an *in vivo* pharmacokinetic interaction of WELCHOL with these drugs is unlikely. WELCHOL was found to have no significant effect on the bioavailability of aspirin, atenolol, digoxin, enalapril, fenofibrate, lovastatin, metoprolol,

phenytoin, pioglitazone, quinidine, rosiglitazone, sitagliptin, valproic acid, and warfarin. The results of additional *in vivo* drug interactions of WELCHOL are presented in Table 5.

Table 5
Mean Change in Drug Exposure ($AUC_{0-\infty}$ and C_{max}) when Administered with WELCHOL (3.75 g)[a]

Drug	Dose	Co-administered		1 hr prior to WELCHOL		4 hr prior to WELCHOL	
		$AUC_{0-\infty}$	C_{max}	$AUC_{0-\infty}$	C_{max}	$AUC_{0-\infty}$	C_{max}
Cyclosporine [d]	200 mg	-34%	-44%	N/A	N/A	N/A	N/A
Ethinyl Estradiol* [b]	0.035 mg	-24%	-24%	-18%	-1%	-12%	0%
Glimepiride [b]	4 mg	-18%	-8%	N/A	N/A	-6%	3%
Glipizide [b]	20 mg	-12%	-13%	N/A	N/A	-4%	0%
Glyburide [b]	3 mg	-32%	-47%	-20%	-15%	-7%	4%
Levothyroxine [b]	600 µg	-22%	-33%	6%	-2%	1%	8%
Metformin ER [c]	1500 mg	44%	8%	N/A	N/A	N/A	N/A
Norethindrone* [b]	1 mg	-1%	-20%	5%	-3%	6%	7%
Olmesartan Medoxomil[b]	40 mg	-39%	-28%	N/A	N/A	-15%	-4%
Repaglinide	2 mg	-7%	-19%	-6%	-1%	N/A	N/A
Verapamil sustained-release	240 mg	-31%	-11%	N/A	N/A	N/A	N/A

[a] With verapamil, the dose of WELCHOL was 4.5 g
[b] Should be administered at least 4 hours prior to WELCHOL *[See Drug Interactions (7)]*.
[c] Patients receiving concomitant metformin ER and colesevelam should be monitored for clinical response as is usual for the use of anti-diabetes drugs *[See Drug Interactions (7)]*.
[d] Cyclosporine levels should be monitored and, based on theoretical grounds, cyclosporine should be administered at least 4 hours prior to WELCHOL *[See Drug Interactions (7)]*.
* Oral contraceptive containing norethindrone and ethinyl estradiol.
N/A – Not Available

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

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

13.2 Animal Toxicology and/or Pharmacology

Reproductive Toxicology Studies

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

14 CLINICAL STUDIES

14.1 Primary Hyperlipidemia

WELCHOL reduces TC, LDL-C, apolipoprotein B (Apo B), and non-HDL-C when administered alone or in combination with a statin in patients with primary hyperlipidemia.

Approximately 1600 patients were studied in 9 clinical trials with treatment durations ranging from 4 to 50 weeks. With the exception of one open-label, uncontrolled, long-term extension study, all studies were multicenter, randomized, double-blind, and placebo-controlled. A maximum therapeutic response to WELCHOL was achieved within 2 weeks and was maintained during long-term therapy.

Monotherapy: In a study in patients with LDL-C between 130 mg/dL and 220 mg/dL (mean 158 mg/dL), WELCHOL was given for 24 weeks in divided doses with the morning and evening meals.

As shown in Table 6, the mean LDL-C reductions were 15% and 18% at the 3.8 g and 4.5 g doses. The respective mean TC reductions were 7% and 10%. The mean Apo B reductions were 12% in both treatment groups. WELCHOL at both doses increased HDL-C by 3%. Increases in TG of 9-10% were observed at both WELCHOL doses but the changes were not statistically different from placebo.

Table 6
Response to WELCHOL Monotherapy in a 24-Week Trial - Percent Change in Lipid Parameters from Baseline

Grams/Day	N	TC	LDL-C	Apo B	HDL-C[a]	Non-HDL-C	TG[a]
Placebo	88	+1	0	0	–1	+1	+5
3.8 g (6 tablets)	95	–7*	–15*	–12*	+3*	–10*	+10
4.5 g (7 tablets)	94	–10*	–18*	–12*	+3	–13*	+9

*p<0.05 for lipid parameters compared to placebo, for Apo B compared to baseline.
[a] Median % change from baseline.

In a study in 98 patients with LDL-C between 145 mg/dL and 250 mg/dL (mean 169 mg/dL), WELCHOL 3.8 g was given for 6 weeks as a single dose with breakfast, as a single dose with dinner, or as divided doses with breakfast and dinner. The mean LDL-C reductions were 18%, 15%, and 18% for the 3 dosing regimens, respectively. The reductions with these 3 regimens were not statistically different from one another.

Combination Therapy: Co-administration of WELCHOL and a statin (atorvastatin, lovastatin, or simvastatin) in 3 clinical studies demonstrated an additive reduction of LDL-C. The mean baseline LDL-C was 184 mg/dL in the atorvastatin study (range 156-236 mg/dL), 171 mg/dL in the lovastatin study (range 115-247 mg/dL), and 188 mg/dL in the simvastatin study (range 148-352 mg/dL). As demonstrated in Table 7, WELCHOL doses of 2.3 g to 3.8 g resulted in an additional 8% to 16% reduction in LDL-C above that seen with the statin alone.

Table 7
Response to WELCHOL in Combination with Atorvastatin, Simvastatin, or Lovastatin - Percent Change in Lipid Parameters

Dose/Day	N	TC	LDL-C	Apo B	HDL-C[a]	Non-HDL-C	TG[a]
Atorvastatin Trial (4-week)							
Placebo	19	+4	+3	–3	+4	+4	+10
Atorvastatin 10 mg	18	–27*	–38*	–32*	+8	–35*	–24*
WELCHOL 3.8 g/ Atorvastatin 10 mg	18	–31*	–48*	–38*	+11	–40*	–1
Atorvastatin 80 mg	20	–39*	–53*	–46*	+6	–50*	–33*
Simvastatin Trial (6-week)							
Placebo	33	–2	–4	–4*	–3	–2	+6*
Simvastatin 10 mg	35	–19*	–26*	–20*	+3*	–24*	–17*
WELCHOL 3.8 g/ Simvastatin 10 mg	34	–28*	–42*	–33*	+10*	–37*	–12*
Simvastatin 20 mg	39	–23*	–34*	–26*	+7*	–30*	–12*
WELCHOL 2.3 g/ Simvastatin 20 mg	37	–29*	–42*	–32*	+4*	–37*	–12*
Lovastatin Trial (4-week)							
Placebo	26	+1	0	0	+1	+1	+1
Lovastatin 10 mg	26	–14*	–22*	–16*	+5	–19*	0
WELCHOL 2.3 g/ Lovastatin 10 mg Together	27	–21*	–34*	–24*	+4	–27*	–1
WELCHOL 2.3 g/ Lovastatin 10 mg Apart	23	–21*	–32*	–24*	+2	–28*	–2

*p<0.05 for lipid parameters compared to placebo, for Apo B compared to baseline.
[a] Median % change from baseline.

In all 3 studies, the LDL-C reduction achieved with the combination of WELCHOL and any given dose of statin therapy was statistically superior to that achieved with WELCHOL or that dose of the statin alone. The LDL-C reduction with atorvastatin 80 mg was not statistically significantly different from the combination of WELCHOL 3.8 g and atorvastatin 10 mg.

The effect of WELCHOL when added to fenofibrate was assessed in 122 patients with mixed hyperlipidemia (Fredrickson Type IIb). Inclusion in the study required LDL-C ≥115 mg/dL and TG 150 mg/dL to 749 mg/dL. Patients were treated with 160 mg of fenofibrate during an 8-week open-label run-in period and then randomly assigned to receive fenofibrate 160 mg plus either WELCHOL 3.8 g or placebo for 6 weeks of double-blind treatment. The overall mean LDL-C at the start of randomized treatment was 144 mg/dL. The results of the study are summarized in Table 8.

Table 8
Response to WELCHOL Added to Fenofibrate in Patients with Mixed Hyperlipidemia (Mean % Change from Treated Baseline[b] at 6 Weeks)

Treatment	N	TC	LDL-C	Apo B	HDL-C	Non-HDL-C	TG[a]
Placebo + Fenofibrate 160 mg	61	2	2	1	-1	2	-3
WELCHOL + Fenofibrate 160 mg	61	-6*	-10*	-7*	0	-8*	6

* p≤0.0002 compared to placebo.
[a] For triglycerides, median % change from baseline.
[b] Treated Baseline: following 8-week treatment with open-label fenofibrate 160 mg.

Pediatric Therapy: The safety and efficacy of WELCHOL in pediatric patients were evaluated in an 8-week, multi-center, randomized, double-blind, placebo-controlled, parallel-group study followed by an open-label phase, in 194 boys and postmenarchal girls 10-17 years of age (mean age 14.1 years) with heterozygous familial hypercholesterolemia (heFH), taking a stable dose of an FDA-approved statin (with LDL-C >130 mg/dL) or naïve to lipid-lowering therapy (with LDL-C >160 mg/dL). This study had 3 periods: a single-blind, placebo stabilization period; an 8-week, randomized, double-blind, parallel-group, placebo-controlled treatment period; and an 18-week, open-label treatment period. Forty-seven (24%) patients were taking statins and 147 (76%) patients were statin-naïve at screening. The mean baseline LDL-C at Day 1 was approximately 199 mg/dL.

During the double-blind treatment period, patients were assigned randomly to treatment: WELCHOL 3.8 g/day (n=64), WELCHOL 1.9 g/day (n=65), or placebo (n=65). In total, 186 patients completed the double-blind treatment period. After 8 weeks of treatment, WELCHOL 3.8 g/day significantly decreased plasma levels of LDL-C, non-HDL-C, TC, and Apo B and significantly increased HDL-C. A moderate, non-statistically significant increase in TG was observed versus placebo (Table 9).

Table 9
Response to WELCHOL 3.8 g Compared to Placebo in Pediatric Patients 10-17 Years of Age – Mean Percent Change in Lipid Parameters from Baseline to Week 8

Treatment Difference	TC (N=128)	LDL-C (N=128)	Apo B (N=124)	HDL-C (N=128)	Non-HDL-C (N=128)	TG[a] (N=128)
WELCHOL 3.8 g vs Placebo	-7*	-13*	-8*	+6*	–11 *	+5

*p≤0.05 for lipid parameters compared to placebo
Values represent LS mean. Only patients with values at both study baseline and endpoint are included in this table. Study baseline was defined as the last value measured before or on Day 1 prior to the first dose of randomized study medication.
[a] For triglycerides, median % change from baseline.
Results were based on the ITT population with LOCF

During the open-label treatment period patients were treated with WELCHOL 3.8 g/day. In total, 173 (89%) patients completed 26 weeks of treatment. Results at Week 26 were consistent with those at Week 8.

14.2 Type 2 Diabetes Mellitus

WELCHOL has been studied as monotherapy and in combination with metformin, pioglitazone, sulfonylureas, and insulin. In these studies, WELCHOL and placebo were

administered either as 3 tablets twice daily with lunch and dinner or as 6 tablets with dinner alone.

Monotherapy: The efficacy of WELCHOL 3.8 g/day as anti-diabetes monotherapy was evaluated in a randomized double-blind, placebo-controlled trial involving 357 patients (176 WELCHOL and 181 placebo) with T2DM who were treatment-naïve or had not received antihyperglycemic medication within 3 months prior to the start of the study. Statin use at baseline was reported in 13% of the WELCHOL-treated patients and 16% of the placebo-treated patients.

WELCHOL resulted in a statistically significant reduction in A1C of 0.27% compared to placebo (Table 10).

The mean baseline LDL-C was 121 mg/dL in the monotherapy trial. WELCHOL treatment resulted in a placebo-corrected 11% reduction in LDL-C. WELCHOL treatment also reduced serum TC, ApoB, and non-HDL-C (Table 11). The mean change in body weight was -0.6 kg for WELCHOL and -0.7 kg for placebo treatment groups.

Table 10
Glycemic Parameters in a 24-Week Placebo-Controlled Study of WELCHOL Monotherapy in Patients with Type 2 Diabetes

	WELCHOL 3.8 g/day	Placebo
A1C (%), Mean		
N	175	169
Baseline	8.25	8.17
Change from baseline[a]	-0.26	0.01
Treatment difference (p-value)	-0.27 (p=0.013)	
FPG (mg/dL), Mean		
N	172	166
Baseline	172	168
Change from baseline[a]	-4.6	5.7
Treatment difference (p-value)	-10.3 (p=0.037[b])	

[a] Least-squares mean change calculated from an Analysis of Covariance model
[b] Nominal p=value, not controlled for multiplicity testing.
A1C = hemoglobin A1C, FPG = fasting plasma glucose

Table 11
Percent Change in Lipid Parameters in a 24-Week Placebo-Controlled Study of WELCHOL Monotherapy in Patients with Type 2 Diabetes

Dose/Day	N[†]	TC	LDL-C	Apo B	HDL-C	Non-HDL-C	TG[a]
WELCHOL 3.8 g	162	-3.3*	-10.0*	-5.6*	1.7	-4.4*	15.5
Placebo	160	1.8	1.2	0.9	-0.1	3.0	5.8

*p<0.001 for lipid parameters compared to placebo (this more stringent criterion for statistical significance accounts for multiplicity testing of the lipid parameters, which were secondary endpoints in the diabetes trials)
[a] Median % change from baseline.
[†] The number of patients with analyzable data, i.e., a baseline and post-treatment value (last-observation carried forward), varied slightly among different parameters. The N given represents the smallest number of patients included in the analysis for any parameter.

Add-on Combination Therapy: The efficacy of WELCHOL 3.8 g/day in patients with type 2 diabetes mellitus was evaluated in 5 double-blind, placebo-controlled add-on therapy trials involving a total of 1691 patients with baseline A1C 7.5-9.5%. Patients were enrolled and maintained on their pre-existing, stable, background anti-diabetic regimen. Statin use at baseline was reported in 41% of the WELCHOL-treated patients and 48% of the placebo-treated patients.

In 3 add-on combination therapy trials (metformin, sulfonylurea and insulin), treatment with WELCHOL resulted in a statistically significant reduction in A1C of 0.5% compared to placebo. Similar placebo-corrected reductions in A1C occurred in patients who received WELCHOL in combination with metformin, sulfonylurea, or insulin monotherapy or combinations of these therapies with other anti-diabetic agents. In the pioglitazone trial, treatment with WELCHOL resulted in a statistically significant reduction in A1C of 0.32% compared to placebo. In the metformin, pioglitazone, and sulfonylurea trials, treatment with WELCHOL also resulted in statistically significant reductions in fasting plasma glucose (FPG) of at least 14 mg/dL compared to placebo.

WELCHOL had consistent effects on A1C across subgroups of age, gender, race, body mass index, and baseline A1C. WELCHOL's effects on A1C were also similar for the two dosing regimens (3 tablets with lunch and with dinner or 6 tablets with dinner alone).

The mean baseline LDL-C was 104 mg/dL in the metformin study (range 32-214 mg/dL), 107 mg/dL in the pioglitazone study (range 48-263 mg/dL), 106 mg/dL in the sulfonylurea study (range 41-264 mg/dL), 102 mg/dL in the insulin study (range 35-204 mg/dL). In these trials, WELCHOL treatment was associated with a 12% to 16% reduction in LDL-C levels. The percentage decreases in LDL-C were of similar magnitude to those observed in patients with primary hyperlipidemia. WELCHOL treatment was associated with statistically significant increases in TG levels in the studies of patients on insulin, patients on a sulfonylurea, and patients on pioglitazone but not in the study of patients on metformin. The clinical significance of these increases is unknown. WELCHOL is contraindicated in patients with TG levels > 500 mg/dL *[See Contraindications (4)]* and periodic monitoring of lipid parameters including TG and non-HDL-C levels is recommended *[See Warnings and Precautions (5.2) and Adverse Reactions (6.1)]*.

Body weight did not significantly increase from baseline with WELCHOL therapy, compared with placebo, in any of the add-on combination diabetes studies.

Add-on Combination Therapy with Metformin: WELCHOL 3.8 g/day or placebo was added to background anti-diabetic therapy in a 26-week trial of 316 patients already receiving treatment with metformin alone (N=159) or metformin in combination with other oral agents (N=157). A total of 60% of these patients were receiving ≥1,500 mg/day of metformin. In combination with metformin, WELCHOL resulted in statistically significant placebo-corrected reductions in A1C and FPG (Table 12). WELCHOL also reduced TC, LDL-C, Apo B, and non-HDL-C (Table 13). The mean percent change in serum LDL-C levels with WELCHOL compared to placebo was -16% among statin users and statin non-users; the median percent change in serum TG levels with WELCHOL compared to placebo was -2% among statin users and 10% among statin non-users. The mean change in body weight was -0.5 kg for WELCHOL and -0.3 kg for placebo.

Table 12
Glycemic Parameters in a 26-Week Placebo-Controlled Study of WELCHOL in Combination with Metformin in Patients with Type 2 Diabetes

	Total Patient Population		Metformin Alone		Metformin in Combination with Other Oral Anti-Diabetic Agents	
	WELCHOL 3.8 g/day	Placebo	WELCHOL 3.8 g/day	Placebo	WELCHOL 3.8 g/day	Placebo
A1C (%), Mean						
N	148	152	79	76	69	76
Baseline	8.1	8.1	8.2	8.2	8.1	8.0
Change from baseline[a]	-0.4	0.2	-0.4	0.0	-0.4	0.3
Treatment difference (p-value)	-0.5 (p<0.001)		-0.5 (p=0.002)		-0.6 (p<0.001)	
FPG (mg/dL), Mean						
N	149	152	79	76	70	76
Baseline	178	174	184	180	171	168
Change from baseline[a]	-3	11	-7	8	0	13
Treatment difference (p-value)	-14 (p=0.01)		-14 (p=0.07)		-14 (p=0.10)	

[a] Least-squares mean change calculated from an Analysis of Covariance model.
A1C = hemoglobin A1C, FPG = fasting plasma glucose

Table 13
Percent Change in Lipid Parameters in a 26-Week Placebo-Controlled Study of WELCHOL in Combination with Metformin in Patients with Type 2 Diabetes

Dose/Day	N[†]	TC	LDL-C	Apo B	HDL-C	Non-HDL-C	TG[a]
Total Patient Population							
WELCHOL 3.8 g	125	-4*	-12*	-4*	1	-6*	12
Placebo	126	3	4	4	0	5	7
Metformin Alone							
WELCHOL 3.8 g	66	-3	-9	-2	1	-4	15
Placebo	61	2	0	1	-2	4	8
Metformin in Combination with Other Oral Anti-diabetic Agents							
WELCHOL 3.8 g	59	-6*	-15*	-6*	1	-7*	8
Placebo	65	4	7	7	2	6	5

*p<0.001 for lipid parameters compared to placebo (this more stringent criterion for statistical significance accounts for multiplicity testing of the lipid parameters, which were secondary endpoints in the diabetes trials)
[a] Median % change from baseline.
[†]The number of patients with analyzable data, i.e., a baseline and post-treatment value (last-observation carried forward), varied slightly among different parameters. The N given represents the smallest number of patients included in the analysis for any parameter.

Add-on Combination Therapy with pioglitazone: WELCHOL 3.8 g/day or placebo was added to background anti-diabetic therapy in a 24-week trial of 562 patients already receiving treatment with pioglitazone alone (N=51) or pioglitazone in combination with other oral agents (N=511). Of these, most were on dual therapy with metformin (N=298) or triple therapy with metformin and a sulfonylurea (N=139). In combination with pioglitazone-based therapy, WELCHOL resulted in statistically significant reductions in A1C and FPG compared to placebo (Table 14). WELCHOL also reduced TC, LDL-C, Apo B, and non-HDL-C but increased serum TG (Table 15). The mean change in body weight was 0.8 kg for WELCHOL and 0.4 kg for placebo.

Table 14
Glycemic Parameters in a 24-Week Placebo-Controlled Study of WELCHOL in Combination with Pioglitazone Based Therapy in Patients with Type 2 Diabetes

	WELCHOL 3.8 g/day	Placebo
A1C (%), Mean		
N	271	276
Baseline	8.2	8.1
Change from baseline[a]	-0.34	-0.02
Treatment difference (p-value)	-0.32 (0.0001)	
FPG (mg/dL), Mean		
N	268	270
Baseline	155	157
Change from baseline[a]	-4.8	+9.9
Treatment difference (p-value)	-14.7 (<0.0001)	

[a] Least-squares mean change calculated from an Analysis of Covariance model.
A1C = hemoglobin A1C, FPG = fasting plasma glucose

Table 15
Percent Change in Lipid Parameters in a 24-Week Placebo-Controlled Study of WELCHOL in Combination with Pioglitazone Based Therapy in Patients with Type 2 Diabetes

Dose/Day	N[†]	TC	LDL-C	Apo B	HDL-C	Non-HDL-C	TG[a]
Total Patient Cohort							
WELCHOL 3.8 g	262	-3*	-9*	-5*	+3	-5*	+14*
Placebo	262	+3	+7	+4	+1	+5	+2

Add-on Combination Therapy with Sulfonylurea: WELCHOL 3.8 g/day or placebo was added to background anti-diabetic therapy in a 26-week trial of 460 patients already treated with sulfonylurea alone (N=156) or sulfonylurea in combination with other oral agents (N=304). A total of 72% of these patients were receiving at least half-maximal doses of sulfonylurea therapy. In combination with a sulfonylurea, WELCHOL resulted in statistically significant placebo-corrected reductions in A1C and FPG (Table 16). WELCHOL also reduced TC, LDL-C, Apo B, and non-HDL-C, but increased serum TG (Table 17). The mean percent change in serum LDL-C levels with WELCHOL compared to placebo was -18% among statin users and -15% among statin non-users; the median percent increase in serum TG with WELCHOL compared to placebo was 29% among statin users and 9% among statin non-users. The mean change in body weight was 0.0 kg for WELCHOL and -0.4 kg for placebo.

Table 16
Glycemic Parameters in a 26-Week Placebo-Controlled Study of WELCHOL in Combination with Sulfonylurea in Patients with Type 2 Diabetes

	Total Patient Population		Sulfonylurea Alone		Sulfonylurea in Combination with Other Oral Anti-diabetic Agents	
	WELCHOL 3.8 g/day	Placebo	WELCHOL 3.8 g/day	Placebo	WELCHOL 3.8 g/day	Placebo
A1C (%), Mean						
n	218	218	69	80	149	138
Baseline	8.2	8.3	8.2	8.4	8.2	8.3
Change from baseline[a]	-0.3	0.2	-0.3	0.5	-0.4	0.0
Treatment difference (p-value)	-0.5 (p<0.001)		-0.8 (p<0.001)		-0.4 (p<0.001)	
FPG (mg/dL), Mean						
n	218	217	70	80	148	137
Baseline	177	181	181	186	175	178
Change from baseline[a]	-4	10	3	15	-11	4
Treatment difference (p-value)	-14 (p=0.009)		-12 (p=0.18)		-14 (p=0.03)	

[a] Least-squares mean change calculated from an Analysis of Covariance model.
A1C = hemoglobin A1C, FPG = fasting plasma glucose

Table 17
Percent Change in Lipid Parameters in a 26-Week Placebo-Controlled Study of WELCHOL in Combination with Sulfonylurea in Patients with Type 2 Diabetes

Dose/Day	N[†]	TC	LDL-C	Apo B	HDL-C	Non-HDL-C	TG[a]
Total Patient Population							
WELCHOL 3.8 g	186	-5*	-16*	-6*	1	-6*	20*
Placebo	193	0	1	1	0	1	1
Sulfonylurea Alone							
WELCHOL 3.8 g	57	-5	-14*	-5	-1	-6	17
Placebo	68	0	1	1	1	0	-1
Sulfonylurea in Combination with Other Oral Anti-diabetic Agents							
WELCHOL 3.8 g	129	-5	-18*	-7*	1	-6	21*
Placebo	125	0	0	1	0	1	2

*p<0.001 for lipid parameters compared to placebo (this more stringent criterion for statistical significance accounts for multiplicity testing of the lipid parameters, which were secondary endpoints in the diabetes trials)
[a] Median % change from baseline.
[†] The number of patients with analyzable data, i.e., a baseline and post-treatment value (last-observation carried forward), varied slightly among different parameters. The N given represents the smallest number of patients included in the analysis for any parameter.

Add-on Combination Therapy with Insulin: WELCHOL 3.8 g/day or placebo was added to background anti-diabetic therapy in a 16-week trial of 287 patients already treated with insulin alone (N=116) or insulin in combination with oral agents (N=171). At baseline, the median daily insulin dose was 70 units in the WELCHOL group and 65 units in the placebo group. In combination with insulin, WELCHOL resulted in a statistically significant placebo-corrected reduction in A1C (Table 18). WELCHOL also reduced LDL-C and Apo B, but increased serum TG (Table 19). The mean percent change in serum LDL-C levels with WELCHOL compared to placebo was -13% among statin users and statin non-users; the median percent increase in serum TG levels with WELCHOL compared to placebo was 24% among statin users and 17% among

statin non-users. The mean change in body weight was 0.6 kg for WELCHOL and 0.2 kg for placebo.

Table 18
Glycemic Parameters in a 16-Week Placebo-Controlled Study of WELCHOL in Combination with Insulin in Patients with Type 2 Diabetes

	Total Patient Population		Insulin Alone		Insulin in Combination with Oral Anti-diabetic Agents	
	WELCHOL 3.8 g/day	Placebo	WELCHOL 3.8 g/day	Placebo	WELCHOL 3.8 g/day	Placebo
A1C (%), Mean						
n	144	136	54	55	90	81
Baseline	8.3	8.2	8.2	8.3	8.3	8.2
Change from baseline[a]	-0.4	0.1	-0.4	0.2	-0.4	0.0
Treatment difference (p-value)	-0.5 (p<0.001)		-0.6 (p<0.001)		-0.4 (p<0.001)	
FPG (mg/dL), Mean						
n	144	136	54	55	90	81
Baseline	165	151	165	163	165	143
Change from baseline[a]	2	16	8	17	-4	14
Treatment difference (p-value)	-15 (p=0.08)		-9 (p=0.51)		-18 (p=0.09)	

[a] Least-squares mean change calculated from an Analysis of Covariance model.
A1C = hemoglobin A1C, FPG = fasting plasma glucose

Table 19
Percent Change in Lipid Parameters in a 16-Week Placebo-Controlled Study of WELCHOL in Combination with Insulin in Patients with Type 2 Diabetes

Dose/Day	N[†]	TC	LDL-C	Apo B	HDL-C	Non-HDL-C	TG[a]
Total Patient Cohort							
WELCHOL 3.8 g	129	-3	-12*	-4	-1	-3	23*
Placebo	121	1	1	1	0	1	0
Insulin Alone							
WELCHOL 3.8 g	46	-3	-12	-5	0	-3	19
Placebo	48	2	4	2	3	2	-2
Insulin in Combination with Oral Anti-diabetic Agents							
WELCHOL 3.8 g	83	-4	-13	-4	-1	-3	25*
Placebo	73	-1	-3	0	-1	-1	2

*p<0.001 for lipid parameters compared to placebo (this more stringent criterion for statistical significance accounts for multiplicity testing of the lipid parameters, which were secondary endpoints in the diabetes trials)
[a] Median % change from baseline.
[†] The number of patients with analyzable data, i.e., a baseline and post-treatment value (last-observation carried forward), varied slightly among different parameters. The N given represents the smallest number of patients included in the analysis for any parameter.

16 HOW SUPPLIED/STORAGE AND HANDLING

WELCHOL (colesevelam hydrochloride) Tablets, 625 mg, are supplied as an off-white, solid tablet imprinted with the word "Sankyo" and "C01" on one side. WELCHOL tablets are available as follows:

- Bottles of 180 - NDC 65597-701-18

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Brief exposure to 40°C (104°F) does not adversely affect the product. Protect from moisture.

WELCHOL (colesevelam hydrochloride) for Oral Suspension is a white to pale yellow powder containing yellow granules. WELCHOL for Oral Suspension is available as follows:

- 3.75 gram single-dose packet
  Cartons of 30 packets – NDC 65597-902-30

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Protect from moisture.

17 PATIENT COUNSELING INFORMATION

Dosing: WELCHOL Tablets: Patients should be advised to take WELCHOL Tablets with a meal and liquid. WELCHOL Tablets can be taken as 6 tablets once daily or 3 tablets twice daily. *[See Dosage and Administration (2)]*.

WELCHOL for Oral Suspension: Patients should be advised to take WELCHOL for Oral Suspension as one 3.75 gram packet once daily. To prepare, empty the entire contents of one packet into a glass or cup. Add 1 cup (8 ounces) of water, fruit juice, or diet soft drinks. 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. Always mix WELCHOL for Oral Suspension with water, fruit juice, or diet soft drinks before ingesting *[See Dosage and Administration (2)]*.

Drug interactions: Drugs with a known interaction with colesevelam (e.g., cyclosporine, glimepiride, glipizide, glyburide, levothyroxine, olmesartan medoxomil, oral contraceptives) should be administered at least 4 hours prior to WELCHOL. In an *in vivo* drug interaction study, there was no significant effect on the bioavailability of phenytoin; however, due to its narrow therapeutic index and post-marketing reports consistent with potential drug-drug interactions, phenytoin should be administered at least 4 hours prior to WELCHOL. Drugs that have not been tested for interaction with colesevelam, especially those with a narrow therapeutic index, should also be administered at least 4 hours prior to WELCHOL. Alternatively the physician should monitor blood levels of the coadministered drug. Patients receiving concomitant metformin ER and colesevelam should be monitored for clinical response as is usual for the use of anti-diabetes drugs *[See Drug Interactions (7)]*.

Gastrointestinal: WELCHOL can cause constipation. WELCHOL is contraindicated in patients with a history of bowel obstruction. WELCHOL is not recommended in patients who may be at risk of bowel obstruction, including patients with gastroparesis, other gastrointestinal motility disorders, or a history of major gastrointestinal surgery. Patients should be instructed to consume a diet that promotes bowel regularity. Patients should be instructed to promptly

discontinue WELCHOL and seek medical attention if severe abdominal pain or severe constipation occurs. Because of the tablet size, WELCHOL Tablets can cause dysphagia or esophageal obstruction and should be used with caution in patients with dysphagia or swallowing disorders. To avoid esophageal distress, WELCHOL for Oral Suspension should not be taken in its dry form. Always mix WELCHOL for Oral Suspension with water, fruit juice, or diet soft drinks before ingesting *[See Warnings and Precautions (5.4)]*.

Hypertriglyceridemia and pancreatitis: Patients should be instructed to discontinue WELCHOL and seek prompt medical attention if the hallmark symptoms of acute pancreatitis occur (e.g., severe abdominal pain with or without nausea and vomiting) *[See Warnings and Precautions (5.2)]*.

17.1 Primary Hyperlipidemia:

Patients should be advised to adhere to their National Cholesterol Education Program (NCEP)-recommended diet.

17.2 Type 2 Diabetes Mellitus:

General: Patients should be advised that it is important to adhere to dietary instructions, a regular exercise program, and regular testing of blood glucose.

Hypertriglyceridemia and cardiovascular disease: Patients should be informed that WELCHOL may increase serum triglyceride concentrations and that the long-term effect of hypertriglyceridemia on the risk of coronary artery disease is uncertain *[See Warnings and Precautions (5.2)]*.

17.3 Females of Reproductive Potential:

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

Marketed by: Daiichi Sankyo, Inc.
Basking Ridge, New Jersey 07920

Active Ingredient: Product of Austria

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