A Supplement to
Family Practice News® and
Internal Medicine News®

CASE STUDIES
COMPENDIUM

Featuring:

Management Decisions in an Adult Comorbid Patient With Type 2 Diabetes Having Primary Hyperlipidemia

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Colesevelam Hydrochloride for Management of a Patient With Type 2 Diabetes Mellitus and Hyperlipidemia

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Drs Handelsman and **Jones** are paid consultants for Daiichi Sankyo, Inc. Please refer to the full disclosure at the end of this compendium.

Management Decisions in an Adult Comorbid Patient With Type 2 Diabetes Having Primary Hyperlipidemia

Key Point: Type 2 diabetes mellitus (T2DM) and primary hyperlipidemia are risk factors for cardiovascular disease (CVD) that warrant timely management of both disorders. An option for treating T2DM and primary hyperlipidemia is Welchol® (colesevelam HCl)*, which represents an effective and safe way to treat patients with elevated glycosylated hemoglobin (A1C) and low-density lipoprotein cholesterol (LDL-C).

Nancy† is a 60-year-old Caucasian woman who works in a corporate office. She has a sedentary job as an administrative assistant. Nancy has two grown children; her elderly mother moved in 3 months ago, and Nancy is now responsible for her care. Nancy is concerned about having to pay for extra medical expenses as her husband recently lost his job. Nancy has not seen her primary care physician (PCP) recently, but now goes for a 6-month follow-up visit. Her PCP had previously started Nancy on lifestyle modification (diet and exercise), metformin, and simvastatin.


Yehuda Handelsman, MD, FACP, FACE

Current Visit

Physical Exam

• Weight	175 lb
• Height	5 ft 4 in
• Body Mass Index (BMI)	30
• Blood Pressure	125/80 mm Hg

†Not an actual Welchol® patient.

Current Treatment Regimen

• Metformin	850 mg daily
• Simvastatin	40 mg daily
• Aspirin	81 mg daily

Health History

- Hyperlipidemia diagnosed 1 year ago
- T2DM diagnosed 1 year ago
- Former smoker (quit 2 years ago; was a 1 pack/day cigarette smoker)
- Diet: Reports that she tries to limit fat intake, has decreased consumption of high-sugar sweets to twice a week, and has wine with dinner on weekends
- Limited exercise mainly on weekends and walks associated with shopping
- Family history: Her mother has a history of CVD; her father, diagnosed with T2DM, died of a heart attack at 65 years of age

Laboratory Results

Laboratory Tests	Current Visit	Previous Visit
Glycated hemoglobin (A1C)	7.5%	7.30%
Fasting plasma glucose (FPG)	135 mg/dL	120 mg/dL
LDL-C	118 mg/dL	180 mg/dL
High-density lipoprotein (HDL)	47 mg/dL	49 mg/dL
Fasting triglyceride levels	182 mg/dL	205 mg/dL

***The effect of Welchol® on cardiovascular morbidity and mortality has not been determined.**

Please see Important Information about Welchol® on page 7.
Please see Brief Summary of Full Prescribing Information for Welchol® on page 8.

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Clinical Discussion

Clearly, Nancy's A1C and LDL-C levels have not improved enough since her last visit to her PCP. The American College of Cardiology Foundation (ACCF) and the American Diabetes Association (ADA) Consensus Statement states that a patient classified as having T2DM has a high risk for CVD: the stated goal is LDL-C <100 mg/dL, and a patient having at least one additional risk factor is at highest risk for CVD and has a stated goal LDL-C <70 mg/dL.[1] Nancy's A1C level has increased to 7.5% despite starting on metformin; the ADA and the American Association of Clinical Endocrinologists/American College of Endocrinology (AACE/ACE) have recommended goals for A1C as <7% and ≤6.5%, respectively; both societies recommend goals for A1C as close to normal as possible and the need to individualize to minimize risk of hypoglycemia.[2,3] Nancy's LDL-C levels have improved, but are still too high at 118 mg/dL. Her HDL cholesterol level is 47 mg/dL, and her fasting triglycerides are 182 mg/dL. She is obese with a BMI of 30.0; her FBG level increased to 135 mg/dL. Nancy's PCP increases her metformin to 1000 mg twice a day, and her simvastatin to 80 mg/day.

Three Months Later

Three months later on this regimen, Nancy's A1C level is at 7.1%, her LDL-C is now at 108 mg/dL, and her triglycerides are at 180 mg/dL. Nancy's current weight is 165 pounds, and her BMI has gone down to 28.3. Given the fact that her glucose and lipid levels are still not at goal, a consultation with an endocrinologist is made.

Endocrinologist Consultation

The endocrinologist considers how to intensify Nancy's treatment as she is not at goal for her lipid and glucose levels. Nancy is already at the upper limit of the recommended dosage for simvastatin, so going beyond 80 mg is not an option; neither is increasing the dose of metformin. Nancy would like to keep the cost of any new medications to a minimum. The endocrinologist considers adding glimepiride, which would be cost-effective. However, with an A1C of 7.1%, she is at risk for hypoglycemia. Adding a dipeptidyl peptidase IV (DPP-IV) inhibitor and Zetia® (ezetimibe) could help improve both glucose and LDL-C levels with low risk of hypoglycemia; however, it would require two expensive co-pays imposed by her health plan to obtain these branded medications*. The endocrinologist reviews the risk-benefit ratio of these agents, with minimal potential of inducing hypoglycemia and liver effect, with Nancy. However, Nancy tells him that she cannot pay for two brand medications. After further consideration, the endocrinologist recommends that Nancy consider taking one drug that could reduce both her A1C and LDL-C levels. He explains that Welchol® (colesevelam HCl) reduced both A1C and LDL-C in clinical studies, and there was no significant increase in body weight. He explains to Nancy that Welchol® may lower both her LDL-C and her A1C without being systemically absorbed, and she will only have to pay one branded co-pay. Nancy was given the choice of the two approved Welchol® formulations, 6 tablets that she can take all at once, or as 3 tablets twice daily, or she can take the once daily Welchol® for Oral Suspension, which is mixed with 4-8 ounces of water.

There are several good reasons for prescribing Welchol® in Nancy's case. Her hyperglycemia and primary hyperlipidemia are still not under control after 1 year of therapy. She is concerned

Table. Suggested Treatment Goals in Patients With CMR and Lipoprotein Abnormalities[1]

	Goals		
	LDL cholesterol (mg/dL)	Non-HDL cholesterol (mg/dL)	ApoB (mg/dL)
Highest-risk patients, including those with 1) known CVD or 2) diabetes plus one or more additional major CVD risk factors*	<70	<100	<80
High-risk patients, including those with 1) no diabetes or known clinical CVD but two or more additional major CVD risk factors or 2) diabetes, but no other major CVD risk factors*	<100	<130	<90

*Other major risk factors (beyond dyslipoproteinemia) include smoking, hypertension, and family history of premature CAD.
ApoB=Apolipoprotein B; CAD=coronary artery disease; CMR=cardiometabolic risk; CVD=cardiovascular disease.
Reprinted with permission from *Diabetes Care*. 2008:31:811-822.

*Cost data do not demonstrate clinical significance or that one product is safer or more effective than another.

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about controlling her CVD risk, but she is worried about accruing more copays than is necessary. She is pleased to hear that the safety of Welchol® (colesevelam HCl) has been established through an extensive clinical trial program; for more than 9 years, it has been an approved treatment option for patients with high LDL-C levels, and it is available in a formulation for oral suspension. Nancy's endocrinologist informs her PCP of the change he has made and returns her to his care for follow-up and long-term management.

Three Months After the Endocrinology Consultation

Three months later, Nancy's laboratory values show she is now closer to goal (see testing results below), and therapy will continue.

- LDL-C 91 mg/dL
- Triglycerides 192 mg/dL
- A1C 6.6%

Comment

Risk factors for T2DM and CVD often cluster and include obesity, insulin resistance, hyperglycemia, dyslipidemia, and hypertension.[1] The AACE/ACE Consensus Statement and the ADA guidelines for T2DM agree that intervention should be early, intensive, and stringently focused on maintaining glycemic levels as close as possible to the nondiabetic range without causing side effects.[2,3] Setting individual goals for A1C levels in patients is dependent on a number of factors, including family history, presenting symptoms, age, comorbidities, and duration of disease.[1] A consensus statement from the ADA and the ACCF (**Table** on page 2) recommends treatment goals for lipid levels in patients with cardiometabolic risk (CMR).[1]

New Treatment Regimen With Add-On Therapy

Welchol® is indicated as an adjunct to diet and exercise to reduce elevated LDL-C in patients with primary hyperlipidemia as monotherapy, or in combination with a statin. Welchol® is also indicated as an adjunct to diet and exercise to improve glycemic control in adults with T2DM (not studied as monotherapy).[4] Welchol® has been used as an oral tablet since its approval in 2000. The most recent formulation, and the one prescribed for Nancy, is Welchol® for Oral Suspension taken once a day mixed with 4-8 oz of water. Adverse events reported in ≥2% of patients in clinical trials with Welchol® were constipation, nasopharyngitis, dyspepsia, hypoglycemia, nausea, and hypertension. Welchol® is not systemically absorbed and is the only agent currently approved by the US Food and Drug Administration for treating both primary hyperlipidemia and hyperglycemia in adult patients with T2DM.

The safety and efficacy of Welchol® in reducing A1C and LDL-C levels have been demonstrated in clinical trials in combination with a sulfonylurea, metformin, and insulin.[5-7] Patients in the metformin study had significant reductions in A1C (-0.54%; $p<0.001$). Welchol® also reduced mean LDL-C. Welchol® should not be used in patients with bowel obstruction, those with serum triglyceride (TG) concentrations of >500 mg/dL, or with a history of hypertriglyceridemia-induced pancreatitis. While not seen in the metformin study, TG levels significantly increased in patients taking insulin or a sulfonylurea. TG levels should be monitored.

Treatment Goals for Nancy

- Continue lower calorie diet for further weight loss
- Increased physical activity
- Consultation with her diabetes educator on a regular basis

Conclusion

Welchol® is a safe and effective add-on therapy to metformin and simvastatin, when A1C and LDL-C levels are not at recommended goals.

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Please see Important Information about Welchol® on page 7.
Please see Brief Summary of Full Prescribing Information for Welchol® on page 8.

Colesevelam Hydrochloride for Management of a Patient With Type 2 Diabetes Mellitus and Primary Hyperlipidemia

Key Point: Welchol® (colesevelam hydrochloride) is indicated for lowering hemoglobin A1C in adult patients with type 2 diabetes mellitus (T2DM) and lowering low-density lipoprotein-cholesterol (LDL-C) in patients with primary hyperlipidemia. This is an important add-on choice for patients with elevated A1C and LDL-C as it provides an option to treat both disorders with one medication. The effect of Welchol® on cardiovascular morbidity and mortality has not been determined.

Alice† is a 63-year-old Caucasian woman who works at her local hospital as a case manager. She presents to her primary care physician (PCP) 7 months after her last visit. Her PCP has the latest reports from her cardiologist to keep him updated on her cardiovascular health. She reports no exertional chest pain, and a recent stress echocardiogram showed normal wall motion with apical dyskinesis and an ejection fraction of 55%. Alice's PCP does a thorough workup to determine her overall health status.

Peter H. Jones, MD, FACP

Current Visit

Exam Findings

- Height 5 ft 4 in
- Weight 163 lb
- Body Mass Index (BMI) 29 kg/m^2
- Waist 35 in
- Blood Pressure (BP) 126/76 mm Hg
- Heart Rate 68 beats per minute (BPM)
- Cardiac exam Normal
- Peripheral pulses Normal and no edema

Current Treatment Regimen

- Atorvastatin 10 mg daily (2004)
- Aspirin 81 mg daily (2007)
- Lisinopril‡ 10 mg daily (2007)
- Metformin 1000 mg at bedtime (2008)
- Low fat diet
- Exercise for 20 minutes 3 times per week

Health History

- Myocardial infarction 2 years ago
- T2DM diagnosed 1 year ago
- Dyslipidemia diagnosed 5 years ago
- A family history of T2DM and coronary heart disease (CHD)

Laboratory Results

	Last Visit (7 months ago)	Current Visit
Glycated hemoglobin (A1C)	6.6%	7.1%↑
Fasting plasma glucose (FPG)	115 mg/dL	125↑
Low-density lipoprotein-cholesterol (LDL-C)	97 mg/dL	100↑
High-density lipoprotein-cholesterol (HDL-C)	45 mg/dL	45
Triglycerides (TG)	210 mg/dL	215↑
Total cholesterol (C)	184 mg/dL	188↑
Non-high-density lipoprotein-cholesterol (non-HDL-C)	142 mg/dL	151↑
Aspartate aminotransferase/alanine aminotransferase (AST/ALT)	WNL	WNL

WNL=within normal limits.

Clinical Discussion

Alice's outstanding health issues are her rise in A1C and LDL-C levels since her last visit to her PCP 7 months ago. Alice's A1C level has gone up from 6.6% to 7.1% despite her treatment with metformin for 1 year, and she has a rise in her LDL-C level. The recommended LDL-C goal by the American Diabetes Association/National Cholesterol Educational Program Adult Treatment Panel III/American College of Cardiology Foundation (ADA/NCEP ATP III/ACCF) consensus statement is <70 mg/dL for an individual with high cardiometabolic risk (CMR)[1]; Alice's LDL-C level of 108 mg/dL is not consistent with current National Cholesterol Educational Program Adult Treatment Panel III (NCEP ATP III) guidelines for patients at high risk of CHD.[2] Alice followed a regimen of diet, exercise, and weight loss, but she feels a recent family trip to Italy lessened her resolve to stick to her regimen; she is still overweight with a BMI of 29 kg/m^2.

A review of Alice's current treatment regimen shows that she was first placed on

†Not an actual Welchol® patient.
‡Welchol® has not been studied with lisinopril.

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atorvastatin (20 mg daily) in 2004 for dyslipidemia. After Alice had a myocardial infarction in 2007, she was started on low dose aspirin (81 mg daily), and lisinopril (10 mg daily) was added to lower her blood pressure. Most recently, metformin (1000 mg at bedtime) was added in 2008. Metformin is the first-line drug for the treatment of T2DM, particularly in overweight people; it is the most commonly prescribed oral antidiabetes agent.[3,4]

Since Alice is in the highest risk category for CHD and is not at goal for LDL-C or A1C levels, her PCP returns her to the cardiologist to further manage her care.

Cardiologist Visit

First and foremost, Alice's cardiologist wants to reduce Alice's LDL-C and A1C levels to goal. According to the NCEP ATP III guidelines, a LDL-C goal <70 mg/dL and a non-HDL-C goal <100 mg/dL are preferred recommendations for a patient such as Alice.[5] The American Heart Association and the American College of Cardiology (AHA/ACC) guidelines for secondary prevention state that these goals are reasonable, rather than optional, targets.[6]

Because of these guidelines, the cardiologist wants to further reduce Alice's LDL-C level. After careful consideration, the cardiologist decides that the best option is to switch Alice's treatment plan from atorvastatin 10 mg/day to atorvastin 40 mg/day to achieve at least an additional 12%-14% reduction in her LDL-C level.[7] He also decides to add Welchol® (colesevelam HCl) 3.75 gm/day because he would like to reduce her LDL-C level by another 15%-20%, as well as reducing her A1C level by an additional 0.5%.[8-10]

The cardiologist could have considered other options, such as switching Alice to rosuvastatin 20 mg/day and/or adding ezetimibe (to reduce her LDL-C level), increasing her metformin dosage to 2000 mg/day, and/or considering the addition of a dipeptidyl peptidase IV (DPP-IV) inhibitor (to reduce her A1C level); none of these options would provide the dual benefits of reducing both her LDL-C and A1C levels with one agent. In addition, prescribing Welchol® would eliminate a branded co-pay for an additional drug. Welchol® is available as 625 mg tablets; she can take 6 all at once, 3 tablets twice daily, or a once-daily Welchol® Oral Suspension, which can be mixed with 4-8 ounces of water. Alice decides to take the oral suspension as she has difficulty swallowing tablets.

Three Months After Visiting the Cardiologist

Three months later, Alice's laboratory values demonstrate a marked improvement in her cholesterol and glucose levels:

- LDL-C 69 mg/dL ↓
- HDL-C 47 mg/dL ↑
- Non-HDL-C 120 mg/dL ↓
- A1C 6.6% ↓

Add-On Therapy With Welchol® for Patients With T2DM and CHD

The addition of a bile acid sequestrant (BAS) to a statin has long been recognized as a safe and effective way to lower LDL-C levels by an additional 20% to 25%. A clinical trial by Hunninghake and colleagues demonstrated that adding colesevelam hydro-chloride 3.8 g to atorvastatin 10 mg resulted in a 48% mean reduction from baseline in LDL-C level, with demonstrated safety and tolerability.[11] T2DM was not an inclusion criterion for this study.

Welchol® is the only BAS that is indicated as an adjunct to diet and exercise to reduce LDL-C and improve glycemic control in adults with T2DM.[12] Welchol® was originally approved in the United States in 2000 as a cholesterol-lowering agent; the US Food and Drug Administration approved Welchol® for use in the treatment of T2DM in 2008. Three pivotal clinical trials were the foundation for the approval of Welchol® as add-on therapy with other antidiabetes medications, including a combination with metformin, a sulfonylurea, or an insulin-based regimen. The baseline levels of A1C in these trials were in the range of 7.5% to 9.5%.[8-10] Welchol® was shown to consistently reduce A1C levels in these studies by a mean treatment difference of 0.5% versus placebo, irrespective of the background T2DM treatment regimen. Adverse events reported in ≥ 2% of patients in clinical trials with Welchol® were constipation, nasopharyngitis, dyspepsia, hypoglycemia, nausea, and hypertension. Welchol® should not be used in patients with bowel obstruction, those with serum triglyceride (TG) concentrations of >500 mg/dL, or with a history of hypertriglyceridemia-induced pancreatitis. While not seen in the metformin study, TG levels significantly increased in patients on insulin or a sulfonylurea. TG levels should be monitored.

In Alice's case, the addition of Welchol® to atorvastin resulted in a 31% reduction over her previous LDL-C level; additionally, Alice had a 0.5% reduction in her A1C level. Welchol® was well tolerated, and Alice did not experience weight gain.

Treatment Goals for Alice

- Compliance with medications
- Continued weight loss
- Consultation with a certified diabetes educator on a more frequent basis
- Practice home glucose monitoring
- More frequent visits with PCP

Conclusion

Based on clinical studies, Welchol® is a safe and effective add-on therapy for adult patients with T2DM who are not at their recommended A1C and LDL-C levels.

As featured in the March 2010 issue of Family Practice News *and* Internal Medicine News.

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IMPORTANT INFORMATION ABOUT WELCHOL® (colesevelam HCl)

Indications

Welchol is indicated as an adjunct to diet and exercise to:

-reduce elevated low-density lipoprotein cholesterol (LDL-C) in patients with primary hyperlipidemia (Fredrickson Type IIa) as monotherapy or in combination with an hydroxymethylglutaryl-coenzyme (HMG CoA) reductase inhibitor

-improve glycemic control in adults with type 2 diabetes mellitus

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 as monotherapy or in combination with a dipeptidyl peptidase 4 inhibitor and has not been extensively studied in combination with thiazolidinediones

-Welchol has not been studied in Fredrickson Type I, III, IV, and V dyslipidemias

Contraindications

Welchol is contraindicated in individuals with bowel obstruction, those with serum triglyceride (TG) concentrations of >500 mg/dL, or with a history of hypertriglyceridemia-induced pancreatitis.

Warnings and Precautions

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

Welchol can increase serum TG concentrations particularly when used in combination with sulfonylureas or insulin. Caution should be exercised when treating patients with TG levels >300 mg/dL.

Welchol may decrease the absorption of fat-soluble vitamins A, D, E and K. Patients on vitamin supplements should take their vitamins at least 4 hours prior to Welchol. Caution should be exercised when treating patients with a susceptibility to vitamin K or fat-soluble vitamin deficiencies.

Caution should also be exercised when treating patients with gastroparesis, gastrointestinal motility disorders, major gastrointestinal tract surgery, and when treating patients with dysphagia and swallowing disorders. Welchol reduces gastrointestinal absorption of some drugs.

Drugs with a known interaction with colesevelam (glyburide, levothyroxine, and oral contraceptives [ethinyl estradiol, norethindrone]) 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.

To avoid esophageal distress, Welchol for Oral Suspension should not be taken in its dry form.

Due to tablet size, Welchol for Oral Suspension is recommended for, but not limited to, any patient who has difficulty swallowing tablets.

Phenylketonurics: Welchol for Oral Suspension contains 48 mg phenylalanine per 3.75 gram packet.

Adverse Reactions

In clinical trials, the adverse reactions observed in ≥ 2% of patients – and more commonly with Welchol than placebo – regardless of investigator assessment of causality seen in:

-Adults with Primary Hyperlipidemia were: constipation (11.0% vs 7.0%), dyspepsia (8.3% vs 3.5%), nausea (4.2% vs 3.9%), accidental injury (3.7% vs 2.7%), asthenia (3.6% vs 1.9%), pharyngitis (3.2% vs 1.9%), flu syndrome (3.2% vs 3.1%), rhinitis (3.2% vs 3.1%) and myalgia (2.1% vs 0.4%)

-Adult patients with Type 2 Diabetes were: constipation (8.7% vs 2.0%), nasopharyngitis (4.1% vs 3.6%) dyspepsia (3.9% vs 1.4%), hypoglycemia (3.0% vs 2.3%), nausea (3.0% vs 1.4%) and hypertension (2.8% vs 1.6%)

Post-marketing experience: Due to the voluntary nature of these reports it is not possible to reliably estimate frequency or establish a causal relationship:

-Increased seizure activity or decreased phenytoin levels have been reported in patients receiving phenytoin concomitantly with Welchol.

-Reduced International Normalized Ratio (INR) has been reported in patients receiving warfarin concomitantly with Welchol.

-Elevated thyroid-stimulating hormone (TSH) has been reported in patients receiving thyroid hormone replacement therapy.

Pregnancy

Welchol is Pregnancy Category B.

WELCHOL

(colesevelam hydrochloride)

Initial U.S. Approval: 2000

BRIEF SUMMARY: See package insert for 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 an 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 the full prescribing information]*.

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) in the full prescribing information]*.

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 as monotherapy or in combination with a dipeptidyl peptidase 4 inhibitor and has not been extensively studied in combination with thiazolidinediones.
- 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.

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 the full prescribing information]*.

In clinical trials in patients with type 2 diabetes, greater increases in TG levels occurred when WELCHOL was used in combination with sulfonylureas (median increase 18% compared to placebo in combination with sulfonylureas) and when WELCHOL was used in combination with insulin (median increase 22% compared to placebo in combination with insulin) *[See Adverse Reactions (6.1) and Clinical Studies (14.2) in the full prescribing information]*. 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 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) in the full prescribing information]*.

5.6 Phenylketonurics

WELCHOL for Oral Suspension contains 24 mg phenylalanine per 1.875 gram packet and 48 mg phenylalanine per 3.75 gram packet *[See Description (11) in the full prescribing information]*.

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.

In the lipid-lowering trials, 807 adult patients received at least one dose of WELCHOL (total exposure 199 patient-years). In the type 2 diabetes trials, 566 patients received at least one dose of WELCHOL (total exposure 209 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. In clinical trials of type 2 diabetes, 60% of patients receiving WELCHOL vs. 56% of patients receiving placebo reported an adverse reaction.

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.

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) in the full prescribing information]*.

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) in the full prescribing information]*.

Type 2 Diabetes Mellitus: The safety of WELCHOL in patients with type 2 diabetes mellitus was evaluated in 4 double-blind, 12-26 week, placebo-controlled clinical trials. These trials involved 1128 patients (566 patients on WELCHOL; 562 patients on placebo) with inadequate glycemic control on metformin, sulfonylurea, or insulin when these agents were used alone or in combination with other anti-diabetic agents. Upon completion of the pivotal trials, 492 patients entered a 52-week open-label uncontrolled extension study during which all patients received WELCHOL 3.8 g/day while continuing background treatment with metformin, sulfonylurea, or insulin alone or in combination with other anti-diabetic agents.

A total of 6.7% of WELCHOL-treated patients and 3.2% 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 pivotal trials discontinued due to body rash and mouth blistering that occurred after the first dose of WELCHOL, which may represent a hypersensitivity reaction to WELCHOL.

Table 3
Placebo-Controlled Clinical Studies of WELCHOL Add-on Combination Therapy with Metformin, Insulin, Sulfonylureas: 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 = 566	Placebo N = 562
Constipation	49 (8.7)	11 (2.0)
Nasopharyngitis	23 (4.1)	20 (3.6)
Dyspepsia	22 (3.9)	8 (1.4)
Hypoglycemia	17 (3.0)	13 (2.3)
Nausea	17 (3.0)	8 (1.4)
Hypertension	16 (2.8)	9 (1.6)

Hypertriglyceridemia: Patients with fasting serum TG levels above 500 mg/dL were excluded from the diabetes clinical trials. In the phase 3 diabetes trials, 637 (63%) patients had baseline fasting serum TG levels less than 200 mg/dL, 261 (25%) had baseline fasting serum TG levels between 200 and 300 mg/dL, 111 (11%) had baseline fasting serum TG levels between 300 and 500 mg/dL, and 9 (1%) had fasting serum TG levels greater than or equal to 500 mg/dL. The median baseline fasting TG concentration for the study population was 172 mg/dL; the median post-treatment fasting TG was 195 mg/dL in the WELCHOL group and 177 mg/dL in the placebo group. WELCHOL therapy resulted in a median placebo-corrected increase in serum TG of 5% (p=0.22), 22% (p<0.001), and 18% (p<0.001) when added to metformin, insulin and sulfonylureas, respectively *[See Warnings and Precautions (5.2) and Clinical Studies (14.2) in the full prescribing information]*. 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) in the full prescribing information]*.

Treatment-emergent fasting TG concentrations ≥500 mg/dL occurred in 4.1% of WELCHOL-treated patients compared to 2.0% of placebo-treated patients. Among these patients, the TG concentrations with WELCHOL (median 604 mg/dL; interquartile range 538-712 mg/dL) were similar to that observed with placebo (median 644 mg/dL; interquartile range 574-724 mg/dL). Two (0.4%) patients on WELCHOL and 2 (0.4%) 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 3% (17/566) in the WELCHOL group and 2% (10/562) 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.

Hypoglycemia: Adverse events of hypoglycemia were reported based on the clinical judgment of the blinded investigators and did not require confirmation with fingerstick glucose testing. The overall reported incidence of hypoglycemia was 3.0% in patients treated with WELCHOL and 2.3% in patients treated with placebo. No WELCHOL treated patients developed severe hypoglycemia.

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 or *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[a]	Glyburide, levothyroxine, and oral contraceptives containing ethinyl estradiol and norethindrone
Drugs 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	cephalexin, ciprofloxacin, digoxin, warfarin[b], fenofibrate, lovastatin, metformin, metoprolol, pioglitazone, quinidine, repaglinide, valproic acid, verapamil

[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 Post-marketing Experience (6.2)]*

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 postmarketing 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 Post-marketing Experience (6.2)]*

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B. There are no adequate and well-controlled studies of colesevelam use in pregnant women. Animal reproduction studies in rats and rabbits revealed no evidence of fetal harm. Requirements for vitamins and other nutrients are increased in pregnancy. However, the effect of colesevelam on the absorption of fat-soluble vitamins has not been studied in pregnant women. This drug should be used during pregnancy only if clearly needed.

In animal reproduction studies, colesevelam revealed no evidence of fetal harm when administered to rats and rabbits at doses 50 and 17 times the maximum human dose, respectively. Because animal reproduction studies are not always predictive of human response, this drug should be used in pregnancy only if clearly needed.

8.3 Nursing Mothers

Colesevelam hydrochloride is not expected to be excreted in human milk because colesevelam hydrochloride is not absorbed systemically from the gastrointestinal tract.

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) in the full prescribing information]*. 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 1128 patients enrolled in the four diabetes studies, 249 (22%) were ≥65 years old, and 12 (1%) 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 1128 patients enrolled in the four diabetes studies, 696 (62%) had mild renal insufficiency (creatinine clearance [CrCl] 50-<80 mL/min), 53 (5%) 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).

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.

17 PATIENT COUNSELING INFORMATION

Dosing: Patients should be advised to take WELCHOL Tablets with a meal and liquid. WELCHOL can be taken as 6 tablets once daily or 3 tablets twice daily. Patients should be advised to take WELCHOL for Oral Suspension as one 3.75 gram packet once daily or one 1.875 gram packet twice daily. To prepare, empty the entire contents of one packet into a glass or cup. Add ½ to 1 cup (4 to 8 ounces) of water. Stir well and drink. WELCHOL for Oral Suspension should be taken with meals. To avoid esophageal distress, WELCHOL for Oral Suspension should not be taken in its dry form. Always mix WELCHOL for Oral Suspension with water before ingesting. *[See Dosage and Administration (2) in the full prescribing information]*

Drug interactions: Drugs with a known interaction with colesevelam (e.g., glyburide, levothyroxine, oral contraceptives) 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 (e.g., phenytoin), should also be administered at least 4 hours prior to WELCHOL. Alternatively the physician should monitor blood levels of the coadministered drug. *[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 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 receiving a sulfonylurea or insulin 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)]*

Welchol™
(colesevelam HCl)

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Parsippany, New Jersey 07054

Active Ingredient: Product of Austria

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