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JOURNAL SCAN

SUMMARY OF KEY ARTICLES

An Approach to the Management of Type 2 Diabetes Mellitus in Patients Receiving Add-On Therapy With Colesevelam HCl

INTRODUCTION BY HAROLD E. BAYS, MD, FACP, FACE,[a] AND PETER H. JONES, MD[b]

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An Approach to the Management of Type 2 Diabetes Mellitus in Patients Receiving Add-On Therapy With Colesevelam HCl

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INTRODUCTION

An Approach to the Management of Type 2 Diabetes Mellitus in Patients Receiving Add-On Therapy With Colesevelam HCl

Introduction by Harold E. Bays, MD, FACP, FACE, and Peter H. Jones, MD

Colesevelam hydrochloride (HCl) is a bile acid sequestrant indicated alone or in combination with a statin, and as an adjunct to diet and exercise, for the reduction of elevated low-density lipoprotein-cholesterol (LDL-C) in patients with primary hypercholesterolemia. Bile acid sequestrants (BAS) augment cholesterol excretion via enhanced conversion to bile acids, increasing hepatic low-density lipoprotein (LDL) receptor removal of LDL particles, and thus act to lower LDL-C, especially when combined with other cholesterol-lowering agents.

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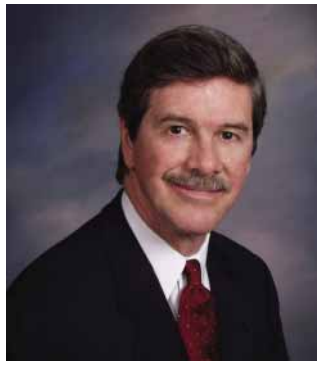

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The clinical trials reviewed in this journal define the road to the indication for colesevelam HCl as add-on therapy for type 2 diabetes mellitus (T2DM); colesevelam HCl is the only agent currently approved to reduce both hypercholesterolemia and hyperglycemia in patients not at treatment goal. However, the effect of colesevelam HCl on cardiovascular morbidity and mortality has not been determined. Colesevelam HCl, when added on to metformin, sulfonylurea, or insulin-based therapies further reduced glycosylated hemoglobin (A1C) levels approximately 0.5% and reduced LDL-C levels approximately 16%. Colesevelam HCl may be particularly useful in patients already being treated with an oral antidiabetes agent and a statin who have not yet achieved the desired A1C or LDL-C goal.

THE HISTORY OF BAS

BAS have a role in the management of dyslipidemia that dates back over 30 years. As a class, BAS have decades of clinical trial support in reducing hypercholesterolemia, and in reducing the risk for atherosclerotic coronary heart disease (CHD), especially in people at high risk for CHD, which includes those with T2DM.[1] Although less appreciated, data for over a decade have also supported BAS as effectively reducing glucose levels.[1] The improvements in both dyslipidemia and hyperglycemia are clinically important because a wealth of clinical experience has shown that improvements in lipid levels with drug therapy generally reduce macrovascular disease; concurrently, drugs that improve hyperglycemia generally reduce microvascular complications in patients with T2DM.[1]

T2DM is a well-known cardiovascular risk factor and a common cause of morbidity and mortality. Two major goals in treating diabetes mellitus include maintaining a level of A1C <7%, and achieving an LDL-C level of <100 mg/dL (or <70 mg/dL for patients at very high CHD risk)—if both goals can be achieved safely. However, the National Health and Nutrition Examination Survey (NHANES) suggest that only 37% of patients with T2DM achieve this goal, and Kennedy et al demonstrated that only 49.4% of patients with T2DM have LDL-C concentrations <100 mg/dL.[2,3]

When the Expert Panel of the National Cholesterol Education Program made its first recommendations in 1988, BAS were a first-line treatment for hypercholesterolemia because they were generally safe with long-term use, and because they reduced the risk for CHD.[4] The Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT) was a landmark study that demonstrated that reducing total cholesterol and LDL-C levels reduced CHD events.[5] The results of this 7-year trial were in concordance with epidemiologic studies, which at the time showed that elevated levels of cholesterol increased CHD risk, and that the relationship between total cholesterol and CHD was continuous, graded, and persistent regardless of other risk factors. The Cholesterol Treatment Trialists' Collaborators meta-analysis and epidemiologic studies suggested that for every 1% reduction in total cholesterol levels, there was a 2% reduction in the risk of CHD.[6]

BAS eventually lost their first-line status for treating hyperlipidemia because although generally safe, they were often poorly tolerated and had a high degree of clinically important drug interactions. Instead, statins became the treatment of choice for hypercholesterolemia because of their efficacy and safety derived from outcome trials. However, even with the advent of statin use, many patients at high risk for CHD are unable to achieve LDL-C treatment goals with statins alone, especially those patients with aggressive LDL-C treatment targets of <70 mg/dL. Overall, approximately 25% of patients with T2DM at high risk for cardiovascular disease require two or more lipid-lowering drugs at maximal dose to attain the <70 mg/dL goal. Tolerability and adherence often decrease due to enhanced adverse effects.[3] Nonetheless, combination use of statins with other lipid-altering drugs such as BAS is an effective therapeutic strategy to achieve lipid treatment goals in patients unable to achieve such goals with statins alone.[1]

THE ROLE OF BAS IN T2DM

For over a decade, controlled clinical trials have consistently demonstrated reductions in glucose and A1C levels in patients with T2DM (**Table 1**).[1,7] Specifically, in earlier clinical trials whose results were

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Table 1. Examples of Clinical Trials Evaluating the Effects of Bile Acid Sequestrants on Glucose Levels

Clinical Trial	Demographics	Duration	Intervention	Lipid Effect	Baseline HbA1c	Results at Study End†
Garg and Grundy (1994)	20 men and 1 woman with T2DM	Crossover study; 6 weeks for each period	Cholestyramine 16 g/day	LDL-C=-28% HDL-C=no change TG=+13.5%	Not reported	FPG=-13% GlyHb=-0.5% (NS)
Yamakawa et al (2007)	70 men and women with T2DM	3 months	Colestimide 6 g/day or pravastatin 10 mg/day	LDL-C=-23% HDL-C=-0.06% (NS) TG=+14% (NS)	7.70%	FPG=-8% HbA1C=-0.9%
Zieve, Kalin, Schwartz, et al (GLOWS) (2007)	65 men and women with T2DM	12 weeks	Colesevelam HCl 3.75 g/day‡	LDL-C=-11.7% HDL-C=-1.5% (NS) TG=+7.8% (NS)	7.90%	HbA1C=-0.5% FPG=-14 mg/dL (NS) PPG=-31.5 mg/dL

T2DM=type 2 diabetes mellitus; LDL-C=low-density lipoprotein cholesterol; HDL-C=high-density lipoprotein cholesterol; TG=triglycerides; FPG=fasting plasma glucose; GlyHb=glycated hemoglobin; NS=not a statistically significant change; PPG=2-hour postprandial glucose; GLOWS=Glucose-Lowering Effect of WelChol Study; OAD=oral antidiabetes drugs.
*Lipid and glucose values were colestimide-treated subjects compared with baseline.
†FPG values represent percent change in glucose levels; HbA1c values reduction in HbA1c percent.
‡In addition to other OAD.
Source: Bays and Goldberg.[1] Used with Permission.

reported between 1994 and 2007, BAS (including cholestyramine, colestimide, and colesevelam HCl) significantly improved both lipid and A1C levels in patients concurrently treated with a variety of glucose-lowering agents.[1] While only 155 patients were evaluated in these illustrative BAS trials (**Table 1**), the clear trend was BAS improved both lipid and glucose levels.[1]

The mechanism of action by which BAS lower glucose is unknown. The most probable explanation involves the farsenoid X receptors (FXR), given that bile acids are natural ligands for intestinal and hepatic FXR, and also that FXR "deactivation" by BAS may lead to increased liver X receptor (LXR) activity, which may lower glucose, lower LDL-C, and increase HDL-C, but raise triglyceride (TG) levels. These are lipid effects found with BAS treatment.[1] Another potential mechanism is that BAS increase bile acid synthesis and thus increase bile acid delivery into the intestine, which may increase incretins such as glucagon-like peptide-1 that may also reduce glucose levels.[1]

Three subsequent clinical trials reported in 2008 evaluated the glucose and lipid-lowering effects of colesevelam HCl, which is a specifically engineered bile acid sequestrant developed in the 1990s as a high-affinity, high-capacity bile acid-binding molecule.

THE DUAL ACTION OF COLESEVELAM HCL AS ADD-ON THERAPY FOR T2DM

Colesevelam HCl was first approved as a cholesterol-lowering drug in the United States in 2000 with the trade name of Welchol®.[1] In early monotherapy trials, six 625 mg tablets/day of colesevelam HCl reduced LDL-C levels by a mean of 15% to 21%, increased HDL-C levels by a mean of 3% to 9%, and increased TG levels by a mean of 2% to 16% over that of placebo.[1] Similar lipid effects were also observed in clinical trials involving colesevelam HCl combined with statins.

One of the preliminary studies demonstrating the glucose-lowering potential of colesevelam HCl in patients with T2DM was entitled the Glucose-Lowering Effect of WelChol Study (GLOWS).[8] GLOWS, a pilot study (n=65), demonstrated that colesevelam HCl produced improved glycemic control in patients with T2DM, resulting in a least squares (LS) mean reduction of -0.5% in A1C level compared with placebo (P=0.007). In this pilot study only, in patients with a higher baseline A1C level (≥8.0%), it was further demonstrated that colesevelam HCl reduced LS mean A1C level by 1% (P=0.002 vs placebo). This pilot study was the predecessor to the three clinical trials described below, which studied the efficacy and safety of colesevelam HCl as add-on therapy when combined with metformin,[9] a sulfonylurea,[10] and insulin-based[11] therapies in people with T2DM. The three trials described in this report were the foundation for approval by the US Food and Drug Administration (FDA) of colesevelam HCl for glycemic control (measured by A1C) in adults with T2DM in combination with metformin, sulfonylureas, or insulin, either alone or in combination with other antidiabetes agents. This made colesevelam HCl the first and only medication approved to reduce both A1C and LDL-C levels. Colesevelam HCl was added to the American College of Endocrinology/American Association of Clinical Endocrinologists (ACE/AACE) "Road Maps to Achieve Glycemic Control in Patients with Type 2 Diabetes Mellitus" as add-on therapy in 2008.[12]

These three double-blind, placebo-controlled, clinical trials studied the add-on efficacy of colesevelam HCl at 3.75 g/day in 1,064 patients with T2DM who had a baseline A1C level ranging from 8.2% to 8.3% (**Table 2**).[1] Patients maintained their preexisting, stable, antidiabetes drug regimens. The three trials demonstrated that colesevelam HCl resulted in a statistically significant reduction in LS mean A1C level (-0.50% to -0.54%) compared to placebo, regardless of the background therapy. In the metformin and sulfonylurea trials, treatment with colesevelam HCl also resulted in a statistically significant reduction of 13.9 mg/dL and 14.6 mg/dL, respectively, in fasting plasma glucose levels compared to placebo. Effects of colesevelam HCl on A1C levels across subgroups of age, gender, race, body mass index, and baseline A1C were consistent, and similar for the once-a-day or twice-a-day dosing regimens. Importantly, this reduction in A1C level occurred without a change in weight.

The LS mean percent change in LDL-C levels for all treatment regimens with colesevelam HCl were of similar magnitude to those observed in patients with primary hyperlipidemia, (ie, 2.8% to 16.7%). There were increases in TG levels in the studies of patients treated with insulin (21.5%) and patients treated with a sulfonylurea (17.7%), as compared with patients treated with metformin (4.7%). The clinical significance of these increases is unknown; however, colesevelam HCl is to be used with caution in patients with TG levels >300 mg/dL. Colesevelam HCl is contraindicated in patients with TG levels >500 mg/dL. Periodic monitoring of lipid parameters including TG and non-HDL-C is recommended.

Colesevelam HCl is generally well tolerated. Adverse experiences (irrespective of causality) reported in adult patients with T2DM during their participation in these clinical trials (colesevelam HCl vs placebo) consisted

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Table 2. Prospective Phase III Clinical Trials Investigating the Effects of Colesevelam HCl on Glucose Levels

Clinical Trial	Demographics of Total Study Participants	Duration	Intervention	Lipid Effect	Baseline HbA1c	Treatment Difference at Study End*
Bays et al (metformin +/- OAD)	316 men and women with T2DM	26 weeks	Colesevelam HCl 3.75 g/day†	LDL-C=–15.9% HDL-C=+0.9% (NS) TG=+4.7% (NS)	8.20%	HbA1C=–0.54% FPG=–13.9 mg/dL
Goldberg and Truitt (insulin +/- OAD)	287 men and women with T2DM	16 weeks	Colesevelam HCl 3.75 g/day‡	LDL-C=–12.8% HDL-C=–0.9% TG=+21.5% (NS)	8.30%	HbA1C=–0.50% FPG=–14.6 mg/dL (NS)
Fonseca et al (sulfonylurea +/- OAD)	461 men and women with T2DM	26 weeks	Colesevelam HCl 3.75 g/day§	LDL-C=–16.7% HDL-C=+0.1% TG=+17.7% (NS)	8.20%	HbA1C=–0.54% FPG=–13.5 mg/dL

T2DM=type 2 diabetes mellitus; LDL-C=low-density lipoprotein cholesterol; HDL-C=high-density lipoprotein cholesterol; TG=triglycerides; FPG=fasting plasma glucose; NS=not a statistically significant change; OAD=oral antidiabetes drugs.
*FPG values represent percent change in glucose levels; HbA1c values reduction in HbA1c percent.
†Study medication mean percent compliance was 93.3% in the colesevelam HCl group and 91.9% in the placebo group.
‡Study medication mean percent compliance was 92.7% in the colesevelam HCl group and 94.5% in the placebo group.
§Study medication mean percent compliance was 92.7% in the colesevelam HCl group and 90.8% in the placebo group.
Source: Bays and Goldberg.[1] Used with Permission.

of 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%). In summary, colesevelam HCl represents a lipid-altering drug that is not systemically absorbed and has demonstrated safety and efficacy. In light of these recent findings with colesevelam HCl, the authors have revisited the evidence supporting BAS as add-on therapy for the treatment of patients with T2DM, along with their established oral antidiabetes drug regimens. ■

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Results of the Glucose-Lowering Effect of WelChol Study (GLOWS): A Randomized, Double-Blind, Placebo-Controlled Pilot Study Evaluating the Effect of Colesevelam Hydrochloride on Glycemic Control in Subjects with Type 2 Diabetes

Key Point: This exploratory pilot study was the first to suggest that adding colesevelam HCl to ongoing oral antidiabetes drugs is associated with improved A1C levels and improved LDL-C control in patients with T2DM whose glucose levels were inadequately controlled on their current antidiabetes drug regimens.*

In clinical practice with current antidiabetes mellitus therapies, only a minority of patients with T2DM attain their recommended goals for glucose or lipid levels. The GLOWS was a proof-of-concept study to investigate the hypoglycemic effect of colesevelam HCl in patients with T2DM on current oral antidiabetes agents.

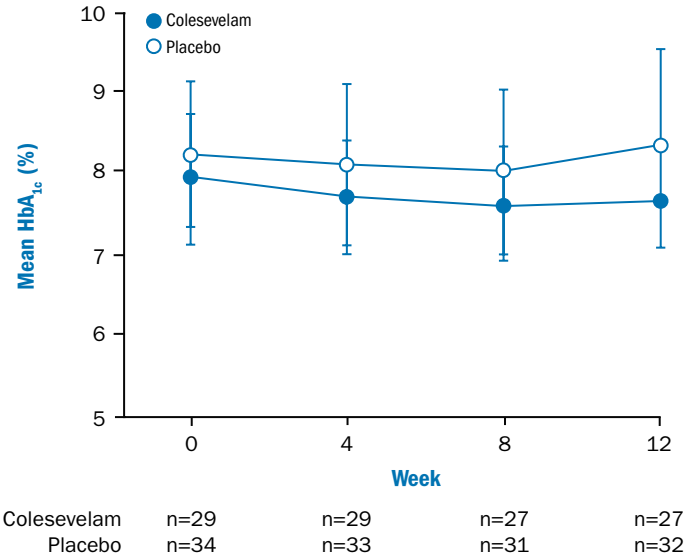
RESEARCH DESIGN AND METHODS

Sixty-five patients with T2DM treated with stable oral hypoglycemic drugs (sulfonylureas±metformin) received either colesevelam HCl at 3.75 g/day or matching placebo for 12 weeks; their A1C values after a 4-week run-in period were from 7.0% to 10.0%. The change in A1C from baseline to week 12 was the primary efficacy endpoint. Secondary endpoints included changes in fructosamine levels, fasting plasma glucose levels, postprandial glucose levels, and mean glucose response, as well as changes in lipid parameters from baseline to week 12. A post hoc analysis evaluated changes in A1C in patient subgroups with A1C values <8.0% and ≥8.0%, as well as changes in A1C levels in patients who were treated with sulfonylurea alone, metformin alone, or sulfonylurea plus metformin.

RESULTS

The difference in LS mean change in A1C between the colesevelam HCl group and the placebo group was -0.5% (P=0.007; A1C ≤8.0%). The time course of the change in mean A1C levels between colesevelam HCl and placebo was both statistically significant and clinically meaningful (**Figure 1**). In this study only, in subjects with a baseline A1C >8% (N=25; Welchol n=10; placebo n=15), the difference in LS mean change in A1C was -1.0% (P=0.002). Compared to placebo, colesevelam HCl significantly reduced LDL-C (11.7%) and apolipoprotein B (apo B) (P=0.003) levels. Constipation was noted more frequently with colesevelam HCl compared to placebo, but no significant differences were found in body weight or occurrences of hypoglycemia between treatment groups.

Figure 1. The Time Course of the Change in Mean A1C Levels



N=65
P=0.007
Source: Zieve et al.[8] Used with Permission.

CONCLUSIONS

Treatment with colesevelam HCl significantly reduced glucose and lipid levels in subjects with T2DM previously treated with sulfonylurea, metformin, or with a regimen containing a combination of both agents. ■

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*Based on Zieve FJ, Kalin MF, Schwartz SL, Jones MR, Bailey WL. Results of the glucose-lowering effect of WelChol study (GLOWS): A randomized, double-blind, placebo-controlled pilot study evaluating the effect of colesevelam hydrochloride on glycemic control in subjects with type 2 diabetes. *Clin Ther*. 2007;29:74-83.

Efficacy and Safety of Colesevelam in Patients With Type 2 Diabetes Mellitus and Inadequate Glycemic Control Receiving Insulin-Based Therapy

Key Point: Colesevelam HCl is both safe and efficacious for improving glycemic control and lipid management in patients with T2DM whose glucose levels were inadequately controlled on insulin-based therapy.*

Colesevelam HCl, a bile acid sequestrant, was shown in the GLOWS study that adding colesevelam HCl to oral antidiabetes medications significantly reduced both lipid and A1C levels.

RESEARCH DESIGN AND METHODS

This prospective study of 287 patients with T2DM was conducted as a 16-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. Subjects had inadequately controlled T2DM (A1C ranging from 7.5% to 9.5%) and received insulin therapy alone or in combination with oral antidiabetes agents. Patients with a mean baseline A1C of 8.3% were randomized to receive either colesevelam HCl 3.75 g/day or placebo.

The primary efficacy variable was the mean change in A1C level from baseline to week 16. Secondary efficacy measures included the mean change in fasting plasma glucose, fructosamine, and A1C levels from baseline to weeks 4, 8, and 16.

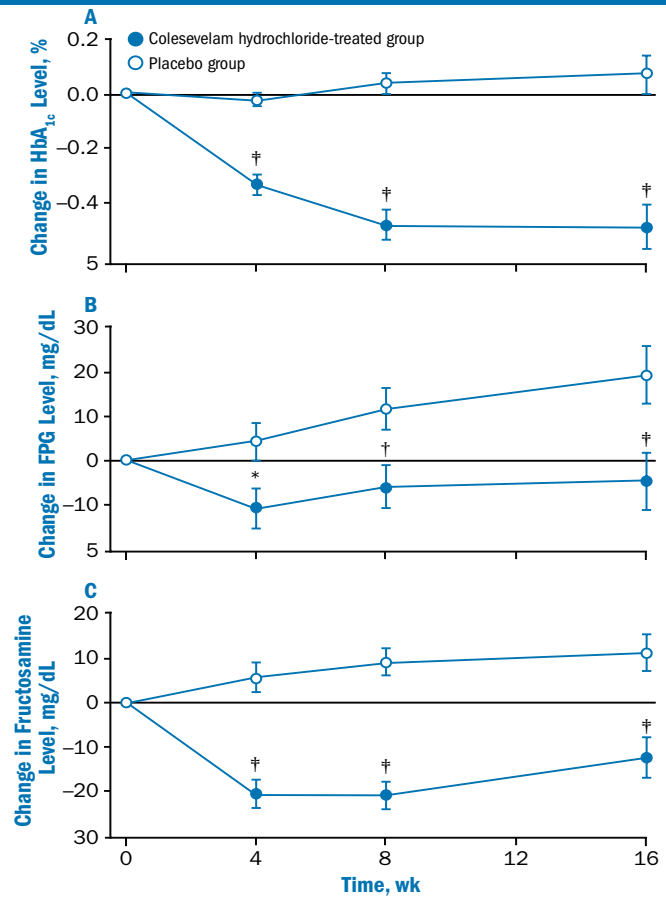
RESULTS

As shown in **Figure 2**, a treatment difference in A1C, fasting plasma glucose, and fructosamine levels was maintained throughout the study. In addition, the reduction in A1C levels in the total study population was consistent across groups, whether patients were receiving insulin alone or insulin in combination with oral antidiabetes agents. The mean change in A1C was -0.50%, and the greatest effect was observed in the subgroup of patients with the higher baseline A1C of >8.0%. Treatment with colesevelam HCl resulted in a significantly greater reduction in LDL-C, and no significant weight gain was noted in any group by study end. In the colesevelam HCl group, the most frequently reported adverse event was constipation (6.8%). The mean percent change in triglycerides from baseline in the colesevelam HCl arm was 21.5%

CONCLUSIONS

Colesevelam HCl improved glycemic control, as shown by a significant mean reduction in A1C level (-0.50%); this improvement in glucose control occurred regardless of the type of insulin regimen. Colesevelam HCl was generally well tolerated, with no change in weight. ■

Figure 2. The Time Course of the Least Squares Mean Change From Baseline in Levels for A1C, Fasting Plasma Glucose, and Fructosamine



N=287
*P<0.05 vs placebo, †P<0.01 vs placebo, ‡P<0.001 vs placebo
Source: Goldberg et al.[11] Used with Permission.

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*Based on Goldberg RB, Fonseca VA, Truitt KE, Jones MR. Efficacy and safety of colesevelam in patients with type 2 diabetes mellitus and inadequate glycemic control receiving insulin-based therapy. *Arch Intern Med*. 2008;168:1531-1540.

Colesevelam HCl Improves Glycemic Control and Reduces LDL Cholesterol in Patients With Inadequately Controlled Type 2 Diabetes on Sulfonylurea-Based Therapy

Key Point: This 26-week study demonstrated that colesevelam HCl represents an effective add-on strategy for improving glycemic and lipid parameters in patients with T2DM inadequately controlled on a sulfonylurea-based regimen.*

Preliminary clinical studies demonstrated that BAS, including colesevelam HCl, reduced A1C and lipid levels when added to stable antidiabetes drug regimens. This study investigated colesevelam HCl as a treatment option for improving glycemic control in patients with T2DM on sulfonylurea-based therapy.

RESEARCH DESIGN AND METHODS

This 26-week, randomized, double-blind, placebo-controlled, parallel-group, multicenter study evaluated the safety and efficacy of colesevelam HCl in reducing A1C in adults with T2DM whose glycemic control was inadequately controlled (defined as A1C value of 7.5%–9.5%) with existing sulfonylurea monotherapy or a sulfonylurea in combination with other oral antidiabetes agents. In total, 461 patients were randomized (230 patients were given colesevelam HCl 3.75 g/day and 231 patients were given placebo). The primary efficacy parameter was mean change in A1C from baseline to week 26 in the intent-to-treat population with the last observation carried forward (LOCF) analysis. Secondary efficacy parameters included several glucose and lipid endpoints, as well as high-sensitivity C-reactive protein (hsCRP) and TG levels.

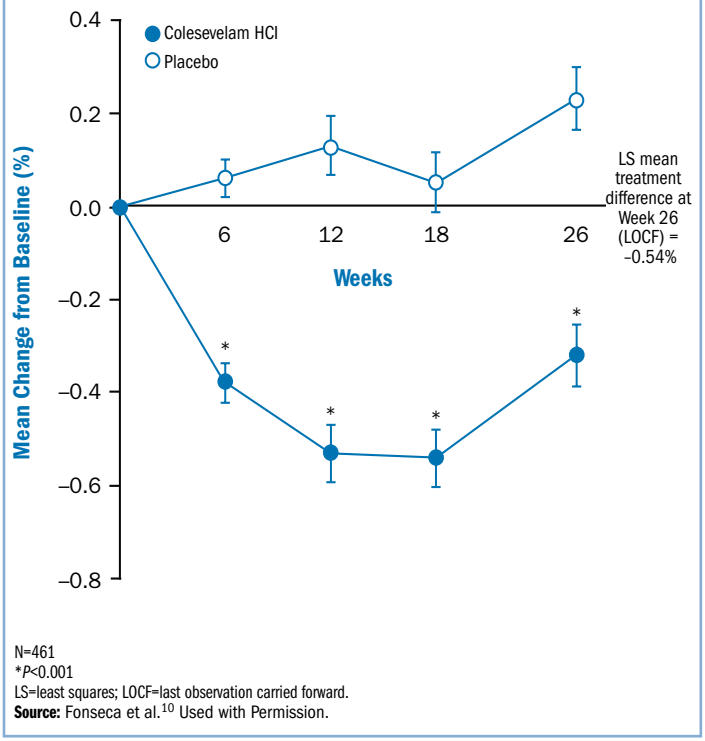
RESULTS

The mean change in A1C from baseline to week 26 resulted in an LS mean treatment difference of -0.54% ($P<0.001$). This effect was consistent irrespective of background therapy. A subgroup analysis according to baseline A1C levels demonstrated a greater treatment effect was observed in the subgroup with A1C >8.0% at baseline (-0.58%; $P<0.0001$). The mean percent change in LDL-C from baseline resulted in a treatment difference of -16.7% ($P<0.001$). Furthermore, at 26 weeks compared to placebo, colesevelam HCl significantly reduced fasting plasma glucose, fructosamine, total cholesterol, non-HDL-C, and apo B levels (**Figure 3**). TG levels were significantly increased by 17.7% ($P<0.001$).

CONCLUSIONS

Colesevelam HCl significantly reduced both A1C values and LDL-C concentrations in patients with T2DM when added to a sulfonylurea-based therapy. No severe hypoglycemia or study withdrawals due to hypoglycemia were reported, and colesevelam HCl did not promote weight gain. Based on the efficacy and safety results, the authors concluded that colesevelam HCl may represent a novel add-on therapeutic strategy for improving A1C and LDL-C in patients with T2DM. ■

Figure 3. Mean Change in A1C (%) From Baseline to Weeks 6, 12, 18, and 26 Versus Placebo



N=461
*$P<0.001$
LS=least squares; LOCF=last observation carried forward.
Source: Fonseca et al.[10] Used with Permission.

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*Based on Fonseca VA, Rosenstock J, Wang AC, Truitt KE, Jones MR. Colesevelam HCl improves glycemic control and reduces LDL cholesterol in patients with inadequately controlled type 2 diabetes on sulfonylurea-based therapy. *Diabetes Care*. 2008;31:1479-1484.

Colesevelam Hydrochloride Therapy in Patients With Type 2 Diabetes Mellitus Treated With Metformin: Glucose and Lipid Effects

Key Point: Colesevelam HCl improved glycemic and lipid parameters in patients with T2DM who had glucose levels inadequately controlled on metformin-based therapy.*

This study evaluated the efficacy and safety of colesevelam HCl in treating patients with T2DM whose A1C was inadequately controlled with metformin monotherapy (N=159), or metformin combination therapy with other oral antidiabetes agents (N=157).

RESEARCH DESIGN AND METHODS

This 26-week, randomized, double-blind, placebo-controlled study was conducted at 54 sites in the United States, and two sites in Mexico. Patients were treated with stable metformin-based therapy but were not at goal for glucose levels. After a placebo run-in period, 316 subjects were randomized 1:1 to colesevelam 3.75 g/day (6 tablets, 625 mg per tablet), or matching placebo for 26 weeks of a double-blind treatment. Patients continued to take their prescribed oral antidiabetes drugs at the same dose and time(s) as before the start of the study. The primary efficacy parameter was the mean change from baseline in A1C level for active drug, compared with placebo, at week 26.

Secondary efficacy parameters included mean changes in A1C, fasting plasma glucose, and fructosamine levels, as well as several other lipid level endpoints, and hsCRP.

RESULTS

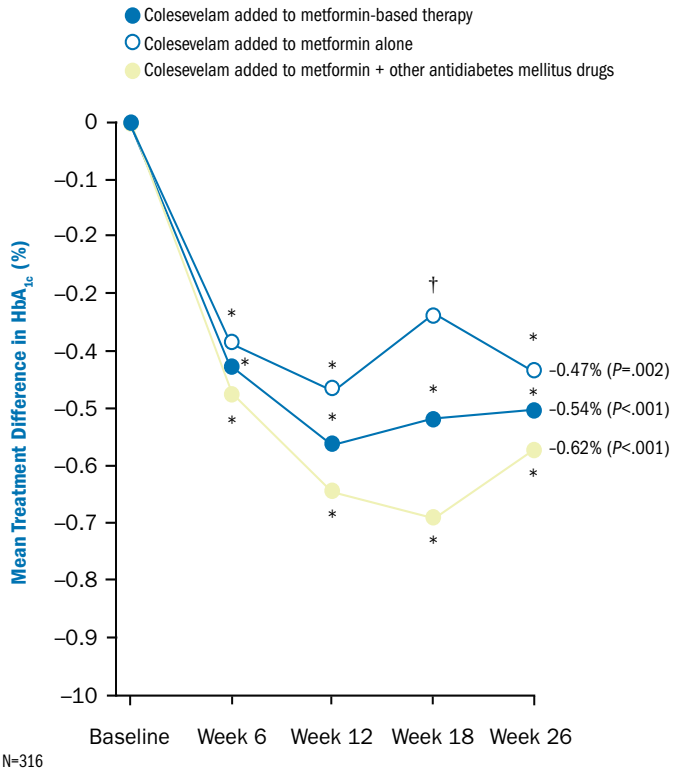
Colesevelam HCl lowered the mean A1C level compared with placebo at week 26 (LS mean treatment difference of -0.54%; $P<0.001$; (**Figure** 4). Results were similar in the metformin monotherapy (LS mean treatment difference of -0.47%; $P=0.002$), and combination therapy cohorts (LS mean treatment difference of -0.62%; $P<0.001$).

In addition, colesevelam HCl significantly lowered LDL-C, fasting plasma glucose, fructosamine, total cholesterol, apo B, non-HDL-C, and hsCRP levels, compared with placebo. Apolipoprotein A1 levels, HDL-C, and TG levels were not significantly increased. Consistent effects on the lipid profile were observed in those subjects who received a concomitant statin. Constipation was the only adverse event that occurred in at least 5% of the patients receiving colesevelam HCl. No weight gain was noted by the end of the study. The mean change in body weight was -0.5 kg for the colesevelam HCl group and -0.3 kg for the placebo group.

CONCLUSIONS

This study supported colesevelam HCl as an effective glucose-lowering agent that also improved various lipid parameters in patients with T2DM who had inadequate glucose control while being treated with a metformin-based therapy. Colesevelam HCl also significantly reduced hsCRP, a finding consistent with colesevelam used as monotherapy or as add-on therapy with statins. Colesevelam HCl was generally well tolerated when added to metformin-based therapy in patients with T2DM. ■

Figure 4. Change From Baseline in A1C (%) During the Course of the 26-Week Study



N=316
*$P \leq 0.002$
†$P \leq 0.001$
Source: Bays et al.[9] Used with Permission.

Please see the Important Safety Information about Welchol® on page 10 and the accompanying Welchol Brief Summary.

*Based on Bays HE, Goldberg RB, Truitt KE, Jones MR. Colesevelam hydrochloride therapy in patients with type 2 diabetes mellitus treated with metformin: Glucose and lipid effects. *Arch Intern Med*. 2008;168:1975-1983.

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.

Welchol for Oral Suspension should not be taken in its dry form.

Phenylketonurics: Welchol for Oral Suspension contains phenylalanine 48 mg 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)

Marketed by: Daiichi Sankyo, Inc.
Parsippany, New Jersey 07054

Active Ingredient: Product of Austria

P1801113