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**

Medical Director/President, Louisville Metabolic and Atherosclerosis Research Center, Louisville, Kentucky

Associate Professor of Medicine, Baylor College of Medicine, Houston, Texas

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**Clinical Therapeutics**


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**Diabetes Care**


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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.

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, sulfonylureas, 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. Although less appreciated, data for over a decade have also supported BAS as effectively reducing glucose levels. 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.

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.

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. 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. 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 Trials’ 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.

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. 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.

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

The mechanism of action by which BAS lower glucose is unknown. The most probable explanation involves the farnesoid X receptor (FXR), which may increase incretins such as glucagon-like peptide-1 (GLP-1), increase bile acid synthesis and thus increase bile acid delivery into the intestine, which, in turn, may increase TC levels 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.

Another potential mechanism is that BAS increase bile acid synthesis and thus increase bile acid delivery into the intestine, which may increase GLP-1 levels. The GLP-1 receptor is a hormone that can increase insulin secretion and decrease glucagon secretion, which may reduce glucose levels.

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®. 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 5% to 9%, and increased TG levels by a mean of 2% to 16% over that of placebo. 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). GLOWS, a pilot study (n=65), demonstrated that colesevelam HCl produced improved glycemic control in patients with T2DM, resulting in a decrease (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 (28.0%), 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, a sulfonylurea, and insulin-based 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.

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 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...
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. ■

REFERENCES


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

**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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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 8.5% 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. ■

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.*


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

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.
5.4 Pharmacokinetics

The median peak concentration (Cmax) of 0.175 mg/g protein was observed at 45 minutes post-dose ingestion. (See『Table』(7) in the full prescribing information).

6. ADVERSE REACTIONS

6.1 Clinical Studies

6.1.1 Clinical Trials

6.1.2 Clinical Pharmacology

6.2 Post-marketing Experience

6.2.1 Hypertriglyceridemia

6.2.2 Increased Seizure Activity

6.3 Nursing Mothers

6.4 Pediatric Use

6.5 Geriatric Use

6.6 Use in Specific Populations

6.7 Patient Counseling Information

6.8 Overdosage

6.8.1 Treatment

7. DRUG INTERACTIONS

7.1 General:

7.2 Hyperglycemia

7.3 Hypertriglyceridemia

7.4 Hypoglycemia

7.5 Increased Seizure Activity

7.6 Oral Contraceptive

7.7 Co-administration with Colesevelam Hydrochloride

7.8 St John’s Wort

7.9 Concomitant Use with Other Medications

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Lactation

8.3 Pediatric Use

8.4 Geriatric Use

8.5 Use In Specific Populations

8.6 Patient Counseling Information

8.7 Overdosage

9. DRUG INTERACTIONS

9.1 General:

9.2 Hyperglycemia

9.3 Hypertriglyceridemia

9.4 Hypoglycemia

9.5 Increased Seizure Activity

9.6 Oral Contraceptive

9.7 Co-administration with Colesevelam Hydrochloride

9.8 St John’s Wort

9.9 Concomitant Use with Other Medications

10. OVERDOSAGE

10.1 Treatment

11. PATIENT COUNSELING INFORMATION

11.1 General:

11.2 Use In Specific Populations

11.3 Patient Counseling Information

11.4 Overdosage

12.2 Use In Specific Populations

12.3 Pediatric Use

12.4 Geriatric Use

12.5 Use In Specific Populations

12.6 Patient Counseling Information

12.7 Overdosage

13. CLINICAL PHARMACOLOGY

13.1 Pharmacokinetics

13.2 Pharmacodynamics

13.3 Clinical Trials

14. CLINICAL STUDIES

14.1 Hypercholesterolemia

14.2 Hypertriglyceridemia

14.3 Increased Seizure Activity

14.4 Oral Contraceptive

14.5 Co-administration with Colesevelam Hydrochloride

14.6 St John’s Wort

14.7 Concomitant Use with Other Medications

15. CLINICAL STUDIES

15.1 Hypercholesterolemia

15.2 Hypertriglyceridemia

15.3 Increased Seizure Activity

15.4 Oral Contraceptive

15.5 Co-administration with Colesevelam Hydrochloride

15.6 St John’s Wort

15.7 Concomitant Use with Other Medications

16. CLINICAL STUDIES

16.1 Hypercholesterolemia

16.2 Hypertriglyceridemia

16.3 Increased Seizure Activity

16.4 Oral Contraceptive

16.5 Co-administration with Colesevelam Hydrochloride

16.6 St John’s Wort

16.7 Concomitant Use with Other Medications

17. PATIENT COUNSELING INFORMATION

17.1 General:

17.2 Use In Specific Populations

17.3 Patient Counseling Information

17.4 Overdosage

18. ADVERSE REACTIONS

18.1 Clinical Trials

18.2 Post-marketing Experience

18.3 Hypercholesterolemia

18.4 Hypertriglyceridemia

18.5 Increased Seizure Activity

18.6 Oral Contraceptive

18.7 Co-administration with Colesevelam Hydrochloride

18.8 St John’s Wort

18.9 Concomitant Use with Other Medications

19. CLINICAL STUDIES

19.1 Hypercholesterolemia

19.2 Hypertriglyceridemia

19.3 Increased Seizure Activity

19.4 Oral Contraceptive

19.5 Co-administration with Colesevelam Hydrochloride

19.6 St John’s Wort

19.7 Concomitant Use with Other Medications

20. ADVERSE REACTIONS

20.1 Clinical Trials

20.2 Post-marketing Experience

20.3 Hypercholesterolemia

20.4 Hypertriglyceridemia

20.5 Increased Seizure Activity

20.6 Oral Contraceptive

20.7 Co-administration with Colesevelam Hydrochloride

20.8 St John’s Wort

20.9 Concomitant Use with Other Medications

21. CLINICAL STUDIES

21.1 Hypercholesterolemia

21.2 Hypertriglyceridemia

21.3 Increased Seizure Activity

21.4 Oral Contraceptive

21.5 Co-administration with Colesevelam Hydrochloride

21.6 St John’s Wort

21.7 Concomitant Use with Other Medications

22. ADVERSE REACTIONS

22.1 Clinical Trials

22.2 Post-marketing Experience

22.3 Hypercholesterolemia

22.4 Hypertriglyceridemia

22.5 Increased Seizure Activity

22.6 Oral Contraceptive

22.7 Co-administration with Colesevelam Hydrochloride

22.8 St John’s Wort

22.9 Concomitant Use with Other Medications

23. CLINICAL STUDIES

23.1 Hypercholesterolemia

23.2 Hypertriglyceridemia

23.3 Increased Seizure Activity

23.4 Oral Contraceptive

23.5 Co-administration with Colesevelam Hydrochloride

23.6 St John’s Wort

23.7 Concomitant Use with Other Medications

24. ADVERSE REACTIONS

24.1 Clinical Trials

24.2 Post-marketing Experience

24.3 Hypercholesterolemia

24.4 Hypertriglyceridemia

24.5 Increased Seizure Activity

24.6 Oral Contraceptive

24.7 Co-administration with Colesevelam Hydrochloride

24.8 St John’s Wort

24.9 Concomitant Use with Other Medications

25. CLINICAL STUDIES

25.1 Hypercholesterolemia

25.2 Hypertriglyceridemia

25.3 Increased Seizure Activity

25.4 Oral Contraceptive

25.5 Co-administration with Colesevelam Hydrochloride

25.6 St John’s Wort

25.7 Concomitant Use with Other Medications

26. ADVERSE REACTIONS

26.1 Clinical Trials

26.2 Post-marketing Experience

26.3 Hypercholesterolemia

26.4 Hypertriglyceridemia

26.5 Increased Seizure Activity

26.6 Oral Contraceptive

26.7 Co-administration with Colesevelam Hydrochloride

26.8 St John’s Wort

26.9 Concomitant Use with Other Medications

27. CLINICAL STUDIES

27.1 Hypercholesterolemia

27.2 Hypertriglyceridemia

27.3 Increased Seizure Activity

27.4 Oral Contraceptive

27.5 Co-administration with Colesevelam Hydrochloride

27.6 St John’s Wort

27.7 Concomitant Use with Other Medications

28. ADVERSE REACTIONS

28.1 Clinical Trials

28.2 Post-marketing Experience

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