

COLESEVELAM HYDROCHLORIDE- colesevelam hydrochloride tablet, coated AvKARE, Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION Colesevelam Hydrochloride Tablets

Rx Only

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

COLESEVELAM hydrochloride tablets, for oral use

Initial U.S. Approval: 2000

INDICATIONS AND USAGE

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

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

Important Limitations of Use (1.3):

- Do not use for glycemic control in type 1 diabetes or for treating diabetic ketoacidosis.
- Colesevelam hydrochloride has not been studied in type 2 diabetes in combination with a dipeptidyl peptidase 4 inhibitor.
- Colesevelam hydrochloride has not been studied in Fredrickson Type I, III, IV, and V dyslipidemias.
- Colesevelam hydrochloride has not been studied in children younger than 10 years of age or in pre-menarchal girls.

DOSAGE AND ADMINISTRATION

- Colesevelam Hydrochloride Tablets: The recommended dose is 6 tablets once daily or 3 tablets twice daily. Colesevelam hydrochloride tablets should be taken with a meal and liquid (2.1).

DOSAGE FORMS AND STRENGTHS

Tablets: 625 mg (3)

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

- The effect of colesevelam hydrochloride on cardiovascular morbidity and mortality has not been determined (5.1).
- Colesevelam hydrochloride can increase TG, particularly when used with insulin or sulfonylureas. Marked hypertriglyceridemia can cause acute pancreatitis. The effect of hypertriglyceridemia on the risk of coronary artery disease is uncertain. Monitor lipids, including TG and non-high density lipoprotein cholesterol (non-HDL-C) (5.2).
- Bile acid sequestrants may decrease absorption of fat-soluble vitamins. Use caution in patients susceptible to fat-soluble vitamin deficiencies (5.3).
- Because of its constipating effects, colesevelam hydrochloride is not recommended in patients at risk of bowel obstruction (e.g., patients with gastroparesis, other gastrointestinal motility disorders or a history of major gastrointestinal surgery) (5.4).
- Colesevelam hydrochloride reduces gastrointestinal absorption of some drugs. Administer drugs with a known interaction with colesevelam at least 4 hours prior to colesevelam hydrochloride. 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 colesevelam hydrochloride. Alternatively, monitor drug levels of the co-administered drug. (5.5, 7, 12.3)

ADVERSE REACTIONS

In clinical trials, the most common (incidence $\geq 2\%$ and greater than placebo) adverse reactions with colesevelam hydrochloride included constipation, dyspepsia, and nausea.

Post-marketing reports with concomitant colesevelam hydrochloride administration include:

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

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

To report SUSPECTED ADVERSE REACTIONS, contact AvKARE, Inc. at 1-855-361-3993; email drugsafety@avkare.com; or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----- **DRUG INTERACTIONS** -----

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

See 17 for PATIENT COUNSELING INFORMATION.

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17.1 Primary Hyperlipidemia

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Primary Hyperlipidemia

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

Colesevelam hydrochloride is indicated as monotherapy or in combination with a statin to reduce LDL-C levels in boys and post-menarchal girls, 10 to 17 years of age, with heterozygous familial hypercholesterolemia if after an adequate trial of diet therapy the following findings are present:

- a. LDL-C remains ≥ 190 mg/dL or
- b. LDL-C remains ≥ 160 mg/dL and
 - there is a positive family history of premature cardiovascular disease or
 - two or more other CVD risk factors are present in the pediatric patient.

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

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

1.3 Important Limitations of Use

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

2 DOSAGE AND ADMINISTRATION

2.1 Primary Hyperlipidemia

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

Colestevam hydrochloride can be dosed at the same time as a statin or the two drugs can be dosed apart [see *Clinical Studies (14.1)*].

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

3 DOSAGE FORMS AND STRENGTHS

- 625 mg tablets are off-white to pale yellow film-coated oval tablets, debossed with "L61" on one side and plain on the other side.

4 CONTRAINDICATIONS

Colestevam hydrochloride 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 colestevam hydrochloride on cardiovascular morbidity and mortality has not been determined.

5.2 Serum Triglycerides

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

Colestevam hydrochloride 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)*].

Hypertriglyceridemia of sufficient severity can cause acute pancreatitis. The long-term effect of hypertriglyceridemia on the risk of coronary artery disease is uncertain. Caution should be exercised when treating patients with TG levels greater than 300 mg/dL. Because most patients in the colestevam hydrochloride 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 colestevam hydrochloride. In addition, the use of colestevam hydrochloride 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 colestevam hydrochloride and periodically thereafter. Colestevam hydrochloride 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 colestevam hydrochloride on the absorption of co-administered dietary or supplemental vitamin therapy. In nonclinical safety studies, rats administered colestevam 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 colestevam hydrochloride. 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, colesevelam hydrochloride 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, colesevelam hydrochloride tablets can cause dysphagia or esophageal obstruction and should be used with caution in patients with dysphagia or swallowing disorders.

5.5 Drug Interactions

Colesevelam hydrochloride reduces gastrointestinal absorption of some drugs. Drugs with a known interaction with colesevelam should be administered at least 4 hours prior to colesevelam hydrochloride. 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 colesevelam hydrochloride. Alternatively, the physician should monitor drug levels of the co-administered drug [see *Drug Interactions (7) and Clinical Pharmacology (12.3)*].

5.7 Macrovascular Outcomes

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

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience

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

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

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

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

	Number of Patients (%)	
	Colesevelam Hydrochloride 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=129), were treated with colesevelam hydrochloride tablets (1.9 to 3.8 g, daily) or placebo tablets [see *Clinical Studies (14.1)*].

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

	Number of Patients (%)	
	Colesevelam Hydrochloride 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 colesevelam hydrochloride 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)*].

Hypertriglyceridemia: Colesevelam hydrochloride 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)*].

6.2 Post-Marketing Experience

The following additional adverse reactions have been identified during post-approval use of colesevelam hydrochloride. 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 colesevelam hydrochloride administration include:

- Increased seizure activity or decreased phenytoin levels in patients receiving phenytoin. Phenytoin should be administered 4 hours prior to colesevelam hydrochloride.
- Reduced International Normalized Ratio (INR) in patients receiving warfarin therapy. In warfarin-treated patients, INR should be monitored frequently during colesevelam hydrochloride 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 colesevelam hydrochloride [see Drug Interactions (7)].

Gastrointestinal Adverse Reactions

Bowel obstruction (in patients with a history of bowel obstruction or resection), dysphagia or esophageal obstruction (occasionally requiring medical intervention), fecal impaction, pancreatitis, abdominal distension, exacerbation of hemorrhoids, and increased transaminases.

Laboratory Abnormalities

Hypertriglyceridemia

7 DRUG INTERACTIONS

Table 4 lists the drugs that have been tested in *in vitro* binding, *in vivo* drug interaction studies with colesevelam and/or drugs with post-marketing 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 colesevelam hydrochloride. Alternatively, the physician should monitor drug levels of the co-administered drug.

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

Drugs with a known interaction with colesevelam: Decrease in exposure of co-administered drug	cyclosporine *, glimepiride †, glipizide †, glyburide †, levothyroxine †, olmesartan medoxomil †, and oral contraceptives containing ethinyl estradiol and norethindrone †
Drugs with a known interaction with colesevelam: Increase in exposure of coadministered drug	metformin extended release (ER) ‡
Drug(s) with post-marketing reports consistent with potential drug-drug interactions when co-administered with colesevelam hydrochloride	phenytoin †, warfarin §
Drugs that do not interact with colesevelam based on <i>in vitro</i> or <i>in vivo</i> testing	aspirin, atenolol, cephalexin, ciprofloxacin, digoxin, enalapril, fenofibrate, lovastatin, metformin, metoprolol, phenytoin †, pioglitazone, rosiglitazone, quinidine, repaglinide, sitagliptin, valproic acid, verapamil, warfarin §

* Cyclosporine levels should be monitored and, based on theoretical grounds, cyclosporine should be administered at least 4 hours prior to colesevelam hydrochloride.

† Should be administered at least 4 hours prior to colesevelam hydrochloride.

‡ Patients receiving concomitant metformin ER and colesevelam should be monitored for clinical response as is usual for the use of anti-diabetes drugs.

§ No significant alteration of warfarin drug levels with warfarin and colesevelam hydrochloride co-administration 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, colesevelam hydrochloride and warfarin co-administration had no effect on warfarin drug levels. This study did not assess the effect of colesevelam hydrochloride and warfarin co-administration on INR. In post-marketing reports, concomitant use of colesevelam hydrochloride and warfarin has been associated with reduced INR. Therefore, in patients on warfarin therapy, the INR should be monitored before initiating colesevelam hydrochloride and frequently

enough during early colesevelam hydrochloride 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 colesevelam hydrochloride as monotherapy or in combination with a statin were evaluated in children, 10 to 17 years of age with heFH [see *Clinical Studies (14.1)*]. The adverse reaction profile was similar to that of patients treated with placebo. In this limited controlled study, there were no significant effects of 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, colesevelam hydrochloride for oral suspension is recommended for use in the pediatric population.

Dose adjustments are not required when colesevelam hydrochloride is administered to children 10 to 17 years of age.

Colesevelam hydrochloride has not been studied in children younger than 10 years of age or in premenarchal 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.

8.6 Hepatic Impairment

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

To report SUSPECTED ADVERSE REACTIONS contact AvKARE, Inc. at 1-855-361-3993; email drugsafety@avkare.com; or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

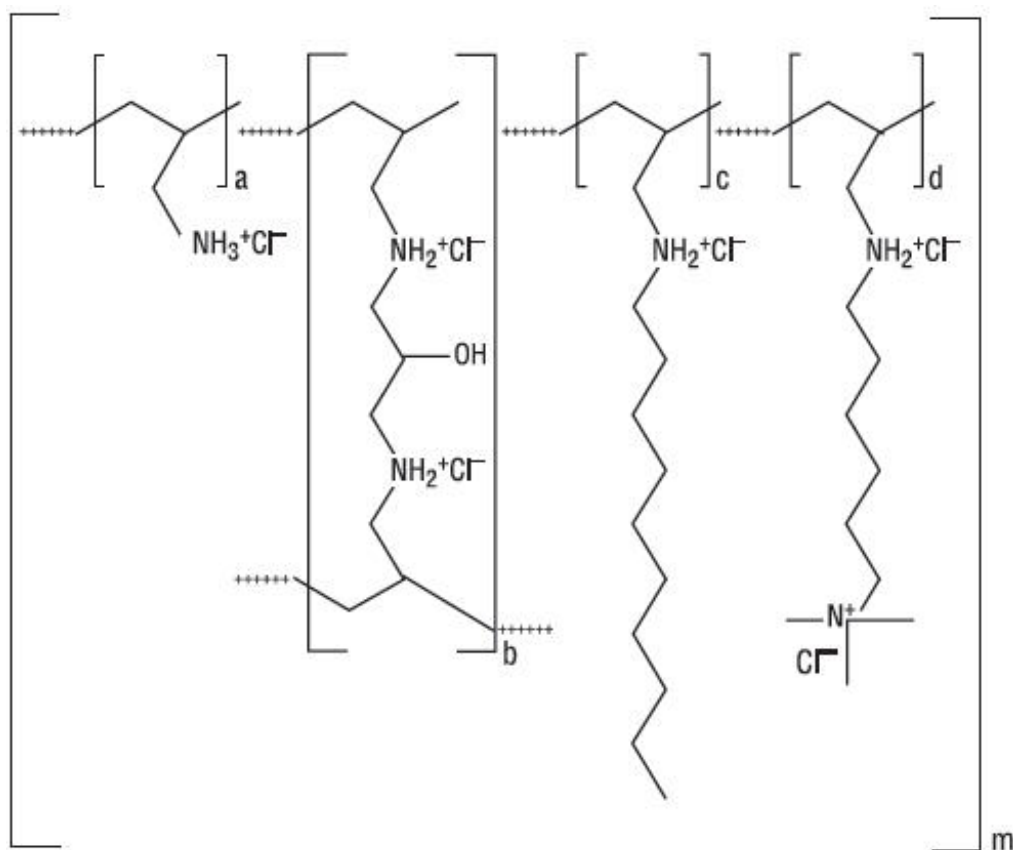
10 OVERDOSAGE

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

11 DESCRIPTION

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

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



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

Cyclosporine †	200 mg	-34%	- 44%	N/A	N/A	N/A	N/A
Ethinyl Estradiol ‡§	0.035 mg	-24%	- 24%	-18%	-1%	-12%	0%
Glimepiride §	4 mg	-18%	-8%	N/A	N/A	-6%	3%
Glipizide §	20 mg	-12%	- 13%	N/A	N/A	-4%	0%
Glyburide §	3 mg	-32%	- 47%	-20%	-15%	-7%	4%
Levothyroxine §	600 mcg	-22%	- 33%	6%	-2%	1%	8%
Metformin ER ¶	1500 mg	44%	8%	N/A	N/A	N/A	N/A
Norethindrone ‡§	1 mg	-1%	- 20%	5%	-3%	6%	7%
Olmesartan Medoxomil §	40 mg	-39%	- 28%	N/A	N/A	-15%	-4%
Repaglinide	2 mg	-7%	- 19%	-6%	-1%	N/A	N/A
Verapamil sustained-release	240 mg	-31%	- 11%	N/A	N/A	N/A	N/A

N/A — Not Available

* With verapamil, the dose of colesevelam hydrochloride was 4.5 g.

† Cyclosporine levels should be monitored and, based on theoretical grounds, cyclosporine should be administered at least 4 hours prior to colesevelam hydrochloride [see Drug Interactions (7)] .

‡ Oral contraceptive containing norethindrone and ethinyl estradiol.

§ Should be administered at least 4 hours prior to colesevelam hydrochloride [see Drug Interactions (7)] .

¶ Patients receiving concomitant metformin ER and colesevelam should be monitored for clinical response as is usual for the use of anti-diabetes drugs [see Drug Interactions (7)] .

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

degradants, decylamine HCl and aminoethyltrimethyl ammonium chloride HCl, were equivocal in the absence of metabolic activation and negative in the presence of metabolic activation. The other 2 degradants, didecylamine HCl and 6-decylaminoethyltrimethyl ammonium chloride HCl, were negative in the presence and absence of metabolic activation.

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

13.2 Animal Toxicology and/or Pharmacology

Reproductive Toxicology Studies

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

14 CLINICAL STUDIES

14.1 Primary Hyperlipidemia

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

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

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

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

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

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

* Median % change from baseline.

† p<0.05 for lipid parameters compared to placebo, for Apo B compared to baseline.

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

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

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

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

* Median % change from baseline.

[†] p<0.05 for lipid parameters compared to placebo, for Apo B compared to baseline.

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

The effect of colessevelam hydrochloride when added to fenofibrate was assessed in 122 patients with mixed hyperlipidemia (Fredrickson Type IIb). Inclusion in the study required LDL-C ≥115 mg/dL and TG 150 mg/dL to 749 mg/dL. Patients were treated with 160 mg of fenofibrate during an 8-week open-label run-in period and then randomly assigned to receive fenofibrate 160 mg plus either colessevelam

hydrochloride 3.8 g or placebo for 6 weeks of double-blind treatment. The overall mean LDL-C at the start of randomized treatment was 144 mg/dL. The results of the study are summarized in Table 8.

Table 8 Response to Colesevelam Hydrochloride Added to Fenofibrate in Patients with Mixed Hyperlipidemia (Mean % Change from Treated Baseline * at 6 Weeks)

Treatment	N	TC	LDL-C	Apo B	HDL-C	Non-HDL-C	TG †
Placebo + Fenofibrate 160 mg	61	2	2	1	-1	2	-3
Colesevelam Hydrochloride + Fenofibrate 160 mg	61	-6 ‡	-10 ‡	-7 ‡	0	-8 ‡	6

* Treated Baseline: following 8-week treatment with open-label fenofibrate 160 mg.

† For triglycerides, median % change from baseline.

‡ p<0.0002 compared to placebo.

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

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

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

Treatment Difference	TC (N=128)	LDL-C (N=128)	Apo B (N=124)	HDL-C (N=128)	Non-HDL-C (N=128)	TG * (N=128)
Colesevelam Hydrochloride 3.8 g vs. Placebo	-7 †	-13 †	-8 †	+6 †	-11 †	+5

* For triglycerides, median % change from baseline. Results were based on the ITT population with LOCF.

† p ≤ 0.05 for lipid parameters compared to placebo. Values represent LS mean. Only patients with values at both study baseline and endpoint are included in this table. Study baseline was defined as the last value measured before or on Day 1 prior to the first dose of randomized study medication.

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

16 HOW SUPPLIED/STORAGE AND HANDLING

Colesevelam hydrochloride tablets, 625 mg, are supplied as off-white to pale yellow film-coated oval tablets, debossed with "L61" on one side and plain on the other side. Colesevelam hydrochloride tablets are available as follows:

- Bottles of 180 – NDC 42291-147-18

Storage: Store at 20°C to 25°C (68°F to 77°F) [see USP Controlled Room Temperature]. Protect from moisture.

17 PATIENT COUNSELING INFORMATION

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

Drug interactions: Drugs with a known interaction with colesevelam (e.g., cyclosporine, glimepiride, glipizide, glyburide, levothyroxine, olmesartan medoxomil, oral contraceptives) should be administered at least 4 hours prior to colesevelam hydrochloride. In an *in vivo* drug interaction study, there was no significant effect on the bioavailability of phenytoin; however, due to its narrow therapeutic index and post-marketing reports consistent with potential drug-drug interactions, phenytoin should be administered at least 4 hours prior to colesevelam hydrochloride. 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 colesevelam hydrochloride. Alternatively the physician should monitor blood levels of the coadministered drug. Patients receiving concomitant metformin ER and colesevelam should be monitored for clinical response as is usual for the use of anti-diabetes drugs [see *Drug Interactions (7)*].

Gastrointestinal: Colesevelam hydrochloride can cause constipation. Colesevelam hydrochloride is contraindicated in patients with a history of bowel obstruction. Colesevelam hydrochloride 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 colesevelam hydrochloride and seek medical attention if severe abdominal pain or severe constipation occurs. Because of the tablet size, colesevelam hydrochloride tablets can cause dysphagia or esophageal obstruction and should be used with caution in patients with dysphagia or swallowing disorders [see *Warnings and Precautions (5.4)*].

Hypertriglyceridemia and pancreatitis: Patients should be instructed to discontinue colesevelam hydrochloride 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.

Hypertriglyceridemia and cardiovascular disease: Patients should be informed that colesevelam hydrochloride 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)*].

Manufactured for:
AvKARE, Inc.
Pulaski, TN 38478

Mfg. Rev. 12/15
AV 06/18 (P)

PRINCIPAL DISPLAY PANEL - 180 Tablet Bottle Label

AvKARE®

NDC 42291-147-18

Colesevelam Hydrochloride Tablets

625 mg

180 Tablets Rx Only

Each tablet contains: Active Ingredient:
Colesevelam hydrochloride 625 mg.

USUAL DOSAGE: See package insert for dosage information.

Dispense in tightly-closed, light-resistant container as defined in the USP, with child-resistant closure, as required.

Store at 20°-25°C (68°-77°F) [See USP Controlled Room Temperature].

Keep out of the reach of children.

Manufactured for:
AvKARE, Inc.
Pulaski, TN 38478

Mfg. Rev. 08/15 AV 06/18 (P)

AVKARE
NDC 42291-147-18

**Colesevelam
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Pulaski, TN 38478

Mfg. Rev. 08/15 AV 06/18 (P)

3 42291 147 18 8

COLESEVELAM HYDROCHLORIDE

colesevelam hydrochloride tablet, coated

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:4229 1-147(NDC:0 115-1320)
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
COLESEVELAM HYDROCHLORIDE (UNII: P4SG24WI5Q) (COLESEVELAM - UNII:1XU104G55N)	COLESEVELAM HYDROCHLORIDE	625 mg

Inactive Ingredients

Ingredient Name	Strength
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
COPOVIDONE (UNII: D9C330MD8B)	
HYPROMELLOSE 2910 (6 MPAS) (UNII: 0WZ8WG20P6)	
HYPROMELLOSE 2910 (15 MPAS) (UNII: 36SF2JZ0W)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
POLYETHYLENE GLYCOL 6000 (UNII: 30IQX730WE)	
TALC (UNII: 7SEV7J4R1U)	

Product Characteristics

Color	white (off-white to pale yellow)	Score	no score
Shape	OVAL	Size	8mm
Flavor		Imprint Code	L61
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:42291-147-18	180 in 1 BOTTLE; Type 0: Not a Combination Product	06/18/2018	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA091600	06/18/2018	

Labeler - AvKARE, Inc. (796560394)