COLESEVELAM HYDROCHLORIDE - colesvelam hydrochloride powder, for suspension
Ascend Laboratories, LLC

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HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use COLESEVELAM HYDROCHLORIDE FOR ORAL SUSPENSION safely and effectively. See full prescribing information for COLESEVELAM HYDROCHLORIDE FOR ORAL SUSPENSION.

COLESEVELAM HYDROCHLORIDE for oral suspension
Initial U.S. Approval: 2000

-------------------------------------  RECENT MAJOR CHANGES ------------------------------------
Dosage and Administration (2.1)  01/2019

-------------------------------------  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 postmenarchal girls, 10 to 17 years of age, with heterozygous familial hypercholesterolemia as monotherapy or in combination with a statin after failing an adequate trial of diet therapy.

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 for Oral Suspension: The recommended dose is one 3.75 gram packet once daily. To prepare, empty the entire contents of one packet into a glass or cup. Add 1 cup (8 ounces) of water, fruit juice, or diet soft drinks. Stir well and drink. Colesevelam hydrochloride for oral suspension should be taken with meals. To avoid esophageal distress, Colesevelam hydrochloride for oral suspension should not be taken in its dry form (2.1).

-------------------------------------  DOSAGE FORMS AND STRENGTHS --------------------------------------
Oral suspension: 3.75 gram packet (3)

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

-------------------------------------  WARNINGS AND PRECAUTIONS ----------------------------------------
• The effect of 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 ≥2% and greater than placebo) adverse reactions with colesevelam hydrochloride included constipation, dyspepsia, and nausea.
Postmarketing 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 postmarketing reports include bowel obstruction, dysphagia, esophageal obstruction, fecal impaction, hypertriglyceridemia, pancreatitis, and increased transaminases (5.5, 6.2, 7, 12.3).

To report SUSPECTED ADVERSE REACTIONS, contact Ascend Laboratories, LLC at 1-877-ASC-RX01 (877-272-7901) or FDA at 1-800-332-1088 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 postmarketing 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.

Revised: 2/2019

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**1 INDICATIONS & 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 postmenarchal girls, 10 to 17 years of age, with heterozygous familial hypercholesterolemia if after an adequate trial of diet therapy the following findings are present:

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

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

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

**1.3 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 & ADMINISTRATION

2.1 Primary Hyperlipidemia

The recommended dose of colesevelam hydrochloride for oral suspension, in adults and children 10 to 17 years of age, is one 3.75 gram packet once daily. To prepare, empty the entire contents of one packet into a glass or cup. Add 1 cup (8 ounces) of water, fruit juice, or diet soft drinks. Stir well and drink. Colesevelam hydrochloride for oral suspension should be taken with meals. To avoid esophageal distress, colesevelam hydrochloride for oral suspension should not be taken in its dry form. Due to tablet size, it is recommended that any patient who has difficulty swallowing tablets use colesevelam hydrochloride for oral suspension. Colesevelam 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 colesevelam hydrochloride, lipid levels should be analyzed within 4 to 6 weeks.

3 DOSAGE FORMS & STRENGTHS

- Colesevelam Hydrochloride for Oral Suspension: a white to yellow granular powder containing yellow granules packaged in single-dose packets: 3.75 gram single-dose packet.

4 CONTRAINDICATIONS

Colesevelam 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 colesevelam hydrochloride on cardiovascular morbidity and mortality has not been determined.

5.2 Serum Triglycerides

Colesevelam hydrochloride, like other bile acid sequestrants, can increase serum TG concentrations. Colesevelam 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 colesevelam 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 colesevelam hydrochloride. In addition, the use of colesevelam hydrochloride is contraindicated in patients with TG levels >500 mg/dL. Lipid parameters, including TG levels and non-HDL-C, should be obtained before starting colesevelam hydrochloride and periodically thereafter. Colesevelam 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 colesevelam hydrochloride 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 colesevelam 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 those who have had major gastrointestinal tract surgery and who may be at risk for bowel obstruction. To avoid esophageal distress, colesevelam hydrochloride for oral suspension should not be taken in its dry form. Always mix colesevelam hydrochloride for oral suspension with water, fruit juice, or diet soft drinks before ingesting.

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)].

5.6 Phenylketonurics

Colesevelam hydrochloride for oral suspension contains 33.6 mg phenylalanine per 3.75 gram packet [See Description (11)].

5.7 Macrovascular Outcomes

There have been no clinical studies establishing conclusive evidence of macrovascular disease risk reduction with colesevelam hydrochloride.

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 ≥ 2% of Patients and More Commonly than in Patients Given Placebo, Regardless of Investigator Assessment of Causality**

<table>
<thead>
<tr>
<th>Number of Patients (%)</th>
<th>Colesevelam Hydrochloride N = 807</th>
<th>Placebo N=258</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constipation</td>
<td>89 (11.0)</td>
<td>18 (7.0)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>67 (8.3)</td>
<td>9 (3.5)</td>
</tr>
<tr>
<td>Nausea</td>
<td>34 (4.2)</td>
<td>10 (3.9)</td>
</tr>
<tr>
<td>Accidental injury</td>
<td>30 (3.7)</td>
<td>7 (2.7)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>29 (3.6)</td>
<td>5 (1.9)</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>26 (3.2)</td>
<td>5 (1.9)</td>
</tr>
<tr>
<td>Flu syndrome</td>
<td>26 (3.2)</td>
<td>8 (3.1)</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>26 (3.2)</td>
<td>8 (3.1)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>17 (2.1)</td>
<td>1 (0.4)</td>
</tr>
</tbody>
</table>

**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 colesevelam hydrochloride tablets (1.9-3.8 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 ≥2% of Patients and More Commonly than in Patients Given Placebo, Regardless of Investigator Assessment of Causality**

<table>
<thead>
<tr>
<th>Number of Patients (%)</th>
<th>Colesevelam Hydrochloride N = 129</th>
<th>Placebo N = 65</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasopharyngitis</td>
<td>8 (6.2)</td>
<td>3 (4.6)</td>
</tr>
<tr>
<td>Headache</td>
<td>5 (3.9)</td>
<td>2 (3.1)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>5 (3.9)</td>
<td>1 (1.5)</td>
</tr>
<tr>
<td>Creatine Phosphokinase Increase</td>
<td>3 (2.3)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>3 (2.3)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3 (2.3)</td>
<td>1 (1.5)</td>
</tr>
</tbody>
</table>

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)].

### 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**

Hypertriglyceridermia

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**7 DRUG INTERACTIONS**

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

<table>
<thead>
<tr>
<th>Drugs with a known interaction with colesevelam: Decrease in exposure of coadministered drug</th>
<th>cyclosporine&lt;sup&gt;c&lt;/sup&gt;, glimepiride&lt;sup&gt;a&lt;/sup&gt;, glipizide&lt;sup&gt;a&lt;/sup&gt;, glyburide&lt;sup&gt;a&lt;/sup&gt;, levothyroxine&lt;sup&gt;a&lt;/sup&gt;, olmesartan medoxomil&lt;sup&gt;a&lt;/sup&gt;, and oral contraceptives containing ethinyl estradiol and norethindrone&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drugs with a known interaction with colesevelam: Increase in exposure of coadministered drug</td>
<td>metformin extended release (ER)&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Drug(s) with postmarketing reports consistent with potential drug-drug interactions when coadministered with colesevelam hydrochloride</td>
<td>phenytoin&lt;sup&gt;a&lt;/sup&gt;, warfarin&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Drugs that do not interact with colesevelam based on in vitro or in vivo testing</td>
<td>aspirin, atenolol, cephalixin, ciprofloxacin, digoxin, enalapril, fenofibrate, lovastatin, metformin, metoprolol, phenytoin&lt;sup&gt;a&lt;/sup&gt;, pioglitazone, rosiglitazone, quinidine, repaglinide, sitagliptin, valproic acid,</td>
</tr>
</tbody>
</table>
Should be administered at least 4 hours prior to colesevelam hydrochloride

No significant alteration of warfarin drug levels with warfarin and colesevelam hydrochloride coadministration in an in vivo study which did not evaluate warfarin pharmacodynamics (INR). [See Adverse Reactions (6.2)]

Cyclosporine levels should be monitored and, based on theoretical grounds, cyclosporine 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.

In an in vivo drug interaction study, colesevelam hydrochloride and warfarin coadministration had no effect on warfarin drug levels. This study did not assess the effect of colesevelam hydrochloride and warfarin coadministration 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 Adverse Reactions (6.2)].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Colesevelam hydrochloride is not absorbed systemically following oral administration, and maternal use is not expected to result in fetal exposure to the drug. Limited available data on the use of colesevelam hydrochloride are insufficient to determine a drug-associated risk of major congenital malformations or miscarriage. In animal reproduction studies, no evidence of either maternal or fetal toxicity was found in rats or rabbits exposed to colesevelam hydrochloride during the period of fetal organogenesis at 8 and 5 times, respectively, the maximum recommended human dose (MRHD) of 3.75 g/day, based on body surface area (mg/m²). No adverse effects on offspring survival and development were observed in rats administered 3 times the MRHD (see Data). Colesevelam hydrochloride may decrease the absorption of fat-soluble vitamins [see Warnings and Precautions (5.3)]. There are no data available on the effect of colesevelam hydrochloride on the absorption of fat-soluble vitamins in pregnant women. If the patient becomes pregnant while taking colesevelam hydrochloride, the patient should be advised of the lack of known clinical benefit with continued use during pregnancy.

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

Data

Human Data

There are no adequate and well-controlled studies of colesevelam hydrochloride use in pregnant women.
In the post-marketing setting there have been infrequent reports of pregnancy with use of colesevelam hydrochloride and a causal association with congenital anomalies has not been established.

Animal Data

In pregnant rats given dietary doses of 0.3, 1.0, 3.0 g/kg/day colesevelam hydrochloride from gestation days 7 through 17, no teratogenic effects were observed. Exposures at 3.0 g/kg/day were 8 times the human exposure at 3.75 g/day MRHD, based on body surface area (mg/m²).

In pregnant rabbits given oral gavage doses of 0.1, 0.5, 1.0 g/kg/day colesevelam hydrochloride from gestation days 6 through 18, no teratogenic effects were observed. Exposures at 1.0 g/kg/day were 5 times the human exposure at 3.75 g/day MRHD, based on body surface area (mg/m²).

In pregnant rats given oral gavage doses of 0.1, 0.3, 1.0 g/kg/day colesevelam hydrochloride from gestation day 6 through lactation day 21 (weaning), no adverse effects on survival and development were observed. Exposures at 1.0 g/kg/day were 3 times the human exposure at 3.75 g/day MRHD, based on body surface area (mg/m²).

8.2 Lactation

Risk Summary

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

8.3 Females and Males of Reproductive Potential

Contraception

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

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 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 of Colesevelam Hydrochloride Tablets, 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 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.

8.6 Hepatic Impairment

No special considerations or dosage adjustments are recommended when colesevelam hydrochloride is administered to patients with hepatic impairment.
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. Colesevelam hydrochloride for oral suspension is a citrus-flavored, a white to yellow granular powder containing yellow granules packaged in single-dose packets containing 3.75 gram colesevelam hydrochloride. In addition, each packet contains the following inactive ingredients: microcrystalline cellulose, medium chain triglycerides, simethicone emulsion, colloidal silicon dioxide, propylene glycol alginate, magnesium trisilicate, lemon-lime flavor, orange flavor, citric acid monohydrate, and aspartame.

PHENYLKETONURICS: Colesevelam hydrochloride for oral suspension contains 33.6 mg phenylalanine per 3.75 gram dose.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.2 Pharmacodynamics

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

12.3 Pharmacokinetics

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

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

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

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

Drug Interactions: Drug interactions between colesevelam and concomitantly administered drugs were
screened through *in vitro* studies and confirmed in *in vivo* studies. *In vitro* studies demonstrated that cephalaxin, metformin, and ciprofloxacin had negligible binding to colesevelam hydrochloride. Therefore, an *in vivo* pharmacokinetic interaction of colesevelam hydrochloride with these drugs is unlikely. Colesevelam hydrochloride was found to have no significant effect on the bioavailability of aspirin, atenolol, digoxin, enalapril, fenofibrate, lovastatin, metoprolol, phenytoin, pioglitazone, quinidine, rosiglitazone, sitagliptin, valproic acid, and warfarin. The results of additional *in vivo* drug interactions of colesevelam hydrochloride are presented in Table 5.

### Table 5

**Mean Change in Drug Exposure (AUC₀-∞ and Cₘₐₓ)** when Administered with Colesevelam Hydrochloride (3.75 g)ᵃ

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Co-administered</th>
<th>1 hr prior to colesevelam hydrochloride</th>
<th>4 hr prior to colesevelam hydrochloride</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>AUC₀-∞</td>
<td>Cₘₐₓ</td>
</tr>
<tr>
<td>Cyclosporineᵈ</td>
<td>200 mg</td>
<td>-34% -44%</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Ethinyl Estradiol*ᵇ</td>
<td>0.035 mg</td>
<td>-24% -24%</td>
<td>-18%</td>
<td>-1%</td>
</tr>
<tr>
<td>Glimepirideᵇ</td>
<td>4 mg</td>
<td>-18% -8%</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Glipizideᵇ</td>
<td>20 mg</td>
<td>-12% -13%</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Glyburideᵇ</td>
<td>3 mg</td>
<td>-32% -47%</td>
<td>-20%</td>
<td>-15%</td>
</tr>
<tr>
<td>Levothyroxineᵇ</td>
<td>600 μg</td>
<td>-22% -33%</td>
<td>6%</td>
<td>-2%</td>
</tr>
<tr>
<td>Metformin ERᶜ</td>
<td>1500 mg</td>
<td>44% 8%</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Norethindrone*ᵇ</td>
<td>1 mg</td>
<td>-1% -20%</td>
<td>5%</td>
<td>-3%</td>
</tr>
<tr>
<td>Olmesartan Medoxomiᵇ</td>
<td>40 mg</td>
<td>-39% -28%</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Repaglinide</td>
<td>2 mg</td>
<td>-7% -19%</td>
<td>-6%</td>
<td>-1%</td>
</tr>
<tr>
<td>Verapamil sustained-release</td>
<td>240 mg</td>
<td>-31% -11%</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

ᵃ With verapamil, the dose of colesevelam hydrochloride was 4.5 g

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

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

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

* Oral contraceptive containing norethindrone and ethinyl estradiol.

N/A – Not Available

### 13 NONCLINICAL TOXICOLOGY

#### 13.1 Carcinogenesis, Mutagenesis, Impairment Of Fertility

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

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

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

### 13.2 Animal Toxicology and/or Pharmacology

**Reproductive Toxicology Studies**

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

### 14 CLINICAL STUDIES

**14.1 Primary Hyperlipidemia**

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 - 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

<table>
<thead>
<tr>
<th>Grams/Day</th>
<th>N</th>
<th>TC</th>
<th>LDL-C</th>
<th>Apo B</th>
<th>HDL-C&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Non-HDL-C</th>
<th>TG&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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 colesevelam 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 - 236 mg/dL), 171 mg/dL in the lovastatin study (range 115 - 247 mg/dL), and 188 mg/dL in the simvastatin study (range 148 - 352 mg/dL). As demonstrated in Table 7, colesevelam 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

<table>
<thead>
<tr>
<th>Dose / Day</th>
<th>N</th>
<th>TC</th>
<th>LDL-C</th>
<th>Apo B</th>
<th>HDL-C&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Non-HDL-C</th>
<th>TG&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Atorvastatin Trial (4-week)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>19</td>
<td>+4</td>
<td>+3</td>
<td>−3</td>
<td>+4</td>
<td>+4</td>
<td>+10</td>
</tr>
<tr>
<td>Atorvastatin 10 mg</td>
<td>18</td>
<td>−27*</td>
<td>−38*</td>
<td>−32*</td>
<td>+8</td>
<td>−35*</td>
<td>−24*</td>
</tr>
<tr>
<td>colesevelam hydrochloride 3.8 g</td>
<td>18</td>
<td>−31*</td>
<td>−48*</td>
<td>−38*</td>
<td>+11</td>
<td>−40*</td>
<td>−1</td>
</tr>
<tr>
<td>Atorvastatin 80 mg</td>
<td>20</td>
<td>−39*</td>
<td>−53*</td>
<td>−46*</td>
<td>+6</td>
<td>−50*</td>
<td>−33*</td>
</tr>
<tr>
<td><strong>Simvastatin Trial (6-week)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>33</td>
<td>−2</td>
<td>−4</td>
<td>−4*</td>
<td>−3</td>
<td>−2</td>
<td>+6*</td>
</tr>
<tr>
<td>Simvastatin 10 mg</td>
<td>35</td>
<td>−19*</td>
<td>−26*</td>
<td>−20*</td>
<td>+3*</td>
<td>−24*</td>
<td>−17*</td>
</tr>
<tr>
<td>colesevelam hydrochloride 3.8 g</td>
<td>34</td>
<td>−28*</td>
<td>−42*</td>
<td>−33*</td>
<td>+10*</td>
<td>−37*</td>
<td>−12*</td>
</tr>
<tr>
<td>Simvastatin 10 mg</td>
<td>34</td>
<td>−33*</td>
<td>−42*</td>
<td>−33*</td>
<td>+10*</td>
<td>−37*</td>
<td>−12*</td>
</tr>
<tr>
<td>Simvastatin 20 mg</td>
<td>39</td>
<td>−23*</td>
<td>−34*</td>
<td>−26*</td>
<td>+7*</td>
<td>−30*</td>
<td>−12*</td>
</tr>
<tr>
<td>colesevelam hydrochloride 2.3 g</td>
<td>37</td>
<td>−29*</td>
<td>−42*</td>
<td>−32*</td>
<td>+4*</td>
<td>−37*</td>
<td>−12*</td>
</tr>
<tr>
<td>Simvastatin 20 mg</td>
<td>37</td>
<td>−29*</td>
<td>−42*</td>
<td>−32*</td>
<td>+4*</td>
<td>−37*</td>
<td>−12*</td>
</tr>
</tbody>
</table>
Lovastatin Trial (4-week)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>TC</th>
<th>LDL-C</th>
<th>Apo B</th>
<th>HDL-C</th>
<th>Non-HDL-C</th>
<th>TG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>26</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td>+1</td>
<td>+1</td>
<td>+1</td>
</tr>
<tr>
<td>Lovastatin 10 mg</td>
<td>26</td>
<td>–14*</td>
<td>–22*</td>
<td>–16*</td>
<td>+5</td>
<td>–19*</td>
<td>0</td>
</tr>
<tr>
<td>Colesevelam hydrochloride 2.3 g/ Lovastatin 10 mg</td>
<td>27</td>
<td>–21*</td>
<td>–34*</td>
<td>–24*</td>
<td>+4</td>
<td>–27*</td>
<td>–1</td>
</tr>
<tr>
<td>Togetherr</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colesevelam hydrochloride 2.3 g/ Lovastatin 10 mg</td>
<td>23</td>
<td>–21*</td>
<td>–32*</td>
<td>–24*</td>
<td>+2</td>
<td>–28*</td>
<td>–2</td>
</tr>
</tbody>
</table>

*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 colesevelam hydrochloride and any given dose of statin therapy was statistically superior to that achieved with colesevelam 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 colesevelam hydrochloride 3.8 g and atorvastatin 10 mg.

The effect of colesevelam hydrochloride when added to fenofibrate was assessed in 122 patients with mixed hyperlipidemia (Fredrickson Type IIb). Inclusion in the study required LDL-C \( \geq 115 \text{ mg/dL} \) 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 colesevelam 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)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>TC</th>
<th>LDL-C</th>
<th>Apo B</th>
<th>HDL-C</th>
<th>Non-HDL-C</th>
<th>TG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo + Fenofibrate 160 mg</td>
<td>61</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>-1</td>
<td>2</td>
<td>-3</td>
</tr>
<tr>
<td>Colesevelam Hydrochloride + Fenofibrate 160 mg</td>
<td>61</td>
<td>-6*</td>
<td>-10*</td>
<td>-7*</td>
<td>0</td>
<td>-8*</td>
<td>6</td>
</tr>
</tbody>
</table>

*p \leq 0.0002 compared to placebo.

a For triglycerides, median % change from baseline.

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

During the double-blind treatment period, patients were assigned randomly to treatment: 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

<table>
<thead>
<tr>
<th>Treatment Difference</th>
<th>TC (N=128)</th>
<th>LDL-C (N=128)</th>
<th>Apo B (N=124)</th>
<th>HDL-C (N=128)</th>
<th>Non-HDL-C (N=128)</th>
<th>TGa (N=128)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colesevelam Hydrochloride 3.8 g vs Placebo</td>
<td>-7*</td>
<td>-13*</td>
<td>-8*</td>
<td>+6*</td>
<td>-11*</td>
<td>+5</td>
</tr>
</tbody>
</table>

*p≤0.05 for lipid parameters compared to placebo

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

a For triglycerides, median % change from baseline.

Results were based on the ITT population with LOCF

During the open-label treatment period patients were treated with 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 for oral suspension is a white to yellow granular powder containing yellow granules. Colesevelam hydrochloride for oral suspension is available as follows:

- 3.75 gram single-dose packet
- Cartons of 30 packets – NDC 67877-523-30
17 PATIENT COUNSELING INFORMATION

**Dosing:** Patients should be advised to take colesevelam hydrochloride for oral suspension as one 3.75 gram packet once daily. To prepare, empty the entire contents of one packet into a glass or cup. Add 1 cup (8 ounces) of water, fruit juice, or diet soft drinks. Stir well and drink. Colesevelam hydrochloride for oral suspension should be taken with meals. To avoid esophageal distress, colesevelam hydrochloride for oral suspension should not be taken in its dry form. Always mix colesevelam hydrochloride for oral suspension with water, fruit juice, or diet soft drinks before ingesting [See Dosage and Administration (2)].

**Drug Interactions:** Drugs with a known interaction with colesevelam (e.g., cyclosporine, glimepiride, glipizide, glyburide, levothyroxine, olmesartan medoxomil, oral contraceptives) should be administered at least 4 hours prior to 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. To avoid esophageal distress, colesevelam hydrochloride for oral suspension should not be taken in its dry form. Always mix colesevelam hydrochloride for oral suspension with water, fruit juice, or diet soft drinks before ingesting [See Warnings and Precautions (5.4)].

**Hypertriglyceridemia and Pancreatitis:** Patients should be instructed to discontinue 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.

17.3 Females of Reproductive Potential

Advise females of reproductive potential that colesevelam hydrochloride may reduce the effectiveness of oral contraceptives, and to take oral contraceptives at least 4 hours before taking colesevelam hydrochloride for oral suspension [see Drug Interactions (7) and Use in Specific Populations (8.3)].
Manufactured by:
Alkem Laboratories Ltd.
Mumbai – 400 013, INDIA

Distributed by:
Ascend Laboratories, LLC
Parsippany, NJ 07054
Revised: 02/2019

PACKAGE LABEL.PRINCIPAL DISPLAY PANEL
PACKAGE LABEL - PRINCIPAL DISPLAY PANEL
ASCEND Laboratories, LLC
NDC 67877-523-30

Colesevelam Hydrochloride for Oral Suspension 3.75g/packet
Rx only
Single Dose Packet

This packet is contained within the Carton NDC 67877-523-30

NDC 67877-523-30

Colesevelam Hydrochloride for Oral Suspension
3.75 g
Citrus flavor
Sugar Free
Rx Only Single Dose Packet

Keep Out of Reach of Children.
Package Not Child Resistant.
Each packet contains 3.75 grams of colesevelam hydrochloride.

Dosage and use: See package insert.

Preparation: To prepare, empty the entire contents of one packet into a glass or cup. Add 1 cup (8 ounces) of water, fruit juice or diet soft drinks. Stir well and drink. Colesevelam Hydrochloride for Oral Suspension should not be taken in its dry form.

Keep Out of Reach of Children. Package Not Child Resistant.

PHENYLETHANOL
CONTAINS PHENYLALANINE 33.6 mg per packet.

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

Manufactured by: Alkem Laboratories Ltd.
Mumbai – 400 013, INDIA

Distributed by: Ascend Laboratories, LLC
Parsippany, NJ 07054

M. L. No.: MNB/05/105
COLESEVELAM HYDROCHLORIDE
colesevelam hydrochloride powder, for suspension

Product Information

Product Type: HUMAN PRESCRIPTION DRUG
Route of Administration: ORAL

Active Ingredient/Active Moiety

<table>
<thead>
<tr>
<th>Ingredient Name</th>
<th>Basis of Strength</th>
<th>Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>COLESEVELAM HYDROCHLORIDE (UNII: P4SG24WE5Q)</td>
<td>COLESEVELAM HYDROCHLORIDE</td>
<td>3.75 g</td>
</tr>
</tbody>
</table>

Inactive Ingredients

<table>
<thead>
<tr>
<th>Ingredient Name</th>
<th>Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>MICROCRYSTALLINE CELLULOSE (UNII: OPIR32DG1U)</td>
<td></td>
</tr>
<tr>
<td>MEDIUM-CHAIN TRIGLYCERIDES (UNII: C9H2L21V7U)</td>
<td></td>
</tr>
<tr>
<td>SILICON DIOXIDE (UNII: ETJ7Z6XBU4)</td>
<td></td>
</tr>
<tr>
<td>MAGNESIUM TRISILICATE (UNII: C2E1C501T)</td>
<td></td>
</tr>
<tr>
<td>CITRIC ACID MONOHYDRATE (UNII: 2968PHW8QP)</td>
<td></td>
</tr>
<tr>
<td>ASPARTAME (UNII: Z0H242BBR1)</td>
<td></td>
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<tr>
<td>DIMETHICOSE (UNII: 92RU3N3Y1O)</td>
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</tr>
<tr>
<td>LEMON (UNII: 24RS0A9880)</td>
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</tr>
<tr>
<td>ORANGE (UNII: 5EVU04NSQU)</td>
<td></td>
</tr>
<tr>
<td>PROPYLENE GLYCOL ALGINATE (UNII: 26CD3J2R0C)</td>
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</tr>
</tbody>
</table>

Product Characteristics

Color: YELLOW (White to Yellow Granular Powder)
Shape: Score
Size:
Flavor  | CITRUS (Lemon-Orange Flavor) |
Contains |

Packaging

<table>
<thead>
<tr>
<th>#</th>
<th>Item Code</th>
<th>Package Description</th>
<th>Marketing Start Date</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>NDC:67877-523-30</td>
<td>30 in 1 PACKET; Type 0: Not a Combination Product</td>
<td>05/09/2019</td>
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</tbody>
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Marketing Information

<table>
<thead>
<tr>
<th>Marketing Category</th>
<th>Application Number or Monograph Citation</th>
<th>Marketing Start Date</th>
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<tbody>
<tr>
<td>ANDA</td>
<td>ANDA210316</td>
<td>05/09/2019</td>
</tr>
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Labeler - Ascend Laboratories, LLC (141250469)

Establishment

<table>
<thead>
<tr>
<th>Name</th>
<th>Address</th>
<th>ID/FEI</th>
<th>Business Operations</th>
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<tbody>
<tr>
<td>Alkem Laboratories Limited</td>
<td>677605851</td>
<td></td>
<td>ANALYSIS(67877-523) , REPACK(67877-523) , MANUFACTURE(67877-523) , PACK(67877-523)</td>
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</tbody>
</table>

Revised: 5/2019