

## PRODUCT MONOGRAPH

<sup>Pr</sup> APO-COLESEVELAM

Colesevelam Hydrochloride

Film-coated Tablets 625 mg

Bile Acid Sequestrant

ATC code: C10A C 04

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## Table of Contents

|  |           |
|--|-----------|
| <b>PART I: HEALTH PROFESSIONAL INFORMATION .....</b> | <b>3</b>  |
| SUMMARY PRODUCT INFORMATION.....                     | 3         |
| INDICATIONS AND CLINICAL USE .....                   | 3         |
| CONTRAINDICATIONS.....                               | 3         |
| WARNINGS AND PRECAUTIONS .....                       | 4         |
| ADVERSE REACTIONS .....                              | 5         |
| DRUG INTERACTIONS .....                              | 9         |
| DOSAGE AND ADMINISTRATION .....                      | 12        |
| OVERDOSAGE .....                                     | 12        |
| ACTION AND CLINICAL PHARMACOLOGY .....               | 13        |
| STORAGE AND STABILITY .....                          | 14        |
| SPECIAL HANDLING INSTRUCTIONS.....                   | 14        |
| DOSAGE FORMS, COMPOSITION AND PACKAGING.....         | 14        |
| <b>PART II: SCIENTIFIC INFORMATION.....</b>          | <b>15</b> |
| PHARMACEUTICAL INFORMATION .....                     | 15        |
| CLINICAL TRIALS.....                                 | 17        |
| DETAILED PHARMACOLOGY.....                           | 21        |
| TOXICOLOGY.....                                      | 22        |
| REFERENCES.....                                      | 24        |
| <b>PART III: CONSUMER INFORMATION .....</b>          | <b>26</b> |

Pr  
APO-COLESEVELAM

Colesevelam Hydrochloride Tablets

**PART I: HEALTH PROFESSIONAL INFORMATION**

**SUMMARY PRODUCT INFORMATION**

| <b>Route of Administration</b> | <b>Dosage Form / Strength</b> | <b>All Nonmedicinal Ingredients</b>  |
|--------------------------------|-------------------------------|--|
| Oral                           | Tablet 625 mg                 | Diacetylated Monoglycerides, Hypromellose, Magnesium Stearate, Microcrystalline Cellulose, Silicon DiOxide |

**INDICATIONS AND CLINICAL USE**

APO-COLESEVELAM (colesevelam) is indicated for the reduction of cholesterol blood level in patients with hypercholesterolemia (Fredrickson Type IIa) as an adjunct to diet and lifestyle changes, when the response to these measures has been inadequate, in patients:

- who are not adequately controlled with an HMG-CoA reductase inhibitor (statin) alone, *or*
- who are unable to tolerate a statin.

**Limitations of Use**

Colesevelam has not been studied in Fredrickson Type I, IIb, III, IV and V dyslipidemias.

**Geriatrics (≥65 years of age):**

There is no need for dose adjustment when APO-COLESEVELAM is administered to elderly patients.

**Pediatrics (<18 years of age):**

The safety and efficacy of colesevelam have not been established in children and adolescent patients; therefore, the use of APO-COLESEVELAM in these patient populations is not recommended.

**CONTRAINDICATIONS**

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of

- the product monograph.
- Bowel or biliary obstruction

## **WARNINGS AND PRECAUTIONS**

### **General**

Prior to initiating therapy with APO-COLESEVELAM (colesevelam), if secondary causes of hypercholesterolemia (i.e., poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinemias, obstructive liver disease) are considered, these should be diagnosed and properly treated.

*For patients on cyclosporine starting or stopping APO-COLESEVELAM or patients on APO-COLESEVELAM with a need to start cyclosporine:* APO-COLESEVELAM reduces the bioavailability of cyclosporine (see **DRUG INTERACTIONS**). Patients starting on cyclosporine already taking APO-COLESEVELAM should have their cyclosporine blood concentrations monitored as normal and their dose adjusted as normal. Patients starting on APO-COLESEVELAM already taking cyclosporine should have their blood concentrations monitored prior to combination therapy and frequently monitored immediately starting co-therapy with the cyclosporine dose adjusted accordingly. It should be noted that stopping APO-COLESEVELAM therapy will result in increased cyclosporine blood concentrations. Therefore, patients taking both cyclosporine and APO-COLESEVELAM should have their blood concentrations monitored prior to and frequently after when APO-COLESEVELAM therapy is stopped with their cyclosporine dose adjusted accordingly.

### **Endocrine and Metabolism:**

When treating hypercholesterolemic patients with type 2 diabetes mellitus who initiate or are currently on antidiabetic pharmacologic treatment regimen, the fasting plasma glucose (FPG) lowering effect of colesevelam as well as subsequent HbA1c monitoring should be considered, since this effect has been observed with colesevelam when administered with some antidiabetic agents

### **Gastrointestinal**

The safety and efficacy of colesevelam in patients with dysphagia, swallowing disorders, severe gastrointestinal motility disorders, inflammatory bowel disease, liver failure or major gastrointestinal tract surgery have not been established. Consequently, caution should be exercised when APO-COLESEVELAM is used in patients with these disorders.

APO-COLESEVELAM can induce or worsen present constipation. The risk of constipation should especially be considered in patients with coronary heart disease and angina pectoris.

### **Hematologic**

Anticoagulant therapy should be monitored closely in patients receiving warfarin or similar agents, since bile acid sequestrants, like APO-COLESEVELAM, have been shown to reduce absorption of vitamin K and therefore interfere with warfarin's anticoagulant effect (see **DRUG INTERACTIONS**).

### **Hepatic/Biliary/Pancreatic**

Caution should be exercised when treating patients with triglyceride levels greater than 3.4 mmol/L due

to the triglyceride increasing effect with APO-COLESEVELAM. Safety and efficacy are not established for patients with triglyceride levels greater than 3.4 mmol/L, since such patients were excluded from the clinical studies.

### **Sexual Function/Reproduction**

APO-COLESEVELAM can affect the bioavailability of the oral contraceptive pill when administered simultaneously. It is important to ensure that APO-COLESEVELAM is administered at least 4 hours after the oral contraceptive pill to minimize the risk of any interaction (see **DRUG INTERACTIONS**).

### **Special Populations**

**Pregnant Women:** No clinical data are available on the use of colesivelam in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonic/fetal development, parturition or post-natal development (see **TOXICOLOGY**). Caution should be exercised when prescribing to pregnant women.

**Nursing Women:** The safety of colesivelam has not been established in breast-feeding women. Caution should be exercised when prescribing to breast-feeding women.

**Pediatrics (<18 years of age):** The safety and efficacy of colesivelam have not been established in children and adolescent patients; therefore, the use of APO-COLESEVELAM in these patient populations is not recommended.

**Geriatrics (≥65 years of age):** 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.

### **Monitoring and Laboratory Tests**

Serum total-C, LDL-C and triglyceride levels should be determined periodically during treatment to confirm favourable initial and adequate long-term responses.

The impact on glycemic levels of colesivelam when used concomitantly with antidiabetic pharmacologic treatment regimens should be monitored by periodic measurements of blood glucose and HbA1c levels. When APO-COLESEVELAM is co-administered with metformin extended release formulation, the physician should monitor glucose more closely.

## **ADVERSE REACTIONS**

### **Adverse Drug Reaction Overview**

In monotherapy clinical trials, the most common (incidence ≥2% and greater than placebo) adverse reactions with colesivelam included constipation, dyspepsia, and nausea.

Post-marketing ADR reports include bowel obstruction, dysphagia, esophageal obstruction, fecal impaction, hypertriglyceridemia, pancreatitis and increased transaminases. Additionally some

interaction reports were received describing changes in phenytoin levels, reduced International Normalized Ratio (INR), and elevated thyroid-stimulating hormone (TSH) (see **DRUG INTERACTIONS**).

**Clinical Trial Adverse Drug Reactions**

*Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

In the lipid-lowering trials, 807 patients received at least one dose of colesevelam (total exposure 199 patient-years). In clinical trials for the reduction of LDL-C, 68% of patients receiving colesevelam vs. 64% of patients receiving placebo reported an adverse reaction.

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

Table 1 summarizes the placebo-controlled monotherapy clinical studies of colesevelam for hyperlipidemia: Adverse reactions reported in ≥1% of patients and numerically more commonly than in patients given placebo, regardless of investigator assessment of causality.

**Table 1 - Placebo-Controlled Monotherapy Clinical Studies of colesevelam for Hyperlipidemia: Adverse Reactions Reported in ≥1% of Patients and Numerically More Commonly than in Patients Given Placebo, Regardless of Investigator Assessment of Causality**

| BODY SYSTEM        | PLACEBO<br>(n=258) |     | Colesevelam ONLY<br>(n=807) |      |
|--------------------|--------------------|-----|-----------------------------|------|
|                    | N                  | %   | N                           | %    |
| Body as a whole    |                    |     |                             |      |
| Flu syndrome       | 8                  | 3.1 | 26                          | 3.2  |
| Asthenia           | 5                  | 1.9 | 29                          | 3.6  |
| Accidental injury  | 7                  | 2.7 | 30                          | 3.7  |
| Chest pain         | 2                  | 0.8 | 11                          | 1.4  |
| Allergic reaction  | 2                  | 0.8 | 9                           | 1.1  |
| Digestive system   |                    |     |                             |      |
| Constipation       | 18                 | 7.0 | 89                          | 11.0 |
| Dyspepsia          | 9                  | 3.5 | 67                          | 8.3  |
| Nausea             | 10                 | 3.9 | 34                          | 4.2  |
| Gastroenteritis    | 1                  | 0.4 | 9                           | 1.1  |
| Respiratory system |                    |     |                             |      |

|                        |   |     |    |     |
|------------------------|---|-----|----|-----|
| Pharyngitis            | 5 | 1.9 | 26 | 3.2 |
| Rhinitis               | 8 | 3.1 | 26 | 3.2 |
| Nervous system         |   |     |    |     |
| Dizziness              | 3 | 1.2 | 13 | 1.6 |
| Anxiety                | 1 | 0.4 | 10 | 1.2 |
| Musculoskeletal system |   |     |    |     |
| Myalgia                | 1 | 0.4 | 17 | 2.1 |
| Arthritis              | 2 | 0.8 | 10 | 1.2 |
| Skin and appendages    |   |     |    |     |
| Rash                   | 3 | 1.2 | 14 | 1.7 |
| Contact dermatitis     | 2 | 0.8 | 10 | 1.2 |

Colesevelam treatment is well-tolerated, though gastrointestinal symptoms (usually mild) are common. In general, the percentages of patients reporting common adverse events were similar in the placebo and colesevelam -only treatment categories. Only constipation and dyspepsia were reported by a higher percentage of colesevelam -only patients.

#### Combination with a HMG-CoA Reductase Inhibitor

Colesevelam has been evaluated for safety in combination studies with a statin in 279 patients. In general, adverse experiences were similar between colesevelam administered with a statin and a statin alone. However, the frequency of constipation was higher (9.3% vs 5.3%) in patients receiving colesevelam administered with a statin than in patients treated with a statin alone, as was the frequency of dyspepsia (5.4% vs 3.8%). No other adverse events were reported in  $\geq 2\%$  of patients and at an incidence significantly greater on the combination than on the statin alone. Nausea occurred less frequently in patients receiving colesevelam administered with a statin (3.2%) than in patients treated with a statin alone (4.3%).

**Table 2** - Placebo-Controlled Combination Clinical Studies of colesevelam for Hyperlipidemia: Adverse Reactions Reported in  $\geq 1\%$  of Patients Regardless of Investigator Assessment of Causality.

| BODY SYSTEM      | STATIN + PLACEBO<br>(n=209) |     | STATIN +<br>Colesevelam<br>(n=279) |     |
|------------------|-----------------------------|-----|------------------------------------|-----|
|                  | N                           | %   | N                                  | %   |
| Body as a whole  |                             |     |                                    |     |
| Headache         | 13                          | 6.2 | 16                                 | 5.7 |
| Flu syndrome     | 6                           | 2.9 | 4                                  | 1.4 |
| Digestive system |                             |     |                                    |     |
| Constipation     | 11                          | 5.3 | 26                                 | 9.3 |
| Flatulence       | 18                          | 8.6 | 18                                 | 6.5 |

|                             |    |     |    |     |
|-----------------------------|----|-----|----|-----|
| Dyspepsia                   | 8  | 3.8 | 15 | 5.4 |
| Diarrhea NOS                | 15 | 7.2 | 9  | 3.2 |
| Nausea                      | 9  | 4.3 | 9  | 3.2 |
| Abdominal tenderness        | 4  | 1.9 | 6  | 2.2 |
| Dry mouth                   | 0  | 0.0 | 3  | 1.1 |
| Abnormal stools             | 1  | 0.5 | 3  | 1.1 |
| Musculoskeletal system      |    |     |    |     |
| Myalgia                     | 9  | 4.3 | 11 | 3.9 |
| Skin and appendages         |    |     |    |     |
| Dry skin                    | 0  | 0.0 | 3  | 1.1 |
| Urogenital system           |    |     |    |     |
| Urinary tract infection NOS | 0  | 0.0 | 4  | 1.4 |

**Less Common Clinical Trial Adverse Drug Reactions (<1%)**

Less common clinical trial treatment-emergent adverse events (<1% and greater than placebo) possibly or probably related to colesevelam:

**Digestive System:** Anorexia, eructation, dysphagia, increased appetite, liver function tests abnormal, colitis, glossitis, stomatitis.

**Body as a Whole:** Asthenia, chest pain, pain, LE syndrome.

**Nervous System:** Hyperkinesia, anxiety, nervousness, paresthesia.

**Musculoskeletal System:** Myalgia, leg cramps.

**Respiratory System:** Pharyngitis, dyspnea, rhinitis, sputum increased.

**Skin and Appendages:** Nail disorder.

**Special Senses:** Taste perversion, conjunctivitis.

**Metabolic and Nutritional Disorders:** SGPT increased, peripheral edema, SGOT increased.

**Urogenital System:** Urinary urgency.

**Cardiovascular System:** Hypertension.

**Post-Market Adverse Drug Reactions**

The following additional adverse reactions have been identified during post-market use of colesevelam. 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 APO-COLESEVELAM administration include:

- Increased seizure activity or decreased phenytoin levels in patients receiving phenytoin. Phenytoin should be administered 4 hours prior to APO-COLESEVELAM.
- Reduced International Normalized Ratio (INR) in patients receiving warfarin therapy. In warfarin-treated patients, INR should be monitored frequently during colesevelam 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 APO-COLESEVELAM [See **DRUG INTERACTIONS**].

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

Metabolism and Nutrition Disorders: hypoglycaemia

## **DRUG INTERACTIONS**

### **Overview**

Colesevelam may affect the bioavailability of other medicinal products. Therefore, when a drug interaction cannot be excluded with a concomitant medicinal product, APO-COLESEVELAM (colesevelam) should be administered at least four hours after the concomitant medication to minimize the risk of reduced absorption of the concomitant medication

When administering medicinal products for which alterations in blood levels could have a clinically significant effect on safety or efficacy, physicians should consider monitoring serum levels or effects.

Interaction studies have only been performed in adults.

In interaction studies in healthy volunteers, colesevelam had no effect on the bioavailability of digoxin, metoprolol, quinidine, valproic acid, and warfarin. Colesevelam decreased the  $C_{max}$  and AUC of sustained-release verapamil by approximately 31% and 11%, respectively. Since there is a high degree of variability in the bioavailability of verapamil, the clinical significance of this finding is unclear.

In pharmacokinetic interaction studies in patients, colesevelam had no effect on the bioavailability of fenofibrate and lovastatin.

There have been very rare reports of reduced phenytoin levels in patients who have received colesevelam administered with phenytoin.

## **Drug-Drug Interactions**

**Table 3** lists the drugs that have been tested in *in vitro* or *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 APO-COLESEVELAM. Alternatively, the physician should monitor drug levels of the co-administered drug.

**Table 3: Drugs Tested in In Vivo Binding or In Vivo Drug Interaction Testing or Post-Marketing Reports**

|   |  |
|---|--|
| Drugs with a known interaction with colesevelam <sup>a</sup>  | Glyburide, levothyroxine, and oral contraceptives containing ethinyl estradiol and norethindrone                                     |
| Drugs with post-marketing reports consistent with potential drug-drug interactions when coadministered with colesevelam | phenytoin <sup>a</sup> , warfarin <sup>b</sup>   |
| Drugs that do not interact with colesevelam based on <i>in vitro</i> or <i>in vivo</i> testing                          | digoxin, warfarin <sup>b</sup> , fenofibrate, lovastatin, metoprolol, pioglitazone, quinidine, repaglinide, valproic acid, verapamil |

<sup>a</sup> Should be administered at least 4 hours prior to colesevelam

<sup>b</sup> No significant alteration of warfarin drug levels with warfarin and colesevelam coadministration in an *in vivo* study which did not evaluate warfarin pharmacodynamics (INR). (see Post-Marketing Adverse Drug Reactions)

### *Anticoagulant therapy*

Anticoagulant therapy should be monitored closely in patients receiving warfarin or similar agents, since bile acid sequestrants have been shown to reduce absorption of vitamin K and therefore interfere with warfarin's anticoagulant effect. Specific clinical interaction studies with colesevelam and vitamin K have not been performed.

### *Levothyroxine*

In an interaction study in healthy volunteers, colesevelam reduced the AUC and C<sub>max</sub> of levothyroxine when administered either concomitantly or after 1 hour. No interaction was observed when colesevelam was administered at least four hours after levothyroxine.

### *Oral contraceptive pill*

In an interaction study in healthy volunteers, colesevelam reduced the C<sub>max</sub> of norethindrone as well as the AUC and C<sub>max</sub> of ethinylestradiol when administered simultaneously with the oral contraceptive pill. This interaction was also observed when colesevelam was administered one hour after the oral contraceptive pill. However no interaction was observed when colesevelam was administered four hours after the oral contraceptive pill.

### *Cyclosporine*

In an interaction study in healthy volunteers, co-administration of colesevelam and cyclosporine significantly reduced the AUC<sub>0-inf</sub> and C<sub>max</sub> of cyclosporine by 34% and 44%, respectively. Therefore, advice is given to closely monitor cyclosporine blood concentrations (see also section 4.4). In addition,

based on theoretical grounds APO-COLESEVELAM should be administered at least 4 hours after cyclosporine in order to further minimize the risks related to the concomitant administration of cyclosporine and APO-COLESEVELAM. Furthermore, APO-COLESEVELAM should always be administered at the same times consistently since the timing of intake of colessevelam and cyclosporine could theoretically influence the degree of reduced bioavailability of cyclosporine.

#### *Statins*

When colessevelam was co-administered with statins in clinical studies, an expected add-on LDL-C lowering effect was observed, and no unexpected effects were observed. Interaction studies with colessevelam in combination with pravastatin, rosuvastatin, or high dose HMG-CoA reductase inhibitors have not been performed.

#### *Antidiabetic agents*

When colessevelam was co administered with some antidiabetic agents in clinical studies (metformin, insulin, sulfonylureas) an add-on fasting plasma glucose lowering, effect was observed.

Co-administration of colessevelam and glyburide caused a decrease in the  $AUC_{0-inf}$  and  $C_{max}$  of glyburide by 32% and 47%, respectively. No interaction was observed when colessevelam was administered four hours after glyburide. colessevelam increased levels of metformin when co-administered with metformin extended release formulation.

Co-administration of colessevelam and repaglinide had no effect on the AUC and caused a 19% reduction in the  $C_{max}$  of repaglinide, the clinical significance of which is unknown. No interaction was observed when colessevelam was administered one hour after repaglinide.

No interaction was observed when colessevelam and pioglitazone were administered simultaneously in healthy volunteers.

#### *Other forms of interaction*

Colessevelam did not induce any clinically significant reduction in the absorption of vitamins A, D, E or K during clinical studies of up to one year. However, caution should be exercised when treating patients with a susceptibility to vitamin K or fat-soluble vitamin deficiencies, such as patients with malabsorption. In these patients, monitoring vitamin A, D and E levels and assessing vitamin K status through the measurement of coagulation parameters is recommended and the vitamins should be supplemented if necessary.

#### **Drug-Food Interactions**

Interactions with food have not been established.

#### **Drug-Herb Interactions**

Interactions with herbal products have not been established.

#### **Drug-Laboratory Interactions**

Interactions with laboratory tests have not been established. Post marketing reports of hypertriglyceridemia (see Post-Market Adverse Drug Reactions).

#### **Drug-Lifestyle Interactions**

Colesevelam has no or negligible influence on the ability to drive and use machines.

## **DOSAGE AND ADMINISTRATION**

### **Dosing Considerations**

Prior to initiating therapy with APO-COLESEVELAM (colesevelam), if secondary causes of hypercholesterolemia (i.e., poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinemias, obstructive liver disease) are considered, these should be diagnosed and properly treated. (see **WARNINGS AND PRECAUTIONS**)

### **Recommended Dose and Dosage Adjustment**

#### *Combination therapy*

The recommended dose of APO-COLESEVELAM is 4 to 6 tablets per day. The maximum recommended dose is 3 tablets taken twice per day with meals or 6 tablets taken once per day with a meal.

Clinical trials have shown that colesevelam and atorvastatin, lovastatin or simvastatin can be co-administered or dosed apart.

#### *Monotherapy*

The recommended starting dose of APO-COLESEVELAM is 3 tablets taken twice per day with meals or 6 tablets once per day with a meal. The maximum recommended dose is 7 tablets per day.

During therapy, the cholesterol-lowering diet should be continued, and serum total-C, LDL-C and triglyceride levels should be determined periodically during treatment to confirm favourable initial and adequate long-term responses.

When a drug interaction cannot be excluded with a concomitant medicinal product, APO-COLESEVELAM should be administered at least four hours after the concomitant medication in order to minimize the risk of reduced absorption of the concomitant medication (see **DRUG INTERACTIONS**).

### **Missed Dose**

If a dose is forgotten, it may be taken with a later meal. But never take in one day more than the total number of tablets prescribed in a single day. Double dosing is not advisable.

### **Administration**

APO-COLESEVELAM tablets should be taken orally with a meal and liquid.

## **OVERDOSAGE**

Since colesevelam is not absorbed, the risk of systemic toxicity is low. Gastrointestinal symptoms could occur. Doses in excess of the maximum recommended dose (4.5 g per day (7 tablets)) have not been tested.

|   |
|---|
| For the management of a suspected drug overdose, contact your regional Poison Control Centre. |
|---|

Should overdosage occur, however, the chief potential harm would be obstruction of the gastrointestinal tract. The location of such potential obstruction, the degree of obstruction and the presence or absence of normal gut motility would determine treatment.

## **ACTION AND CLINICAL PHARMACOLOGY**

### **Mechanism of Action**

The mechanism of action for the activity of colestevlam, the active substance in colestevlam, has been evaluated in several *in vitro* and *in vivo* studies. These studies have demonstrated that colestevlam binds bile acids, including glycocholic acid, the major bile acid in humans. Cholesterol is the sole precursor of bile acids. During normal digestion, bile acids are secreted into the intestine. A major portion of bile acids is then absorbed from the intestinal tract and returned to the liver via the enterohepatic circulation.

Bile acid sequestrants alter the bile acid pool composition, which might explain the impact on glycemic levels associated with these drugs, although the mechanism is unknown.

### **Pharmacodynamics**

Colestevlam is a non-absorbed, lipid-lowering polymer that binds bile acids in the intestine, impeding their reabsorption. The LDL-C lowering mechanism of bile acid sequestrants has been previously established as follows: as the bile acid pool becomes depleted, the hepatic enzyme, cholesterol 7- $\alpha$  -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 effects of increasing transcription and activity of the cholesterol biosynthetic enzyme, hydroxymethyl-glutaryl-coenzyme A (HMG-CoA) reductase, and increasing the number of hepatic low-density lipoprotein receptors. A concomitant increase in very low density lipoprotein synthesis can occur. These compensatory effects result in increased clearance of LDL-C from the blood, resulting in decreased serum LDL-C levels.

In a 6-month dose-response study in patients with primary hypercholesterolemia receiving 3.8 or 4.5 g colestevlam, a 15 to 18% decrease in LDL-C levels was observed, which was evident within 2 weeks of administration. In addition, total-C decreased 7 to 10%, HDL-C increased 3% and triglycerides increased 9 to 10%. Apo B decreased by 12%. In comparison, in patients given placebo, LDL-C, total-C, HDL-C and apo-B were unchanged, while triglycerides increased 5%. Studies examining administration of colestevlam as a single dose with breakfast, a single dose with dinner, or as divided doses with breakfast and dinner did not show significant differences in LDL-C reduction for different dosing schedules. However, in one study triglycerides tended to increase more when colestevlam was given as a single dose with breakfast. Multicentre, randomized, double-blind, placebo-controlled studies in 487 patients demonstrated an additive reduction of 8 to 16% in LDL-C when 2.3 to 3.8 g colestevlam and a statin (atorvastatin, lovastatin or simvastatin) were administered at the same time. Initiation of add-on treatment with colestevlam subsequent to statin therapy has not been specifically studied. Colestevlam has not been compared directly to other bile acid sequestrants in clinical trials.

In a 6 week study 129 patients with mixed hyperlipidemia were randomized to fenofibrate 160 mg plus 3.8 g colestevlam or fenofibrate alone. The fenofibrate plus colestevlam group (64 patients) demonstrated a 10% reduction in LDL-C levels versus 2% increase for the fenofibrate group (65 patients). Reductions were also seen for non-HDL-C, total-C and apo-B. A small 5%, non-significant

increase in triglycerides was noted. The effects of combination of fenofibrate and colessevelam on the risks of myopathy or hepatotoxicity are not known.

**Pharmacokinetics**

Colesevelam is not absorbed from the gastrointestinal tract.

**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 <sup>14</sup>C-labeled colessevelam hydrochloride dose was excreted in the urine.

**STORAGE AND STABILITY**

Store at room temperature 15°C to 30°C. Protect from moisture.

**SPECIAL HANDLING INSTRUCTIONS**

No special requirements.

**DOSAGE FORMS, COMPOSITION AND PACKAGING**

APO-COLESEVELAM 625 mg tablets: Each tablet contains 625 mg colessevelam hydrochloride. White to off white, oval, biconvex coated tablet. Engraved “APO” on one side, “C625” on the other side. Available in bottles of 180 and 500.

*Tablet core:* Magnesium stearate, Microcrystalline Cellulose, Silicon Dioxide

*Film-coating:* Diacetylated Monoglycerides, Hypromellose

## PART II: SCIENTIFIC INFORMATION

### PHARMACEUTICAL INFORMATION

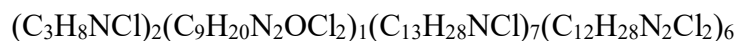
#### Drug Substance

Common name: Colesevelam Hydrochloride

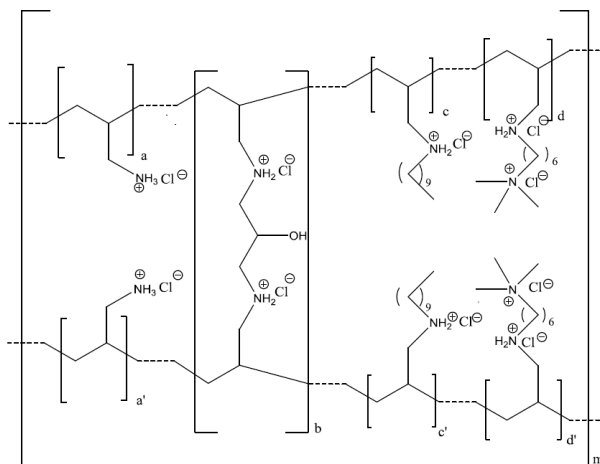
Chemical name: Allylamine polymer with 1-chloro-2,3-epoxypropane, [6-(allylamino)-hexyl] trimethylammonium chloride and N-allyldecylamine, hydrochloride;

1-Hexanaminium, N,N,N-trimethyl-6-(2-propenylamine)-, chloride, polymer with (chloromethyl)oxirane, 2-propen-1-amine and N-2-propenyl-1-decanamine, hydrochloride

Molecular formula and molecular mass:



Structural formula:



Where:

a = number of primary amine groups  
b = number of cross-linked amine groups  
c = decylbromide alkylated amine groups  
d = monoquat alkylated amine groups  
m > 100 to indicate extended polymer network

a + a' = about 0.14  
b = about 0.12  
c + c' = about 0.35  
d + d' = about 0.38

Colesevelam hydrochloride is achiral.

Physicochemical properties:

Physical description:

Colesevelam hydrochloride is a white to off-white, non-crystalline powder with a slight odour characteristic of amines.

Physical form:

Non-crystalline powder.

Solubilities:

Insoluble in all tested aqueous (water, 0.1N HCl, 0.1N HCl/50°C, 1N ammonium hydroxide) and organic solvents (methylene chloride, acetonitrile, octanol and methanol).

pH and pKa values:

The pH is 3.6. The pK value (pK<sub>3</sub>) is approximately 9.3



## CLINICAL TRIALS

### Comparative Bioavailability Studies

Colesevelam hydrochloride resin is not absorbed from the gastrointestinal (GI) tract but passes through the GI tract and complexes with bile acids. The complexes are then excreted with unchanged resin in the feces. Consequently, conventional comparative bioavailability studies are not considered to be a valid test of product performance for the purpose of demonstrating bioequivalence.

Comparative *in vitro* equilibrium and kinetic binding studies with bile acids were conducted in order to demonstrate bioequivalence between the APO-COLESEVELAM film-coated tablets, 625 mg (Apotex Inc.) and LODALIS<sup>®</sup> tablets, 625 mg (Valeant Canada LP/Valeant Canada S.E.C.).

Twelve randomized, placebo-controlled efficacy studies were conducted in 1,740 patients with hyperlipidemia. A total of 1,193 patients were treated with colesevelam: 807 received colesevelam alone, 279 received a colesevelam /HMG-CoA reductase inhibitor combination, and 107 received colesevelam combined with another lipid lowering agent.

Colesevelam administered alone or with a statin was shown to be effective in reducing LDL-C and total-C and in increasing HDL-C in patients with primary hypercholesterolemia.

#### *Study demographics and trial design*

The patient population included men and women 18 years of age or older with primary hypercholesterolemia. The mean age was 56 years; 51% of the population was male. Patients had a serum LDL-cholesterol of at least 3.36 mmol/L. All patients followed a low-fat, low-cholesterol diet, avoided fasting or binge eating, and ate at least 2 meals on most days.

All studies were randomized, placebo-controlled, double-blind, parallel-group studies; eight of the studies had an active control group (**Table 4**).

**Table 4** - Summary of Design and Patient Demographics for all Efficacy Studies

| Study #    | Design                | Route of administration and duration | Dosage     | Study subjects (n) | Mean age (Range)  | Percent male |
|------------|-----------------------|--------------------------------------|------------|--------------------|-------------------|--------------|
| GTC-37-201 | Randomized DB, PC, PG | p.o.<br>6 weeks                      | Placebo    | 29                 | 56.0 y<br>(31-80) | 44%          |
|            |                       |                                      | 0.8 g bid  | 30                 |                   |              |
|            |                       |                                      | 1.2 g bid  | 30                 |                   |              |
|            |                       |                                      | 1.6 g bid  | 31                 |                   |              |
|            |                       |                                      | 2.0 g bid  | 29                 |                   |              |
| GTC-37-202 | Randomized DB, PC, PG | p.o.<br>4 weeks                      | Placebo    | 32                 | 55.4 y<br>(21-83) | 57%          |
|            |                       |                                      | 1.6 g q AM | 30                 |                   |              |
|            |                       |                                      | 1.6 g q PM | 30                 |                   |              |
|            |                       |                                      | 0.8 g bid  | 30                 |                   |              |

|            |                          |                  |  |  |                   |     |
|------------|--------------------------|------------------|--|--|-------------------|-----|
| GTC-37-203 | Randomized<br>DB, PC, PG | p.o.<br>4 weeks  | Placebo<br>2.4 g q PM<br>Lovastatin 10 mg q PM<br>2.4 g q PM + lovastatin 10 mg q PM<br>2.4 g q PM + lovastatin<br>10 mg q HS                                | 26<br>29<br>26<br>29<br>25             | 57.7 y<br>(23-88) | 45% |
| GTC-48-204 | Randomized<br>DB, PC, PG | p.o.<br>6 weeks  | Placebo<br>1.2 g bid<br>2.0 g bid<br>Simvastatin 10 mg qd<br>Simvastatin 20 mg qd<br>1.2 g bid + simvastatin 20 mg qd<br>2.0 g bid + simvastatin<br>10 mg qd | 35<br>38<br>38<br>36<br>39<br>37<br>35 | 54.3 y<br>(18-82) | 58% |
| GTC-48-205 | Randomized<br>DB, PC, PG | p.o.<br>4 weeks  | Placebo<br>2.0 g bid<br>Atorvastatin 10 mg qd<br>2.0 g bid + atorvastatin 10 mg qd<br>Atorvastatin 80 mg qd  | 19<br>17<br>19<br>19<br>20             | 57.3 y<br>(28-79) | 70% |
| GTC-48-301 | Randomized<br>DB, PC, PG | p.o.<br>6 months | Placebo<br>1.2 g bid<br>1.6 g bid<br>2.0 g bid<br>2.4 g bid  | 94<br>102<br>98<br>101<br>99           | 55.5 y<br>(18-86) | 50% |
| GTC-48-302 | Randomized<br>DB, PC, PG | p.o.<br>6 weeks  | Placebo<br>4.0 g q AM<br>4.0 g q PM<br>2.0 g bid   | 23<br>27<br>24<br>24                   | 55.2 y<br>(24-70) | 45% |
| WEL-403    | Randomized<br>DB, PC, PG | p.o.<br>6 weeks  | 3.75 g qd + fenofibrate 160 mg qd<br>Placebo + fenofibrate<br>160 mg qd  | 64<br>65                               | 54.8 y<br>(31-70) | 56% |
| WEL-405    | Randomized<br>DB, PC, PG | p.o.<br>6 weeks  | 3.75 g qd + simvastatin<br>Simvastatin mean of 28 mg/day   | 47<br>25                               | 60 y<br>(31-82)   | 50% |
| WEL-406    | Randomized<br>DB, PC, PG | p.o.<br>6 weeks  | 3.75 g qd + atorvastatin<br>Atorvastatin mean of 16 mg/day   | 40<br>25                               | 57.7 y<br>(32-78) | 44% |
| WEL-407    | Randomized<br>DB, PC, PG | p.o.<br>6 weeks  | 3.75 g qd + pravastatin<br>Pravastatin mean of 25 mg/day   | 47<br>20                               | 54.8 y<br>(29-80) | 40% |
| WEL-408    | Randomized<br>DB, PC, PG | p.o.<br>10 weeks | 3.75 g qd + ezetimibe 10 mg/day<br>Placebo + ezetimibe 10 mg/day   | 43<br>43                               | 59.1 y<br>(24-79) | 43% |

### Monotherapy

The efficacy and safety of colessevelam monotherapy was evaluated in seven randomized, double-blind,

placebo-controlled studies (**Table 5**). Three of these studies included an active control of atorvastatin, pravastatin, or simvastatin.

### Study results

The primary efficacy parameter in all of the studies was the percent change in serum LDL cholesterol concentration from the end of the diet period to the end of an active treatment period. Secondary efficacy variables included the percent change in total cholesterol, HDL cholesterol, and triglycerides.

Compared to baseline, colesevelam reduced LDL-C at all doses studied, whether taken as a single daily dose or as divided doses. In dose-ranging studies, there was a clear dose-response relationship over the range of doses studied. The decreases were greater than on placebo at all doses studied. In the largest phase 3 study, all pairwise comparisons were significant except for 12 g bid compared to 1.6 g bid and g bid compared to 2.0 g bid. In studies with an active control, HMG-CoA reductase inhibitor resulted in a greater reduction of LDL-C than did colesevelam.

Colesevelam also reduced total cholesterol, and tended to increase HDL-C and triglycerides.

A maximum therapeutic response to colesevelam was generally achieved within 2 weeks and was maintained during long-term therapy.

Colesevelam is equally effective in a variety of patient populations with hypercholesterolemia: men and women, under or over 65 years of age, pre- and post-menopausal women, Caucasians and non-Caucasians.

**Table 5** - Summary of Monotherapy Study Results (mean % change from baseline)

| Study<br>Treatment       | LDL-C  |         | TOT-C |         | HDL-C |        | TG    |        |
|--------------------------|--------|---------|-------|---------|-------|--------|-------|--------|
|                          | % ■    | p       | % ■   | p       | % ■   | p      | % ■   | p      |
| <b>GTC-37-201</b>        |        |         |       |         |       |        |       |        |
| Placebo                  | 1.36   | 0.3910  | 0.52  | 0.6158  | -1.11 | 0.5088 | -0.20 | 0.9673 |
| 0.8 g bid                | -4.24  | 0.0328  | -2.16 | 0.0829  | 3.27  | 0.2304 | 3.34  | 0.3819 |
| 1.2 g bid                | -7.63  | 0.0002  | -5.1  | 0.0008  | 0.82  | 0.6324 | 1.85  | 0.7151 |
| 1.6 g bid                | -11.46 | 0.0001  | -7.55 | 0.0001  | 4.1   | 0.0649 | 4.84  | 0.3980 |
| 2.0 g bid                | -15.21 | 0.0001  | -7.53 | 0.0001  | 4.71  | 0.0348 | 23.14 | 0.0212 |
| <b>GTC-37-202</b>        |        |         |       |         |       |        |       |        |
| Placebo                  | 1.27   | 0.5062  | 1.1   | 0.4433  | -0.76 | 0.7056 | 4.91  | 0.3734 |
| 1.6 g q AM               | -7.23  | 0.0002  | -2.84 | 0.0242  | 1.97  | 0.2714 | 21.20 | 0.0050 |
| 1.6 g q PM               | -7.18  | 0.0001  | -3.78 | 0.0087  | 2.1   | 0.2334 | 9.06  | 0.1348 |
| 0.8 g bid                | -6.31  | 0.0004  | -4.48 | 0.0045  | 0.49  | 0.8175 | 0.79  | 0.8313 |
| <b>GTC-37-203</b>        |        |         |       |         |       |        |       |        |
| Placebo                  | 0.5    | 0.8297  | 0.6   | 0.7015  | 1.2   | 0.5207 | 2.00  | 0.5934 |
| 2.4 g q PM               | -6.9   | 0.0064  | -2.6  | 0.1076  | 4.6   | 0.0041 | 14.20 | 0.0013 |
| Lovastatin 10 mg q<br>PM | -22.5  | <0.0001 | -14.5 | <0.0001 | 3.2   | 0.0917 | 5.40  | 0.3819 |
| <b>GTC-48-204</b>        |        |         |       |         |       |        |       |        |

|                       |       |         |       |         |      |         |        |         |
|-----------------------|-------|---------|-------|---------|------|---------|--------|---------|
| Placebo               | -3.7  | 0.0044  | -2.2  | 0.0906  | -2.2 | 0.2219  | 5.50   | 0.2553  |
| 1.2 g bid             | -8.5  | <0.0001 | -3.9  | 0.0047  | 4.3  | 0.0043  | 12.60  | 0.0963  |
| 2.0 g bid             | -16   | <0.0001 | -9    | <0.0001 | 1.9  | 0.3000  | 15.00  | 0.0070  |
| Simvastatin 10 mg qd  | -25.5 | <0.0001 | -18.7 | <0.0001 | 4.9  | 0.0177  | -11.60 | 0.0112  |
| Simvastatin 20 mg qd  | -33.8 | <0.0001 | -23.4 | <0.0001 | 6.5  | 0.0010  | -9.70  | 0.0028  |
| GTC-48-205            |       |         |       |         |      |         |        |         |
| Placebo               | -0.6  | 0.2753  | 1.1   | 0.0434  | 4.4  | 0.0494  | 9.50   | 0.1956  |
| 2.0 g bid             | -12.5 | 0.0021  | -5.9  | 0.0182  | 2.7  | 0.0067  | 9.90   | 0.1754  |
| Atorvastatin 10 mg qd | -38.5 | <0.0001 | -28.9 | <0.0001 | 8.3  | 0.0093  | -24.40 | 0.0268  |
| GTC-48-301            |       |         |       |         |      |         |        |         |
| Placebo               | 0.8   | 0.7905  | 0.6   | 0.3091  | -1.1 | 0.2681  | 4.60   | 0.0701  |
| 1.2 g bid             | -9.3  | <0.0001 | -4.9  | <0.0001 | 2.6  | 0.0003  | 8.60   | 0.0022  |
| 1.6 g bid             | -12.4 | <0.0001 | -6.2  | <0.0001 | 3.9  | <0.0001 | 4.80   | 0.0148  |
| 2.0 g bid             | -16.3 | <0.0001 | -8.1  | <0.0001 | 2.9  | 0.0001  | 9.90   | <0.0001 |
| 2.4 g bid             | -19.6 | <0.0001 | -10.3 | <0.0001 | 2.6  | 0.0003  | 9.40   | 0.0017  |
| GTC-48-302            |       |         |       |         |      |         |        |         |
| Placebo               | 0.8   | 0.7729  | 2     | 0.6261  | 1.9  | 0.4477  | 9.60   | 0.5604  |
| 4.0 g q AM            | -18.4 | <0.0001 | -9.3  | 0.0002  | 3    | 0.4091  | 25.40  | 0.0031  |
| 4.0 g q PM            | -13.9 | <0.0001 | -7    | 0.0002  | 7.5  | 0.0022  | 12.20  | 0.1014  |
| 2.0 g bid             | -18.4 | <0.0001 | -9.3  | <0.0001 | 9.5  | 0.0010  | 9.40   | 0.0717  |

### **Combination Therapy**

Colesevelam was co-administered with an HMG-CoA reductase inhibitor (atorvastatin, lovastatin, pravastatin, or simvastatin) in 6 clinical studies. Combination therapy resulted in an additive effect on LDL-C.

Each of the lovastatin- colesevelam combination therapies in study 37-203 reduced LDL-C to a greater extent than either lovastatin or colesevelam alone ( $p<0.005$ ); the combination therapy groups did not differ from each other ( $p=0.480$ ). In study 37-204, LDL-C decreased more in each simvastatin-colesevelam combination therapy group compared to each simvastatin group ( $p<0.006$ ); there was no difference between the two simvastatin groups ( $p=0.0546$ ) or between the two combination therapy groups ( $p=0.674$ ). The decrease in LDL-C in study 34-205 was greater after treatment with the combination atorvastatin- colesevelam than after treatment with atorvastatin 10 mg alone ( $p=0.007$ ), but not different from atorvastatin 80 mg alone ( $p=0.070$ ).

In studies WEL-405, WEL-406, and WEL-407, the patients were first stabilized on an individualized dose of the statin before randomization. In study WEL-405, LDL-C did not change in the active control group ( $p=0.763$ ); LDL-C decreased more on the combination simvastatin- colesevelam than on simvastatin alone ( $p=0.0003$ ). In the two other studies, the decreases in LDL-C in the combination therapy groups were similar to that seen in the combination therapy group in study WEL-403, but there were also unexpected smaller decreases in LDL-C in the control groups.

**Table 6** - Summary of Combination Therapy Study Results (mean % change from baseline)

| Study<br>Treatment                 | LDL-C |         | TOT-C |         | HDL-C |         | TG    |         |
|------------------------------------|-------|---------|-------|---------|-------|---------|-------|---------|
|                                    | % ■   | p       | % ■   | p       | % ■   | p       | % ■   | p       |
| <i>GTC-37-203</i>                  |       |         |       |         |       |         |       |         |
| Lovastatin 10 mg q PM              | -22.5 | <0.0001 | -14.5 | <0.0001 | 3.2   | 0.0917  | 5.4   | 0.3819  |
| 2.4 g q PM + lovastatin 10 mg q PM | -34.0 | <0.0001 | -20.8 | <0.0001 | 3.4   | 0.1     | 8.6   | 0.2173  |
| 2.4 g q PM + lovastatin 10 mg q HS | -31.8 | <0.0001 | -21   | <0.0001 | 3.1   | 0.0788  | -2.9  | 0.4879  |
| <i>GTC-48-204</i>                  |       |         |       |         |       |         |       |         |
| Simvastatin 10 mg qd               | -25.5 | <0.0001 | -18.7 | <0.0001 | 4.9   | 0.0177  | -11.6 | 0.0112  |
| Simvastatin 20 mg qd               | -33.8 | <0.0001 | -23.4 | <0.0001 | 6.5   | 0.001   | -9.7  | 0.0028  |
| 1.2 g bid + simvastatin 20 mg qd   | -42.3 | <0.0001 | -29.1 | <0.0001 | 6.1   | 0.0017  | -4.8  | 0.0493  |
| 2.0 g bid + simvastatin 10 mg qd   | -41.5 | <0.0001 | -28.3 | <0.0001 | 10.2  | <0.0001 | -3.2  | 0.2013  |
| <i>GTC-48-205</i>                  |       |         |       |         |       |         |       |         |
| Atorvastatin 10 mg qd              | -38.5 | <0.0001 | -28.9 | <0.0001 | 8.3   | 0.0093  | -24.4 | 0.0268  |
| 2.0 g bid + atorvastatin 10 mg qd  | -49.1 | <0.0001 | -28   | <0.0001 | 10.8  | 0.001   | -1.3  | 0.865   |
| Atorvastatin 80 mg qd              | -56.3 | <0.0001 | -42.4 | <0.0001 | 5.5   | 0.0336  | -32.8 | <0.0001 |
| <i>WEL-405</i>                     |       |         |       |         |       |         |       |         |
| Simvastatin mean of 28 mg qd       | -1.1  | 0.7626  | -0.7  | 0.7819  | 1     | 0.6676  | 2.1   | 0.9223  |
| 3.75 g qd + simvastatin            | -18.6 | <0.0001 | -8.2  | <0.0001 | 2     | 0.2459  | 17.8  | 0.5774  |
| <i>WEL-406</i>                     |       |         |       |         |       |         |       |         |
| Atorvastatin mean of 16 mg qd      | -13.5 | 0.0004  | -6.6  | 0.0089  | -1    | 0.6539  | 9.4   | 0.7751  |
| 3.75 g qd + atorvastatin           | -17.2 | <0.0001 | -8.4  | <0.0001 | 1     | 0.5599  | 15.5  | 0.6256  |
| <i>WEL-407</i>                     |       |         |       |         |       |         |       |         |
| Pravastatin mean of 25 mg qd       | -4.7  | 0.2320  | -3    | 0.1895  | -1.1  | 0.6382  | 4.7   | 0.8074  |
| 3.75 g qd + pravastatin            | -11.9 | 0.0001  | -5.3  | 0.0010  | -2.5  | 0.1485  | 16.4  | 0.6589  |

## DETAILED PHARMACOLOGY

Colesevelam hydrochloride is a novel polymeric substance designed to be administered orally to sequester bile acids and reduce their reabsorption.

Colesevelam hydrochloride was designed to incorporate both ionic and hydrophobic characteristics into the polymer in a pattern that would be complementary to the ionic and hydrophobic characteristics of bile acids. The resulting polymer should allow for enhanced binding of trihydroxy bile acids such as cholic acid as well as sufficiently tight binding to allow for retention of bile acids as they pass through the colon. Studies were conducted to confirm *in vitro* and *in vivo* binding to bile acids.

The physical chemical properties of colesevelam hydrochloride are such that it is unlikely to be absorbed after oral administration as confirmed by [<sup>14</sup>C]- studies in rats, dogs and humans. Recovery of radiolabel was complete in the rat study and in one dog study, but only 75-80% in the other dog study and in the human studies. In none of the studies was there evidence of the [<sup>14</sup>C]- labeled material in

tissues or plasma. Since colestevam hydrochloride is not absorbed, no metabolism or distribution studies were conducted.

Findings in rats, dogs and man correlated well. The high doses administered to laboratory species resulted in reductions in plasma concentrations of fat-soluble vitamins. However, assays of fat-soluble vitamins in human studies did not indicate any evidence of reductions.

Pharmacological studies confirmed that colestevam hydrochloride binds bile acids in man, hamsters and rats, and reduces plasma cholesterol in man and dogs (but not in rats).

## **TOXICOLOGY**

### General Toxicology Studies

Colestevam hydrochloride was tolerated after daily oral dosing of up to 2 g/kg/day (32 times human maximal dose based on a mg/kg basis) for 52 weeks in dogs and in rats after 1.2 g/kg/day (19 times human dose) for 6 months. In dogs, treatment at 0.67 and 2 g/kg resulted in discolored feces and mucoid discharge. There were local gastrointestinal effects in some dogs which may be related to the large amount of administered compound. After 2.4 g/kg/day for 5 weeks, male rats died secondary to hemorrhage, presumed to be secondary to reduced vitamin K absorption. Lifetime administration (2 year) in rodents (rat and mice) were conducted with diet supplemented with vitamins and doses of 2.4 g/kg/day and 3 g/kg/day were tolerated. Serum vitamin K levels were not determined in repeat dose studies in rats but serum levels of vitamin D and E were decreased in rat at 1.2 mg/kg and at 0.6 mg/kg in the dog. Thus, for chronic administration, careful attention has to be paid to effect secondary to reduced uptake of fat-soluble vitamins.

### Reproductive Toxicology Studies

Colestevam hydrochloride had no effects on male or female fertility or early embryonic development in male and female rats administered 2 g/kg/day (approximately 32 times the maximum human dose, based on body weight, mg/kg) orally prior to and during mating and early pregnancy.

Colestevam hydrochloride administered orally during organogenesis at doses up to 3 g/kg/day and 1 g/kg/day in rats and rabbits, respectively (approximately 48 and 16 times the maximum human dose, based on body weight, mg/kg) and have revealed no evidence of harm to the fetus. There were no effects on pre- and post-natal development in rats treated with colestevam hydrochloride from gestation day 6 through lactation day 20 at doses up to 1 g/kg.

*Carcinogenesis:* A 104-week carcinogenicity study with colestevam hydrochloride was conducted in CD-1 mice (n=50 per sex per dose group), at oral dietary doses up to 3 g/kg/day. Cholangioma (bile duct adenoma) was noted only at the mid-dose (1 male at 1 g/kg/day; 16 times the maximum recommended human dose of 4.5 g/day, based on body weight, mg/kg ) and at the high dose (1 male and 1 female at 3 g/kg/day; 48 times the maximum recommended human dose of 4.5 g/day, based on body weight). This is a spontaneous but uncommon tumor in mice. The relevance of this finding to humans has not been established. In a 104-week carcinogenicity study with colestevam 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 19 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.

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**PART III: CONSUMER INFORMATION**

<sup>Pr</sup>**APO-COLESEVELAM**  
Colesevelam Hydrochloride Tablets

This leaflet is part III of a three-part "Product Monograph" published when APO-COLESEVELAM was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about APO-COLESEVELAM. Contact your doctor or pharmacist if you have any questions about the drug.

**ABOUT THIS MEDICATION**

What the medication is used for:

- APO-COLESEVELAM may be prescribed on its own (called monotherapy) in addition to a diet low in fat and cholesterol when treatment with a statin (a class of cholesterol-lowering medicines that work in the liver) is inadequate.
- APO-COLESEVELAM may be used together with a statin (called combination therapy) and the diet low in fat and cholesterol when patients are not appropriately controlled by the statin on its own.

What it does:

Taking APO-COLESEVELAM helps to lower the level of cholesterol in your blood. Your doctor should only give you APO-COLESEVELAM if a diet low in fat and cholesterol did not work well enough on its own.

APO-COLESEVELAM works in your intestinal system by binding bile acids produced by your liver and carrying the bile acids out of your body with your feces. This prevents your body from recycling the bile acids from your intestines in the usual way. Without the recycling process, your liver has to make additional bile acids. Your liver uses cholesterol from your blood to do this, which lowers the level of cholesterol in your blood.

When it should not be used:

**Do not take APO-COLESEVELAM**

- if you are allergic (hypersensitive) to colesevelam or to any of the other ingredients of APO-COLESEVELAM
- if you have a blockage in your intestines or bile ducts (tubes that carry bile)

What the medicinal ingredient is:

Colesevelam hydrochloride

What the nonmedicinal ingredients are:

APO-COLESEVELAM Tablets: Diacetylated Monoglycerides, Hypromellose, Magnesium Stearate, Microcrystalline Cellulose, Silicon DiOxide.

What dosage forms it comes in:

Tablet 625 mg

**WARNINGS AND PRECAUTIONS**

**BEFORE** you use APO-COLESEVELAM talk to your doctor or pharmacist if:

- your triglyceride levels (a blood fat) are greater than 3.4 mmol/L
- you have difficulty in swallowing, or have a major stomach or intestinal disorder
- you are taking another medication called cyclosporine (a medicine used to suppress the immune system)
- you are taking antidiabetic treatments
- you are taking the oral contraceptive pill
- you are taking anticoagulant therapy
- you suffer from constipation, as APO-COLESEVELAM may induce or worsen this condition. This is especially important for patients with coronary heart disease and angina pectoris
- you are pregnant, planning on becoming pregnant or are breastfeeding
- you have any allergies to this drug or its ingredients or components of the container

**INTERACTIONS WITH THIS MEDICATION**

To ensure that the effectiveness of the following medications is not affected, it is important that you take the following medications at least 4 hours before taking APO-COLESEVELAM.

**Drugs that may interact with APO-COLESEVELAM include:**

- Anticoagulant therapy (medicines, such as warfarin, used to thin blood)
- Thyroid replacement therapy (medicines, such as thyroxine or levothyroxine, used to treat low thyroid hormone levels)
- Oral contraceptives (medicines to prevent pregnancy)
- Verapamil (a medicine used to treat high blood pressure)
- Antidiabetic medications (medicines, such as pioglitazone, repaglinide, glyburide metformin and insulin used to treat diabetes)
- Anti-epileptic medicines (medicines, such as phenytoin, used to treat epilepsy).

## IMPORTANT: PLEASE READ

- Cyclosporine (a medicine used to suppress the immune system).

If you are going to take APO-COLESEVELAM and one of these medicines, your doctor may want to do tests to make sure that APO-COLESEVELAM does not interfere with these medicines.

Additionally, if you have any condition that could cause you to have a deficiency of vitamins A, D, E or K, your doctor may want to check your vitamin levels periodically while you are taking APO-COLESEVELAM. If necessary, your doctor may advise you to take vitamin supplements.

### PROPER USE OF THIS MEDICATION

Before starting therapy with APO-COLESEVELAM, you should be advised to follow a cholesterol-lowering diet and you should continue this diet during treatment.

Take APO-COLESEVELAM with a meal.

APO-COLESEVELAM Tablets: Swallow the tablets with liquid.

Always take APO-COLESEVELAM exactly as your doctor has instructed you. You should check with your doctor or pharmacist if you are unsure. If you will be taking another medicine along with APO-COLESEVELAM it is possible that your doctor will advise you to take this other medicine at least 4 hours prior to taking APO-COLESEVELAM.

If you take a drug called cyclosporine, please ensure to take it with APO-COLESEVELAM in a consistent pattern over the day; either always together or always separate for a set number of hours.

#### Usual dose:

##### Monotherapy:

The usual starting dose for APO-COLESEVELAM is 3 tablets taken twice a day with meals or 6 tablets a day with a meal. Your doctor may increase your dose to a maximum of 7 tablets per day.

##### Combination therapy:

The usual dose for APO-COLESEVELAM, when used with a statin, is 4 to 6 tablets a day. The maximum recommended dose is 6 tablets per day. Your doctor may tell you to take the APO-COLESEVELAM dose either once a day or twice a day. APO-COLESEVELAM should be taken with a meal. The dosing of the statin should follow the instructions for that particular statin. The two

medicines may be taken at the same time or at separate times according to what your doctor has prescribed.

#### Overdose:

Please contact your doctor. Constipation or bloating could occur.

If you think you have taken too much APO-COLESEVELAM contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

#### Missed Dose:

You may take a missed dose with a later meal, but do not take a double dose of APO-COLESEVELAM to make up for missed doses.

### SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, APO-COLESEVELAM can cause side effects, although not everybody gets them.

The following side effects have been reported in patients taking APO-COLESEVELAM: Constipation, flatulence (gas), diarrhea, indigestion, muscle pain, abdominal pain, abnormal stools, feeling sick (nausea), headache, raised levels of triglycerides (fats) in your blood, raised levels of liver enzymes in your blood. You may notice that hemorrhoids get worse.

Side effects were usually mild or moderate in intensity.

### SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

| Symptom / effect |  | Talk to your healthcare professional |              | Stop taking drug and get immediate medical help |
|------------------|--|--------------------------------------|--------------|---|
|                  |  | Only if severe                       | In all cases |   |
| <b>Un common</b> | <ul style="list-style-type: none"> <li>• Bowel obstruction (abdominal pain, cramps or distension, vomiting, fecal vomiting, constipation)</li> </ul> |                                      |              | ✓   |
|                  | <ul style="list-style-type: none"> <li>• Difficulty swallowing</li> </ul>  |                                      |              | ✓   |

## IMPORTANT: PLEASE READ

### SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

| Symptom / effect   | Talk to your healthcare professional | Stop taking drug and get immediate medical help |
|--|--------------------------------------|---|
|  | Only if severe                       | In all cases                                    |
| <ul style="list-style-type: none"> <li>Fecal impaction (chronic constipation (sometimes with overflow diarrhea as liquid stool passes around the obstruction), abdominal pain and bloating, loss of appetite)</li> </ul> |                                      | ✓   |
| <ul style="list-style-type: none"> <li>Pancreatitis (severe upper abdominal pain that radiates to the back, nausea, vomiting).</li> </ul>  |                                      | ✓   |

*This is not a complete list of side effects. For any unexpected effects while taking APO-COLESEVELAM, contact your doctor or pharmacist.*

### HOW TO STORE IT

Keep out of the reach and sight of children. Store at room temperature 15°C to 30°C. Protect from moisture.

Do not use after the expiry date.

#### Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html>) for information on how to report online, by mail or by fax; or

- Calling toll-free at 1-866-234-2345.

*NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.*

### MORE INFORMATION

#### **If you want more information about APO-COLESEVELAM:**

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Consumer Information by visiting the Health Canada website (<https://health-products.canada.ca/dpd-bdpp/index-eng.jsp>). Find the Consumer Information on the manufacturer's website (<http://www.apotex.ca/products>), or by calling 1-800-667-4708.

This leaflet was prepared by Apotex Inc., Toronto, Ontario, M9L 1T9.

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