PRODUCT MONOGRAPH

PrLODALIS™

Colesevelam Hydrochloride

Film-coated Tablets 625 mg

Powder for Oral Suspension, 3.75 g.

Bile Acid Sequestrant

ATC code: C10A C 04

Valeant Canada LP
2150 Blvd. St-Elzear West
Laval, Quebec
H7L 4A8

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Table of Contents

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Colesevelam Hydrochloride Tablets
Colesevelam Hydrochloride Powder for Oral Suspension

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Oral	Tablet 625 mg	Microcrystalline cellulose, colloidal anhydrous silica, magnesium stearate, water, hypromellose, diacetylated monoglycerides, iron oxide black, propylene glycol
	Powder for Oral Suspension, 3.75g	Lemon flavor, orange flavor, propylene glycol alginate, simethicone, aspartame, citric acid, medium chain triglycerides, and magnesium trisilicate.

INDICATIONS AND CLINICAL USE

LODALIS (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

LODALIS (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 LODALIS is administered to elderly patients.

Pediatrics (<18 years of age):
The safety and efficacy of LODALIS have not been established in children and adolescent patients; therefore, the use of LODALIS 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 LODALIS (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 LODALIS or patients on LODALIS with a need to start cyclosporine: LODALIS reduces the bioavailability of cyclosporine (see DRUG INTERACTIONS). Patients starting on cyclosporine already taking LODALIS should have their cyclosporine blood concentrations monitored as normal and their dose adjusted as normal. Patients starting on LODALIS 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 LODALIS therapy will result in increased cyclosporine blood concentrations. Therefore, patients taking both cyclosporine and LODALIS should have their blood concentrations monitored prior to and frequently after when LODALIS 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 LODALIS 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 LODALIS is used in patients with these disorders.

LODALIS 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 LODALIS, 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 LODALIS. 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

LODALIS can affect the bioavailability of the oral contraceptive pill when administered simultaneously. It is important to ensure that LODALIS 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 LODALIS 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 LODALIS 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 LODALIS have not been established in children and adolescent patients; therefore, the use of LODALIS 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 colesevelam when used concomitantly with antidiabetic pharmacologic treatment regimens should be monitored by periodic measurements of blood glucose and HbA1c levels. When LODALIS 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 LODALIS (colesevelam) 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 LODALIS (total exposure 199 patient-years). In clinical trials for the reduction of LDL-C, 68% of patients receiving LODALIS 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 LODALIS 1.5 g/day to 4.5 g/day from 4 to 24 weeks.

Table 1 summarizes the placebo-controlled monotherapy clinical studies of LODALIS 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 LODALIS 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 (n=258)		LODALIS™ ONLY (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

LODALIS 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 LODALIS-only treatment categories. Only constipation and dyspepsia were reported by a higher percentage of LODALIS-only patients.

Combination with a HMG-CoA Reductase Inhibitor
LODALIS has been evaluated for safety in combination studies with a statin in 279 patients. In general, adverse experiences were similar between LODALIS administered with a statin and a statin alone. However, the frequency of constipation was higher (9.3% vs 5.3%) in patients receiving LODALIS 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 ≥2% of patients and at an incidence significantly greater on the combination than on the statin alone. Nausea occurred less frequently in patients receiving LODALIS administered with a statin (3.2%) than in patients treated with a statin alone (4.3%).

Table 2 - Placebo-Controlled Combination Clinical Studies of LODALIS for Hyperlipidemia: Adverse Reactions Reported in ≥1% of Patients Regardless of Investigator Assessment of Causality.

BODY SYSTEM	STATIN + PLACEBO (n=209) N	%	STATIN + LODALIS™ (n=279) 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

BODY SYSTEM	STATIN + PLACEBO (n=209) N	%	STATIN + LODALIS™ (n=279) N	%
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 LODALIS:

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 LODALIS. 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 LODALIS administration include:

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

LODALIS may affect the bioavailability of other medicinal products. Therefore, when a drug interaction cannot be excluded with a concomitant medicinal product, LODALIS (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, LODALIS had no effect on the bioavailability of digoxin, metoprolol, quinidine, valproic acid, and warfarin. LODALIS 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, LODALIS 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 LODALIS 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 LODALIS. 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[a]	Glyburide, levothyroxine, and oral contraceptives containing ethinyl estradiol and norethindrone
Drugs with post-marketing reports consistent with potential drug-drug interactions when coadministered with LODALIS	phenytoin[a], warfarin[b]
Drugs that do not interact with colesevelam based on *in vitro* or *in vivo* testing	digoxin, warfarin[b], fenofibrate, lovastatin, metoprolol, pioglitazone, quinidine, repaglinide, valproic acid, verapamil

[a] Should be administered at least 4 hours prior to LODALIS

[b] No significant alteration of warfarin drug levels with warfarin and LODALIS 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, LODALIS reduced the AUC and C_{max} of levothyroxine when administered either concomitantly or after 1 hour. No interaction was observed when LODALIS was administered at least four hours after levothyroxine.

Oral contraceptive pill

In an interaction study in healthy volunteers, LODALIS reduced the C_{max} of norethindrone as well as the AUC and C_{max} of ethinylestradiol when administered simultaneously with the oral contraceptive pill. This interaction was also observed when LODALIS was administered one hour after the oral contraceptive pill. However no interaction was observed when LODALIS was administered four hours after the oral contraceptive pill.

Cyclosporine

In an interaction study in healthy volunteers, co-administration of LODALIS and cyclosporine significantly reduced the $AUC_{0\text{-}inf}$ and C_{max} 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 LODALIS should be administered at least 4 hours after cyclosporine in

order to further minimize the risks related to the concomitant administration of cyclosporine and LODALIS. Furthermore, LODALIS should always be administered at the same times consistently since the timing of intake of LODALIS and cyclosporine could theoretically influence the degree of reduced bioavailability of cyclosporine.

Statins
When LODALIS 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 colesevelam in combination with pravastatin, rosuvastatin, or high dose HMG-CoA reductase inhibitors have not been performed.

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

Co-administration of LODALIS 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 LODALIS was administered one hour after repaglinide.

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

Other forms of interaction
LODALIS 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
LODALIS has no or negligible influence on the ability to drive and use machines.

DOSAGE AND ADMINISTRATION

Dosing Considerations

Prior to initiating therapy with LODALIS (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 LODALIS 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. The recommended dose of LODALIS Powder for Oral Suspension is one 3.75 g packet once daily with a meal.

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

Monotherapy

The recommended starting dose of LODALIS 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. . The recommended dose of LODALIS Powder for Oral Suspension is one 3.75 g packet once daily with a meal.

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, LODALIS 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

LODALIS tablets should be taken orally with a meal and liquid.

LODALIS Powder for Oral suspension should be taken with a meal. To prepare, empty the entire contents of one packet into a glass or cup. Add ½ to 1 cup (4 to 8 ounces) of water, fruit juice, or diet soft drinks. Stir well and drink. To avoid esophageal distress, LODALIS Powder for Oral Suspension should not be taken in its dry form.

OVERDOSAGE

Since LODALIS (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 colesevelam, the active substance in LODALIS, has been evaluated in several *in vitro* and *in vivo* studies. These studies have demonstrated that colesevelam 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

Colesevelam 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-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 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 LODALIS, 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 LODALIS 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 LODALIS 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 LODALIS and a statin (atorvastatin, lovastatin or simvastatin) were administered at the same time. Initiation of

add-on treatment with LODALIS subsequent to statin therapy has not been specifically studied. LODALIS 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 LODALIS or fenofibrate alone. The fenofibrate plus LODALIS 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 LODALIS on the risks of myopathy or hepatotoxicity are not known.

Pharmacokinetics

LODALIS 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 14C-labeled colesevelam hydrochloride dose was excreted in the urine.

STORAGE AND STABILITY

Store at 25° C; excursions permitted to 15-30° C.
Protect from moisture.

SPECIAL HANDLING INSTRUCTIONS

No special requirements.

DOSAGE FORMS, COMPOSITION AND PACKAGING

LODALIS (colesevelam) 625 mg film-coated tablets, each tablet contains 625 mg colesevelam hydrochloride. Off white, capsule-shaped, film-coated tablets imprinted with “LODALIS” on one side.

Tablet core:
Cellulose (E460), microcrystalline
Silica, colloidal anhydrous
Magnesium stearate
Water, purified

Film-coating:
Hypromellose (E464)

Diacetylated monoglycerides

Printing ink:
Iron oxide black (E172)
Hypromellose (E464)
Propylene glycol

High density polyethylene bottles with a polypropylene cap without outer carton.
Package size: 180 tablets (1 X 180)
Physician sample: 18 tablets (1 X 18)

LODALIS (colesevelam) for oral suspension is a citrus-flavoured, white to pale yellow powder containing yellow granules packaged in single-dose packets containing 3.75 g colesevelam hydrochloride. Each packet contains the following inactive ingredients: Lemon flavor, orange flavor, propylene glycol alginate, simethicone, aspartame, citric acid, medium chain triglycerides, and magnesium trisilicate.

LODALIS for Oral Suspension contains 27 mg phenylalanine per 3.75 g dose.

Package sizes: 3.75 g -dose packet available in cartons of 30 packets.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

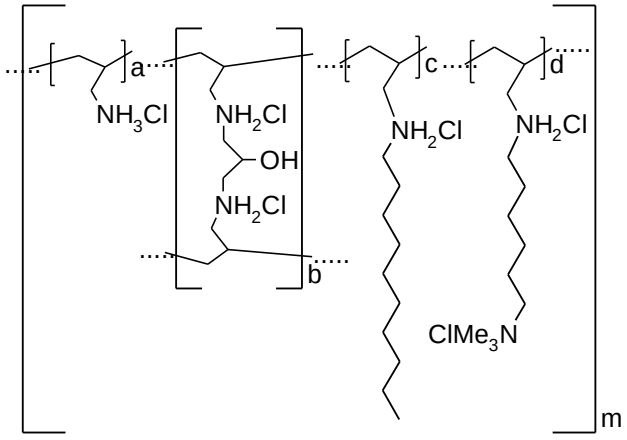
Drug Substance

Common name: Colesevelam Hydrochloride

Chemical name: 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:
$(C_3H_8NCl)_2(C_9H_{20}N_2OCl_2)_1(C_{13}H_{28}NCl)_7(C_{12}H_{28}N_2Cl_2)_6$

Structural formula:



Where:

a = number of primary amine groups	a = 0.14
b = number of cross-linked amine groups	b = 0.12
c = monoquat alkylated amine groups	c = 0.34
d = decylbromide alkylated amine groups	d = 0.40
m > 100 to indicate extended polymer network	

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_3) is approximately 9.3

CLINICAL TRIALS

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

LODALIS 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. 6 weeks	Placebo 0.8 g bid 1.2 g bid 1.6 g bid 2.0 g bid	29 30 30 31 29	56.0 y (31-80)	44%
GTC-37-202	Randomized DB, PC, PG	p.o. 4 weeks	Placebo 1.6 g q AM 1.6 g q PM 0.8 g bid	32 30 30 30	55.4 y (21-83)	57%
GTC-37-203	Randomized DB, PC, PG	p.o. 4 weeks	Placebo 2.4 g q PM Lovastatin 10 mg q PM 2.4 g q PM + lovastatin 10 mg q PM 2.4 g q PM + lovastatin 10 mg q HS	26 29 26 29 25	57.7 y (23-88)	45%
GTC-48-204	Randomized DB, PC, PG	p.o. 6 weeks	Placebo 1.2 g bid 2.0 g bid Simvastatin 10 mg qd Simvastatin 20 mg qd 1.2 g bid + simvastatin 20 mg qd 2.0 g bid + simvastatin 10 mg qd	35 38 38 36 39 37 35	54.3 y (18-82)	58%
GTC-48-205	Randomized DB, PC, PG	p.o. 4 weeks	Placebo 2.0 g bid Atorvastatin 10 mg qd 2.0 g bid + atorvastatin 10 mg qd Atorvastatin 80 mg qd	19 17 19 19 20	57.3 y (28-79)	70%
GTC-48-301	Randomized DB, PC, PG	p.o. 6 months	Placebo 1.2 g bid 1.6 g bid 2.0 g bid 2.4 g bid	94 102 98 101 99	55.5 y (18-86)	50%
GTC-48-302	Randomized DB, PC, PG	p.o. 6 weeks	Placebo 4.0 g q AM 4.0 g q PM 2.0 g bid	23 27 24 24	55.2 y (24-70)	45%
WEL-403	Randomized DB, PC, PG	p.o. 6 weeks	3.75 g qd + fenofibrate 160 mg qd Placebo + fenofibrate 160 mg qd	64 65	54.8 y (31-70)	56%
WEL-405	Randomized DB, PC, PG	p.o. 6 weeks	3.75 g qd + simvastatin Simvastatin mean of 28 mg/day	47 25	60 y (31-82)	50%
WEL-406	Randomized DB, PC, PG	p.o. 6 weeks	3.75 g qd + atorvastatin Atorvastatin mean of 16 mg/day	40 25	57.7 y (32-78)	44%
WEL-407	Randomized DB, PC, PG	p.o. 6 weeks	3.75 g qd + pravastatin Pravastatin mean of 25 mg/day	47 20	54.8 y (29-80)	40%
WEL-408	Randomized DB, PC, PG	p.o. 10 weeks	3.75 g qd + ezetimibe 10 mg/day Placebo + ezetimibe 10 mg/day	43 43	59.1 y (24-79)	43%

Monotherapy

The efficacy and safety of LODALIS 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, LODALIS 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 1.6 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 LODALIS.

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

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

LODALIS 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	LDL-C		TOT-C		HDL-C		TG	
Treatment	% Δ	p	% Δ	p	% Δ	p	% Δ	p
GTC-37-201								
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
GTC-37-202								
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
GTC-37-203								
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 PM	-22.5	<0.0001	-14.5	<0.0001	3.2	0.0917	5.40	0.3819
GTC-48-204								
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

LODALIS 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-LODALIS combination therapies in study 37-203 reduced LDL-C to a greater extent than either lovastatin or LODALIS 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-LODALIS 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-LODALIS 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- LODALIS 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	**LDL-C**		**TOT-C**		**HDL-C**		**TG**	
Treatment	% Δ	p	% Δ	p	% Δ	p	% Δ	p
GTC-37-203								
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
GTC-48-204								
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
GTC-48-205								
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
WEL-405							*0*	
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
WEL-406								
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
WEL-407								
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 [^{14}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 [^{14}C]- labeled material in tissues or plasma. Since colesevelam 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 colesevelam 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

Colsevelam 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

Colesevelam 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.

Colsevelam 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 colesevelam hydrochloride from gestation day 6 through lactation day 20 at doses up to 1 g/kg.

Carcinogenesis: A 104-week carcinogenicity study with colesevelam 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 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 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.

REFERENCES

1. Avorn J, Monette J, Lacour A, et al. Persistence of use of lipid-lowering medications: a cross-national study. *JAMA*. 1998;279:1458-62.

2. Expert Panel. Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. *Arch Intern Med*. 1988;148:36-69.

3. Brown MS, Goldstein, J.L. Drugs used in the treatment of hyperlipoproteinemias. In: Goodman LS, Gilman, A., ed. *The Pharmacologic Basis of Therapeutics*. 8 ed. New York: McGraw-Hill Book Co.; 1990:874-96.

4. Levine GN, et al. Cholesterol reduction in cardiovascular disease. *New Engl. J. Med.* 1995;332:512-21.

5. Eisenberg DA. Cholesterol lowering in the management of coronary artery disease: the clinical implications of recent trials. *Am J Med*. 1998;104:2S-5S.

6. Gotto AM, Jr. Lipid lowering and coronary risk. *Isr J Med Sci*. 1996;32:355-9.

7. Lipid Research Clinic Program. The Lipid Research Clinics Coronary Primary Prevention Trial results. II. The relationship of reduction in incidence of coronary heart disease to cholesterol lowering. *JAMA*. 1984;251:365-74.

8. Rossouw JE. The effects of lowering serum cholesterol on coronary heart disease risk. *Med Clin North Am*. 1994;78:181-95.

9. Law MR, Wald NJ, Thompson SG. By how much and how quickly does reduction in serum cholesterol concentration lower risk of ischaemic heart disease? *Br. Med. J.* 1994;308:367-72.

10. McPherson R, et al. Canadian Cardiovascular Society position statement - Recommendations for the diagnosis and treatment of dyslipidemia and prevention of cardiovascular disease. *Can J Cardiol* 2006; 22 (11); 913-927.

11. Graham I, et al. European Guidelines on cardiovascular disease prevention in clinical practice: Executive summary. *Atheroscelerosis* 2007; 197; 1-45.

12. Jelinek DF, Andersson S, Slaughter CA, Russell DW. Cloning and regulation of cholesterol 7 alpha-hydroxylase, the rate- limiting enzyme in bile acid biosynthesis. *J Biol Chem*. 1990;265:8190-7.

13. Illingworth DR. New horizons in combination drug therapy for hypercholesterolemia. *Cardiology*. 1989;76:83-94; discussion -100.

14. Setchell KDR, Street JM, Sjövall J. Fecal bile acids. In: Setchell KDR, Kritchevsky D, Nair PP, eds. *The Bile Acids. Chemistry, Physiology, and Metabolism*. New York: Plenum Press; 1988:441-570.

15. Czubayko F, Beumers B, Lammsfuss S, Lutjohann D, von Bergmann K. A simplified micro-method for quantification of fecal excretion of neutral and acidic sterols for outpatient studies in humans. *J Lipid Res*. 1991;32:1861-7.

16. Lindenthal B, Simatupang A, Dotti MT, Federico A, Lutjohann D, von Bergmann K. Urinary excretion of mevalonic acid as an indicator of cholesterol synthesis. *J Lipid Res*. 1996;37:2193-201.

17. Wasserhess P, Becker M, Staab D. Effect of taurine on synthesis of neutral and acidic sterols and fat absorption in preterm and full-term infants. *Am J Clin Nutr*. 1993;58:349-53.

18. Rossi SS, Wayne ML, Smith RB, Wright CE, Andreadis NA, Hofmann AF. Effect of the bile-acid sequestrant colestipol on postprandial serum bile-acid concentration: evaluation by bioluminescent enzymic analysis. *Aliment Pharmacol Ther*. 1989;3:41-6.

19. Knapp HH, Schrott H,Ma P, Knopp R, Chin B. Gaziano JM, Donovan JM, Burke S, Davidson M. Efficacy and safety of combination simvastatin and colesevelam in patients with Primary hypercholesterolemia. *Am J Med.* 2001;110: 352-360.

20. Hunninghake D, Insull W, Toth P, Davidson D, Donovan JM, Burke SK. Coadministration of colesevelam hydrochloride with atorvastatin lowers LDL cholesterol additively. *Atherosclerosis.* 2001; 158:407-416.

21. Bays H, Rhyne J, Abby S, Lai Y, Jones M. Lipid-lowering effects of colesevelam HCl in combination with ezetimibe. *Current Medical Research Opinion.* 2006; 11:2191-2200.

22. Insull W. Clinical utility of bile acid sequestrants in the treatment of dyslipidemia: a scientific review. *Southern Med J.* 2006; 99(3): 257-273.

23. Corsini, A. Colesevelam hydrochloride: usefulness of a specifically engineered bile acide sequesterant for lowering LDL-cholesterol. *European Journal of Cardiovascular Prevention &Rehabilitation*. Feb 2009.

24. McKenney J, Jones M, Abby S. Safety and efficacy of colesevelam hydrochloride in combination with fenofibrate for the treatment of mixed hyperlipodemia. *Current Medical Research Opinion.* 2005;21:9:1403-1412.

25. Corsini A, Eberhard W, Farnier, Colesevelam hydrochloride: usefulness of a specifically engineered bile acid sequestrant for lowering LDL-cholesterol. *European Journal of Cardiovascular Prevention & Rehabilitation*. 2009;16:1-9.

26. Studer M, Briel M, Leimenstoll B, Glass TR, Bucher HC. Effect of different antilipidemic agents and diets on mortality. *Arch Intern Med*. 2005;165:725-730.

27. Grundy SM, Cleeman JI, Merz CNB, Brewer HB, Clark LT, Hunninghake DB, Pasternak RC, Smith SC, Stone NJ. Implications of recent clinical trials for the national cholesterol education program adult treatment panel III guidelines. *Arterioscler Thromb Vasc Biol*. 2004;24:e149-e161.

28. Braunlin W, Zhorov E, Smisek D, Guo A, Appruzese W, Xu Q, Hook P, Holmes-Farley R, Mandeville. In vitro comparison of bile acid binding to colesevelam HCl and other bile acid sequestrants. *Polymer preprints*. 2000;41(1):708-709.

29. Bays H, Dujovne C. Colesevelam HCl: a non-systemic lipid-altering drug. *Expert Opin. Pharmacother*.2003;4(5):779-790.

30. Holmes-Farley SR, Mandeville WH, Miller KL, Petersen J, Ward J, Sacchiero B, Maloney C, Brochi S, Rosenbaum D, Goldberg D, Norton KA, Chen X, Mazzeo JR. Colesevelam hydrochloride:synthesis and testing of a novel polymer gel pharmaceutical. *Poylmer preprints*. 2000;41(1):735-736.

31. Davidson MH, Dicklin MR, Maki KC, Kleinpell RM. Colesevelam hydrochloride: a non-absorbed, polymeric cholesterol-lowering agent. *Exp. Opin. Invest. Drugs*. 2000;9(11):2663-2671.

32. Heller DP, Burke SK, Davidson DM, Donovan JM. Absorption of colesvelam hydrochloride in healthy volunteers. *Ann Pharmacother*.2002;36:398-403.

33. Insull W, Toth P, Mullican W, Hunninghake D, Burke S, Donovan JM, Davidson MH. Effectiveness of colesevelam hydrochloride in decreasing LDL cholesterol in patients with primary hypercholesterolemia: a 24-week randomized controlled trial. *Mayo Clin Proc*.2001;76:971-982.

34. Steinmetz KL, Schonder KS. Colesevelam: Potential uses for the newest bile resin. *Cardiovascular Drug Reviews*.2005;23(1):15-30.

35. Bays HE., Goldberg RB. The Forgotten Bile Acid Sequestrants: Is Now a Good Time to Remember? American Journal of Therapeutics. 2007; 14: 567-580.

PART III: CONSUMER INFORMATION

PrLODALIS™
Colesevelam Hydrochloride Tablets
Colesevelam Hydrochloride Powder for Oral Suspension

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

ABOUT THIS MEDICATION

What the medication is used for:

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

LODALIS 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 LODALIS
- **if you are allergic (hypersensitive) to colesevelam or to any of the other ingredients of LODALIS**
- **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:
LODALIS Tablets: Diacetylated monoglycerides, hypromellose, iron oxide black, magnesium stearate, microcrystalline cellulose, propylene glycol, purified water, and silica colloidal anhydrous.

LODALIS Powder for Oral Suspension:
Aspartame, citric acid, lemon flavor, magnesium trisilicate, medium chain triglycerides, orange flavor, propylene glycol alginate and simethicone.

LODALIS contains phenylalanine

What dosage forms it comes in:
Tablet 625 mg
Oral Suspension: 3.75 g/packet

WARNINGS AND PRECAUTIONS

BEFORE you use LODALIS 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 LODALIS 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 LODALIS.

Drugs that may interact with LODALIS 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).**

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

If you are going to take LODALIS and one of these medicines, your doctor may want to do tests to make sure that LODALIS 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 LODALIS. If necessary, your doctor may advise you to take vitamin supplements.

PROPER USE OF THIS MEDICATION

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

Take LODALIS with a meal.

LODALIS Tablets: Swallow the tablets with liquid.

LODALIS Powder for Oral Suspension: Empty the entire contents of one packet into a glass or cup. Add ½ to 1 cup (4 to 8 ounces) of water, fruit juice, or diet soft drinks. Stir well and drink. To avoid esophageal distress, LODALIS Powder for Oral Suspension should not be taken in its dry form.

Always take LODALIS 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 LODALIS it is possible that your doctor will advise you to take this other medicine at least 4 hours prior to taking LODALIS.

If you take a drug called cyclosporine, please ensure to take it with LODALIS 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 LODALIS 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. The usual dose of LODALIS powder for oral suspension is one packet (3.75 g of colesevelam resin) a day with a meal.

Combination therapy:
The usual dose for LODALIS, 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 LODALIS dose either once a day or twice a day. The usual dose of LODALIS powder for oral suspension when used with a statin is one packet (3.75 g of colesevelam resin) a day with a meal. LODALIS 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.

In case of drug overdose, contact a health care practitioner, 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 doseof LODALIS to make up for missed doses.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, LODALIS can cause side effects, although not everybody gets them.

The following side effects have been reported in patients taking LODALIS:
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 with your doctor or pharmacist		Stop taking the drug and seek immediate emergency medical attention
		Only if severe	In all cases	
Uncommon	• Bowel obstruction (abdominal pain, cramps or distension, vomiting, fecal vomiting, constipation)			√
	• Difficulty swallowing			√

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

Symptom / effect		Talk with your doctor or pharmacist		Stop taking the drug and
	• Fecal impaction (chronic constipation (sometimes with overflow diarrhea as liquid stool passes around the obstruction), abdominal pain and bloating, loss of appetite)			√
	• Pancreatitis (severe upper abdominal pain that radiates to the back, nausea, vomiting).			√

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

HOW TO STORE IT

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

Do not use after the expiry date.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada through the Canada Vigilance Program collects information on serious and unexpected effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug, you may notify Canada Vigilance.

You can report any suspected adverse reactions associated with the use of health products in the Canada Vigilance Program by one of the following 3 ways:

Report online at www.healthcanada.gc.ca/medeffect
Call toll-free telephone at 1-866-234-2345
Complete a Canada Vigilance Reporting Form and:
Fax toll-free to 1-866-678-6789
Mail to: Canada Vigilance Program
Health Canada
Postal Locator 0701C
Ottawa, ON, K1A 0K9
Postage paid labels, Canada Vigilance Report Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect

NOTE: Should you require information related to the management of the side effect, please contact your health care professional. The Canada Vigilance program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be obtained:
by contacting the sponsor:
Valeant Canada LP
2150 Blvd. Dt-Elzear west
Laval, Quebec, H7L 4A8

1-800-361-4261

This leaflet was prepared by Valeant Canada LP.

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