**PRODUCT MONOGRAPH**

# COLESTID® Granules

**(colestipol hydrochloride for oral suspension USP)**

# COLESTID® ORANGE Granules

**(colestipol hydrochloride for oral suspension)**

# COLESTID® Tablets

**(colestipol hydrochloride tablets)**

**Oral Antihypercholesterolemic**

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## ACTION AND CLINICAL PHARMACOLOGY

Colestipol hydrochloride is hygroscopic, water insoluble, and it is neither hydrolyzed by digestive enzymes nor is it absorbed. Colestipol hydrochloride binds with bile acids in the intestine forming a complex that is excreted in the feces. This non-systemic action results in a continuous, partial removal of bile acids from the enterohepatic circulation preventing their reabsorption. This increased fecal loss of bile acids due to colestipol hydrochloride administration leads to an increased oxidation of cholesterol to bile acids. This results in an increase in the number of hepatic low density lipoprotein (LDL) receptors, and consequently an increased uptake of LDL and a decrease in serum/plasma beta lipoprotein or total and LDL cholesterol levels. Although hydrochloride produces an increase in the hepatic synthesis of cholesterol in man, serum cholesterol levels fall.

## INDICATIONS AND CLINICAL USE

COLESTID Granules, COLESTID ORANGE Granules and COLESTID Tablets (colestipol hydrochloride) are indicated as adjunctive therapy to diet and exercise for the reduction of elevated serum cholesterol in patients with primary hypercholesterolemia (elevated low density lipoproteins). Such a reduction of serum cholesterol may reduce the risks of atherosclerotic coronary artery disease and myocardial infarction. In patients with combined hypercholesterolemia and hypertriglyceridemia, COLESTID Granules, COLESTID ORANGE Granules and COLESTID Tablets may be useful in lowering elevated cholesterol but is not indicated where hypertriglyceridemia is the abnormality of most concern.

Patients should be placed on a standard cholesterol-lowering diet at least equivalent to the American Heart Association (AHA) Step 1 Diet, which should be continued during treatment. If appropriate, a programme of weight control and physical exercise should be implemented.

## CONTRAINDICATIONS

COLESTID products (colestipol hydrochloride) are contraindicated in patients with complete biliary obstruction where bile is not secreted into the intestine.

COLESTID Granules, COLESTID ORANGE Granules and COLESTID Tablets are contraindicated in individuals who have shown hypersensitivity to colestipol hydrochloride or any of the components of the products.

In addition, COLESTID ORANGE Granules is contraindicated in phenylketonurics as each 7.5 g COLESTID ORANGE Granules contains 18.2 mg phenylalanine.

## WARNINGS

**COLESTID Granules and COLESTID ORANGE Granules (colestipol hydrochloride) should never be taken in its dry form.** Esophageal spasm or respiratory distress can result from attempting to swallow the granules dry. COLESTID Granules and COLESTID ORANGE Granules should always be mixed with water, beverages, cereals, soups or other foods with sufficient fluid for mixing.

## PRECAUTIONS

Studies have suggested that control of elevated cholesterol and triglycerides may not lessen the danger of cardiovascular related mortality, although the incidence of nonfatal myocardial infarctions is decreased.

Before instituting therapy with COLESTID products (colestipol hydrochloride), diseases contributing to increased serum cholesterol such as hypothyroidism, diabetes mellitus, nephrotic syndrome, dysproteinemias and obstructive liver disease should be ruled out or specifically treated.

In addition, the current medications of the patient should be reviewed for their potential to increase serum LDL-C or total cholesterol.

It should be verified that an elevated LDL-C is responsible for the high total cholesterol level, especially in those patients with marked elevations of HDL-C and elevations of triglyceride over 4.5 mmol/L (400 mg/100 mL). An LDL-C level may be estimated using the following formula:

$$\text{LDL-C} = \text{total cholesterol} - \text{HDL-C} - \frac{\text{triglyceride}}{2.19}$$

All units are in mmol/L. The accuracy of this approximation falls when triglycerides are greater than 4.5 mmol/L. Patients with triglyceride levels above 4.5 mmol/L should not be considered for initial therapy with COLESTID alone. Instead, the use of COLESTID products given in combination with another lipid lowering agent like a fibrate or niacin would be more beneficial.

When used as the sole therapy, COLESTID Granules, COLESTID ORANGE Granules and COLESTID Tablets do not improve hypertriglyceridemia and in fact may elevate serum triglycerides. This elevation is generally transient, but may sometimes persist. If a significant rise in triglyceride level occurs consideration should be given to dose reduction, drug discontinuation or combination therapy with another lipid lowering agent.

Appropriate use of serum lipid profiles (with LDL-C and triglyceride levels) at regular intervals is advised so that therapeutic effect can be determined.

COLESTID products may produce or worsen pre-existing constipation. In patients with pre-existing constipation, the starting dose should be 5 g colestipol granules, or 2 g colestipol tablets, given once or twice daily. Increased fluid and fiber intake is encouraged to alleviate the constipation. A stool softener may be added if needed. If the initial dose is well tolerated, the dosage may be increased (by daily increments of 5 g colestipol granules or 2 to 4 g colestipol tablets) at monthly intervals. If the constipation worsens or the desired therapeutic response is not achieved at the maximum recommended dose, then combination lipid-lowering therapy or alternate therapy should be considered. Particular effort should be made to avoid constipation in patients with symptomatic coronary artery disease. Constipation may aggravate hemorrhoids.

Since COLESTID is a chloride form of an anion exchange resin, there is a possibility that prolonged use may lead to the development of hyperchloremic acidosis.

**Carcinogenesis and Mutagenesis**

In studies conducted in rats in which cholestyramine resin (a bile acid sequestering agent similar to colestipol hydrochloride) was used as a tool to investigate the role of various intestinal factors, such as fat, bile salts and microbial flora, in the development of intestinal tumours induced by potent carcinogens, the incidence of such tumours was observed to be greater in cholestyramine resin treated rats than in control rats. The relevance of this laboratory observation from studies in rats with cholestyramine resin to the clinical use of COLESTID is not known.

In the Lipid Research Clinics (LRC) Coronary Primary Prevention Trial (CPPT), a randomized double-blind, placebo-controlled trial of cholestyramine (n=1907) versus placebo (n=1899) treatment, the incidence of total tumors was similar in cholestyramine and placebo groups. When the many different categories of tumors are examined, various alimentary system cancers were somewhat more prevalent in the cholestyramine group. The small numbers and the multiple categories prevent conclusions from being drawn. After the treatment period participants in the LRC-CPPT trial were followed up annually for six years. After 13.4 years of in-trial plus post-trial follow-up, the cholestyramine and placebo groups had similar mortality rates from cancer, other medical causes and similar cancer incidence rates. However, 13.4-year incidences of benign colorectal tumors (50 vs 34) and cancer of the buccal cavity and pharynx (8 vs 2) were numerically (but not statistically) higher in the cholestyramine group compared to the placebo group. There were factors unrelated to treatment that may have influenced these findings. The incidences of gallbladder disease (68 vs 53) and gallbladder surgery (58 vs 40) also were numerically higher in the cholestyramine group compared to the placebo group.

Since the action of colestipol is limited to the gastrointestinal tract, careful evaluation of signs and symptoms related to the gastrointestinal tract is needed in patients receiving chronic bile acid sequestering therapy.

**Fertility, Pregnancy and Lactation:**

Pregnancy and Lactation

No clinical data are available on the use of colestipol hydrochloride in pregnant women and during lactation. Colestipol hydrochloride does not appear to be absorbed systematically (see HUMAN PHARMACOLOGY, Drug Kinetics). Due to its known interference with absorption of fat-soluble vitamins, the use of COLESTID products in pregnancy or lactation or by women of childbearing potential requires that the benefits of drug therapy be weighed against the possible hazards to the mother and the child.

Evidence from a non-regulatory reproduction and development study showed no teratogenic effects of colestipol hydrochloride when administered to rats and rabbits during gestation at doses up to 2 times the maximum recommended human dose (MRHD), which is 30 g/day. No drug-related effects on reproductive parameters were seen when colestipol hydrochloride was administered to female rats from 14 days before breeding through weaning of the $F_1$ generation at 21 days post-parturition (see **TOXICOLOGY**, **Teratology and Reproduction**).

Fertility

There are no data on the effect of colestipol hydrochloride on fertility in humans. A non-regulatory reproduction study conducted in rats at doses up to 2 times the MHRD did not report any drug-related effect on fertility and reproductive parameters (see TOXICOLOGY, Teratology and Reproduction).

**Effect on Vitamin Absorption:**

Due to the action of colestipol HCl in sequestering bile acids, COLESTID products may theoretically interfere with normal fat absorption and thus may reduce the absorption of folic acid and fat soluble vitamins A, D and K. In general, supplementation of vitamins A, D and K is not needed unless a deficiency is shown to exist.

Chronic use of COLESTID products has been rarely associated with an increased bleeding tendency due to hypoprothrombinemia resulting from vitamin K deficiency. This deficiency can be corrected with oral vitamin K.

**Use in Children:**

The use of colestipol hydrochloride in children is limited. Clinical trials conducted in children with COLESTID Granules have usually employed doses of 5 to 20 g/day. The National Cholesterol Education Program (NCEP) Expert Panel recommends drug therapy be considered in children 10 years or older, who have previously undergone an adequate trial of diet therapy but still have unacceptably high serum cholesterol levels. In certain situations where a young child has extremely high serum cholesterol levels, drug treatment may even be initiated before 10 years of age. If the child is started on drug therapy, a carefully assessed diet therapy should also be continued in order to obtain optimal results.
However the safety of using COLESTID Tablets in patients under the age of 18 years has not been established.

Because bile acid sequestrants may interfere with the absorption of fat-soluble vitamins, appropriate monitoring of growth and development is essential if colestipol hydrochloride is used in children.

**Use in the Elderly:**

Appropriate studies on the relationship of age to the effects of colestipol hydrochloride have not been performed in the geriatric population. However, patients over 60 years of age may be more likely to experience gastrointestinal side effects, as well as adverse nutritional effects.

**Effect on Ability to Drive and Use Machinery**

Based on the pharmacodynamics and general safety profiles of colestipol hydrochloride, it is not expected to affect the ability to drive or use machines

**Drug Interaction: (also see HUMAN PHARMACOLOGY)**

Since colestipol hydrochloride is an anion-exchange resin, it may have a strong affinity for anions other than the bile acids. Colestipol hydrochloride does not bind *in vivo* with an affinity and to an extent that results in clinically significant drug-drug interactions with all anionic compounds or weak acids. Clinically relevant reductions in bioavailability have been found for several weakly acid drugs (summarized below). However, other weakly acid (anionic) drugs have been studied and found not to be affected by colestipol hydrochloride co-administration. The drugs that are affected by co-administration of colestipol hydrochloride vary widely in pharmacologic effect and mechanisms, in magnitude of doses, and in physicochemical characteristics. Therefore, it is not possible to predict a priori whether or not co-administration with colestipol hydrochloride will interfere with absorption. Unless a particular drug has been studied, it should be assumed that concomitantly administered drugs have the potential for interacting with colestipol hydrochloride.

**SINCE COLESTIPOL HYDROCHLORIDE MAY BIND OTHER DRUGS GIVEN CONCURRENTLY, PATIENTS SHOULD TAKE OTHER DRUGS AT LEAST ONE HOUR BEFORE OR FOUR HOURS AFTER COLESTID (OR AT AS GREAT AN INTERVAL AS POSSIBLE) TO AVOID IMPEDING THEIR ABSORPTION.**

Interactions between colestipol hydrochloride and drugs can be divided into two major categories:

- Substantially decreased bioavailability (defined as a decrease of > 20%), and
- Little or no effect on bioavailability (defined as a decrease of < 20%).

***Drug Interactions with Other Lipid-Lowering Drugs:***

**Fibric acid derivatives** - Based upon the definitions above, colestipol hydrochloride reduced the bioavailability of *gemfibrozil* (Cmax reduced 27%, AUC reduced 30%) when both drugs were administered together; this interaction was avoided by dosing gemfibrozil either two hours before or after

colestipol hydrochloride. Colestipol hydrochloride had little or no effect on the bioavailability of *clofibrate* and *fenofibrate*.

**Niacin (nicotinic acid)** - *Niacin* plasma concentrations were highly variable among subjects due in part to rapid absorption and elimination of niacin. The median Cmax and AUC were 35% and 48% lower when niacin was given with colestipol, but were not statistically significantly different from a niacin alone treatment. Concomitant multiple dosing of colestipol hydrochloride and niacin had minimal effect on niacin absorption. The interaction between colestipol hydrochloride and niacin does not appear to be clinically significant as evidenced by the additive efficacy of combination colestipol hydrochloride and niacin.

**Other classes of lipid-lowering drugs** - Colestipol hydrochloride drug interaction studies have not been conducted with HMG-CoA reductase inhibitors (ie. *lovastatin, simvastatin*, etc) or with *probucol*. However, clinical studies indicate that the cholesterol-lowering effects of colestipol hydrochloride and HMG-CoA reductase inhibitors are additive; therefore a clinically significant drug interaction is unlikely. Other drug interaction studies have been conducted with cholestyramine (another bile acid sequestrant) and various HMG-CoA reductase inhibitors. Cholestyramine significantly reduced the bioavailability of fluvastatin and pravastatin when the HMG-CoA reductase inhibitor was given one hour before and up to four hours after the cholestyramine dose. However, in clinical studies cholestyramine and HMG-CoA reductase inhibitors had additive cholesterol-lowering effects. The relevance of these cholestyramine drug interaction findings to colestipol is unknown.

***Drug Interactions with Other Drugs:***

**Antibiotics** - When co-administered, colestipol hydrochloride significantly reduced the bioavailability of *penicillin G* (Cmax reduced 79%, AUC reduced 84%) and *tetracycline hydrochloride* (Cmax reduced 52% and AUC reduced 59%). Colestipol hydrochloride had little effect on *clindamycin hydrochloride* bioavailability.

**Anticoagulants** - Colestipol hydrochloride had little effect on the bioavailability of *warfarin sodium* or *phenprocoumon*.

**Anticonvulsants** - Colestipol hydrochloride had little or no effect on the bioavailability of *phenytoin* or *carbamazepine*.

**Antihypertensives** - Repeated doses of colestipol hydrochloride given prior to a single dose of *propranolol* have been reported to decrease propranolol absorption. However, in a follow-up study involving healthy volunteers, single dose administration of colestipol hydrochloride and propranolol, twice-a-day administration for five doses of both agents, did not affect the extent of propranolol absorption, but had a small yet statistically significant effect on its rate of absorption.
The time to reach maximum concentration was delayed approximately 30 minutes. Therefore, patients on propranolol should be observed when COLESTID products are either added or deleted from a therapeutic regimen. The effects on the absorption of other beta-blockers have not been determined.
Colestipol hydrochloride had little effect on the bioavailability of *methyldopa*.

**Anti-inflammatory Agents** - Colestipol hydrochloride had little effect on the bioavailability of *A.S.A.*

**Cardiac Glycosides** - Particular caution should be exercised with digitalis preparations because there are conflicting results about the effects of colestipol hydrochloride on the bioavailability of *digoxin* and *digitoxin* in clinical and animal studies. In a single-dose, crossover study in healthy volunteers, the Cmax and AUC of digoxin did not differ when digoxin was co-administered with colestipol hydrochloride vs. when digoxin was given alone (Cmax was 118% and AUC was 97% of the values determined with digoxin alone). Since the potential for binding of digoxin and digitoxin to colestipol hydrochloride may exist, the serum digoxin and digitoxin levels should be monitored during periods of administration or discontinuation of COLESTID products.

**Diuretics** - Colestipol hydrochloride significantly lowered the bioavailability of *hydrochlorothiazide* (Cmax reduced 14%, 24-hour urinary excretion reduced 31%), *chlorothiazide* (urinary excretion reduced 58%) and *furosemide* (Cmax reduced 86%, AUC reduced 79%).

**Hypoglycemic Agents** - Colestipol hydrochloride had little effect on the bioavailability of *tolbutamide.*

**Mycophenolate Mofetil** - A study has shown that cholestyramine binds bile acids and reduces mycophenolic acid exposure. As colestipol also binds bile acids, colestipol may reduce mycophenolic acid exposure and potentially reduce efficacy of mycophenolate mofetil.

**Non-Medicinal Components: (also see PHARMACEUTICAL INFORMATION for a list of components)**

i) **Colloidal Silicon Dioxide** - COLESTID Granules and COLESTID Tablets contain colloidal silicon dioxide that can adversely influence patients with irritable bowel syndrome, diverticulosis and diverticulitis.

ii) **Aspartame** - COLESTID ORANGE Granules contain aspartame. Phenylketonurics are sensitive to the phenylalanine in aspartame.

## ADVERSE REACTIONS

The most frequently encountered adverse effects in clinical trials with COLESTID products (colestipol hydrochloride) are gastrointestinal. Constipation is the major single complaint and at times is severe and occasionally accompanied by fecal impaction. Most instances of constipation are mild, transient and controlled with standard treatment. See **PRECAUTIONS** for recommendation on how to minimize constipation side effect. Predisposing factors for most complaints of constipation are high dose and increasing age (more than 60 years of age).

Very common (≥10%) gastrointestinal complaints are abdominal discomfort and abdominal pain. Abdominal distension, flatulence, dyspepsia, nausea, vomiting, diarrhea, haemorrhoidal haemorrhage and

haematochezia were reported as common (≥1 - <10%). Dysphagia* and oesophageal obstruction* have been reported as uncommon (≥0.1 - <1%) in patients taking COLESTID Tablets.

Chest pain*, angina pectoris* and tachycardia * have been reported as uncommon (≥0.1-<1%).

Transient and modest elevations of serum aspartate aminotransferase (AST, SGOT)*, serum alanine aminotransferase (ALT, SGPT)* and serum alkaline phosphatise* were uncommonly (≥0.1-<1%) observed in patients treated with colestipol hydrochloride.

During initial registration studies for COLESTID Granules, adverse reactions occurring at a frequency of 0.1% or more are listed by body system as follows:

1. **Gastrointestinal disorders**

   Very common (≥10%): constipation, abdominal pain, abdominal discomfort

   Common (≥1- <10%): abdominal distension, belching, flatulence, nausea, vomiting, diarrhea

   Uncommon (≥0.1-<1%): peptic ulceration*, GI irritation and bleeding, haemorrhoids *

2. **Skin and subcutaneous tissue disorders**

   Common ((≥1 - <10%): rash

   Uncommon (≥0.1-<1%): urticaria *, dermatitis *

3. **Musculoskeletal and connective tissue disorders**

   Common (≥1 - <10%): muscle and joint pains, arthritis, arthralgia, back pain, musculoskeletal pain, pain in extremity

4. **Nervous system disorders**

   Very Common (≥10%): migraine, sinus headache, headache

   Uncommon (≥0.1-<1%): dizziness*, anxiety, vertigo, drowsiness

5. **Hepatobiliary disorders**

   Uncommon (≥0.1-<1%): cholecystitis*, cholelithiasis*

6. **Metabolism and nutrition disorders**

   Uncommon (≥0.1-<1%): decreased appetite *, anorexia

7. **Psychiatric disorders**

   Uncommon (≥0.1-<1%): insomnia *

8. **Respiratory, thoracic and mediastinal disorders**

Uncommon (≥0.1-<1%): dyspnoea *

9. **General disorders and administration site conditions**

Common (≥1 - <10%): fatigue

Uncommon (≥0.1-<1%): oedema peripheral*, asthenia *

10. **Miscellaneous**

Uncommon (≥0.1-<1%): weakness, shortness of breath

** events identified from post-marketing reports*

## SYMPTOMS AND TREATMENT OF OVERDOSAGE

For Management of a suspected drug overdose, contact your regional Poison Control Center.

Overdosage with COLESTID products (colestipol hydrochloride) has not been reported. Should overdosage occur, 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.

## DOSAGE AND ADMINISTRATION

Treatment for elevated serum cholesterol levels should begin with dietary therapy. Patients should be placed on a standard cholesterol-lowering diet at least equivalent to the American Heart Association (AHA) Step 1 Diet, which should be continued during treatment. If appropriate, a programme of weight control and physical exercise should be implemented. A minimum of six months of dietary therapy and counselling should usually be undertaken before initiating drug therapy. Shorter periods can be considered in patients with severe elevations of LDL-C (greater than 225 mg/100 mL or

5.85 mmol/L) or with definite coronary heart disease. Drug therapy should be added to dietary therapy and not substituted for it.

For adults, COLESTID Granules and COLESTID ORANGE Granules (colestipol hydrochloride) are recommended in doses of 5 to 30 g/day of colestipol hydrochloride given once or in divided doses. Initiation of therapy is recommended at 5 g colestipol hydrochloride either once or twice a day, with daily increments of 5 g colestipol hydrochloride no more frequently than at one month intervals.

For adults, COLESTID Tablets are recommended in doses of 2 to 16 g/day given once or in divided doses. Initiation of therapy is recommended at 2 g either once or twice a day. Dosage increments of 2 g once or twice daily may be instituted no more frequently than at one month intervals.

Serum cholesterol (total, fractionated and triglyceride levels) should be monitored periodically. Consideration should be given to reducing the dosage of COLESTID if serum cholesterol levels fall below the targeted range, such as that recommended by the Second Report of the U.S. National Cholesterol Education Program (NCEP). If the desired serum cholesterol levels are not obtained at maximal COLESTID doses with good compliance and acceptable side effects, combination lipid lowering therapy or alternate treatment should be considered.

According to the U.S. NCEP Expert Panel, children 10 years and older can be considered for drug therapy after an adequate trial of diet therapy alone is unsuccessful. If drug therapy is initiated, diet therapy should be continued in order to make the entire treatment regimen as effective as possible. The dose of colestipol hydrochloride used is not related to the body weight of the child but to the levels of total and LDL cholesterol after an adequate trial of diet therapy. Initially start the child on the lowest dose of COLESTID Granules or COLESTID ORANGE Granules. If needed, this dose is increased gradually over time in order to achieve the required total and LDL cholesterol levels. Breakfast and dinner are

preferred times for the administration of this medication to children. **(also see Use in Children under PRECAUTIONS)**

COLESTID Granules and COLESTID ORANGE Granules should always be taken mixed in a liquid such as water or a beverage; or in foods such as cereals, soups, yogurt, pudding, cottage cheese or pulpy fruits.

***To avoid accidental inhalation or esophageal distress, COLESTID Granules and COLESTID ORANGE Granules should not be taken in their dry form.***

With beverages:

1. Add the prescribed amount of COLESTID Granules or COLESTID ORANGE Granules to a glass (100 mL or more) of water, milk, flavoured drink, juice (orange, tomato, pineapple, etc.), or carbonated beverage. A heavy or pulpy juice may minimize complaints relative to consistency. An unsweetened juice may improve palatability.
2. Stir the mixture until the medication is completely suspended. COLESTID Granules and COLESTID ORANGE Granules will not dissolve in the liquid.
3. After drinking the mixture, rinse the glass with a small amount of additional beverage to make sure all the medication is taken.

With cereals, soups and fruits:

COLESTID Granules or COLESTID ORANGE Granules may be taken with milk in hot or regular breakfast cereals, or in soups with a high fluid content. It may also be added to fruits that are pulpy such as crushed pineapple, pears, peaches, or fruit cocktail.

COLESTID Tablets should be swallowed whole. Do not cut, chew or crush the tablets. The prescribed amount of COLESTID Tablets can be taken with water or any other appropriate fluid based on patient preference. COLESTID Tablets should be taken with meals.

**Missed Dose:** If the patient misses a dose, it should be taken as soon as possible provided it is NOT almost time for the next dose. The patient should be instructed to only take the dose prescribed at this time. COLESTID should not be taken as a double dose to make up for missed doses.

## PHARMACEUTICAL INFORMATION

### 1. Drug Substance:

Proper Name: colestipol hydrochloride

Chemical Name: copolymer of diethylenetriamine and 1-chloro-2,3-epoxpropane (hydrochloride) with at least one out of five amine nitrogens protonated

Chemical Structure: Anion-exchange copolymer of diethylenetriamine and 1-chloro-2,3-epoxypropane with one out of five amine nitrogens pronated.

Molecular Weight: varies between one to five million

Description:

- non-crystalline, water-insoluble resin which occurs as yellow to orange beads
- insoluble in common organic solvents
- decomposes without melting above 260°C
- hygroscopic and swells when suspended in aqueous fluids
- 10% (w/w) suspension in water is within pH of 6.0 to 7.5
- tasteless, odorless

### 2. Composition:

COLESTID Granules contains colestipol hydrochloride and colloidal silicon dioxide.

COLESTID ORANGE Granules has a light orange colour appearance and is orange flavoured. The product contains the active ingredient colestipol hydrochloride. The non-medicinal ingredients include mannitol, methylcellulose, citric acid, aspartame (each 7.5 g of COLESTID ORANGE Granules contains 18.2 mg phenylalanine), maltol, beta carotene, glycerin, artificial and natural flavour.

COLESTID Tablets are light yellow coloured, oval or elliptical, tasteless and odourless film coated tablets containing colestipol hydrochloride 1 g as active ingredient. The non-medicinal ingredients include: povidone, colloidal silicon dioxide, magnesium stearate, cellulose acetate phthalate, triacetin, hypromellose, carnauba wax. COLESTID Tablets contain no calories.

**3. Storage:**

Controlled room temperature (15°-30°C). Protect from heat, direct sunlight, moisture and humidity.

## AVAILABILITY OF DOSAGE FORMS

COLESTID Granules are available in cartons of 30 foil packets.

Each packet contains 5 g colestipol hydrochloride

COLESTID ORANGE Granules are available in cartons of 30 foil packets.

Each packet contains approximately 7.5 g COLESTID ORANGE Granules (5 g colestipol hydrochloride).

COLESTID Tablets 1 g are available in bottles of 120 tablets.

# PHARMACOLOGY

## ANIMAL PHARMACOLOGY

### Drug Kinetics

Following oral administration of $^{14}C$-labelled polymerized colestipol hydrochloride to dogs at a dosage level of 0.2 g/kg, 0.043% of the radioactivity was excreted in the urine over a seven day period. Seventy-three percent of the material ultimately excreted in the urine was voided during the first day.

Recovery of radioactivity, almost exclusively in the feces was 96.8% of the administered dose. No drug related radioactivity was found in plasma samples taken at intervals during a three day period following drug administration. The sensitivity of the plasma measurements was such that 0.002% of the administered dose, distributed in total body plasma, would have been detected.

### Antihypercholesterolemic Properties

Colestipol hydrochloride significantly reduced serum cholesterol in cholesterol-fed cockerels and pigeons and in cholesterol-cholic acid-fed rats. In the study of (1,2-$^{3}H$) - cholesterol turnover in normal rats, colestipol hydrochloride significantly increased cholesterol production and excretion rates without altering the size of the rapidly miscible cholesterol pool or serum cholesterol concentration. These results are compatible with an agent capable of enhancing bile acid excretion in the rat, which compensates for bile acid loss by increasing cholesterol biosynthesis. Colestipol hydrochloride feeding enhanced incorporation of (1-$^{14}C$) - acetate into cholesterol and conversion of (4-$^{14}C$) - cholesterol into 7-hydroxy-cholesterol by rat liver homogenates approximately 2-fold, confirming the effects on cholesterol synthesis and catabolism determined mathematically from the turnover studies. In dogs, colestipol hydrochloride feeding reduced serum cholesterol, enhanced fecal lipid excretion and fecal bile acid, but not fecal neutral steroid excretion.

**Drug Interactions**

Colestipol hydrochloride has been shown to bind a number of drugs in vitro and the degree of binding was influenced by ionic strength, pH, type of competing ion and whether association could occur with other molecules. In vivo, the effects of colestipol hydrochloride on the gastrointestinal absorption of radioactive drugs were measured in unanesthetized rats by following changes in serum radioactivity levels after concomitant administration of single doses of drug and resin. Colestipol hydrochloride or a microcrystalline cellulose control was given in doses of 71.5 and 214.5 mg/kg, which are equivalent on a body weight basis to 5 g (the usual human therapeutic dose) and 15 g in a 70 kg person. Drug doses also were equivalent to those in the human dose range on a body weight basis. Data were analyzed statistically at each sampling period and, whenever possible, by a one compartment model. The results are described as follows:

Colestipol hydrochloride did not significantly affect absorption of phenobarbital, cortisone acetate, tetracycline, chlorpromazine, sulfadiazine or clofibrate. In a repeat study comparing colestipol hydrochloride and cholestyramine at 3 times the usual human dose (214.5 mg/kg), both resins had minor effects on phenobarbital blood levels at some sampling periods, but area under the time-concentrations curves, representing total drug availability, was not significantly reduced with either resin. The high dose of colestipol hydrochloride significantly lowered serum levels of acetylsalicylic acid at several time periods. One compartment model parameter estimations showed a reduced rate of absorption and of peak serum radioactivity, but area under the model time-concentration curve (0-4) (calculated drug availability) was not significantly different from control. However, observed drug availability (0-12h) was reduced.

Serum l-thyroxine levels at most time periods were reduced by both the high and low doses of colestipol hydrochloride. The polymer significantly reduced peak serum radioactivity and drug availability. Absorption of nicotinic acid was reduced at 15 minutes by the low dose of colestipol hydrochloride and at 15 and 30 minutes by the high dose.

High dose of colestipol hydrochloride reduced serum warfarin levels at 0.5 and 1 hour.
Colestipol hydrochloride had no significant effect on serum digoxin levels, but the high dose of resin caused a statistically significant increase in digitoxin levels at 22 and 28 hours. Affinity of digitoxin for colestipol hydrochloride may have been decreased as the resin-bound drug reached a region of higher pH in the more distal small intestine or as newly secreted bile salts displaced the drug from colestipol HCl, giving an effect on serum levels similar to that seen with a sustained release preparation.

Effects of colestipol hydrochloride at 3 times the usual human dose (214.5 mg/kg) on the absorption of hydrochlorothiazide were determined. Colestipol hydrochloride did not inhibit the absorption of concomitantly administered hydrochlorothiazide.

Anionic dietary constituents such as amino acids also might be expected to bind to colestipol hydrochloride. To investigate possible effects on amino acid absorption, weaning rats were placed on a low protein diet containing enzymatically hydrolyzed casein amino acids as the only protein source with and without colestipol hydrochloride. An additional group of animals was fed the same diet containing 25% less protein as a means of comparing any effects of colestipol hydrochloride on weight gain or physical condition with a decrease in amino acid intake of known magnitude. After 14 weeks animals fed the basic diet plus 2% colestipol hydrochloride weighed approximately 12% less than animals fed basic diet alone; animals fed diet containing 25% less protein weighed 16% less than controls. If comparison of growth rate of the colestipol hydrochloride -fed rats with the rats fed the diet containing 25% less protein (7.5%) provides a valid estimate of the decrease in amino acid absorption, this amounts to only about 400 mg/day.

In a diet containing normal amounts of protein (25-30%) a decrease of 400 mg/day would have no significant effect on growth rate. In addition, since the dose of colestipol hydrochloride used in this study is about six-fold higher than the usual human therapeutic dose, significant effects on protein absorption in humans on nutritionally adequate diets would not be expected during hypercholesterolemic therapy.

## HUMAN PHARMACOLOGY

### Drug Kinetics

Following oral ingestion of $^{14}C$-labelled colestipol HCl by humans, at a dosage level of 0.07 g/kg body weight, 0.0214% of the radioactivity was excreted in urine over a seven-day period. Eighty percent of the material excreted in urine was voided during the first day. Recovery of radioactivity in the feces accounted for an additional 93.4% of the administered dose. No drug-related radioactivity was found in plasma samples taken at intervals during the 4 day period following drug administration. In this case, the sensitivity of the plasma measurements was such that 0.01% of the administered dose, distributed in total body plasma, would have been detected.

Colestipol hydrochloride is hydrophilic, but it is virtually water insoluble (99.75%) and it is not hydrolyzed by digestive enzymes. The high molecular weight polymer in colestipol hydrochloride apparently is not absorbed in the gastrointestinal tract: colestipol hydrochloride action is limited to the lumen of the gastrointestinal tract and it is passed in the feces. It binds bile acids in the intestinal lumen and causes them to be excreted in the feces together with the polymer. In humans, less than 0.17% of a single $^{14}C$-labeled colestipol hydrochloride dose is excreted in the urine when given following 60 days of dosing of 20 grams of colestipol hydrochloride per day.

For the treatment of hypercholesterolemia, initial response occurs at 24-48 hours while the peak occurs at 1 month after the oral administration of colestipol.

### Antihypercholesterolemic Properties

To confirm the mode of action of colestipol hydrochloride, young normal volunteers were given $^{14}C$-cholate intravenously and the fecal excretion rate was measured during 4 days of placebo medication, followed by two 4-day periods on either 30 g/day colestipol hydrochloride, 15 g/day colestipol

hydrochloride or 12 g/day cholestyramine. Diet was stable. Both drugs significantly increased fecal excretion of radio-labeled bile salts. In a second study, volunteer subjects were intravenously injected with $^{14}$C-cholesterol and the serum decay curves were examined. Colestipol hydrochloride significantly reduced the serum cholesterol concentration (21%) and produced a large increase in the production rate of cholesterol (86%). The turnover rate of cholesterol increased by 46%.

More than 2500 patients have taken 15-30 g a day of colestipol hydrochloride for periods up to 60 months. The decline in serum cholesterol is evident after one month's therapy and cholesterol does not return to baseline levels at any time during administration of the drug. On discontinuation of colestipol hydrochloride, within one month serum cholesterol returns to and does not exceed pretreatment levels. On reintroduction of colestipol hydrochloride, serum cholesterol responds as it did initially without evidence of ineffectiveness on successive exposures. Serum triglyceride levels usually remain unchanged in colestipol hydrochloride-treated patients, but they may increase in some.

In the various controlled studies using 15 g/day, the average cholesterol decline compared to placebo has been 45 mg/100 mL (1.2 mmol/L) with a range of 35-85 mg/100 mL (0.9 - 2.2 mmol/L). A lowering of serum cholesterol by 19% has been demonstrated with 10 g of colestipol hydrochloride given twice a day.

In a multi clinic study in 2278 hypercholesterolemic patients, men treated with 15 g/day of colestipol hydrochloride for up to 3 years had significantly lower coronary heart disease mortality rates than placebo-treated men ($p=0.01$). Colestipol hydrochloride -treated men also developed significantly fewer total (fatal or non-fatal) coronary heart disease events ($p=0.01$). Colestipol hydrochloride had no significant effect on mortality or coronary heart disease rates in women.

In 183 patients treated with 15 g/day of colestipol hydrochloride and 188 patients treated with placebo, each patient was given a comprehensive ophthalmological examination before drug administration and

again one year after initial exposure. There was no evidence of eye damage after the chronic administration of colestipol hydrochloride.

Patients given 15 g/day colestipol hydrochloride or placebo had platelet counts performed at or before Week 0 and again at Months 1, 3, 6, 9 and 12 and in a smaller group at Months 16, 20 and 24. This analysis was performed on data from 192 patients on colestipol hydrochloride and 196 on placebo. There was no evidence of colestipol hydrochloride affecting platelets.

In a double-blind, parallel, randomized, placebo-controlled study in 152 patients with mild primary hypercholesterolemia, three different dosages (5 g, 10 g, and 15 g per day) of colestipol HCl were evaluated. The greatest percentage of patients were adequately treated with the 15 g/day regimen. However, a LDL-C of less than 3.4 mmol/L (130 mg/100 mL) was achieved in some patients taking only 5 g or 10 g/day of colestipol hydrochloride.In a study previous to the one above, patients with average LDL-C levels in the range of 4.5 - 6.5 mmol/L (175-250 mg/100 mL) were treated with either 5 g, 10 g or 20 g of colestipol hydrochloride per day. Some patients in all dosage groups achieved a LDL-C level of less than 3.9 mmol/L (150 mg/100 mL). The greatest percentage of patients were adequately treated using 20 g/day of colestipol hydrochloride.

In a double-blind, parallel, randomized, placebo-controlled study in 312 patients with primary moderate hypercholesterolemia, treatment with colestipol tablets and granules at dosages of 4 and 16 g/day over an 8 week period, were compared. At 4 g/day LDL cholesterol levels decreased 11.5% and 12.1%; at 16 g/day the decreases were 24.1% and 24.6% respectively.

In another double-blind, parallel, randomized, placebo-controlled study, 193 patients with primary moderate hypercholesterolemia were treated with colestipol tablets for 8 weeks at dosages of 2, 4, 8 and 16 g/day. Reductions in LDL cholesterol levels were 5.2%, 10.9%, 19.8% and 25.8% respectively.

When compared to conventional measures, intensive lipid-lowering combination therapy using colestipol HCl plus either niacin or lovastatin, has been shown to significantly reduce the frequency of progression, and increase the frequency of regression of coronary atherosclerotic lesions in patients with or at risk for symptomatic coronary artery disease. However, it remains to be established to what extent these findings can be extrapolated to other segments of the hypercholesterolemic population not studied.

Treatment with colestipol hydrochloride results in a significant increase in lipoprotein LpA1. Lipoprotein LpA1 is one of the two major lipoprotein particles within the high density lipoprotein (HDL) density range. Lipoprotein LpA1 has been shown in cell culture to promote cholesterol efflux or removal from cells. Although the significance of this finding has not been established in clinical studies, the elevation of the lipoprotein LpA1 particle within the HDL fraction is consistent with an anti-atherogenic effect of colestipol hydrochloride, even though little change is observed in HDL cholesterol.

**Drug Interactions (also see PRECAUTIONS)**

Colestipol hydrochloride was shown to reduce plasma concentrations of **propranolol** in 12 healthy volunteers given propranolol tablets. Peak plasma concentrations and area under the curve for propranolol and the metabolite, 4'-hydroxypropranolol, were reduced. In another study involving 24 healthy volunteers, co-administration of propranolol tablets and colestipol hydrochloride did not result in a significant change in the rate or extent of propranolol absorption.

The effect of colestipol hydrochloride on the absorption of **penicillin G** was examined in 18 healthy adult male subjects. Colestipol hydrochloride significantly reduced the peak serum levels and the area under the serum concentration vs. time curve for penicillin G.

The effect on the bioavailability of oral **tetracycline HCl** when administered concomitantly with colestipol hydrochloride was examined in 18 healthy volunteers. Colestipol hydrochloride significantly reduced the serum levels of tetracycline hydrochloride.

The effect of colestipol hydrochloride on the gastrointestinal absorption of **chlorothiazide** was compared to placebo in 10 patients. Colestipol hydrochloride significantly reduced the gastrointestinal absorption of chlorothiazide measured by the cumulative 24 hour excretion of chlorothiazide in urine, both when the drugs were ingested simultaneously and when they were taken 1 hour apart.

Colestipol hydrochloride administration to 6 healthy adult male volunteers decreased total urinary excretion and plasma levels of **hydrochlorothiazide**.

The absorption and diuretic effect of **furosemide** were significantly diminished by colestipol hydrochloride in 6 patients. The bioavailability of furosemide was reduced to 80%.

The absorption of oral **phosphate supplements** can be affected by bile acid binding resins.
Ten patients received **gemfibrozil** together with colestipol hydrochloride, or two hours before or two hours after colestipol hydrochloride. No significant difference in gemfibrozil bioavailability was noted when gemfibrozil was administered two hours before or two hours after colestipol hydrochloride.

The concomitant administration of colestipol hydrochloride and **clindamycin** to 12 healthy volunteers did not affect clindamycin serum levels. There was however a slight decrease in the rate and extent of clindamycin availability.
The effect of colestipol hydrochloride on the absorption of concomitantly administered **clofibrate** was examined in 24 healthy subjects. Although there was little effect on the bioavailability parameters studied, concomitant colestipol hydrochloride did result in some higher serum levels of clofibrate.

When colestipol hydrochloride and a single dose of **methyldopa** were administered concomitantly in normal volunteers, the absorption of methyldopa was only very slightly reduced.

The effect of single doses of colestipol hydrochloride on the bioavailability of concomitantly administered **warfarin** was examined in 18 healthy subjects. Colestipol hydrochloride did not affect the bioavailability of warfarin in these subjects.

The effect of single doses of colestipol hydrochloride on the absorption of **phenprocoumon** in 4 human subjects was determined in a randomized crossover study with microcrystalline cellulose placebo. The mean plasma phenprocoumon concentrations were not significantly altered compared to placebo after the simultaneous administration of the drug and colestipol hydrochloride.

Colestipol hydrochloride did not affect the absorption of **phenytoin** in 6 adult male volunteers who received both medications together.

The effect of colestipol hydrochloride on the absorption of orally administered **digitalis** was examined in patients on chronic cardiac maintenance with digitalis. Four patients on placebo and 8 patients on colestipol hydrochloride were followed for up to 24 months. Digitalis was taken at least 1 hour after colestipol hydrochloride. Colestipol hydrochloride appeared to have no effect on the maintenance of serum digoxin levels in these patients.

In 12 healthy male volunteers, concurrent administration with colestipol hydrochloride did not affect plasma levels of **A.S.A.** or **tolbutamide.**

The serum levels of **vitamin A** in 84 subjects on colestipol hydrochloride and 73 subjects on placebo were examined for over 2 years, and colestipol hydrochloride had no effect on the vitamin A blood levels.

Determinations of the **vitamin D** levels in the serum of patients on colestipol hydrochloride or placebo for 1 to 2 years showed that colestipol hydrochloride had only a small effect on vitamin D levels as compared

to placebo treatment. This supports the absence of significant changes in serum calcium and phosphorous in all clinical studies.

A study of 11 subjects on placebo and 6 subjects on 15 g/day of colestipol hydrochloride showed that colestipol hydrochloride had no influence on the serum **folic acid** levels after 1 year of therapy.

A study in 25 healthy adult males indicated that the co-administration of colestipol hydrochloride tablets with **nicotinic acid** did not significantly alter the absorption of nicotinic acid.

A study has shown that cholestyramine binds bile acids and reduces mycophenolic acid exposure. As colestipol also binds bile acids, colestipol may reduce mycophenolic acid exposure and potentially reduce efficacy of mycophenolate mofetil.

## TOXICOLOGY

### Acute Toxicity

Because colestipol hydrochloride takes up several times its weight of water and swells, it was not practicable to administer more than 4000 mg/kg acutely. For reference, a clinical dose of 15 g/day is approximately 200 mg/kg. The $LD_{50}$ values for colestipol hydrochloride, expressed as mg/kg of body weight are as follows:

| Species | Route | $LD_{50}$ |
|---|---|---|
| Mouse | intraperitoneal | >4000 mg/kg |
| Rat | intraperitoneal | >4000 mg/kg |
| Rat | oral | >4000 mg/kg |

**Subacute Toxicity**

Colestipol hydrochloride was given to groups of 5 male and 5 female rats via the diet at dosage levels of 500, 1000 and 2000 mg/kg/day over a one-month period. An additional group of 10 animals received the diet alone and served as controls. The compound was judged non-toxic at the dosage levels administered.

Colestipol hydrochloride was given by gastric intubation to a group of New Zealand white rabbits at the rate of 4000 mg/kg/day in divided doses over a two-week period. A similar group of New Zealand white rabbits received an equal volume of vehicle alone and served as controls.
The compound was judged non-toxic in this study but somewhat irritating, as indicated by the resistance to dosing and the elevated heterophil percentage in the treated rabbits as compared to controls.

Colestipol hydrochloride was given in the feed to a group of 2 male and 2 female immature purebred beagle dogs for an 11-day period at a dosage level of 4000 mg/kg/day. A similar group of dogs received microcrystalline cellulose placebo at the same rate in the feed and served as controls. Colestipol hydrochloride appeared at this high dose to interfere with the absorption of certain elements of nutrition which are in increased demand during the growing period.

Colestipol hydrochloride was administered in the feed of two male purebred beagles for a one-month period at the single dosage level of 3000 mg/kg/day. A similar group received the non-treated diet and served as controls. The compound was judged essentially non-toxic in this study. A marked drop was produced in the serum cholesterol, triglycerides and phospholipids, which was an anticipated therapeutic effect. The only other drug-related changes observed were soft odorous feces and a decrease in body weight.

**Chronic Toxicity**

Colestipol hydrochloride was administered in the feed of 3 groups of rats consisting of 15 male and female rats at dosage levels of 500, 1000 and 2000 mg/kg/day over an eighteen-month period. A similar

group was given the diet only and served as controls. The compound was judged non-toxic in this study. An examination of the femur weights and bone calcium concentrations after 18 months on colestipol hydrochloride showed no significant change which indicates no significant effect of colestipol hydrochloride on calcium intestinal absorption.

Colestipol hydrochloride was given in the feed to 3 groups of 2 male and 2 female purebred beagles at dosage levels of 500, 1000 and 2000 mg/kg/day, respectively, over a one-year period. A fourth and similar group received the diet only and served as controls. In this study, clinical, clinical pathological, gross and microscopic observations were made. No drug-related adverse effects were observed, except for losses in body weight of approximately 15% which occurred during the first thirty days of the study and persisted throughout.

**Electron Microscopy Study - Rat Liver**

Colestipol hydrochloride was administered in the feed to a single group of 3 male and 2 female rats at a dosage level of 500 mg/kg/day over a 5-month period. A similar group received the diet alone and served as controls. Under the conditions of this experiment, the drug had no apparent effect on hepatic tissue as judged from electron photomicrographs.

**Fat Absorption**

Bile acids are required for optimal fat digestion and absorption. Decrease in the intraluminal concentration of bile acids by binding to colestipol hydrochloride might be expected to have some effect on fat absorption. In purebred beagle dogs given colestipol hydrochloride in doses of 500, 1000 and 2000 mg/kg daily in the diet for 1 year, total fecal lipids were increased by the two higher doses; the low dose had no effect on fat excretion. Caloric loss due to increased fat excretion at the highest dose, equivalent to approximately 10 times the human therapeutic dose on a body weight basis, resulted in weight loss of about 15%. However, there was no evidence of fat soluble vitamin deficiencies or other toxicity.

**Teratology and Reproduction**

In a non-regulatory reproduction and development study, colestipol hydrochloride administered as bulk drug via gastric intubation to pregnant rabbits on gestation day 6 through 18 at dosages of 300 and 1000 mg/kg/day (comparable to 0.6 and 2 times the MRHD) was judged non-teratogenic. The reproductive performance of treated dams was comparable to controls. The 1000 mg/kg group exhibited a slightly higher incidence of resorptions than the controls but the average litter size was unaffected.

Colestipol hydrochloride was not teratogenic when given to pregnant rats by gastric intubation on gestation day 6 through 15 in two separate studies at dosages of 300 and 1000 mg/kg/day (comparable to 0.6 and 2 times the MRHD), respectively. Visceral and skeletal examination results between treated and control groups were comparable.

Colestipol hydrochloride administered in the diet at 500 and 1000 mg/kg/day (comparable to 1 and 2 times the MRHD) had no significant effect upon the reproductive performance of male and female rats for one generation. No significant abnormalities were noted by gross observation at birth or by necropsy at weaning (21 days post-parturition).

**Carcinogenesis and Mutagenesis:**

When colestipol hydrochloride was administered in the diet to rats for 18 months, there was no evidence of any drug related intestinal tumour formation. In the Ames assay, colestipol hydrochloride was not mutagenic.

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**PART III: CONSUMER INFORMATION**

**COLESTID® Granules**
**(colestipol hydrochloride for oral suspension USP)**
**COLESTID® ORANGE Granules**
**(colestipol hydrochloride for oral suspension)**
**COLESTID® Tablets**
**(colestipol hydrochloride tablets)**

**This leaflet is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about COLESTID. Contact your doctor or pharmacist if you have any questions about this drug.**

## ABOUT THIS MEDICATION

**What the medication is used for:**

In addition to a standard diet to lower cholesterol and exercise, COLESTID can be used to reduce the amount of cholesterol in the blood.
Your doctor may also prescribe weight loss while you are taking COLESTID.

Your doctor will put you on a special diet to help lower your cholesterol. Follow the diet while you are taking COLESTID. Taking COLESTID **does not replace** the need to be on a special diet. It is important for your treatment that you do both.

**What it does:**
COLESTID works by preventing bile acids from being taken up in the blood.

Bile acids are formed when your body breaks down cholesterol. The medicine in COLESTID acts by trapping bile acids in the bowels. Bile acids trapped by COLESTID pass out of your body instead of going into the blood. When there are less bile acids, your body is forced to break down more cholesterol, which will lower the cholesterol level in your blood.

**When it should not be used:**
Do not take COLESTID

- if you are allergic (hypersensitive) to colestipol hydrochloride or to any of the other ingredients of COLESTID
- if you have a blockage in your intestines or bile ducts (tubes that carry bile)
- if you have phenylketonuria you should not take COLESTID ORANGE granules. They contain aspartame. Phenylketonurics are sensitive to the phenylalanine in aspartame.

**What the medicinal ingredient is:**
Colestipol hydrochloride

**What the nonmedicinal ingredients are:**
**COLESTID granules:**
Colloidal silicon dioxide

**COLESTID ORANGE Granules**:
Aspartame, beta-carotene, citric acid, glycerine, mannitol, maltol, methyl cellulose, artificial and natural flavor

**COLESTID Tablets:**
Carnauba wax, cellulose acetate phthalate, colloidal silicon, dioxide, hypromellose, magnesium stearate, povidone, triacetin

**What dosage forms it comes in:**
COLESTID Granules for oral suspension USP in foil packet. Each packet contains 5g colestipol hydrochloride.

COLESTID ORANGE Granules for oral suspension in foil packet. Each packet contains 5g colestipol hydrochloride.

COLESTID Tablets in bottles. Each tablet contains 1 g of colestipol hydrochloride

## WARNINGS AND PRECAUTIONS

**BEFORE you use COLESTID talk to your doctor or pharmacist if:**

- **You have or have had in the past any health problems as some conditions can affect your cholesterol level and should be treated before you take COLESTID.**
- **You have dysproteinemia (an abnormality in protein content of the blood, usually in the content of immunoglobulins), diabetes, thyroid, gallbladder, kidney or liver disease**
- **You have a deficiency of vitamins A, D, or K.**
- **You are pregnant, if you become pregnant or if you are breastfeeding your baby.**
- **You are taking other medicines, even medicine without prescription.**
- **you have irritable bowel syndrome, diverticulosis and diverticulitis, as these conditions can be influenced by the non-medicinal ingredient colloidal silicon present in these products**

## INTERACTIONS WITH THIS MEDICATION

COLESTID can reduce the effect of other medications taken at the same time. **Take other medications at least 1 hour before or, wait 4 hours after you take COLESTID before taking other medications**

Drugs that may interact with COLESTID include:

- Antibiotics
- Beta-blockers (used to decrease blood pressure)
- Digoxin or digitoxin

- Diuretics (water pills)
- Warfarin (anticoagulant)
- Mycophneolate mofetil (immunosuppressant)

## PROPER USE OF THIS MEDICATION

**Usual Adult Dose:**
**COLESTID Granules or COLESTID ORANGE Granules:**
5 to 30 g per day once or in divided doses. Usual starting dose is 5 g once or twice a day.

**COLESTID Tablets:**
2 to 16 g per day once or in divided doses. Usual starting dose is 2 g once or twice a day.

Dosages can be increased at one month intervals. Your doctor will decide the best dosage for you.

**Usual dose for Children 10 years and older:** Will be determined by the doctor. The lowest dose of the granules is recommended.

**COLESTID Granules or COLESTID ORANGE Granules:**

**Never take COLESTID ORANGE granules USP or COLESTID granules in its dry form, as it can cause you to choke.**

A heavy or pulpy juice may reduce the "gritty" feel of the medicine.

Unsweetened juice may make COLESTID taste better.

**PREPARATION**
Always mix COLESTID with liquids or foods.
* For liquids you may choose: water, milk, flavoured drink, juice or any other liquid of your choice.

* For foods you may choose: cereals (hot or cold), soups (avoid chunky soups), yogurt, pudding, cottage cheese or pulpy fruits (crushed pineapple, pears, peaches or fruit cocktail).

Step 1. Add the amount of your dose (packets) of COLESTID to at least 100 mL (3-4 oz) of liquid or food.

Step 2. Stir the medicine until it is evenly mixed. The medicine will not completely dissolve; you will still be able to see the granules.

Step 3. Drink or eat all of the mixture. When you are finished, rinse the glass or bowl with a small amount of liquid that you drink to make sure you have taken all the medicine.

**COLESTID Tablets:**
**Do not cut, chew or crush the tablets.**

Swallow COLESTID Tablets whole. Take them with a full glass of liquid. You may choose water, milk, flavoured drink, juice, pop or soda, or any other liquid of your choice.

Take COLESTID Tablets with your meals. If you take COLESTID Tablets more than once a day, take one dose at breakfast or lunch, and a second dose in the evening.

**Overdose:**

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:**
If you miss a dose of this medicine, take it as soon as possible. For the rest of the day continue on your regular schedule. But, if you miss a dose and it is almost time for the next dose, do not take the 2 doses together. Take only the dose you should be taking at this time.
**Do not take a double dose of COLESTID to make up for missed doses.**

## SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Side effects may include:

- worsened haemorrhoids and bleeding from haemorrhoids
- nausea, bloating, gas, heartburn, vomiting, loss of appetite,
- headache, anxiety, dizziness, drowsiness,
- fatigue, weakness, insomnia

Call your doctor, if these effects continue or worsen. If you feel any other unusual effects not listed here, see your doctor.

| SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM | | | | |
|---|---|---|---|---|
| **Symptom / effect** | | **Talk with your doctor or pharmacist** | | **Stop taking drug and Seek immediate medical help** |
| | | **Only if severe** | **In all cases** | |
| **Frequency** | | | | |
| Very Common | Constipation | | √ | |
| | Stomach pain | | √ | |
| Common | Diarrhea | | √ | |
| | Joint and muscle pains, back pain | | √ | |
| | Blood in feces | | √ | |
| | Shortness of breath | | √ | |
| | Vertigo | | √ | |
| | Ulcers | | √ | |
| | Skin Reaction: rash | | √ | |
| | Inflammation of the gallbladder, gall stone: symptoms like abdominal pain so intense that you can't sit still or find a comfortable position | | √ | |
| Uncommon | Elevated liver enzyme levels | | √ | |
| | Allergic Reaction: symptoms like hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing | | | √ |
| | Chest pain | | √ | |
| | Rapid heart beats | | √ | |

***This is not a complete list of side effects. For any unexpected effects while taking* COLESTID*, contact your healthcare professional.***

## HOW TO STORE IT

Keep out of the sight and reach of children. Store COLESTID Tablets away from heat, direct sunlight and humid places like your bathroom. COLESTID is best kept at room temperature (15°-30°C) in a dry place.

## 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

This document plus the full product monograph, prepared for health professionals can be found at:
http://www.pfizer.ca
or by contacting the sponsor, Pfizer Canada ULC at:
1-800-463-6001.

This leaflet was prepared by Pfizer Canada ULC

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