

PRODUCT INFORMATION

COLESTID[®] (colestipol hydrochloride)

NAME OF THE MEDICINE

COLESTID (colestipol hydrochloride) 5 g granules for oral suspension.

DESCRIPTION

COLESTID Granules for Oral Suspension consist of colestipol hydrochloride which is a hypolipidaemic agent for oral use. COLESTID is an insoluble, high molecular weight basic anion-exchange copolymer of diethylenetriamine and 1-chloro-2, 3-epoxypropane, with approximately 1 out of 5 amine nitrogens protonated (chloride form). It is a light yellow water-insoluble resin which is hygroscopic and swells when suspended in water or aqueous fluids. COLESTID is tasteless and odourless.

Inactive ingredient: Silicon dioxide.

PHARMACOLOGY

Cholesterol is the major, and probably the sole precursor of bile acids. During normal digestion, bile acids are secreted via the bile from the liver and gall bladder into the intestines. Bile acids emulsify the fat and lipid materials present in food, thus facilitating absorption. A major portion of the bile acids secreted is reabsorbed from the intestines and returned via the portal circulation to the liver, thus completing the enterohepatic cycle. Only very small amounts of bile acids are found in normal serum.

COLESTID binds bile acids in the intestine forming a complex that is excreted in the faeces. This nonsystemic action results in a partial removal of the bile acids from the enterohepatic circulation, preventing their reabsorption. Since COLESTID is an anion-exchange resin, the chloride anions of the resin can be replaced by other anions, usually those with a greater affinity for the resin than chloride ions.

COLESTID is hydrophilic, but it is virtually water insoluble (99.75%) and it is not hydrolysed by digestive enzymes. The high molecular weight polymer in COLESTID apparently is not absorbed. Less than 0.05% of ¹⁴C-labelled COLESTID is excreted in the urine.

The increased faecal loss of bile acids due to COLESTID administration leads to an increased oxidation of cholesterol to bile acids, a decrease in beta lipoprotein or low density lipoprotein serum levels, and a decrease in serum cholesterol levels. Although COLESTID produces an increase in the hepatic synthesis of cholesterol in man, serum cholesterol levels fall.

There is evidence to show that this fall in cholesterol is secondary to an increased rate of clearance of cholesterol rich lipoproteins (beta or low density lipoproteins) from the plasma. Serum triglyceride levels may increase or remain unchanged in colestipol treated patients.

Treatment with colestipol hydrochloride results in a significant increase in lipoprotein LpAI. Lipoprotein LpAI is one of the two major lipoprotein particles within the HDL density range and has been shown in cell culture to promote cholesterol efflux or removal from cells. The significance of this finding has not been established in clinical studies.

The decline in serum cholesterol levels with COLESTID treatment is usually evident by one month. When COLESTID is discontinued, serum cholesterol levels usually return to baseline levels within one month. Cholesterol may rise even with continued use of COLESTID and serum levels should be determined periodically to confirm that a favourable initial response is maintained.

INDICATIONS

Since no drug is innocuous, strict attention should be paid to the indications and contraindications, particularly when selecting drugs for chronic long-term use.

COLESTID is indicated as adjunctive therapy to diet for the reduction of elevated serum cholesterol in patients with primary hypercholesterolaemia (elevated low density lipoproteins [LDL] cholesterol) who do not respond adequately to diet. COLESTID has been shown to have no effect on or to increase triglyceride levels.

It has not been established whether the drug-induced lowering of serum cholesterol or triglyceride levels has a beneficial, no effect, or a detrimental effect on the morbidity or mortality due to atherosclerosis including coronary heart disease. Investigations now in progress may yield an answer to this question.

CONTRAINDICATIONS

COLESTID is contraindicated in those individuals who have shown hypersensitivity to colestipol hydrochloride or any other components in the formulation.

PRECAUTIONS

TO AVOID ACCIDENTAL INHALATION OR OESOPHAGEAL DISTRESS, COLESTID SHOULD NOT BE TAKEN IN ITS DRY FORM. ALWAYS MIX COLESTID WITH WATER OR OTHER FLUIDS BEFORE INGESTING.

Before instituting therapy with COLESTID, diseases contributing to increased blood cholesterol such as hypothyroidism, diabetes mellitus especially poorly controlled cases, nephrotic syndrome, dysproteinaemias, other drug therapy, alcoholism and obstructive liver disease should be looked for and specifically treated. The patient's current medications should be reviewed for their potential to increase serum LDL-cholesterol or total cholesterol.

Effect on Vitamin Absorption

Because it sequesters bile acids, COLESTID may interfere with normal fat absorption and thus may prevent absorption of folic acid and fat soluble vitamins such as A, D and K. If

COLESTID resin is to be given for long periods of time, supplemental vitamin A and D should be considered.

Hypoprothrombinaemia

Chronic use of COLESTID may be associated with an increased bleeding tendency due to hypoprothrombinaemia from vitamin K deficiency. This will usually respond promptly to parenteral vitamin K₁, and recurrences can be prevented by oral administration of vitamin K₁.

Elevation of Serum Triglycerides

Serum cholesterol and triglyceride levels should be measured periodically to detect significant changes. COLESTID may raise the serum triglycerides in long term use and, in some patients, the cholesterol levels return to baseline or rise above baseline. A significant rise in triglyceride level should be considered as an indication for dose reduction, drug discontinuation, or combined or alternate therapy.

Constipation

COLESTID may produce or severely worsen pre-existing constipation. The dosage should be decreased in these patients since impaction may occur. Particular effort should be made to avoid constipation in patients with symptomatic coronary artery disease. Constipation associated with COLESTID may aggravate haemorrhoids.

Hypothyroidism

While there have been no reports of hypothyroidism induced in individuals with normal thyroid function, the theoretical possibility exists, particularly in patients with limited thyroid reserve.

Use in Pregnancy - Category B2

The physiological hyperlipidaemia of pregnancy does not require treatment.

The safe use of COLESTID by pregnant women has not been established.

Due to its known interference with absorption of fat-soluble vitamins, the use of COLESTID in pregnancy or lactation or by women of childbearing age requires that the potential benefits of drug therapy be weighed against the possible hazards to the mother and child.

Use in Lactation

The safety of COLESTID has not been established in breast-feeding women. Caution should be exercised when prescribing to breast-feeding women.

Paediatric Use

Safety and effectiveness in children have not been established.

Genotoxicity

In the Ames assay, COLESTID was not mutagenic.

Carcinogenicity

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 LRC-CPPT study referred to above, the total incidence of fatal and non-fatal neoplasms was similar in both treatment groups. When the many different categories of tumours 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. Further follow-up of the LRC-CPPT participants by the sponsors of that study is planned for cause-specific mortality and cancer morbidity.

When COLESTID was administered in the diet to rats for 18 months, there was no evidence of any drug related intestinal tumour formation.

INTERACTIONS WITH OTHER MEDICINES

Since COLESTID is an anion-exchange resin, it may have a strong affinity for anions other than the bile acids. *In vitro* studies have indicated that COLESTID binds a number of drugs. Therefore, COLESTID resin may delay or reduce the absorption of concomitant oral medication. The interval between the administration of COLESTID and any other medication should be as long as possible. Patients should take other drugs at least one hour before or four hours after COLESTID to avoid impeding their absorption.

Effect of COLESTID on Other Medicines

Propranolol

Human studies have demonstrated that COLESTID may decrease propranolol absorption. Effects on the absorption of other beta-blockers have not been determined. Therefore, patients on propranolol should be observed when COLESTID is either added or deleted from a therapeutic regimen.

Chlorothiazide

Studies in humans show that the absorption of chlorothiazide as reflected in urinary excretion is markedly decreased even when administered one hour before COLESTID.

Tetracycline/Frusemide/Penicillin G/Hydrochlorothiazide/Gemfibrozil

The absorption of tetracycline, frusemide, penicillin G, hydrochlorothiazide and gemfibrozil was significantly decreased when given simultaneously with colestipol hydrochloride; however, colestipol hydrochloride and gemfibrozil can be used in the same patient when administered two hours apart.

Digoxin/Digitoxin

Particular caution should be observed with digitalis preparations since there are conflicting results for the effect of COLESTID on the availability of digoxin and digitoxin. The potential for binding of these drugs if given concomitantly is present. Discontinuing COLESTID could pose a hazard to health if a potentially toxic drug that is significantly bound to the resin has been titrated to a maintenance level while the patient was taking COLESTID. The serum digoxin and digitoxin levels should be monitored during periods of administration or discontinuation of COLESTID.

Oral Phosphate Supplements

Bile acid binding resins may also interfere with the absorption of oral phosphate supplements.

Mycophenolic Acid/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.

Medicines not Affected by COLESTID

Concurrent administration of colestipol hydrochloride with phenytoin, aspirin, tolbutamide, clofibrate, methyldopa, nicotinic acid, clindamycin or warfarin does not affect the bioavailability of the respective drugs.

ADVERSE EFFECTS

The most common adverse reactions are confined to the gastrointestinal tract. Constipation, reported by about one patient in ten, is the major single complaint and at times is severe. Most instances of constipation are mild, transient, and controlled with standard treatment. Some patients require decreased dosage or discontinuation of therapy.

The following table lists adverse events described by system organ class and frequency (very common $\geq 1/10$; common $\geq 1/100$ to $< 1/10$; uncommon $\geq 1/1,000$ to $< 1/100$; rare $\geq 1/10,000$ to $< 1/1,000$; very rare $< 1/10,000$).

MedDRA System Organ Class	Frequency	Undesirable Effects
Metabolism and nutrition disorders	Uncommon	Decreased appetite
Psychiatric disorders	Uncommon	Insomnia
Nervous system disorders	Very common	Migraine, Sinus headache, Headache
	Uncommon	Dizziness
	Rare	Anxiety, Vertigo, Drowsiness
Cardiac disorders	Uncommon	Angina pectoris, Tachycardia
Respiratory, thoracic and mediastinal disorders	Uncommon	Dyspnoea
Gastrointestinal disorders	Very common	Constipation, Abdominal pain, Abdominal discomfort
	Common	Haematochezia, Haemorrhoidal haemorrhage, Abdominal distention, Dyspepsia, Nausea, Vomiting, Diarrhoea, Flatulence
	Uncommon	Belching, Gastrointestinal bleeding, Peptic ulcer, Haemorrhoids
Hepatobiliary disorders	Uncommon	Cholecystitis, Cholelithiasis
Skin and subcutaneous tissue disorders	Common	Rash
	Uncommon	Urticaria, Dermatitis
Musculoskeletal and connective tissue disorders	Common	Arthritis, Arthralgia, Back pain, Musculoskeletal pain, Pain in extremity
General disorders and administration site conditions	Common	Fatigue
	Uncommon	Chest pain, Oedema peripheral, Asthenia
Investigations	Uncommon	Alanine aminotransferase increased, Aspartate aminotransferase increased, Blood alkaline phosphatase increased

Some patients have shown an increase in serum phosphorus and chloride with a decrease in sodium and potassium. Asthma and wheezing were not reported in the COLESTID studies but have been noted during treatment with other cholesterol - lowering agents.

DOSAGE AND ADMINISTRATION

For adults, COLESTID is recommended in doses of 15 - 30 grams/day taken in divided doses two to four times daily. To avoid accidental inhalation or oesophageal distress, COLESTID should not be taken in its dry form. COLESTID should always be mixed with water or other fluids before ingesting. Patients should take other drugs at least one hour before or four hours after COLESTID to minimise possible interference with their absorption (see INTERACTIONS WITH OTHER MEDICINES).

Before COLESTID Administration

1. Define the type of hyperlipoproteinaemia.
2. Institute a trial of diet and weight reduction.
3. Establish baseline serum cholesterol and triglyceride levels.

During COLESTID Administration

1. The patient should be carefully monitored clinically, including serum cholesterol and triglyceride levels.
2. Failure of cholesterol to fall or significant rise in triglyceride level should be considered as indications to discontinue medication.

Mixing and Administration Guide

COLESTID should always be taken mixed in a liquid such as orange or tomato juice, water, milk or carbonated beverage. It may also be taken in soups or with cereals or pulpy fruits.

COLESTID SHOULD NEVER BE TAKEN IN ITS DRY FORM.

With Beverages

1. Add the prescribed amount of COLESTID to a glassful (100 – 150 mL) of water, milk, flavoured drink, or a favourite juice (orange, tomato, pineapple, or other fruit juice).
2. Stir the mixture until the medication is completely mixed. (COLESTID will not dissolve in the liquid.) COLESTID may also be mixed with carbonated beverages, slowly stirred in a large glass. Rinse the glass with a small amount of additional beverage to make sure all the medication is taken.

With Cereals, Soups and Fruits

COLESTID may be taken mixed with milk in hot or regular breakfast cereals, or even mixed in soups that have a high fluid content (tomato or chicken noodle soup). It may also be added to fruits that are pulpy such as crushed pineapple, pears, peaches or fruit cocktail.

OVERDOSAGE

Overdosage of COLESTID has not been reported. 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.

Monitor serum electrolytes and fluid status in all patients with persistent vomiting or symptomatic patients. Monitor liver enzymes after significant overdose. Assess bowel motion in all patients. If obstruction is ruled out, a polyethylene glycol electrolyte oral solution may be used to expedite the evacuation of colestipol resin. In minimal to moderate ingestions, increased fluid intake, fibre and stool softener should be instituted.

Colestipol is largely not absorbed in the gastrointestinal tract. Attempts at gastrointestinal decontamination are generally not warranted.

Contact the Poisons Information Centre on 13 11 26 for advice on the management of an overdose.

PRESENTATION AND STORAGE CONDITIONS

COLESTID Granules for Oral Suspension are available in packs containing 120 foil sachets (4 boxes of 30 sachets). Each sachet supplies 5 grams of COLESTID.

Storage Conditions

Store below 30°C.

NAME AND ADDRESS OF THE SPONSOR

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POISON SCHEDULE OF THE MEDICINE

S4 - Prescription Only Medicine.

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS

2 August 1991.

DATE OF MOST RECENT AMENDMENT

19 September 2013

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