

COLESTID®

Colestipol hydrochloride, 100% granule

Presentation

COLESTID is a colourless, tasteless, light yellow, water-insoluble resin of 100% colestipol hydrochloride, which is hygroscopic and swells when suspended in water or aqueous fluids.

Uses

Actions

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 (colestipol hydrochloride) 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 ion.

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 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.

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.

Pharmacokinetics

Colestipol hydrochloride is hydrophilic, but it is virtually water insoluble (99.75%) and it is not hydrolysed 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 faeces. It binds bile acids in the intestinal lumen and causes them to be excreted in the faeces together with the polymer. In humans, less than 0.17% of a single ¹⁴C-labeled COLESTID dose is excreted in the urine when given following 60 days of dosing of 20 grams of COLESTID 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 COLESTID.

Indications

COLESTID is indicated as adjunctive therapy to diet for the reduction of elevated serum cholesterol and low-density lipoprotein (LDL) cholesterol in patients with primary hypercholesterolaemia (elevated low density lipoproteins (LDL) cholesterol) who do not respond adequately to diet and to reduce the risks of atherosclerotic coronary artery disease and myocardial infarction.

It may be used as the sole agent or in combination with additional lipid lowering agents.

When compared to conventional measures, intensive lipid-lowering combination therapy, which included COLESTID plus either niacin or lovastatin, significantly reduced the frequency of progression and increased the frequency of regression of coronary atherosclerotic lesions in patients with, or at risk for, symptomatic coronary artery disease.

Dosage and Administration

Treatment for elevated serum cholesterol levels should begin with dietary therapy. 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-cholesterol or definite coronary heart disease. Drug therapy should be added to dietary therapy, and not substituted for it.

COLESTID should never be taken in its dry form. Oesophageal spasm or respiratory distress can result from attempting to swallow the granules dry.

For adults, COLESTID is recommended in doses of 5 - 30 grams/ day taken one to two times daily. Initiation of therapy is recommended at 5 grams either once or twice daily with daily increments of 5 grams no more frequently than at one to two month intervals. Appropriate use of lipid profiles including LDL-cholesterol and triglycerides is advised so that optimal, but not excessive doses are used to obtain the desired therapeutic effect. If the desired therapeutic effect is not obtained at a dose of 5 - 30 grams/day with good compliance and acceptable side effects, combined therapy or alternate treatment should be considered.

The prescribed amount of COLESTID should be taken with fluids. Each sachet should be added to 100-150ml of any appropriate fluid (fruit juice, water) based on patient preference. Stir the mixture until the medication is completely suspended. COLESTID may also be mixed with cereals, soups and other foods provided that sufficient fluid is also ingested.

Contraindications

COLESTID is contraindicated in those individuals who have shown hypersensitivity to any of its components.

Warnings and Precautions

Before instituting therapy with COLESTID, a vigorous attempt should be made to control serum cholesterol by an appropriate dietary regimen and weight reduction; any underlying disorder that may contribute to the hypercholesterolaemia such as hypothyroidism, diabetes mellitus, nephrotic syndrome, dysproteinemias and obstructive liver disease should be treated. The patients current medications should be reviewed for their potential to increase serum LDL-cholesterol or total cholesterol.

Because it sequesters bile acids, COLESTID may interfere with normal fat absorption and thus may prevent absorption of fat soluble vitamins such as A, D, E and K. A study done in humans found only one patient in whom a prolonged prothrombin time was noted. Most studies did not show a decrease in vitamin A, D or E levels during the administration of COLESTID.

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.

When used as sole therapy, COLESTID will not improve hypertriglyceridaemia and may elevate serum triglycerides. This elevation is generally transient but may persist in some individuals. A significant rise in triglyceride level should be considered as an indication for dose reduction, drug discontinuation, or combined or alternate therapy.

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.

Carcinogenesis, Mutagenesis and Impairment of Fertility

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 colestipol hydrochloride is not known. In the LRC-CPPT study, 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 colestipol hydrochloride was administered in the diet to rats for 18 months, there was no evidence of any drug related intestinal tumor formation. In the Ames assay, colestipol hydrochloride was not mutagenic.

Use in Children

Clinical trials of COLESTID tablets have not been conducted in patients under 18 years of age. The use of COLESTID in children is limited; therefore, dosage and long-term safety have not been established. If COLESTID therapy is indicated in children, a titration approach is recommended to obtain optimal cholesterol-lowering effect with the lowest possible dose. Clinical trials conducted with COLESTID granules in children have usually employed doses of 5 - 20 grams/day. The NCEP Report of the Expert Panel on Blood Cholesterol Levels in Children and Adolescents recommends a titration approach in children ages 10 and older, based on cholesterol levels and therapeutic response as an adjunct to dietary measures. Because bile acid sequestrants may interfere with the absorption of fat-soluble vitamins, appropriate monitoring of growth and development is recommended if used to treat children.

Children under 2 years of age should not have their cholesterol levels manipulated, either by drug or diet treatment.

Use in Pregnancy

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

Adverse Effects

Gastrointestinal Disorders

The most common adverse reactions are confined to the gastrointestinal tract. To achieve minimal GI disturbance with an optimal LDL-cholesterol lowering effect, a gradual increase in dosage starting with 2 grams, once or twice a day is recommended.

Constipation, reported by about one patient in ten, is the major single complaint and at times is severe and occasionally accompanied by faecal impaction. Haemorrhoids may be aggravated. Most instances of constipation are mild, transient, and controlled with standard treatment. Increased fluid intake and inclusion of additional dietary fibre should be the first step; a stool softener may be added if needed. Some patients require decreased dosage or discontinuance of therapy.

Less frequent gastrointestinal complaints consist of: Abdominal discomfort (abdominal pain and cramping), abdominal distention, flatulence, dyspepsia, nausea, vomiting, diarrhoea, bleeding haemorrhoids, haematochezia, peptic

<i>Hepatobiliary Disorders</i>	ulceration Cholecystitis, cholelithiasis
<i>Investigation</i>	Alanine aminotransferase increased, aspartate aminotransferase increased, alkaline phosphatase increased, transient and modest elevations of aspartate aminotransferase (AST,SGOT), alanine aminotransferase (ALT,SGPT) and alkaline phosphatase were observed on one or more occasions in various patients treated with COLESTID.
<i>Metabolism and Nutrition Disorders</i>	Anorexia, decreased appetite
<i>Cardiovascular Disorders</i>	Chest Pain, angina pectoris, tachycardia
<i>Respiratory, Thoracic and Mediastinal Disorders</i>	Dyspnoea
<i>General Disorders and Administration Site Conditions:</i>	Fatigue, asthenia, oedema peripheral
<i>Skin and Subcutaneous Tissue Disorders</i>	Urticaria, rash, dermatitis
<i>Nervous System Disorders</i>	Headache, migraine, sinus headache, dizziness
<i>Psychiatric Disorders</i>	Insomnia
<i>Miscellaneous</i>	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.

Interactions

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 colestipol hydrochloride 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 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.

Repeated doses of colestipol hydrochloride given prior to a single dose of propranolol in human trials have been reported to decrease propranolol absorption. However, in a follow-up study in normal subjects, single dose administration of colestipol hydrochloride and propranolol or multiple dose administration of both agents did not affect the extent of propranolol absorption.

Effects on the absorption of other beta-blockers have been determined. Patients on propranolol should be observed when COLESTID is either added or deleted from a therapeutic regimen.

Studies in humans show that absorption of chlorothiazide is markedly decreased even when administered one hour before or after COLESTID administration.

The absorption of hydrochlorothiazide, tetracycline, frusemide, gemfibrozil and penicillin G was significantly decreased when given concurrently with COLESTID. However, COLESTID and gemfibrozil can be used in the same patient when administered two hours apart.

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

Particular caution should be observed with digitalis preparations since there are conflicting results of the effect of COLESTID on the availability of digoxin and digitoxin. The potential for binding of these drugs if given concomitantly is present. The serum digoxin and digitoxin levels should be monitored during periods of administration or discontinuation of COLESTID.

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

Overdosage

Overdosage of COLESTID has not been reported. Should over-dosage occur, however, the chief harm would be obstruction of the gastrointestinal tract. Treatment would be determined by the location and degree of obstruction.

Pharmaceutical Precautions

Store at 15 - 50 degrees C.

Medicine Classification

Prescription medicine.

Package Quantities

COLESTID is available in packs of 30 x 5g sachets.

Further Information

Nil

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