NEW ZEALAND DATA SHEET

1. PRODUCT NAME

COLESTID® 5 g granules for oral suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each sachet contains 5 g colestipol hydrochloride.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Granules for oral suspension

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

COLESTID is indicated as adjunctive therapy to diet for the reduction of elevated serum cholesterol and low-density lipoprotein cholesterol (LDL-C) in patients with primary hypercholesterolaemia (elevated LDL-C) 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 of, symptomatic coronary artery disease.

4.2 Dose and method of administration

Dose

Treatment for elevated serum cholesterol levels should begin with dietary therapy. A minimum of 6 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 or definite coronary heart disease. Drug therapy should be added to dietary therapy, and not substituted for it.

For adults, COLESTID is recommended in doses of 5 g/day to 30 g/day taken once or in divided doses, twice daily. Initiation of therapy is recommended at 5 g either once or twice

daily, with increments of 5 g/day no more frequently than at 1- to 2-month intervals. Appropriate use of lipid profiles, including LDL-C 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 g/day to 30 g/day with good compliance and acceptable side effects, combined therapy or alternate treatment should be considered.

Method of administration

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

The prescribed amount of COLESTID should be taken with fluids. Each sachet should be added to 100 mL to 150 mL 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.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

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 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-C or total cholesterol.

Effect on vitamin absorption

Because it sequesters bile acids, COLESTID may interfere with normal fat absorption and may thus prevent the absorption of folic acid and fat-soluble vitamins such as A, D, E and K. A study done in humans found only 1 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.

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

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.

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.

Paediatric population

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 g/day to 20 g/day. The National Cholesterol Education Program (NCEP) Report of the Expert Panel on Blood Cholesterol Levels in Children and Adolescents recommends a titration approach in children aged 10 years 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.

4.5 Interaction with other medicines and other forms of interaction

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 1 hour before or 4 hours after the administration of COLESTID to avoid impeding their absorption.

Effect of COLESTID on other medicines

Propranolol

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 the agents did not affect the extent of propranolol absorption. Effects on the absorption of other beta-blockers have not been determined. Patients on propranolol should be observed when COLESTID is either added or deleted from a therapeutic regimen.

Chlorothiazide

Studies in humans have shown that the absorption of chlorothiazide is markedly decreased even when administered 1 hour before COLESTID administration.

Tetracycline/frusemide/penicillin G/hydrochlorothiazide/gemfibrozil

The absorption of tetracycline, frusemide, penicillin G, hydrochlorothiazide and gemfibrozil was significantly decreased when given concurrently with COLESTID. However, COLESTID and gemfibrozil can be used in the same patient when administered 2 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. 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 with phenytoin, aspirin, tolbutamide, clofibrate, methyldopa, nicotinic acid (niacin), clindamycin, phenprocoumon or warfarin does not affect the bioavailability of the respective drugs.

4.6 Fertility, pregnancy and lactation

Fertility

There are no data on the effect of COLESTID on fertility in humans. A study conducted in rats did not result in any differences in reproductive parameters that might imply reproductive effects attributable to COLESTID.

Pregnancy

No clinical data are available on the use of COLESTID in pregnant women. Though animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonic/fetal development, parturition or postnatal development, caution should be exercised when prescribing to pregnant women.

Due to its known interference with the 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 the drug therapy be weighed against the possible hazards to the mother and child.

Lactation

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

4.7 Effects on ability to drive and use machinery

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

4.8 Undesirable effects

Gastrointestinal Disorders

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

Constipation, reported by about 1 patient in 10, 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.

The following table lists adverse events described by system organ class and frequency (very common ≥1/10; common ≥1/100 to <1/10; uncommon ≥1/1,000 to <1/100; rare ≥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
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 distension, dyspepsia, nausea, vomiting, diarrhoea, flatulence
	Uncommon	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

Reporting of Suspected Adverse Reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

4.9 Overdose

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

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

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 ions.

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 (LDL) 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 high-density lipoprotein (HDL) density range, and 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 LpAI particle within the HDL fraction is consistent with an antiatherogenic effect of colestipol hydrochloride, even though little change is observed in HDL cholesterol.

The decline in serum cholesterol levels with COLESTID treatment is usually evident by 1 month. When COLESTID is discontinued, serum cholesterol levels usually return to baseline levels within 1 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.

5.2 Pharmacokinetic properties

Colestipol hydrochloride is hydrophilic, but it is virtually water insoluble (99.75%) and is not hydrolysed by digestive enzymes. The high molecular weight polymer in colestipol hydrochloride is apparently not absorbed in the gastrointestinal (GI) tract. Colestipol

hydrochloride action is limited to the lumen of the GI tract and 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 ^{14}C-labeled COLESTID dose is excreted in the urine when given following 60 days of dosing of 20 g of COLESTID per day.

For the treatment of hypercholesterolaemia, initial response occurs at 24 to 48 hours, while the peak occurs at 1 month after the oral administration of COLESTID.

5.3 Preclinical safety data

Genotoxicity

In the Ames assay, colestipol hydrochloride 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.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal anhydrous silica.

6.2 Incompatibilities

No data available.

6.3 Shelf life

60 months.

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

COLESTID is packaged in paper/aluminium foil/vinyl sachets in packs of 30 x 5 g sachets.

6.6 Special precautions for disposal

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Prescription medicine.

8. SPONSOR

Pfizer New Zealand Limited
P O Box 3998
Auckland, New Zealand

Toll Free Number: 0800 736 363

9. DATE OF FIRST APPROVAL

14 April 1977.

10. DATE OF REVISION OF THE TEXT

16 April 2019.

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SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
All	Reformat to MedSafe Data Sheet guidance