SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Colestyramine Powder for Oral Suspension.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each sachet contains 4 g of Colestyramine resin (a basic anion-exchange resin).

Excipients with known effect:
Each sachet contains sunset yellow (E110), 50 mg aspartame and 300 mg propylene glycol (as alginate).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for oral suspension

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Colestyramine is indicated for:

1. The primary prevention of coronary heart disease in middle aged men (35 - 59 years of age) with primary hypercholesterolaemia who have not responded to diet and other appropriate measures.
2. Reduction of plasma cholesterol in patients with hypercholesterolaemia, either alone or as an adjunct to diet, exercise and HMG-CoA reductase inhibitors.
3. Symptomatic relief of pruritus in patients with primary biliary cirrhosis and partial biliary obstruction.
4. Relief of diarrhoea associated with ileal resection, Crohn’s disease, vagotomy and diabetic vagal neuropathy.
5. Control of radiation-induced diarrhoea.

4.2 Posology and method of administration

Posology
Adults

Monotherapy:-
For primary prevention of coronary heart disease and to reduce cholesterol:-
After an introduction period of three to four weeks, the dose is 12 to 24 grams of colestyramine resin (i.e. three to six sachets) to be taken in single or divided doses up to four times daily, according to dosage requirements and patient acceptability. Dosage may be modified according to response up to 36 grams (nine sachets) a day in resistant cases.

Occasional slight gastrointestinal upsets, e.g. constipation, may occur when starting Colestyramine. These usually pass with continued usage of Colestyramine and are minimised by starting therapy gradually.

Final dose required	**Week 1**	**Week 2**	**Week 3**	**Week 4**
	Sachets per day			
3	1	2	3	3
4	1	2	3	4
6	1	2	3	6

Combination therapy:-
The cholesterol-lowering effect of colestyramine on total and LDL-cholesterol is enhanced when it is combined with an HMG-CoA reductase inhibitor (e.g. pravastatin, simvastatin, lovastatin). Enhanced lowering of LDL-cholesterol is also seen with combined nicotinic acid/colestyramine therapy. There is also evidence to support the addition of colestyramine to gemfibrozil therapy in order to further lower LDL-cholesterol in patients with high LDL-cholesterol and triglycerides and low HDL-cholesterol.

For the relief of diarrhoea:-
As in prevention of coronary heart disease and reduction of cholesterol above, but it may be possible to reduce this dose. In all patients presenting with diarrhoea induced by bile acid malabsorption, if a response is not seen within 3 days, then alternative therapy should be initiated.

For the relief of pruritus:-
Four to eight grams (one to two sachets) a day should be sufficient.

Doses of more than 24 g a day of colestyramine resin may interfere with normal fat absorption.

Paediatric population:
Children aged 6 to 12 years
The initial dose is determined by the following formula:

$$\frac{\text{Child's weight in Kg} \times \text{adult dose}}{70}$$

Subsequent dosage adjustment may be required where clinically indicated.

To minimise potential gastrointestinal side effects, it is desirable to begin all therapy in children with one dose of colestryamine daily. The dosage is then increased gradually, every five to seven days to the desired level for effective control.

Children under 6 years of age
Colestyramine should not be used in children under 6. There are no data to support its use.

Colestyramine should not be used in patients with exudative or bloody diarrhoea.

Elderly:
No dosage adjustment is necessary.

Method of administration
Colestyramine is administered orally. To minimise possible interactions, other concomitantly administered drugs should be given at least one hour before or, four to six hours following, colestyramine administration.

To avoid oesophageal irritation or blockage or intestinal blockage, colestyramine should not be taken in its dry form. Colestyramine should always be mixed with an appropriate fluid prior to ingestion. The contents of one sachet of colestyramine are placed on the surface of 120 - 180ml of water or non-carbonated beverage such as skimmed milk or fruit juice and stirred for one to two minutes to produce a uniform dispersion. Colestyramine may also be mixed in thin soups or pulpy fruits with a high moisture content.

To minimise gastro-intestinal side effects and to familiarise the patient with colestyramine, it is desirable to begin with one dose daily. After one to two days the dosage can be increased to meet the patient's needs.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Patients with complete biliary obstruction, since colestyramine cannot be effective where bile is not secreted into the intestine.

4.4 Special warnings and precautions for use

Before instituting therapy with colestyramine, diseases contributing to increased blood cholesterol such as hypothyroidism, diabetes mellitus, nephrotic syndrome, dysproteinaemias and obstructive liver disease should be investigated and specifically treated. An attempt should be made to control serum cholesterol by appropriate dietary regimen, weight reduction, and the treatment of any underlying disorder which might be the cause of the hypercholesterolaemia. Serum cholesterol levels should be determined frequently during the first few months of therapy and periodically thereafter. A favourable trend in cholesterol reduction should occur during the first month of colestyramine therapy. The therapy should be continued to sustain cholesterol reduction. Serum triglyceride levels should be measured periodically to detect whether significant changes have occurred.

Prolonged use of colestyramine resin may be associated with an increased bleeding tendency as a result of hypoprothrombinaemia secondary to vitamin K deficiency. If

bleeding occurs in patients receiving colestyramine, parenteral administration of vitamin K_1 is usually valuable in restoring normal clotting time and oral administration of vitamin K_1 can be used to prevent recurrent bleeding.

Because colestyramine is a chloride-containing anion exchange resin, the possibility that prolonged use of the drug may produce hyperchloraemic acidosis should be considered, particularly in children and smaller patients where the relative dosage may be higher.

Colestyramine may produce or aggravate pre-existing constipation or related conditions, such as haemorrhoids. In patients with constipation, the dosage of colestyramine should be decreased, since it may produce impaction. In patients presenting with clinically symptomatic coronary artery disease, where straining of the stool is to be avoided, the dosage of colestyramine should be titrated to avert constipation.

Serum or red cell folate deficiency has been reported with long term administration of colestyramine resin. Supplementation with folic acid should be considered in these cases.

Reduction of serum folate concentrations has been reported in children with familial hypercholesterolaemia. Supplementation with folic acid should be considered in these cases.

Colestyramine Powder for Oral Suspension contains 50 mg aspartame in each sachet. Aspartame is hydrolysed in the gastrointestinal tract when orally ingested. One of the major hydrolysis products is phenylalanine. It may be harmful for patients with phenylketonuria (PKU). Neither non-clinical nor clinical data are available to assess aspartame use in infants below 12 weeks of age.

Colestyramine Powder for Oral Suspension contains 2.7 mg sunset yellow (E110) in each sachet. May cause allergic reactions.

Colestyramine Powder for Oral Suspension contains 300 mg propylene glycol (as alginate) in each sachet. Co-administration with any substrate for alcohol dehydrogenase such as ethanol may induce adverse effects in children less than 5 years old.. For propylene glycol doses exceeding 50 mg/kg/day, medical monitoring is required in patients with impaired renal or hepatic function.

4.5 Interaction with other medicinal products and other forms of interaction

Colestyramine, being a basic anion exchange resin, has the potential to interfere with the absorption of a number of drugs including digitalis, chlorothiazide, thyroxine, tetracycline and warfarin. It is possible that it may interfere with the absorption or elimination of other drugs and so patients receiving concomitant therapies should be advised to report any perceived change in efficacy of their medication. The response should be closely monitored and appropriate adjustments made if necessary.

Patients should take other drugs at least one hour before or 4-6 hours after Colestyramine to minimise possible interference with their absorption.

The separation of doses may not prevent interaction with drugs that undergo enterohepatic circulation.

In patients receiving long-term high dose colestyramine therapy, absorption of fat-soluble vitamins from the intestine may be impaired. Vitamin D deficiencies, bleeding deficiencies due to hypoprothrombinaemia secondary to vitamin K deficiency and night blindness secondary to vitamin A deficiency have been reported only rarely. Daily administration of vitamin A and D should be considered in patients receiving prolonged high dose colestyramine therapy or when malabsorption is suspected. Vitamin K deficiency and hypoprothrombinaemia can be treated or prevented with phytomenadione or menadiol sodium phosphate.

Several cases of hyperchloraemic metabolic acidosis have been reported following colestyramine administration.

Tabulated list of colestyramine drug-drug interactions:

Drug Class	Drug(s)
Anti-arrhythmics	Amiodarone
Anti-convulsants	Valproate
Anti-infectives	Vancomycin, tetracycline
Antimetabolites	Methotrexate
Bile acids	Ursodeoxycholic acid
Cholesterol lowering drugs	Ezetimibe
Combined hormonal contraceptive	Ethinylestradiol
Coumarins	Phenprocoumon, warfarin
Digitalis glycosides	Digitoxin, digoxin
Disease-modifying antirheumatics	Leflunomide
Immunosuppressants	Mycophenolate
Loop Diuretics	Furosemide
Nonsteroidal anti-inflammatory drugs	Diclofenac, meloxicam, piroxicam, sulindac, tenoxicam
Potassium sparing diuretics	Spironolactone
Thiazide diuretics	Chlorothiazide, hydrochlorothiazide
Thyroid hormones	Levothyroxine, liothyronine, thyroid extract

4.6 Fertility, pregnancy and lactation

The safety of colestyramine in pregnancy and lactation has not been established and the possibility of interference with absorption of fat-soluble vitamins should be considered.

4.7 Effects on ability to drive and use machines

Colestyramine has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Frequency categories are defined according to the following convention: 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), not known (cannot be estimated from the available data).

The most common adverse reaction is constipation. Predisposing factors for most of these complaints when colestyramine is used as a cholesterol lowering agent are: high dose and increased age (more than 60 years old). Most instances of constipation are mild, transient and controlled with conventional therapy. Some patients require a temporary decrease in dosage or discontinuation of therapy.

Tabulated list of adverse reactions:

System Organ Class	Frequency	Adverse Reaction(s)
Blood and lymphatic system disorders	Uncommon	Bleeding tendencies due to hypoprothrombinaemia (Vitamin K deficiency) as well as Vitamin A (night blindness has been reported rarely) and D deficiencies
	Not known	Anaemia
Metabolism and nutrition disorders	Uncommon	Anorexia, hyperchloremic acidosis in children and patients with renal impairment
	Not known	Oedema
Gastrointestinal disorders	Very common	Constipation
	Uncommon	Abdominal discomfort, flatulence, nausea, vomiting, diarrhoea, heartburn, dyspepsia and steatorrhea
	Rare	Reports of intestinal obstruction have been received post marketing, including deaths in paediatric patients
	Not known	Acute abdominal symptom complex ("pasty mass" in the transverse colon on X-ray), eructation
Skin and subcutaneous tissue disorders	Uncommon	Rash and irritation of skin, tongue and perianal area
Musculoskeletal and connective tissue disorders	Uncommon	Osteoporosis
	Not known	Arthritis, backache
Renal and urinary disorders	Not known	Calcified material has occasionally been observed in the biliary tree (including calcification of the gall bladder), burnt odour to urine

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

One case of medication error experienced heartburn and nausea after taking colestyramine 27 g t.i.d. for a week. Should overdosage occur however, the chief potential harm would be obstruction of the gastrointestinal tract. The location of such potential obstruction and the presence or absence of normal gut motility would determine treatment.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Bile acid sequestrants, ATC code: C10AC01.

Colestyramine resin is the chloride form of a basic quaternary ammonium anion exchange resin in which the basic groups are attached to a styrene-divinylbenzene co-polymer.

Following oral administration, colestyramine resin releases chloride ions and absorbs bile acids in the intestine forming a non-absorbable complex which is excreted together with unchanged resin in the faeces. This results in a continuous, though partial, removal of bile acids from the enterohepatic circulation by preventing their reabsorption. Colestyramine is hydrophilic but it is not soluble in water, nor is it hydrolysed by digestive enzymes.

Colestyramine resin absorbs and combines with the bile acids in the intestine to form an insoluble complex which is excreted in the faeces. This results in a continuous, though partial, removal of bile acids from the enterohepatic circulation by preventing their reabsorption. The increased faecal loss of bile acids leads to an increased oxidation of cholesterol to bile acids and a decrease in serum cholesterol levels and low-density lipoprotein serum levels. Colestyramine is hydrophilic but it is not soluble in water, nor is it hydrolysed by digestive enzymes.

In addition to the bile acids, cholestyramine can also bind other substances (e.g. certain drugs, fat-soluble vitamins) and interfere with their absorption and/or enterohepatic circulation.
In patients with partial biliary obstruction, the reduction of bile acid levels following colestyramine resin administration reduces bile acids deposited in the dermal tissue with resultant decrease in pruritus.

5.2 Pharmacokinetic properties

Colestyramine resin is not absorbed from the digestive tract.

5.3 Preclinical safety data

In studies conducted in rats in which colestyramine 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 colestyramine-treated rats than in control rats. The relevance of laboratory observation from studies in rats to the clinical use of colestyramine is not known. A long-term study in humans does not reveal any significant difference between patients treated with cholestyramine and those treated with placebo with respect to the incidence of cancer.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Aspartame powder

Propylene glycol alginate

Colloidal silicon dioxide

Citric acid anhydrous

Sunset Yellow (E110)

Orange flavour WL16739

6.2 Incompatibilities

None known

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store in a dry place, below 30^{o}C

6.5 Nature and contents of container

The individual sachets consist of a layer of polyethylene, then a layer of aluminium, another layer of polyethylene and finally a layer of paper printed with the product details. The sachets contain 5g of powder.

Sachets are packed in cartons of 30, 50, 60 or 180 (The 180 pack comprises six cartons of 30 in a fully labelled outer box).

6.6 Special precautions for disposal

No special instructions.

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

7 MARKETING AUTHORISATION HOLDER

Resolution Chemicals Ltd.,
Wedgwood Way,
Stevenage, Herts,
SG1 4QT,
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 10321/0218

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

24 April 1997

10 DATE OF REVISION OF THE TEXT

09/12/2024