PRODUCT MONOGRAPH

NOVO-CHOLAMINE POWDER FOR ORAL SUSPENSION

NOVO-CHOLAMINE LIGHT POWDER FOR ORAL SUSPENSION

(Cholestyramine Resin)

USP

4 g Powder

Antidiarrheal, Antihypercholesterolemic

Novopharm Ltd.
Toronto, Canada

Control Numbers 09113, 26947

Date of Preparation:

October 26, 1994

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THERAPEUTIC CLASSIFICATION

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ACTION AND CLINICAL PHARMACOLOGY

Cholesterol is believed to be the sole precursor of bile acids which are secreted into the intestines during normal digestion. A major portion of the bile acids is absorbed from the intestinal tract and, via the enterohepatic circulation, is then returned to the liver. In normal serum only very small amounts of bile acids are found.

NOVO-CHOLAMINE (cholestyramine resin) absorbs and combines with the bile acids in the intestine to form an insoluble complex. This is then excreted in the feces. As a result, bile acids are partially removed from the enterohepatic circulation by preventing their absorption.

Due to cholestyramine resin administration, the increased fecal loss of bile acids leads to an increased oxidation of cholesterol to bile acids, a decrease in beta lipoprotein or low density lipoprotein plasma levels and a decrease in serum cholesterol levels.

Although cholestyramine resin causes an increase in hepatic synthesis of cholesterol in man, plasma cholesterol levels fall.

INDICATIONS AND CLINICAL USE

NOVO-CHOLAMINE (cholestyramine resin) is 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, NOVO-CHOLAMINE may be useful to lower elevated cholesterol but it is not indicated where hypertriglyceridemia is the abnormality of most concern.

NOVO-CHOLAMINE is indicated as a symptomatic control of bile acid induced diarrhea as a result of short bowel syndrome.

NOVO-CHOLAMINE is also indicated for the relief of pruritus which accompanies partial biliary obstruction.

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 program of weight control and physical exercise should be implemented.

CONTRAINDICATIONS

NOVO–CHOLAMINE (cholestyramine resin) is contraindicated in patients with complete biliary obstruction where bile is not excreted into the intestine. It is also contraindicated in those individuals who have shown hypersensitivity to any of its components and in those individuals who have phenylketonuria (sensitivity to phenylalanine in aspartame, which is a sweetener in both NOVO-CHOLAMINE and NOVO-CHOLAMINE LIGHT. See PHARMACEUTICAL INFORMATION section).

WARNINGS

NOVO-CHOLAMINE (cholestyramine resin) SHOULD NEVER BE INGESTED IN ITS DRY FORM. BEFORE TAKING, ALWAYS ADMIX NOVO-CHOLAMINE WITH WATER OR OTHER FLUIDS.

SINCE NOVO-CHOLAMINE (cholestyramine resin) MAY BIND OTHER DRUGS GIVEN CONCURRENTLY, TO AVOID IMPEDING THEIR ABSORPTION, PATIENTS SHOULD TAKE OTHER DRUGS AT LEAST ONE HOUR BEFORE OR 4-6 HOURS AFTER NOVO-CHOLAMINE (OR AT AS GREAT AN INTERVAL AS POSSIBLE).

Pregnancy

NOVO-CHOLAMINE is not expected to cause fetal harm when administered during pregnancy in recommended dosages since it is not absorbed systemically. There are, however, no adequate and well controlled studies in pregnant women and, the known interference with absorption of fat soluble vitamins may be harmful to the fetus even in the presence of supplementation.

Nursing Mothers

When administering NOVO-CHOLAMINE to a nursing mother, caution should be exercised. Poor vitamin absorption as described in the "Pregnancy" section may have an effect on nursing infants.

Pediatric Use

The effect of NOVO-CHOLAMINE in maintaining lowered cholesterol levels in pediatric patients and long-term effects of drug administration has not yet been determined. A dosage schedule in children has not yet been established.

Geriatrics

Appropriate studies on the relationship of age to the effects of cholestyramine 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.

Carcinogenesis and Mutagenesis

Cholestyramine resin was used as a tool in studies conducted in rats to determine the role of various intestinal factors (e.g. fat, bile salts and microbial flora). In cholestyramine treated rats, the incidence of intestinal tumors induced by potent carcinogens was greater than in control rats. The significance of this observation is not evident, as the results in one study indicated a statistically insignificant increase in tumor incidence whereas a more recent study did not demonstrate any presence of tumors following cholestyramine administration. Therefore, the relevance of these studies conducted in rats to clinical use of NOVO-CHOLAMINE has not been determined.

PRECAUTIONS

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 hypercholesterolemia before instituting therapy with NOVO-CHOLAMINE (cholestyramine resin). Serum cholesterol and triglyceride concentration should be determined prior to and regularly during cholestyramine therapy. During the first month of NOVO-CHOLAMINE therapy a favorable trend in cholesterol should occur. In order to sustain cholesterol reduction, therapy should be continued.

With chronic use of NOVO-CHOLAMINE a tendency of increased bleeding due to hypoprothrombinemia associated with Vitamin K deficiency may occur. Parenteral Vitamin K_1 will usually promptly rectify this and recurrences can be prevented by oral administration of Vitamin K_1. Long-term administration of NOVO-CHOLAMINE has been reported to cause a reduction of serum or red cell folate. In these cases, supplementation of folic acid should be considered.

Since NOVO-CHOLAMINE is a chloride form of anion exchange resin there is a possibility that prolonged use may produce hyperchloremic acidosis. In younger and smaller patients where the relative dosage may be higher, this would especially be true.

Pre-existing constipation may occur or be worsened with use of NOVO-CHOLAMINE. In such cases, dosage should be reduced or discontinued. Aggravation of hemorrhoids and fecal impaction may occur. In those patients with clinically symptomatic coronary artery disease, every effort should be made to avert severe constipation and its inherent problems.

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

Laboratory Tests

Serum cholesterol and serum triglyceride determinations should be made prior to intiation of therapy with cholestyramine and at periodic intervals during therapy to confirm efficacy and to determine that a positive response is maintained.

Drug Interactions

BECAUSE NOVO-CHOLAMINE POWDER AND NOVO-CHOLAMINE LIGHT POWDER MAY BIND OTHER DRUGS GIVEN CONCURRENTLY, PATIENTS SHOULD TAKE OTHER DRUGS AT LEAST ONE HOUR BEFORE OR 4 TO 6 HOURS AFTER NOVO-CHOLAMINE POWDER AND NOVO-CHOLAMINE LIGHT POWDER (OR AT AS GREAT AN INTERVAL AS POSSIBLE) TO AVOID IMPEDING THEIR ABSORPTION.

Since cholestyramine is the chloride form of anion-exchange resin, it is capable of binding to a number of drugs in the GI tract and may delay or reduce their absorption. Acidic drugs are strongly absorbed to cholestyramine, neutral and basic drugs may be non specifically bound.

Patients should be instructed to allow as long a time interval as possible between ingestion of other drugs and cholestyramine resin, however separation of doses may not prevent interaction with drugs that undergo enterohepatic circulation (See WARNINGS).

Drug Interactions with Other Lipid-Lowering Drugs:

Concomitant therapy with other lipid-lowering agents should be approached with caution as information from controlled clinical trials is limited.

HMG-CoA reductase Inhibitors:

The cholesterol-lowering effects of cholestyramine and HMG-CoA reductase inhibitors (i.e. lovastatin, simvastatin, pravastatin, etc.) are additive. 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.

When fluvastatin was administered concomitantly 2 to 4 hours after cholestyramine, fluvastatin decreases of more than 50% for the fluvastatin AUC and 50-80% for the fluvastatin C_{max} occurred. However, administration of fluvastatin 4 hours after cholestyramine resulted in a clinically significant additive effect in reducing total-cholesterol and LDL-cholesterol compared with that achieved with either component drug.

Fibric Acid Derivatives and Niacin:

Cholestyramine had little effect on the bioavailability of gemfibrozil, clofibrate, fenofibrate and niacin.

Probucol:

The combination of cholestyramine and probucol demonstrated an additive effect with no additional side effects.

Drug Interactions with Other Drugs

Antibiotics:

Concurrent use with cholestyramine may result in binding of medications such as oral tetracyclines and oral Penicillin G, thus decreasing their absorption; an interval of several hours between administration of cholestyramine and any of these medications is recommended.

Cholestyramine has been shown to bind oral vancomycin significantly when used concurrently, resulting in decreased stool concentrations and marked reduction in antibacterial activity of vancomycin; Concurrent use is not recommended; patients should be advised to take oral vancomycin and cholestyramine several hours apart.

Anticoagulants:

Concurrent use may significantly increase the anticoagulant effect as a results of depletion of vitamin K, but cholestyramine may also bind with oral anticoagulants in the gastrointestinal tract and reduce their effects; administration at least 6 hours before cholestyramine and adjustment of anticoagulant dosage based on frequent prothrombin-time determinations are recommended.

Antihypertensives and Cardiac Glycosides:

Antihypertensives (i.e. propranolol) concomitantly administered with cholestyramine may interact depending on the amounts of each component drug administered.

Cholestyramine may reduce the half-life of these medications by decreasing intestinal reabsorption and enterohepatic circulation; caution is recommended, especially when cholestyramine is withdrawn from a patient who was stabilized on the digitalis glycoside while receiving cholestyramine, because of the potential for serious

toxicity; some clinicians recommend administration of cholestyramine approximately 8 hours after the digitalis glycoside.

Anti-inflammatory Agents:

Concurrent use of anti-inflammatory agents such as phenylbutazone or ASA with cholestyramine may retard or reduce absorption of the anti-inflammatory agents, depending on the amount of each component drug administered.

Chenodiol or ursodiol:

The effect may be decreased when chenodiol or ursodiol is used concurrently with cholestyramine, which binds these medications and decreases their absorption and also tends to increase cholesterol saturation of bile.

Diuretics:

Depending on the amounts of cholestyramine or diuretic (i.e. thiazides) administered, concomitant administration may reduce plasma thiazide levels.

Fat-Soluble Vitamins:

Cholestyramine may interfere with absorption of fat-soluble vitamins as result of its interference with fat absorption; supplemental vitamin A and D in water-miscible or parenteral form are recommended in patients receiving cholestyramine for prolonged periods; supplemental vitamin K may be required in some patients who develop bleeding tendencies.

Folic acid:

Concurrent use with cholestyramine may interfere with absorption of folic acid; folic acid supplementation is recommended in patients receiving cholestyramine for prolonged periods.

Thyroid hormones:

Concurrent use with cholestyramine may decrease the effects of thyroid hormones by binding and delaying or preventing absorption; an interval of 4 to 5 hours between administration of the two medications and regular monitoring of thyroid function tests are recommended.

ADVERSE REACTIONS

Constipation is the most common adverse reaction. Predisposing factors for most complaints of constipation are high dose and increased age (more than 60 years old), when cholestyramine is used as a cholesterol lowering agent. Conventional therapy controls most instances of constipation which are usually mild and transient. A temporary decrease in dosage or discontinuance of therapy may be required by some patients.

Less frequently reported adverse reactions: abdominal discomfort, flatulence, nausea, vomiting, diarrhea, heartburn, anorexia, indigestive feeling and steatorrhea, bleeding tendencies due to hypoprothrombinemia (Vitamin K deficiency) as well as Vitamin A (one case of night blindness reported) and D deficiencies, hyperchloremic acidosis in children, osteoporosis, rash and irritation of the skin, tongue and perianal area.

In patients to whom cholestyramine resin has been given, occasional calcified material has been observed in the biliary tree, including calcification of the gall bladder. This may be a manifestation of the liver disease and not related to drug therapy.

Other adverse reactions (not necessarily drug related) include:

Gastrointestinal: GI–rectal bleeding, black stools, hemmorhoidal bleeding, bleeding from known duodenal ulcer, dysphagia, hiccups, ulcer attack, sour taste, pancreatitis, rectal pain, diverticulitis.

Hematologic: increased prothrombin time, ecchymosis, anemia, dental bleeding.

Hypersensitivity: urticaria, asthma, wheezing, shortness of breath.

Metabolic and electrolyte effects: Hyperchloremic acidoses and increased urinary calcium excretion have been seen with high doses or usual doses in small patients or children. Increased urinary excretion of calcium may lead to osteoporosis.

Muskoskeletal: backache, muscle and joint pains, arthritis.

Neurologic: headache, anxiety, vertigo, dizziness, fatigue, tinnitus, syncope, drowsiness, femoral nerve pain, paresthesia.

Eye: uveitis

Renal: hematuria, dysuria, burnt odor of urine, diuresis.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

There have been no reported overdosages with cholestyramine resin. Should overdosage occur the chief potential problem would be obstruction of the gastrointestinal tract. Treatment would be determined by the location of such potential obstruction, the degree of obstruction, and the presence or absence of normal gut motility.

DOSAGE AND ADMINISTRATION

NOVO-CHOLAMINE SHOULD NOT BE TAKEN IN ITS DRY FORM.

To avoid accidental inhalation or esophageal distress or intestinal blockage, the drug should be mixed with at least 120 or 180 mL of water or other fluids before being ingested. See PREPARATION instructions. 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 program of weight control and physical exercise should be implemented.

It is desirable to begin all therapy with one dose of NOVO-CHOLAMINE (cholestyramine resin) daily, in order to familiarize the patient with NOVO-CHOLAMINE and to minimize gastrointestinal side effects. Dosage is then increased within a day or two to the desired level for effective control.

Motivation of the patient to continue the prescribed regimen in spite of gastrointestinal problems is important. Physician encouragement and supervision are essential for successful management.

The recommended adult dose is 4 grams of cholestyramine resin, one to six times daily. Dosage may be adjusted as required to meet the patient's needs. A pediatric dosage schedule has not been established.

Cholesterol levels should be monitored periodically and consideration should be given to reducing the dosage of NOVO-CHOLAMINE if cholesterol levels fall below the targeted range, such as that recommended by the Second Report of the U.S. National Cholesterol Education Program (NCEP). See **REFERENCES**.

Preparation

Place the contents of one packet (4 grams of anhydrous cholestyramine or one level scoop (4 grams of anhydrous cholestyramine) of Novo-Cholamine Powder on the surface of 120 to 180 mL of water or non-carbonated beverage such as milk or fruit juice. After 1 to 2 minutes mix thoroughly by stirring.

Novo-Cholamine may also be mixed in thin soups or pulpy fruits with a high moisture content.

In calculating dosages, one packet or level scoop of Novo-Cholamine (sweetening agents; sucrose and aspartame) contains 9 grams of powder which is equivalent to 4 grams of anhydrous cholestyramine resin or one packet of Novo-Cholamine Light (sweetening agent, aspartame) contains 5.5 grams of powder which is equivalent to 4 grams of anhydrous cholestyramine resin.

INFORMATION FOR THE PATIENT

NOVO–CHOLAMINE Powder (cholestyramine resin) has been prescribed for you by your physician because many studies have shown that lowering blood cholesterol leads to a decrease in your risk for coronary heart disease (heart attacks and angina).

The following practical indications are made so that NOVO–CHOLAMINE and NOVO–CHOLAMINE LIGHT are pleasant and easy to take. It is best to get into a routine of making up and taking NOVO–CHOLAMINE regularly. NOVO–CHOLAMINE is available in cartons of 30 pouches (each pouch contains one dose of NOVO–CHOLAMINE) or cans containing 42 doses of NOVO–CHOLAMINE. NOVO–CHOLAMINE LIGHT is available in cartons only.

Preparation

NOVO-CHOLAMINE SHOULD NOT BE TAKEN IN ITS DRY FORM. To avoid accidental choking or indigestion, the drug should be mixed with at least 120 to 180 mL of water or other fluids before ingested.

Place the contents of one packet (4 grams of anhydrous cholestyramine or one level scoop (4 grams of anhydrous cholestyramine) of Novo-Cholamine Powder on the surface of 120 to 180 mL of water or non-carbonated beverage such as milk or fruit juice. After 1 to 2 minutes mix thoroughly by stirring.

Novo-Cholamine may also be mixed in thin soups or pulpy fruits with a high moisture content.

In calculating dosages, one packet or level scoop of Novo-Cholamine (sweetening agents; sucrose and aspartame) contains 9 grams of powder which is equivalent to

4 grams of anhydrous cholestyramine resin or one packet of Novo-Cholamine Light (sweetening agents, aspartame) contains 5.5 grams of powder which is equivalent to 4 grams of anhydrous cholestyramine resin.

One Day's Dose

Experience has shown that pre–mixing the day's dose helps to improve taste and reduce gastrointestinal discomfort.

Add the amount of NOVO–CHOLAMINE or NOVO–CHOLAMINE LIGHT prescribed by your doctor using the ratio of 1 pouch or 1 level scoop of NOVO–CHOLAMINE with 120–180 mL (4 to 6 oz.) of a preferred beverage.

1. Evening Beverage

Mix an entire day's dose in a container with a tight fitting lid, or in a blender.

Add the powder to the fluid or beverage and shake vigorously or blend well until the powder is dispersed through the liquid.

Place in a sealed container and refrigerate overnight.

2. Breakfast

Shake the container well and drink approximately one–third (1/3) of the volume before, during or after the meal.

Seal the container and refrigerate.

3. Dinner

Shake the container well and drink the remainder (2/3) before, during or after the meal.

NOTE: The small dose is taken with the smaller meal. The large dose is taken with the larger meal. Do not miss a dose because a meal is missed. The small dose can be taken with a light meal such as coffee/tea/toast.

Although certain medicines should not be used together at all, in other cases two different medicines may be used together even if an interaction might occur. If you take other medications they should not be taken with NOVO–CHOLAMINE. OTHER MEDICATIONS SHOULD BE TAKEN AT LEAST 1 HOUR BEFORE OR 4 HOURS (MINIMUM 2 HOURS) AFTER NOVO-CHOLAMINE TO AVOID PREVENTING THEIR ABSORPTION. In these cases, your doctor may want to change the dose, or other precautions may be necessary. When you are taking NOVO-CHOLAMINE or NOVO-CHOLAMINE LIGHT it is especially important that your doctor and pharmacist know if you are taking any of the following:

- Anticoagulants (blood thinners) - The effects of the anticoagulant may be altered.
- Digitalis glycosides (heart medicine) or
- Diuretics (water pills) or
- Penicillin G, taken by mouth or
- Phenylbutazone or
- Propranolol or
- Tetracyclines, taken by mouth (medicine for infection) or
- Thyroid hormones or
- Vancomycin, taken by mouth.

Cholestyramine may prevent these medicines from working properly.

The presence of other medical problems may affect the use of NOVO-CHOLAMINE.

Make sure you tell your doctor if you have any other medical problems, especially:

- Bleeding problems or
- Constipation or
- Gallstones or
- Heart or blood vessel disease or
- Hemorrhoids or
- Stomach ulcer or other stomach problems or
- Underactive thyroid - Cholestyramine may make these conditions worse.

- Kidney disease - There is an increased risk of the developing electrolyte problems.

- Phenylketonuria - NOVO-CHOLAMINE and NOVO-CHOLAMINE LIGHT contains aspartame, which can cause problems in people with this condition. It is best if you avoid using this product. Phenylalanine in aspartame should be avoided.

Note: Phenylalanine content in: 1) NOVO-CHOLAMINE – 5 mg/dose

2) NOVO-CHOLAMINE LIGHT – 25 mg/dose

If you should have problems with constipation, add to your diet stewed prunes or prune juice, bran or extra glasses of water. Increasing your exercise is also recommended.

If you miss a dose of this medicine, take it as soon as possible. Then go back to your regular dosing schedule. However, if it is almost time for your next dose, skip the missed dose and go back to your regular dosing schedule. Do not double doses.

If you have any problems or questions, please contact your physician immediately.

Novopharm Ltd.
Toronto, Canada

PHARMACEUTICAL INFORMATION

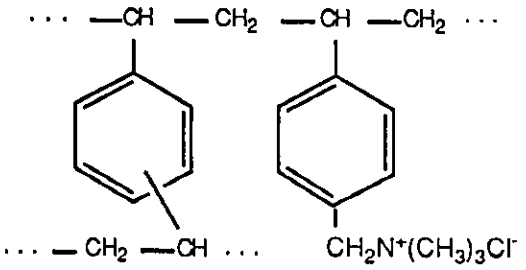
DRUG SUBSTANCE:

Proper Name: Cholestyramine Resin

Common Name: Cholestyramine Resin

Chemical Name: Cholestyramine

Structural Formula:



Description: White to buff–coloured, hygroscopic, fine powder which is odourless or has not more than a slight amine–like odour. It is insoluble in water, alcohol, chloroform, and ether.

Note: Phenylalanine content in: 1) NOVO-CHOLAMINE – 5 mg/dose

2) NOVO-CHOLAMINE LIGHT – 25 mg/dose

STABILITY AND STORAGE RECOMMENDATIONS: Store between 15° and 30°C.

AVAILABILITY OF DOSAGE FORMS

NOVO-CHOLAMINE Powder (sweetened with sugar and aspartame) and NOVO-CHOLAMINE LIGHT Powder (sweetened with aspartame) are available in cartons of thirty packets (each packet contains one dose of NOVO–CHOLAMINE). NOVO-CHOLAMINE Powder is also available in cans containing 378 g (42 doses of NOVO–

CHOLAMINE). Each dose of NOVO-CHOLAMINE Powder (sweetened and unsweetened) contains 4 grams of anhydrous cholestyramine resin.

PHARMACOLOGY

ANIMAL

Binding of Bile Acids

Since cholestyramine is an anion exchange resin, other anions, usually those with a greater affinity for the resin than chloride, can replace the chloride anion attached to the quaternary ammonium groups of the resin. *In vitro* studies have shown that bile acids are strongly bound by the resin. A study conducted in male albino rats of 130–140 g in weight reported a 3–fold increase in fecal bile acid excretion after 10 days. This effect continued during nine weeks of administration of a normal diet containing 2% cholestyramine.

Binding of Drugs

Cholestyramine has a strong affinity for acidic materials since it is an anion exchange resin. It may also absorb neutral or, less likely, to some extent, basic materials.

Both *in vitro* and *in vivo* studies have been conducted with various drugs for possible binding with cholestyramine. Basic drugs studied were chlorpheniramine maleate, dextromethorphan, dihydrocodeinone bitartrate and quinidine sulfate; acidic drugs were acetylsalicylic acid, chlorothiazide, phenobarbital, phenylbutazone, tetracycline and warfarin, and one neutral drug, digoxin. The basic and neutral drugs were not bound by cholestyramine *in vitro*, or were bound only slightly. Buffer at various pH levels was able to easily wash from the resin those drugs which were weakly bound. Although acetylsalicylic acid is an acidic drug, it had much less affinity than cholic acid

and was more easily eluted from the cholestyramine resin. The concomitant oral administration of acetylsalicylic acid at a dose of 4.65 mg/kg and cholestyramine, at a dose of 71.5 mg/kg to rats caused only a moderate depression of blood levels of salicyclic acid in the first half hour following drug administration, which supports the *in vitro* studies. Blood salicyclate levels were not affected by the resin after two hours. Similar results were seen with phenobarbital and tetracycline both *in vivo* and *in vitro*. Rat studies have suggested that the absorption of phenylbutazone may be delayed but not decreased.

In dogs given chlorothiazide 30 minutes before the administration of cholestyramine no significant effects on chlorothiazide absorption or excretion were noted.

The anticoagulent activity of a large single dose of warfarin in rats was unaffected by the administration of cholestyramine, irregardless of whether warfarin was given 30 minutes before or simultaneously within the resin. When the two drugs were given together plasma warfarin levels were lower.

Fat Absorption

The administration of 5% cholestyramine decreased the absorption of medium chain triglycerides by 3% in a study with male weanling rats, whereas absorption of the other dietary fats was more markedly affected. The net absorption of coconut oil was decreased by 15%, the highly unsaturated vegetable oils by 19 to 40%, olive oil by 40% and butter and lard by 47 and 55%, respectively, by administration of 5% cholestyramine.

Fat–Soluble Vitamins A and K Absorption

Decreased liver stores of Vitamin A in young rats resulted from the inclusion of 1 or 2% cholestyramine in rations containing 5–20% fat and minimal levels of Vitamin A. There was no obvious evidence of a nutritional deficiency of this essential vitamin observed. At the lower levels of dietary fat intake, rates of weight gain and efficiency of caloric utilization were unaffected. The addition of 2% cholestyramine to the diet of 1 to 8–day old chicks fed minimal or adequate amounts of menadione (a synthetic analog of Vitamin K) had no significant effect on prothrombin time after 2 or 4 weeks.

HUMAN

Binding of Bile Acids

Cholestyramine is a quaternary ammonium anion exchange resin which has a polystyrene polymer skeleton. As the chloride salt, it binds bile acids, exchanging chloride for bile acid, both *in vitro* and *in vivo*. When cholestyramine resin is administered to experimental animals and in humans it sequesters bile acids in the gut, preventing their reabsorption and thereby promoting their excretion in the feces.

In Vitro Bile Salt Binding

A comparative *in vitro* bile salt binding assay was conducted for cholestyramine resin to demonstrate *in vitro* equivalence of Novo-Cholamine Powder with Questran® Powder. This study was designed to evaluate the comparative bile-salt binding capacities of Novopharm Cholestyramine for Oral Suspension and Cholestyramine for Oral Suspension (Light) with Bristol-Myers Questran® and Bristol-Myers Questran® (Light), respectively. The experimental design and data analysis was based upon information received from the FDA Division of Bioequivalence.

Cholestyramine resin (at a concentration of 1 mg/mL) was incubated with a bile salt mixture consisting of a 2:2:1 ratio of the sodium salts of Glycocholic,

Taurodeoxycholic and Glycochenodeoxycholic acids. The total salt concentration varied from 0.1 to 30mM, a total of eight concentrations being studied. Incubations were carried out at 37°C, with shaking. The incubation time for the 0.1, 0.3, 1 and 3mM samples was 2 hours, whilst for the 7, 10, 20 and 30mM samples the incubation time was 24 hours. The amounts of bile acids not bound by the resin were determined using an HPLC method (#C-110, which was developed in-house), and from these values the amounts bound by the resin calculated.

The total amount of bile salts bound by the resin was then summed, and this value expressed as the amount of bile acids bound (in µMoles) per milligram of resin. The results are summarized below:

CHOLESTYRAMINE BILE SALT BINDING STUDY - SUMMARY OF RESULTS

Regular Formulation

Total Bile Salt Concentration (mM)	Total Amount Bound (mM/mg) Novopharm	Total Amount Bound (mM/mg) Questran
0.1	0.08	0.08
0.3	0.24	0.22
1	0.74	0.72
3	2.13	2.15
7	3.93	4.27
10	4.01	4.09
20	4.05	4.48
30	3.89	4.49

Light Formulation

Total Bile Salt Concentration (mM)	Total Amount Bound (mM/mg) Novopharm	Total Amount Bound (mM/mg) Questran
0.1	0.08	0.08
0.3	0.23	0.23
1	0.72	0.72
3	2.14	2.20
7	4.04	4.53
10	3.94	4.58
20	3.63	4.47
30	3.52	4.43

The total of bile acids bound *in vitro* by Novopharm and Bristol products are comparable.

Fat Absorption

A study was conducted in healthy subjects where gross steatorrhea was induced by the administration of a large daily dose (30 g) of cholestyramine for 11–17 days. Fecal fat excretion increased by factors of 4 and 5, respectively, however when cholestyramine was withdrawn levels promptly returned to pretreatment values.

Studies were conducted in 5 healthy subjects which were maintained on regular diet and given radioactive labelled triolein before and during administration of 30 g/day of cholestyramine. A depression in the level of blood radioactivity over the 8–hour sampling period and a significant increase in fecal radioactivity during the 48–hour period of cholestyramine administration was observed.

In contrast, there was no significant difference in radioactivity of blood and feces between control and experimental periods in 7 subjects maintained on regular diet and given radioactive labelled oleic acid.

From these studies it was concluded that the binding of bile acids by cholestyramine prevents their participation in the hydrolytic digestion of dietary triglycerides. This leads to the steatorrhea induced by large doses of cholestyramine.

During treatment with cholestyramine serum bile acids, phospholipids, triglycerides, cholesterol and total lipids may be lowered as seen in studies in a limited number of patients with partial biliary obstruction, however, another study showed significant decreases in serum triglyceride levels in only 4 of 15 patients.

Fat–Soluble Vitamins A and K Absorption

A study in four healthy young adults demonstrated that when 8 g of cholestyramine was ingested simultaneously with a normal meal with 250,000 USP units of vitamin A acetate, during a 9–hour post–prandial period the plasma vitamin A levels were significantly reduced (below the values obtained with the control meal). No significant effect was observed with a 4 g addition of cholestyramine.

Clinical Studies

(a) Hypercholesterolemia

Administration of cholestyramine resin in the proper dosage usually leads to a significant reduction (15% or more) in serum cholesterol levels. This occurs as a result of the increased fecal loss of bile acids bound to the resin and the compensatory formation of additional bile acids from cholesterol. The effect of lower serum cholesterol levels due to cholestyramine has been observed both in subjects with "normal" cholesterol levels (100–250 mg/100 mL) as well as in patients with elevated values.

A careful, long–term metabolic study was conducted in 10 patients with hypercholesterolemia. Results indicated that over periods of 12 months for 7 patients and 6 months for 3 patients with varying dosage levels of cholestyramine (12–24 g/day) the decrease in cholesterol ranged from 15 to 76% of an average of pretreatment values, with the mean decrease being 43%.

Another study was conducted in 17 patients with hypercholesterolemia where most patients were prescribed 4–8 g of cholestyramine resin daily. (Two patients received

12 g/day). In many of these patients significant cholesterol reduction occurred with an average decrease of 23.5%.

It is necessary to emphasize the importance of carefully determining the etiology of the hypercholesterolemia that is to be treated. It was found that patients who are truly idiopathic, and not basically hypertriglyceridemic, respond to cholestyramine resin with significant lowering of serum cholesterol. A study involving 13 patients with idiopathic hypercholesterolemia demonstrated an average cholesterol reduction of 26% with dosage of 8 to 16 g daily, for a period of one month to two years.

A 10 year, multicenter, randomized, double–blind, placebo–controlled study was conducted by the National Institutes of Health in 12 lipid research clinics on the effect of lowering plasma cholesterol on the risk of coronary heart disease defined as CHD death and/or non–fatal myocardial infarction. The 3,806 subjects who participated in the study were predominantly college or high school–educated whites. The mean age was 47.8 years. At the start of the study, all participants had a plasma cholesterol level of 265 mg/dL or greater and an LDL–C level of 190 mg/dL or greater. Exclusions from the study were participants with coronary heart disease or conditions associated with secondary hyperlipoproteinemia. The effect of Total–C on the incidence of CHD is shown in Table 2.

TABLE 2
CHOLESTEROL LOWERING AND CORONARY HEART DISEASE

	N	Mean Total–C+	No. of CHD Cases++
Cholestyramine Group	1,906	257	155
Placebo Group	1,900	277	187

+Average of annual post–treatment levels for participants attending clinic. Total–C indicates plasma total cholesterol.
++Definite non–fatal myocardial infarction or CHD death.

A combination of a modest cholesterol–lowering diet and cholestyramine resin lowered plasma cholesterol. The dose response relationship between the daily dosage of cholestyramine resin, the lowering of total plasma cholesterol and the reduction in CHD risk is summarized in Table 3.

TABLE 3

RELATION OF REDUCTION IN CHOLESTEROL TO REDUCTION IN CORONARY HEART DISEASE RISK

Dose of Cholestyramine	Package Count	Patient Population	Total Cholesterol Lowering	Reduction in CHD Risk
0 – 8 g	0 – 2	439	4.4%	10.9%
8 – 20 g	2 – 5	496	11.5%	20.1%
20 – 24 g	5 – 6	965	19.0%	39.3%

(b) Partial Biliary Obstruction

Bile acids are formed from cholesterol in the liver and then are excreted into the intestine via the bile. There they aid in the digestive processes, emulsifying the fats and fatty materials which are present in ingested foods. A large proportion of the bile acids is reabsorbed and returned to the liver via the portal circulation.

In normal sera, very small amounts of bile acids are found. Serum concentrations may increase 10 to 20–fold or more; however, when the normal secretion of bile is partially blocked, an intractable pruritis often intervenes when this occurs. Some patients become extremely depressed because the pruritis may be so severe.

Several recent reports have shown that in such patients administration of cholestyramine reduced serum bile acids and relieved pruritis. Withdrawing the

cholestyramine resin for a few days resulted in a return of pruritis and increased serum bile acid levels.

This evidence supports the hypothesis of a casual relationship between high serum bile acid concentrations and the pruritis of jaundice. The lag periods of several days between administration of the resin and relief of itching, and between withholding cholestyramine and the return of itching suggest that the reason may not be bile acid in the serum but that which accumulated in the skin or adjacent tissues.

After cholestyramine administration to man, increased fecal bile acid excretion has been consistently observed. One study reported an increase in fecal bile acid from 54 to 500 mg/day in a patient following cholestyramine ingestion.

An increase in fecal bile acids from a mean of 81 mg/day during a 10–day control period to 364 mg/day during 54 days of cholestyramine therapy (dosage 1.7–6.6 g/day) was observed in another study.

Pruritis associated with partial biliary obstruction was seen in four patients who had an average serum bile acid concentration of 25 µg/mL. During cholestyramine treatment, the serum bile acids averaged only 6 µg/mL and the itching was relieved.

Human studies have conclusively demonstrated that an important effect of cholestyramine resin is to increase fecal bile acid excretion and reduce serum bile acids.

(c) Diarrhea in Post Ileal Resection Patients

A report involving fifteen patients with persistent diarrhea of more than one year's duration following ileal resection found that thirteen patients had a 50% reduction in stool frequency and 14 had an improvement in consistency on an average dose of 5.4 g of cholestyramine per day. In most cases urgency, perianal soreness and flatus also decreased.

Another study showed that the stool frequency in 11 patients decreased when cholestyramine was added to the diet and was further decreased when Portagen® was substituted for part of the dietary fat.

TOXICOLOGY

Chronic Toxicity

Oral chronic toxicity studies of one year duration have been conducted in rats and in dogs. Dosages of cholestyramine exceeding those used in man exhibited no toxic effects and caused no observable histological changes in either species.

In these studies, rats were fed 0.5, 1, or 2 g/kg/day cholestyramine and beagle dogs received 5, 10, or 20 g/day. No adverse effects on weight or other gross clinical signs of toxicity were noted in either species studied.

Periodic measurements of total red cells, hematocrit, hemoglobin, sedimentation rate and differential leukocyte counts were made in the dogs. Serum glucose, BUN, carbonate, chloride, sodium, potassium and pH measurements were not remarkable.

Urinary tests for protein, sugar, pH, chloride, sodium and potassium were also unremarkable.

In the rat, during the year study, similar measurements were made as far as samples of blood and urine could be obtained. No abnormal values which could be attributed to cholestyramine were observed.

Teratology:

Three successive litters of rats were bred, whelped and weaned from dams and sires receiving 2 g/kg/day cholestyramine, beginning 60 days before the initial breeding and continuing through all periods of pregnancy, lactation and intervening rest. With regards to the parent animals, there was no evidence of gross toxicity. Reproduction performance was normal and pregnancy and lactation proceeded without any remarkable occurences. Fetal development was considered normal. No gross teratogenic effects which could be attributed to cholestyramine were observed. Pup growth rates, and body weights at birth and weaning were normal. Both in control and treated animals, occasional oral, nasal and ocular porphyrin discharges were observed. Toward the end of the 37-week study one treated animal exhibited corneal opacity, and another, a growth on the right side. Neither occurrences were considered unusual nor cholestyramine-induced. Other anomalous changes common in rats included hydronephrosis and disphragmatic hernia in a few animals. These observations were seen in proportionately equivalent numbers among the control and experimental groups. No gross pathology due to cholestyramine was observed in any parental animals. No evaluation of possible skeletal anomalies was made in the offspring.

When the standard diet was supplemented with vitamins, extra care was required to assure the nutritional adequacy of the ration for the cholestyramine-fed animals, as evidenced by decreased pup mortality.

When cholestyramine was fed at levels 10 times the usual human dose, under the conditions of these studies, the only adverse effects were nutritional, due to sequestration of one or more essential vitamins by the agent.

Carcinogenesis and Mutagenesis

Cholestyramine resin was used as a tool in studies conducted in rats to determine the role of various intestinal factors (e.g. fat, bile salts and microbial flora). In cholestyramine treated rats, the incidence of intestinal tumors induced by potent carcinogens was greater than in control rats. The significance of this observation is not evident, as the results in one study indicated a statistically insignificant increase in tumor incidence whereas a more recent study did not demonstrate any presence of tumors following cholestyramine administration.

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