CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 74-771

FINAL PRINTED LABELING
PREPARATION OF CHOLESTYRAMINE FOR ORAL SUSPENSION, USP:
Cholestyramine for oral suspension, USP can be mixed with your choice of noncarbonated beverage.

1. Pour contents of one Cholestyramine for Oral Suspension, USP packet into a glass or cup.
2. Add 2 to 6 ounces of your favorite beverage (orange juice is a popular choice) and stir vigorously.
3. Add at least 2-4 more ounces of beverage to suit individual taste and stir vigorously again.
4. The slightly-tasteless slurry of Cholestyramine for Oral Suspension, USP mixture is now ready to drink.

NOTE: More than one packet can be mixed at one time depending upon the amount of beverage you wish to consume when using your Cholestyramine for Oral Suspension, USP. You may take 2 to add your individual taste.

Zenith Goldline

CHOLESTYRAMIN FOR ORAL SUSPENSION, US
4 grams cholestyramine resin, USP, per packet.

Usual Dosage: See package insert. Store between 15 and 30°C (59 and 86°F).
*Each packet contains 4 grams of anhydrous cholestyramine for Oral Suspension.

CAUTION: FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION.

 Zenith Goldline Pharmaceutical
 distributes and markets
 27672
PREPARATION OF CHOLESTYRAMINE FOR ORAL SUSPENSION, USP:
Cholestryamine for oral suspension, USP can easily be mixed with
easily with highly fluid foods or fruits.

1. Pour contents of one Cholestryamine for Oral Suspension, USP
   packet in bowl.

2. Add at least 6
   Tablespoons of applesauce or
   other food

3. Mix well.

4. The slightly-textured Cholestryamine for Oral Suspension, USP
   mixture is now ready to eat.

WARNING: more than one packet can be used if needed depending upon the amount of food you wish to consume after taking your
Cholestryamine for Oral Suspension, USP. You may also eat your normal foods.
CHOLESTYRAMINE
FOR ORAL SUSPENSION, USP

DESCRIPTION
Cholestyramine for Oral Suspension, USP, the chloride salt of a basic ion exchange resin, a cholesterol lowering agent, is intended for oral administration. Cholestyramine resin is quite hydrophilic, but insoluble in water. The cholestyramine resin in this product is not adsorbed from the digestive tract. Late granules of cholestyramine for oral suspension USP contain 4 grams of anhydrous cholestyramine resin. It is represented by the following structural formula:

![Representation of structure of resin polymeric groups]

Cholestyramine for Oral Suspension USP contains the following inactive ingredients: distilled water, citric acid (anhydrous) USP, natural lemon flavor, sucrose NF (Malters special), xanthan gum NF.

CLINICAL PHARMACOLOGY
Cholesterol is probably the sole precursor of bile acids. During normal digestion, bile acids are secreted into the intestines. A major portion of the bile acids is absorbed from the proximal tract and returned to the liver via the enterohepatic circulation. Only very small amounts of bile acids are found in normal serum.

Cholestyramine resin absorbs and combines with the bile acids in the intestines to form an indigestible complex which is excreted in the feces. This results in a partial removal of bile acids from the enterohepatic circulation by preventing their absorption.

The increased fecal loss of bile acids due to cholestyramine resin. USP administration leads to an increased oxidation of cholesterol to bile acids, a decrease in total cholesterol and low density lipoprotein plasma cholesterol levels, and a decrease in serum cholesterol levels. Although in man, cholestyramine resin USP produces an increase in hepatic synthesis of cholesterol, plasma cholesterol levels fall.

In patients with partial biliary obstruction, the reduction of serum bile acid levels by
The effects of intensive blood-pressure lowering therapy on coronary atherosclerosis has been assessed by arteriography in hypertensive patients in these randomized, controlled clinical trials. Patients were treated for two to four years by either conventional measures (diet, drugs, or in some cases low dose resin) or intensive combination therapy using diet plus clofibrate (an ion exchange resin). The patients in the diet group were randomized to a diet designed to lower blood pressure to levels similar to that of Clofibrate for Oral Suspension plus either four to six months of treatment. When compared to conventional measures, intensive blood-pressure lowering combination therapy significantly reduced the frequency of progression and increased the frequency of regression of coronary atherosclerotic lesions in patients with or at risk for coronary artery disease.

INDICATIONS AND USAGE

1. Clofibrate for Oral Suspension, USP is indicated as an antihypertensive therapy for the...
CHOLESTEROL REDUCTION

CHOLESTEROL REDUCTION

1. Cholesterol reduction is indicated for persons with hypercholesterolemia.
2. Individuals with familial hypercholesterolemia or those with high levels of LDL cholesterol should be treated with diet and/or medication.
3. Treatment should be continued lifelong to maintain cholesterol levels below target levels.

INDICATIONS AND USAGE

1. Hypercholesterolemia: In patients with hypercholesterolemia, this drug may be used to lower total serum cholesterol and LDL cholesterol. It is also indicated for the prevention of acute coronary events in patients with known coronary artery disease.

2. Coronary heart disease: In patients with coronary heart disease, this drug may be used to reduce the risk of myocardial infarction.

3. Peripheral vascular disease: In patients with peripheral vascular disease, this drug may be used to reduce the risk of cardiovascular events.

4. Diabetes mellitus: In patients with diabetes mellitus, this drug may be used to lower cholesterol levels and reduce the risk of cardiovascular events.

5. Hypertension: In patients with hypertension, this drug may be used to lower cholesterol levels and reduce the risk of cardiovascular events.

6. Dyslipidemia: In patients with dyslipidemia, this drug may be used to lower cholesterol levels and reduce the risk of cardiovascular events.

7. Hypertriglyceridemia: In patients with hypertriglyceridemia, this drug may be used to lower cholesterol levels and reduce the risk of cardiovascular events.

8. Familial hypercholesterolemia: In patients with familial hypercholesterolemia, this drug may be used to lower cholesterol levels and reduce the risk of cardiovascular events.

9. Familial combined hyperlipidemia: In patients with familial combined hyperlipidemia, this drug may be used to lower cholesterol levels and reduce the risk of cardiovascular events.

10. Familial lipoprotein lipase deficiency: In patients with familial lipoprotein lipase deficiency, this drug may be used to lower cholesterol levels and reduce the risk of cardiovascular events.

11. familial apoE deficiency: In patients with familial apoE deficiency, this drug may be used to lower cholesterol levels and reduce the risk of cardiovascular events.

12. Familial lipoprotein(a) deficiency: In patients with familial lipoprotein(a) deficiency, this drug may be used to lower cholesterol levels and reduce the risk of cardiovascular events.

13. Hypercholesterolemia and familial hypertriglyceridemia: In patients with hypercholesterolemia and familial hypertriglyceridemia, this drug may be used to lower cholesterol levels and reduce the risk of cardiovascular events.

14. Hypercholesterolemia and familial combined hyperlipidemia: In patients with hypercholesterolemia and familial combined hyperlipidemia, this drug may be used to lower cholesterol levels and reduce the risk of cardiovascular events.

15. Hypercholesterolemia and familial lipoprotein lipase deficiency: In patients with hypercholesterolemia and familial lipoprotein lipase deficiency, this drug may be used to lower cholesterol levels and reduce the risk of cardiovascular events.

16. Hypercholesterolemia and familial apoE deficiency: In patients with hypercholesterolemia and familial apoE deficiency, this drug may be used to lower cholesterol levels and reduce the risk of cardiovascular events.

17. Hypercholesterolemia and familial lipoprotein(a) deficiency: In patients with hypercholesterolemia and familial lipoprotein(a) deficiency, this drug may be used to lower cholesterol levels and reduce the risk of cardiovascular events.

18. Hypercholesterolemia and hypertriglyceridemia: In patients with hypercholesterolemia and hypertriglyceridemia, this drug may be used to lower cholesterol levels and reduce the risk of cardiovascular events.
**Clinical heart disease or peripheral vascular disease (including symptomatic carotid artery disease).**

Other risk factors for coronary heart disease (CHD):
- Male age 55 years, female age 65 years or premature menopause without estrogen replacement therapy,
- Family history of premature CHD,
- Current cigarette smoking,
- Hypertension: confirmed HDL-C <35 mg/dl (<0.9 mmol/L), and
diabetes mellitus. Subtract one risk factor if HDL-C is >50 mg/dl (>1.3 mmol/L).

**Cholestyramine Resin Monotherapy** has been demonstrated to reduce the rate of progression and increase the rate of regression of coronary artery disease. In addition to its CRP trial, cholestyramine resin therapy reduced the combined rate of coronary heart disease death and non-fatal MI.

2) Cholestyramine for Oral Suspension USP is indicated for the relief of pruritus associated with partial or complete biliary obstruction. Cholestyramine for Oral Suspension USP has been shown to have a variable effect on serum cholesterol in these patients. Patients with primary biliary cirrhosis may exhibit an elevated cholesterol as part of their disease.

**Contraindications**
Cholestyramine Resin USP is contraindicated in patients with complete biliary obstruction where bile is not secreted into the intestine and in those individuals who have shown hypersensitivity to any of its components.

**Precautions**
- **Gastrointestinal:**
  - Cholestyramine Resin USP may be associated with increased bleeding tendency to hypercoagulable states associated with vitamin K deficiency. This can usually respond to prompt administration of vitamin K and recurrences may be prevented by oral administration of vitamin K. Reduction of serum or red cell count has been reported in long-term administration of cholestyramine resin USP. Supplementation with low and should be considered in these cases.

There is a possibility that prolonged use of cholestyramine resin USP can result in a chronic form of anion exchange resin, which may produce hyperkalemia and acidosis. This should especially be true in younger patients or those with renal insufficiency or volume depletion and in those receiving concurrent potassium supplements.

Cholestyramine Resin USP may produce or worsen pre-existing constipation. The dosage should be increased gradually in patients to minimize the risk of developing fecal incontinence. In patients with pre-existing constipation, the starting dose should be 1 packet or 1 scoop once daily for 3 to 7 days, increasing to twice daily with monitoring of constipation and serum electrolytes, at least once every 4 to 6 weeks. Increased fluid intake and fiber intake should be encouraged to alleviate constipation and a stool softener may occasionally be indicated. If the initial dose is well tolerated, the dose may be increased as needed by one dose/day (at monthly intervals) with periodic monitoring of serum electrolytes.

If constipation worsens or the desired therapeutic response is not achieved at one to six doses/day, combination therapy or alternate therapy should be considered. Particular effort should be made to avoid constipation in patients with sympto-
music coronary artery disease.

Consultation with a doctor and
cholesterol levels may help in this

Assessment of Baseline Levels

Patients with elevated cholesterol levels may benefit from

Procedures

1. Establish a baseline cholesterol level.
2. Establish a target level for cholesterol reduction.

High Risk Groups

Patients with high cholesterol levels may include:

- Patients with a family history of heart disease.
- Patients with a history of high blood pressure.
- Patients with diabetes.
- Patients with a history of smoking.
- Patients who are overweight.

Medications

- Statins (e.g., atorvastatin, simvastatin).
- Fibric acid derivatives (e.g., fenofibrate).
- Niacin.
- HMG-CoA reductase inhibitors (e.g., lovastatin).

Dietary Changes

- Increase intake of dietary fiber.
- Decrease intake of saturated and trans fats.
- Increase intake of polyunsaturated and monounsaturated fats.
- Reduce intake of cholesterol.
- Increase intake of fruits and vegetables.

Lifestyle Modifications

- Regular physical activity.
- Maintaining a healthy weight.
- Quitting smoking.
- Reducing alcohol consumption.

Other Considerations

- Avoiding long periods of stress.
- Reducing sodium intake.
- Ensuring adequate sleep.

Conclusion

By implementing lifestyle changes and possibly medication, patients can significantly reduce their cholesterol levels and lower their risk of developing heart disease.

References

IT IS RECOMMENDED THAT PATIENTS SHOULD TAKE OTHER DRUGS AT LEAST ONE HOUR BEFORE OR AFTER TREATMENT WITH CHOLESTYRAMINE RESIN. USP (OR AT AS GREAT AN INTERVAL AS POSSIBLE TO AVOID IMPENDING THEIR ABSORPTION.

Concomitant Drugs, Measurements, Assessment of Effectibility in studies conducted in rats in which cholestyramine resin was used to investigate the role of various intestinal factors, such as fat, bile salts and micellar forms, in the development of intestinal tumors induced by potent carcinogens, the incidence of intestinal tumors was observed to be greater in cholestyramine-induced rats than in controls.

The relevance of this laboratory observation from studies in rats to the clinical use of cholestyramine resin in humans is unknown. In the human study referred to above, the total incidence of fatal and nonfatal neoplasms was similar in both treatment groups. When the many different categories of tumors are examined, various alimentary tract cancers were somewhat more prevalent in the cholestyramine group. The small numbers and the multiple categories prevent conclusions from being drawn. However, in view of the fact that cholestyramine resin is used in the GI tract and not absorbed, and in light of the above observations referred to above, a long-term placebo-controlled study of the cholestyramine patient population has been completed in 134 patients of all ages, and it has revealed no statistically significant difference in incidence of cause-specific mortality or cause-specific morbidity between cholestyramine and placebo treated patients.

Pregnancy: Teratogenic Effects. Pregnancy Category C.

Since cholestyramine resin is not absorbed systemically, it is not expected to cause fetal harm when administered during pregnancy. However, in animals and in humans, cholestyramine is not excreted in breast milk. The possible effect of cholestyramine on the nursing mother is unknown.

Pediatric Use

Experience in the pediatric population is limited. A practical dosage schedule has not been established.

Recommendations in patients under 12 years of age are as follows: in patients weighing 35 kg or less, administer 24 mg of cholestyramine resin per day; in patients weighing 36 to 71 kg, administer 48 mg of cholestyramine resin per day; in patients weighing over 71 kg, administer 72 mg of cholestyramine resin per day.

The effects of long-term drug administration, as well as its effect on maintaining lowered cholesterol levels in pediatric patients, are unknown.

ADVERSE REACTIONS

The most common adverse reaction is constipation. When used as a cholesterol-lowering agent, predisposable factors (i.e., recent meals, intake of high fat and increased age) may be responsible for this. In over 50 patients treated with cholestyramine resin for the first time, constipation was reported by 60% of patients treated for at least 30 days. Some patients require a temporary decrease in dosage or discontinuation of therapy.

Less Common Adverse Reactions:

Abdominal discomfort and/or pain, flatulence, nausea, vomiting, diarrhea, constipation, dermatitis, eczematous, bleeding, tenderness due to hepato-biliary hepatomegaly (Vitamin K deficiency) when used as a vitamin A, a case of acute myeloid leukemia (unknown cause).
ADVERSE REACTIONS

The most common adverse reaction is constipation. When used as a cholesterol-lowering agent, gastrointestinal factors must be considered in the side effects of cholestyramine, especially if the 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.

Less frequent adverse reactions:
Abdominal discomfort and/or pain, diarrhea, nausea, vomiting, cramps, diarrhea, constipation, and urination.

Occasionally, bleeding tendencies d due to hypoprothrombinemia (Vitamin K deficiency) as well as Vitamin A (one case of light bruising reported) and D deficiencies. Hypoprothrombinemia is found in children with profound rash and malnutrition of the brain. In the elderly, these patients have developed coagulation disorders due to cholestyramine. The usual dosage is 3 grams daily. One patient with a history of high blood pressure had an episode presumed to be due to cholestyramine. The usual dosage is 3 grams daily. One patient developed acute mesenteric ischemia and died.

Occasional allergic material has been observed in the biliary tree, including calcification of the gallbladder. In patients to whom cholestyramine resin has been given, this may be a manifestation of the liver disease and not drug related.

One patient experienced jaundice on one of three occasions on which he took cholestyramine for oral suspension. This patient had jaundice as his presenting symptom. The patient was not found to have a "pasty" mass in the transverse colon on a barium enema.

Other adverse effects (not necessarily drug-related) reported in patients taking cholestyramine resin are:

Gastrointestinal—Diarrhea, constipation, back pain, hemorrhoidal bleeding, bleeding from the colon, vomiting, and liver disease.

Laboratory test changes—Liver function abnormalities

Hematological—Prolonged prothrombin time, eosinophilia, anemia

Hypersensitivity—Urticaria, arthralgia, wheezing, shortness of breath

Musculoskeletal—Backache, muscle pain, joint pain, arthritis

Neurological—Headache, seizure, vertigo, dizziness, lupus, bullous, syringomyelia, tremor, paresthesia

Skin: Urticaria, rash, dryness, pruritus, urticaria, rash, pruritus

Miscellaneous—Weight loss, anorexia, nausea, pyrosis, burn or rise, diarrhea

OVERDOSAGE

Overdosage with cholestyramine resin (UST) has been reported in a patient taking 150% of the maximum recommended daily dosage for a period of several weeks. No ill effects were reported. Should an overdose occur, the chief potential harm would be obstructions 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.

DOSE AND ADMINISTRATION

The recommended starting adult dose for cholestyramine for oral suspension (UST) is one packet or one level scoopful (9 grams of cholestyramine resin) once or twice daily. The recommended maintenance dose for cholestyramine for oral suspension (UST) is 2 to 4 packets or...
Dosage and Administration

The recommended starting adult dose for cholestyramine for oral suspension, USP is one packet or one level scoopful (5 grams of cholestyramine for oral suspension, USP contains 4 grams of anhydrous cholestyramine resin) once or twice a day. The recommended maintenance dose for cholestyramine for oral suspension, USP is 2 to 6 packets or scoopfuls daily (10 to 18 grams of anhydrous cholestyramine resin) divided into two doses. It is recommended that increases in dose be gradual with periodic assessment of lipid-lowering response at intervals of not less than 4 weeks. The maximum recommended daily dose is six packets or scoopfuls of cholestyramine for oral suspension, USP (24 grams of anhydrous cholestyramine resin). The suggested time of administration is at meals but may be modified to avoid interference with absorption of other medications. Although the recommended dosage schedule is twice daily, cholestyramine for oral suspension, USP may be administered in 1-6 doses per day.

Cholestyramine for Oral Suspension should not be taken in its dry form. Always mix cholestyramine resin, USP with water or other fluids before ingesting. See Preparation Instructions.

Concomitant Therapy

Preparatory evidence suggests that the lipid-lowering effects of cholestyramine on total and low density lipoprotein are enhanced when combined with a HMG CoA reductase inhibitor, e.g. lovastatin, simvastatin, atorvastatin and pravastatin. Additive effects on LDL cholesterol are also seen when combined with niacin or niacinamide therapy. See the Drug Interactions section of the PRECAUTIONS section for recommendations on administering concomitant therapy.

Preparation

The color of cholestyramine resin, USP may vary somewhat from batch to batch but this variation does not affect the performance of the product. Place the contents of one single-dose packet or one level scoopful of cholestyramine resin, USP in 1 glass or cup, and at least 2 to 6 ounces of water or the beverage of your choice. Stir to a uniform consistency.

Cholestyramine resin, USP may also be mixed with high fiber soups or puréeed foods with a high moisture content such as applesauce or crushed bananas.

How Supplied

Cholestyramine for oral suspension, USP is available in cans of ten 90-gram packets and in cans containing 375 grams, nine grams of cholestyramine for oral suspension, USP contain 4 grams of anhydrous cholestyramine resin. Store between 15°C and 30°C.

NDC 0177-2930-90
Cans of 10 packets
NDC 0177-2930-36
Cans, 375 g

REFERENCES

1. The Lipid Research Clinics Coronary Primary Prevention Trial Results (II) Reduction in Incidence of Coronary Heart Disease: (III) The Reversing of Reduction in Incidence of Coronary Heart Disease to Cholesterol Lowering: JAMA 1984, 251:351-374

The level of cholesterol in the body can be lowered by medication called cholestyramine. This medication is usually taken in conjunction with a special diet. Cholestyramine is a resin that binds with bile salts, preventing them from being reabsorbed into the bloodstream. It is available as a powder that is mixed with water or a beverage to form a suspension. The suspension is then taken by mouth. The resin binds with fats and cholesterol in the digestive tract, preventing them from being absorbed into the bloodstream. This process helps to reduce the amount of cholesterol in the body, which can help to reduce the risk of heart disease.

Cholestyramine is often used in combination with other medications and lifestyle changes to manage cholesterol levels. It is important to follow a healthy diet and exercise regularly to maintain good cholesterol levels. Cholestyramine may cause side effects such as constipation, bloating, and flatulence. In some cases, it may cause more serious side effects such as liver problems or interactions with other medications.

Precautions

Cholestyramine may cause serious side effects. Do not use if you have certain medical conditions, such as kidney or liver disease. Do not use if you are allergic to cholestyramine or any other ingredients in the medication. Follow all instructions carefully.

Cholestyramine may interact with other medications. Tell your doctor and pharmacist all prescription and over-the-counter medications you use. Keep a list of all your medications and show it to your doctor and pharmacist.

Reference:


Single Dose

Zenith Goldline

CHOLESTYRAMINE
FOR ORAL SUSPENSION, USP

CAUTION: FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION.

Usual Dosage: See Package Insert.

Store between 15 and 30°C (59 and 86°F).

Preparation: Place the contents of one packet in a glass or cup.
Add at least 2 to 6 ounces of water or the beverage of your choice.
Stir to a uniform consistency.

Keep this and all medication out of the reach of children.
This package is not child-resistant.
Each packet contains 4 grams of anhydrous cholestyramine
in 9 grams of Cholestyramine For Oral Suspension, USP.

This product contains sucrose.

ZENITH GOLDLINE PHARMACEUTICALS, INC.

APPROVED

04/07/2
CAUTION: Federal law prohibits dispensing without prescription.

Preparation
1. A scoop is enclosed to help you measure accurately. Do not force or pack the powder into the scoop.
2. Place one level scoopful of CHOLESTYRAMINE FOR ORAL SUSPENSION, USP in a glass or cup.
3. Add 2 to 6 ounces of water or the beverage of your choice and stir vigorously.
4. Add at least 2-4 more ounces of beverage to suit individual taste and stir vigorously again.
5. The slightly textured CHOLESTYRAMINE FOR ORAL SUSPENSION, USP is now ready to drink.

Always mix CHOLESTYRAMINE FOR ORAL SUSPENSION, USP with water, or the beverage of your choice, or other highly fluid foods or fruits before using.

Keep this and all medication out of the reach of children. This package is not child-resistant.

Always replace plastic lid after using.

Usual Dosage: See package insert for dosage information.

*Each level scoopful (9 grams) of CHOLESTYRAMINE FOR ORAL SUSPENSION, USP contains 4 grams of cholestyramine resin, USP.