CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 77-203

Name: Cholestyramine for Oral Suspension USP, (Light), packaged in multiple-dose containers providing 4 g resin/scoopful and single-use packets containing 4 g resin/packet

Sponsor: Par Pharmaceutical, Inc.

Approval Date: August 26, 2005

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 77-203

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 77-203

APPROVAL LETTER

ANDA 77-203

AUG 26 2005

Par Pharmaceutical, Inc.
Attention: Julie Szozda
Sr. Associate, Regulatory Affairs
One Ram Ridge Road
Spring Valley, NY 10977

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated July 2, 2004, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Cholestyramine for Oral Suspension USP, (Light), packaged in multiple-dose containers providing 4 g resin/scoopful and single-use packets containing 4 g resin/packet.

Reference is also made to your amendments dated March 3, June 6, July 14, July 18, and August 9, 2005.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the application is approved. The Division of Bioequivalence has determined your Cholestyramine for Oral Suspension USP, (Light), to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Questran® Light Powder for Oral Suspension of Bristol Myers Co.).

Under Section 506A of the Act, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Postmarketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

Promotional materials may be submitted to FDA for comment prior to publication or dissemination. Please note that these submissions are voluntary. If you desire comments on proposed launch promotional materials with respect to compliance with

applicable regulatory requirements, we recommend you submit, in draft or mock-up form, two copies of both the promotional materials and package insert(s) directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising, and Communications, HFD-42
5600 Fishers Lane
Rockville, MD 20857

We call your attention to 21 CFR 314.81(b)(3) which requires that all promotional materials be submitted to the Division of Drug Marketing, Advertising, and Communications (HFD-42) with a completed Form FDA 2253 at the time of their initial use.

Sincerely yours,

Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 77-203
Division File
Field Copy
HFD-610/R. West
HFD-205
HFD-610/Orange Book Staff

Approved Electronic Labeling Located at:
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Endorsements:
HFD-625/K.Furnkranz/ for [signature] (Monika Setrau) 8/25/2005.
HFD-625/M.Smela/ ES for MS 8/25/05
HFD-617/P.Chen/ [signature] 8/29/05
HFD-613/A.Payne/ } SEE ATTACHED EMAIL
HFD-613/J.Grace/ }
[signature] 8/26/05
Rec'd 8/24/05

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F/T by

APPROVAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 77-203

LABELING

NDC 49884-466-63

Cholestyramine for Oral Suspension USP, Light

POWDER

Rx only

SINGLE DOSE

Sugar Free Orange Flavor*

*Contains the artificial sweetener Aspartame

Preparation: Place the contents of one packet in a glass or cup. Add at least 2-6 ounces of water, milk or the noncarbonated beverage of your choice. Stir to a uniform consistancy and drink.

PHENYLKETONURICS: CONTAINS PHENYLALANINE, 14.0 mg per 5 mg DOSE.

KEEP THIS AND ALL DRUGS OUT OF REACH OF CHILDREN.

This packet is not child-resistant.

This packet contains 4 grams of anhydrous cholestyramine in 5 grams of Cholestyramine Light.

Mfd by:
Par Pharmaceutical, Inc.
Spring Valley, NY 10977

I01/05
PO466-63-1-01

N 3 49884-466-63 3

NDC 49884-466-65

Cholestyramine for Oral Suspension USP, Light

POWDER

4 GRAMS
CHOLESTYRAMINE RESIN USP,
PER PACKET

Sugar Free Orange Flavor*

Rx only

60 X 5 g SINGLE DOSE PACKETS

*Contains the artificial sweetener Aspartame

Mfd by:
Par Pharmaceutical, Inc.
Spring Valley, NY 10977

I01/05 UC466-65-1-01

PREPARATION OF CHOLESTYRAMINE LIGHT
Cholestyramine Light can be easily mixed with highly fluid foods or fruits.

1. Pour contents of one Cholestyramine Light packet into bowl.

2. Add at least 2-3 ounces of highly fluid food such as applesauce.

3. Mix well.

4. The slightly textured Cholestyramine Light mixture is now ready to eat.

NOTE: More than one packet can be mixed at one time depending upon the amount of food you wish to consume when taking your Cholestyramine Light. You may mix to suit your individual taste.

PHARMACY LABEL

HEALTHFUL HINTS

- Maintain diet and exercise as directed by your physician.
- Find a suitable time to take your medication daily (it may be useful to take Cholestyramine Light with meals).
- Cholestyramine Light can be mixed ahead of time and kept refrigerated for three days (remember to mix well each time before drinking or eating a dose).
- Cholestyramine Light can also be easily mixed in a blender
- Ask your pharmacist or physician for new and different ways to prepare Cholestyramine Light.

• Always mix Cholestyramine Light with water, the beverage of your choice, or highly fluid foods or fruits before using.

- See package insert for dosage information.

KEEP THIS AND ALL DRUGS OUT OF REACH OF CHILDREN.

This carton is not child-resistant.

WARNING: PHENYLKETONURICS:
CONTAINS PHENYLALANINE, 14.0 mg per 5 g DOSE.

Store between 20°-25°C (68°-77°F). [See USP Controlled Room Temperature]. Excursion permitted to 15°-30°C (59°-86°F).

NDC 49884-466-65

Cholestyramine for Oral Suspension USP, Light

POWDER

4 GRAMS
CHOLESTYRAMINE RESIN USP,
PER PACKET

Sugar Free Orange Flavor*

Rx only

60 X 5 g SINGLE DOSE PACKETS

*Contains the artificial sweetener Aspartame

Mfd by:
Par Pharmaceutical, Inc.
Spring Valley, NY 10977

I01/05 UC466-65-1-01

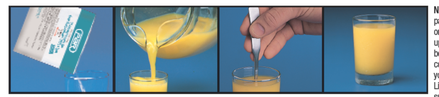
PREPARATION OF CHOLESTYRAMINE LIGHT
Cholestyramine Light can be easily mixed with water, milk, juice or noncarbonated beverage of your choice.

1. Pour contents of one Cholestyramine Light packet into a glass or cup.

2. Add 2 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-textured Cholestyramine Light mixture is now ready to drink.



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NOTE: More than one packet can be mixed at one time depending upon the amount of beverage you wish to consume when taking your Cholestyramine Light. You may mix to suit your individual taste.

Usual Dosage:
One level scoop one to six times daily, as directed. Each level scoop of Cholestyramine Light supplies 4 grams of anhydrous cholestyramine in 5 grams of powder.

Preparation

1. A scoop is enclosed to help you measure accurately. Do not force or pack the powder into the scoop. Scoop is not interchangeable with scoops from other products.
2. Place one level scoopful of Cholestyramine Light in a glass or cup.
3. Add 2 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 Light is now ready to drink.

Always mix Cholestyramine Light with a liquid or highly fluid food before using.

N 3 49884-466-67 1

NDC 49884-466-67

Cholestyramine for Oral Suspension USP, Light

Powder

4 GRAMS CHOLESTYRAMINE RESIN USP, PER SCOOPFUL

Rx only

Sugar Free Orange Flavor*

42 MEASURED DOSES
CONTENTS 210 G (168 G ANHYDROUS CHOLESTYRAMINE)

WARNINGS:
PHENYLKETONURICS: CONTAINS PHENYLALANINE 14.0 mg per 5 g DOSE.

KEEP THIS AND ALL DRUGS OUT OF REACH OF CHILDREN.

This container is not child-resistant.

Always replace plastic lid after using.

Store between 20°-25°C (68°-77°F). [See USP Controlled Room Temperature]. Excursion permitted to 15°-30°C (59°-86°F).

***Contains the artificial sweetener Aspartame**

I01/05 LA466-67-1-01

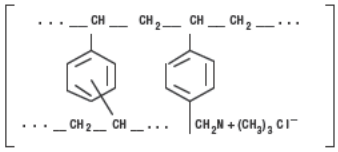
Mfd by:
Par Pharmaceutical, Inc.
Spring Valley, NY 10977

Lot

Exp.

DESCRIPTION

Cholestyramine for Oral Suspension USP, the chloride salt of a basic anion exchange resin, a cholesterol lowering agent, is intended for oral administration. Cholestyramine resin is quite hydrophilic, but insoluble in water. The cholestyramine resin in Cholestyramine is not absorbed from the digestive tract. Four grams of anhydrous cholestyramine resin is contained in 9 grams of Cholestyramine for Oral Suspension USP. Four grams of anhydrous cholestyramine resin is contained in 5 grams of Cholestyramine for Oral Suspension USP, Light. It is represented by the following structural formula:



Representation of structure of main polymeric groups

Cholestyramine for Oral Suspension USP contains the following inactive ingredients: acacia, citric acid, D&C Yellow No. 10, FD&C Yellow No. 6, flavor (natural and artificial Orange), polysorbate 80, propylene glycol alginate and sucrose. Cholestyramine for Oral Suspension USP, Light contains the following inactive ingredients: aspartame, citric acid, colloidal silicon dioxide, D&C Yellow No. 10, FD&C Red No. 40, flavor (natural and artificial Orange), maltodextrin, propylene glycol alginate and xanthan gum.

ACTIONS/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 intestinal tract and returned to the liver via the enterohepatic circulation. Only very small amounts of bile acids are found in normal serum.

Cholestyramine resin adsorbs and combines with the bile acids in the intestine to form an insoluble 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 administration 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 in man, Cholestyramine 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 Cholestyramine reduces excess bile acids deposited in the dermal tissue with resultant decrease in pruritus.

Clinical Studies

In a large, placebo-controlled, multi-clinic study, LRC-CPPT[1], hypercholesterolemic subjects treated with Cholestyramine had mean reductions in total and low-density lipoprotein cholesterol (LDL-C) which exceeded those for diet and placebo treatment by 7.2% and 10.4%, respectively. Over the seven-year study period the Cholestyramine group experienced a 19% reduction (relative to the incidence in the placebo group) in the combined rate of coronary heart disease death plus non-fatal myocardial infarction (cumulative incidences of 7% Cholestyramine and 8.6% placebo). The subjects included in the study were men aged 35–59 with serum cholesterol levels above 265 mg/dL and no previous history of heart disease. It is not clear to what extent these findings can be extrapolated to females and other segments of the hypercholesterolemic population. (See also **PRECAUTIONS: Carcinogenesis, Mutagenesis, Impairment of Fertility**.)

Two controlled clinical trials have examined the effects of Cholestyramine monotherapy upon coronary atherosclerotic lesions using coronary arteriography. In the NHLBI Type II Coronary Intervention Trial[2], 116 patients (80% male) with coronary artery disease (CAD) documented by arteriography were randomized to Cholestyramine or placebo for five years of treatment. Final study arteriography revealed progression of coronary artery disease in 49% of placebo patients compared to 32% of the Cholestyramine group ($p<0.05$).

In the St. Thomas Atherosclerosis Regression Study (STARS)[3], 90 hypercholesterolemic men with CAD were randomized to three blinded treatments: usual care, lipid-lowering diet, and lipid-lowering diet plus Cholestyramine. After 36 months, follow-up coronary arteriography revealed progression of disease in 46% of usual care patients, 15% of patients on lipid-lowering diet and 12% of those receiving diet plus Cholestyramine ($p<0.02$). The mean absolute width of coronary segments decreased in the usual care group, increased slightly (0.003mm) in the diet group and increased by 0.103mm in the diet plus Cholestyramine group ($p<0.05$). Thus in these randomized controlled clinical trials using coronary arteriography, Cholestyramine monotherapy has been demonstrated to slow progression [2,3] and promote regression[3] of atherosclerotic lesions in the coronary arteries of patients with coronary artery disease.

The effect of intensive lipid-lowering therapy on coronary atherosclerosis has been assessed by arteriography in hyperlipidemic patients. In these randomized, controlled clinical trials, patients were treated for two to four years by either conventional measures (diet, placebo, or in some cases low dose resin), or intensive combination therapy using diet plus colestipol (an anion exchange resin with a mechanism of action and an effect on serum lipids similar to that of Cholestyramine for Oral Suspension USP and Cholestyramine for Oral Suspension USP, Light) plus either nicotinic acid or lovastatin. When compared to conventional measures, intensive lipid-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) Cholestyramine for Oral Suspension USP is indicated as adjunctive therapy to diet for the reduction of elevated serum cholesterol in patients with primary hypercholesterolemia (elevated low density lipoprotein [LDL] cholesterol) who do not respond adequately to diet. Cholestyramine may be useful to lower LDL cholesterol in patients who also have hypertriglyceridemia, but it is not indicated where hypertriglyceridemia is the abnormality of most concern.

Therapy with lipid-altering agents should be a component of multiple risk factor intervention in those individuals at significantly increased risk for atherosclerotic vascular disease due to hypercholesterolemia. Treatment should begin and continue with dietary therapy specific for the type of hyperlipoproteinemia determined prior to initiation of drug therapy. Excess body weight may be an important factor and caloric restriction for weight normalization should be addressed prior to drug therapy in the overweight.

Prior to initiating therapy with Cholestyramine, secondary causes of hypercholesterolemia (e.g., poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinemias, obstructive liver disease, other drug therapy, alcoholism), should be excluded, and a lipid profile performed to assess Total cholesterol, HDL-C, and triglycerides (TG). For individuals with TG less than 400 mg/dL (<4.5 mmol/L), LDL-C can be estimated using the following equation:-

$$\text{LDL-C} = \text{Total cholesterol} - [(\text{TG}/5) + \text{HDL-C}]$$

For TG levels >400 mg/dL, this equation is less accurate and LDL-C concentrations should be determined by ultracentrifugation. In hypertriglyceridemic patients, LDL-C may be low or normal despite elevated Total-C. In such cases Cholestyramine may not be indicated.

Serum cholesterol and triglyceride levels should be determined periodically based on NCEP guidelines to confirm initial and adequate long-term response. A favorable trend in cholesterol reduction should occur during the first month of Cholestyramine therapy. The therapy should be continued to sustain cholesterol reduction. If adequate cholesterol reduction is not attained, increasing the dosage of Cholestyramine or adding other lipid-lowering agents in combination with Cholestyramine should be considered.

Since the goal of treatment is to lower LDL-C, the NCEP[4] recommends that LDL-C levels be used to initiate and assess treatment response. If LDL-C levels are not available then Total-C alone may be used to monitor long-term therapy. A lipoprotein analysis (including LDL-C determination) should be carried out once a year. The NCEP treatment guidelines are summarized below.

		LDL-Cholesterol mg/dL (mmol/L)	
Definite Atherosclerotic Disease*	Two or More Other Risk Factors**	Initiation Level	Goal
NO	NO	≥190 (≥4.9)	<160 (<4.1)
NO	YES	≥160 (≥4.1)	<130 (<3.4)
YES	YES or NO	≥130 (≥3.4)	≤100 (≤2.6)

*Coronary heart disease or peripheral vascular disease (including symptomatic carotid artery disease).

**Other risk factors for coronary heart disease (CHD) include: age (males ≥45 years; females ≥55 years or premature menopause without estrogen replacement therapy); family history of premature CHD; current cigarette smoking; hypertension; confirmed HDL-C <35 mg/dL (<0.91 mmol/L); and diabetes mellitus. Subtract one risk factor if HDL-C is ≥60 mg/dL (≥1.6 mmol/L).

Cholestyramine monotherapy has been demonstrated to retard the rate of progression[2,3] and increase the rate of regression[3] of coronary atherosclerosis.

2) Cholestyramine for oral suspension is indicated for the relief of pruritus associated with partial biliary obstruction. Cholestyramine for oral suspension 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 for oral suspension 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.

WARNINGS

PHENYLKETONURICS: CHOLESTYRAMINE for ORAL SUSPENSION USP, LIGHT CONTAINS 14.0 mg PHENYLALANINE PER 5 GRAM DOSE.

PRECAUTIONS

General

Chronic use of cholestyramine resin may be associated with increased bleeding tendency due to hypoprothrombinemia associated with Vitamin K deficiency. This will usually respond promptly to parenteral Vitamin K_1 and recurrences can be prevented by oral administration of Vitamin K_1. Reduction of serum or red cell folate has been reported over long term administration of cholestyramine resin. Supplementation with folic acid should be considered in these cases.

There is a possibility that prolonged use of cholestyramine resin, since it is a chloride form of anion exchange resin, may produce hyperchloremic acidosis. This would especially be true in younger and smaller patients where the relative dosage may be higher. Caution should also be exercised in patients with renal insufficiency or volume depletion, and in patients receiving concomitant spironolactone.

Cholestyramine resin may produce or worsen pre-existing constipation. The dosage should be increased gradually in patients to minimize the risk of developing fecal impaction. In patients with pre-existing constipation, the starting dose should be 1 packet or 1 scoop once daily for 5–7 days, increasing to twice daily with monitoring of constipation and of serum lipoproteins, at least twice, 4–6 weeks apart. 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 lipoproteins. 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 symptomatic coronary artery disease. Constipation associated with cholestyramine resin may aggravate hemorrhoids.

Information for Patients

Inform your physician if you are pregnant or plan to become pregnant or are breastfeeding. Drink plenty of fluids and mix each 9 gram dose of Cholestyramine for Oral Suspension USP in at least 2 to 6 ounces of fluid. Mix each 5 gram dose of Cholestyramine for Oral Suspension USP, Light in at least 2 to 6 ounces of fluid before taking. Sipping or holding the resin suspension in the mouth for prolonged periods may lead to changes in the surface of the teeth resulting in discoloration, erosion of enamel or decay; good oral hygiene should be maintained.

Laboratory Tests

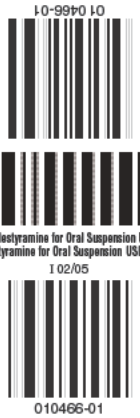
Serum cholesterol levels should be determined frequently during the first few months of therapy and periodically thereafter. Serum triglyceride levels should be measured periodically to detect whether significant changes have occurred.

The LRC-CPPT showed a dose-related increase in serum triglycerides of 10.7%–17.1% in the cholestyramine-treated group, compared with an increase of 7.9%–11.7% in the placebo group. Based on the mean values and adjusting for the placebo group, the cholestyramine-treated group showed an increase of 5% over pre-entry levels the first year of the study and an increase of 4.3% the seventh year.

Drug Interactions

Cholestyramine for Oral Suspension USP may delay or reduce the absorption of concomitant oral medication such as phenylbutazone, warfarin, thiazide diuretics (acidic), or propranolol (basic), as well as tetracycline, penicillin G, phenobarbital, thyroid and thyroxine preparations, estrogens and progestins, and digitalis. Interference with the absorption of oral phosphate supplements has been observed with another positively-charged bile acid sequestrant. Cholestyramine may interfere with the pharmacokinetics of drugs that undergo enterohepatic circulation. The discontinuance of Cholestyramine could pose a hazard to health if a potentially toxic drug such as digitalis has been titrated to a maintenance level while the patient was taking Cholestyramine.

Because cholestyramine binds bile acids, Cholestyramine may interfere with normal fat digestion and absorption and thus may prevent absorption of fat-soluble vitamins such as A, D, E and K. When Cholestyramine is given for long periods of time, concomitant supplementation with water-miscible (or parenteral) forms of fat-soluble vitamins should be considered.



SINCE CHOLESTYRAMINE MAY BIND OTHER DRUGS GIVEN CONCURRENTLY, IT IS RECOMMENDED THAT PATIENTS TAKE OTHER DRUGS AT LEAST ONE HOUR BEFORE OR 4 TO 6 HOURS AFTER CHOLESTYRAMINE (OR AT AS GREAT AN INTERVAL AS POSSIBLE) TO AVOID IMPEDING THEIR ABSORPTION.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In studies conducted in rats in which cholestyramine resin 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 tumors induced by potent carcinogens, the incidence of such tumors was observed to be greater in cholestyramine resin-treated rats than in control rats.

The relevance of this laboratory observation from studies in rats to the clinical use of Cholestyramine is not known. In the LRC-CPPT 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 system 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 confined to the GI tract and not absorbed, and in light of the animal experiments referred to above, a six-year post-trial follow-up of the LRC-CPPT[5] patient population has been completed (a total of 13.4 years of in-trial plus post-trial follow-up) and revealed no significant difference in the incidence of cause-specific mortality or cancer morbidity between cholestyramine and placebo treated patients.

Pregnancy

Pregnancy Category C

There are no adequate and well controlled studies in pregnant women. The use of Cholestyramine in pregnancy or lactation or by women of childbearing age requires that the potential benefits of drug therapy be weighed against the possible hazards to the mother and child. Cholestyramine is not absorbed systemically, however, it is known to interfere with absorption of fat-soluble vitamins; accordingly, regular prenatal supplementation may not be adequate (see **PRECAUTIONS: Drug Interactions**).

Nursing Mothers

Caution should be exercised when Cholestyramine is administered to a nursing mother. The possible lack of proper vitamin absorption described in the **"Pregnancy"** section may have an effect on nursing infants.

Pediatric Use

Although an optimal dosage schedule has not been established, standard texts[6,7] list a usual pediatric dose of 240 mg/kg/day of anhydrous cholestyramine resin in two to three divided doses, normally not to exceed 8 gm/day with dose titration based on response and tolerance.

In calculating pediatric dosages, 44.4 mg of anhydrous cholestyramine resin are contained in 100 mg of Cholestyramine for Oral Suspension USP and 80 mg of anhydrous cholestyramine resin are contained in 100 mg of Cholestyramine for Oral Suspension USP, Light.

The effects of long-term administration, as well as its effect in maintaining lowered cholesterol levels in pediatric patients, are unknown. (Also see **ADVERSE REACTIONS**.)

ADVERSE REACTIONS

The most common adverse reaction is constipation. When used as a cholesterol-lowering agent predisposing factors for most complaints of constipation 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.

Less Frequent Adverse Reactions: Abdominal discomfort and/or pain, flatulence, nausea, vomiting, diarrhea, eructation, anorexia, 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. Rare reports of intestinal obstruction, including two deaths, have been reported in pediatric patients.

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

One patient experienced biliary colic on each of three occasions on which he took cholestyramine resin. One patient diagnosed as acute abdominal symptom complex was found to have a "pasty mass" in the transverse colon on x-ray.

Other events (not necessarily drug related) reported in patients taking cholestyramine resin include:

Gastrointestinal—GI-rectal bleeding, black stools, hemorrhoidal bleeding, bleeding from known duodenal ulcer, dysphagia, hiccups, ulcer attack, sour taste, pancreatitis, rectal pain, diverticulitis.

Laboratory test changes—Liver function abnormalities.

Hematologic—Prolonged prothrombin time, ecchymosis, anemia.

Hypersensitivity—Urticaria, asthma, wheezing, shortness of breath.

Musculoskeletal—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 to urine, diuresis.

Miscellaneous—Weight loss, weight gain, increased libido, swollen glands, edema, dental bleeding, dental caries, erosion of tooth enamel, tooth discoloration.

OVERDOSAGE

Overdosage with Cholestyramine 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 overdosage occur, the chief potential harm would be obstruction 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.

DOSAGE AND ADMINISTRATION

The recommended starting adult dose for all cholestyramine for oral suspension powdered products (Cholestyramine for Oral Suspension USP and Cholestyramine for Oral Suspension USP, Light) is one packet or one level scoopful once or twice a day. The recommended maintenance dose for all cholestyramine for oral suspension powdered products is 2 to 4 packets or scoopfuls daily (8-16 grams anhydrous cholestyramine resin) divided into two doses. Four grams of anhydrous cholestyramine resin is contained in each measured dose of Cholestyramine as follows:

Cholestyramine for Oral Suspension USP	9 grams
Cholestyramine for Oral Suspension USP, Light	5 grams

It is recommended that increases in dose be gradual with periodic assessment of lipid/lipoprotein levels at intervals of not less than 4 weeks. The maximum recommended daily dose is six packets or scoopfuls of cholestyramine for oral suspension (24 grams of anhydrous cholestyramine resin). The suggested time of administration is at mealtime but may be modified to avoid interference with absorption of other medications. Although the recommended dosing schedule is twice daily, cholestyramine for oral suspension may be administered in 1–6 doses per day.

Cholestyramine should not be taken in its dry form. Always mix Cholestyramine with water or other fluids before ingesting. See Preparation Instructions.

Concomitant Therapy

Preliminary evidence suggests that the lipid-lowering effects of Cholestyramine on total and LDL-cholesterol are enhanced when combined with a HMG-CoA reductase inhibitor, e.g., pravastatin, lovastatin, simvastatin, and fluvastatin. Additive effects on LDL-cholesterol are also seen with combined nicotinic acid/Cholestyramine therapy. See the **Drug Interactions** subsection of the **PRECAUTIONS** section for recommendations on administering concomitant therapy.

PREPARATION

The color of Cholestyramine 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 in a glass or cup. Add an amount of water or other non-carbonated beverage of your choice depending on the product being used:

Product Formula	Amount of Water or other Non-Carbonated Liquid
Cholestyramine for Oral Suspension USP	2-6 ounces per dose
Cholestyramine for Oral Suspension USP, Light	2-6 ounces per dose

Stir to a uniform consistency and drink.

Cholestyramine may also be mixed with highly fluid soups or pulpy fruits with a high moisture content such as applesauce or crushed pineapple.

HOW SUPPLIED

Cholestyramine for Oral Suspension USP is available in cans containing 378 grams and in cartons of sixty 9 gram packets. Four grams of anhydrous cholestyramine resin are contained in 9 grams of Cholestyramine for Oral Suspension USP. The 378 g can includes a 15 cc scoop. The scoop is not interchangeable with scoops from other products.

NDC 49884-465-66	**Can, 378 g**
NDC 49884-465-65	**Carton of 60, 9 g packets**

Cholestyramine for Oral Suspension USP, Light is available in cans containing 210 grams and in cartons of sixty 5 gram packets. Four grams of anhydrous cholestyramine resin are contained in 5 grams of Cholestyramine for Oral Suspension USP, Light. The 210 g can includes a 9 cc scoop. The scoop is not interchangeable with scoops from other products.

NDC 49884-466-67	**Can, 210 g**
NDC 49884-466-65	**Carton of 60, 5 g packets**

Storage

Store between 20º-25ºC (68º-77ºF). [See USP Controlled Room Temperature]. Excursions permitted to 15º-30ºC (59º-86ºF).

REFERENCES

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

2. Brensike JF, Levy RI, Kelsey SF, et al. Effects of therapy with cholestyramine on progression of coronary arteriosclerosis: results of the NHLBI type II coronary intervention study. *Circulation* 1984;69:313-24.

3. Watts, GF, Lewis B, Brunt JNH, Lewis ES, et al. Effects on coronary artery disease of lipid-lowering diet, or diet plus cholestyramine, in the St Thomas Atherosclerosis Regression Study (STARS). *Lancet* 1992;339:563-69.

4. National Cholesterol Education Program. Second Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II). *Circulation* 1994 Mar; 89(3):1333-445.

5. The Lipid Research Clinics Investigators. The Lipid Research Clinics Coronary Primary Prevention Trial: Results of 6 Years of Post-Trial Follow-up. *Arch Intern Med* 1992; 152:1399-1410.

6. Behrman RE et al (eds): *Nelson, Textbook of Pediatrics*, ed 15. Philadelphia, PA, WB Saunders Company, 1996.

7. Takemoto CK et al (eds): *Pediatric Dosage Handbook*, ed 3. Cleveland/Akron, OH, Lexi-Comp, Inc., 1996-1997.

Manufactured by:
PAR PHARMACEUTICAL, INC.
Spring Valley, NY 10977

Issued: 02/05 0S466-65-1-01

NDC 49884-937-65

QUESTRAN® LIGHT

(Cholestyramine for Oral Suspension USP)

POWDER

4 GRAMS
CHOLESTYRAMINE RESIN USP,
PER PACKET

Sugar Free Orange Flavor*

Rx only

60 X 5 g SINGLE DOSE PACKETS

***Contains the artificial sweetener Aspartame**

®Registered trademark of
Par Pharmaceutical, Inc.

Mfd by:
Par Pharmaceutical, Inc.
Spring Valley, NY 10977

I01/05

UC937-65-1-01

N 3 49884-937-65 2

PREPARATION OF QUESTRAN® LIGHT
QUESTRAN® LIGHT can be easily mixed with highly fluid foods or fruits.

1. Pour contents of one QUESTRAN® LIGHT packet into bowl.

2. Add at least 2-3 ounces of highly fluid food such as applesauce.

3. Mix well.

4. The slightly-textured QUESTRAN® LIGHT mixture is now ready to eat.

NOTE: More than one packet can be mixed at one time depending upon the amount of food you wish to consume when taking your QUESTRAN® LIGHT. You may mix to suit your individual taste.

PHARMACY LABEL

HEALTHFUL HINTS

- Maintain diet and exercise as directed by your physician.
- Find a suitable time to take your medication daily (it may be useful to take QUESTRAN® LIGHT with meals).
- QUESTRAN® LIGHT can be mixed ahead of time and kept refrigerated for three days (remember to mix well each time before drinking or eating a dose).
- QUESTRAN® LIGHT can also be easily mixed in a blender
- Ask your pharmacist or physician for new and different ways to prepare QUESTRAN® LIGHT.

• Always mix QUESTRAN® LIGHT with water, the beverage of your choice, or highly fluid foods or fruits before using.

- See package insert for dosage information.

KEEP THIS AND ALL DRUGS OUT OF REACH OF CHILDREN.

This carton is not child-resistant.

WARNING: PHENYLKETONURICS: CONTAINS PHENYLALANINE 14.0 mg per 5 g DOSE.

Store between 20°-25°C (68°-77°F). [See USP Controlled Room Temperature]. Excursion permitted to 15°-30°C (59°-86°F).

NDC 49884-937-65

QUESTRAN® LIGHT

(Cholestyramine for Oral Suspension USP)

POWDER

4 GRAMS
CHOLESTYRAMINE RESIN USP,
PER PACKET

Sugar Free Orange Flavor*

Rx only

60 X 5 g SINGLE DOSE PACKETS

***Contains the artificial sweetener Aspartame**

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Par Pharmaceutical, Inc.
Spring Valley, NY 10977

I01/05

UC937-65-1-01

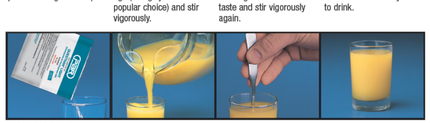
PREPARATION OF QUESTRAN® LIGHT
QUESTRAN® LIGHT can be easily mixed with water, milk, juice or noncarbonated beverage of your choice.

1. Pour contents of one QUESTRAN® LIGHT packet into a glass or cup.

2. Add 2 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-textured QUESTRAN® LIGHT mixture is now ready to drink.



NDC 49884-937-65

NOTE: More than one packet can be mixed at one time depending upon the amount of beverage you wish to consume when taking your QUESTRAN® LIGHT. You may mix to suit your individual taste.

Usual Dosage:
One level scoop one to six times daily, as directed. Each level scoop of QUESTRAN® LIGHT supplies 4 grams of anhydrous cholestyramine in 5 grams of powder.

Preparation

1. A scoop is enclosed to help you measure accurately. Do not force or pack the powder into the scoop. Scoop is not interchangeable with scoops from other products.
2. Place one level scoopful of QUESTRAN® LIGHT in a glass or cup.
3. Add 2 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 QUESTRAN® LIGHT is now ready to drink.

Always mix QUESTRAN® LIGHT with a liquid or highly fluid food before using.

N 3 49884-937-67 6

NDC 49884-937-67

QUESTRAN® LIGHT

(Cholestyramine for Oral Suspension USP)

Powder

4 GRAMS CHOLESTYRAMINE RESIN USP, PER SCOOPFUL

Rx only

Sugar Free Orange Flavor*

42 MEASURED DOSES
CONTENTS 210 G (168 G ANHYDROUS CHOLESTYRAMINE)

WARNINGS:
PHENYLKETONURICS: CONTAINS PHENYLALANINE 14.0 mg per 5 g DOSE.

KEEP THIS AND ALL DRUGS OUT OF REACH OF CHILDREN.

This container is not child-resistant.

Always replace plastic lid after using.

Store between 20°-25°C (68°-77°F). [See USP Controlled Room Temperature]. Excursion permitted to 15°-30°C (59°-86°F).

***Contains the artificial sweetener Aspartame**

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Spring Valley, NY 10977

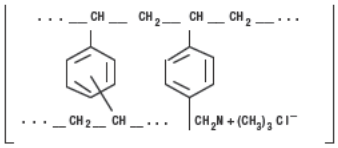
I01/05
LA937-67-1-01

Lot

Exp.

DESCRIPTION

QUESTRAN® (Cholestyramine for Oral Suspension USP), the chloride salt of a basic anion exchange resin, a cholesterol lowering agent, is intended for oral administration. Cholestyramine resin is quite hydrophilic, but insoluble in water. The cholestyramine resin in QUESTRAN is not absorbed from the digestive tract. Four grams of anhydrous cholestyramine resin is contained in 9 grams of QUESTRAN powder. Four grams of anhydrous cholestyramine resin is contained in 5 grams of QUESTRAN LIGHT. It is represented by the following structural formula:



Representation of structure of main polymeric groups

QUESTRAN powder contains the following inactive ingredients: acacia, citric acid, D&C Yellow No. 10, FD&C Yellow No.6, flavor (natural and artificial Orange), polysorbate 80, propylene glycol alginate and sucrose. QUESTRAN LIGHT contains the following inactive ingredients: aspartame, citric acid, colloidal silicon dioxide, D&C Yellow No. 10, FD&C Red No.40, flavor (natural and artificial Orange), maltodextrin, propylene glycol alginate and xanthan gum.

ACTIONS/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 intestinal tract and returned to the liver via the enterohepatic circulation. Only very small amounts of bile acids are found in normal serum.

QUESTRAN resin adsorbs and combines with the bile acids in the intestine to form an insoluble 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 QUESTRAN administration 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 in man, QUESTRAN 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 QUESTRAN reduces excess bile acids deposited in the dermal tissue with resultant decrease in pruritus.

Clinical Studies

In a large, placebo-controlled, multi-clinic study, LRC-CPPT[1], hypercholesterolemic subjects treated with QUESTRAN had mean reductions in total and low-density lipoprotein cholesterol (LDL-C) which exceeded those for diet and placebo treatment by 7.2% and 10.4%, respectively. Over the seven-year study period the QUESTRAN group experienced a 19% reduction (relative to the incidence in the placebo group) in the combined rate of coronary heart disease death plus non-fatal myocardial infarction (cumulative incidences of 7% QUESTRAN and 8.6% placebo). The subjects included in the study were men aged 35-59 with serum cholesterol levels above 265 mg/dL and no previous history of heart disease. It is not clear to what extent these findings can be extrapolated to females and other segments of the hypercholesterolemic population. (See also **PRECAUTIONS: Carcinogenesis, Mutagenesis, Impairment of Fertility**.)

Two controlled clinical trials have examined the effects of QUESTRAN monotherapy upon coronary atherosclerotic lesions using coronary arteriography. In the NHLBI Type II Coronary Intervention Trial[2], 116 patients (80% male) with coronary artery disease (CAD) documented by arteriography were randomized to QUESTRAN or placebo for five years of treatment. Final study arteriography revealed progression of coronary artery disease in 49% of placebo patients compared to 32% of the QUESTRAN group ($p<0.05$).

In the St. Thomas Atherosclerosis Regression Study (STARS)[3], 90 hypercholesterolemic men with CAD were randomized to three blinded treatments: usual care, lipid-lowering diet, and lipid-lowering diet plus QUESTRAN. After 36 months, follow-up coronary arteriography revealed progression of disease in 46% of usual care patients, 15% of patients on lipid-lowering diet and 12% of those receiving diet plus QUESTRAN ($p<0.02$). The mean absolute width of coronary segments decreased in the usual care group, increased slightly (0.003mm) in the diet group and increased by 0.103mm in the diet plus QUESTRAN group ($p<0.05$). Thus in these randomized controlled clinical trials using coronary arteriography, QUESTRAN monotherapy has been demonstrated to slow progression[2,3] and promote regression[3] of atherosclerotic lesions in the coronary arteries of patients with coronary artery disease.

The effect of intensive lipid-lowering therapy on coronary atherosclerosis has been assessed by arteriography in hyperlipidemic patients. In these randomized, controlled clinical trials, patients were treated for two to four years by either conventional measures (diet, placebo, or in some cases low dose resin), or intensive combination therapy using diet plus colestipol (an anion exchange resin with a mechanism of action and an effect on serum lipids similar to that of QUESTRAN and QUESTRAN LIGHT) plus either nicotinic acid or lovastatin. When compared to conventional measures, intensive lipid-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) QUESTRAN (Cholestyramine for Oral Suspension USP), is indicated as adjunctive therapy to diet for the reduction of elevated serum cholesterol in patients with primary hypercholesterolemia (elevated low density lipoprotein [LDL] cholesterol) who do not respond adequately to diet. QUESTRAN may be useful to lower LDL cholesterol in patients who also have hypertriglyceridemia, but it is not indicated where hypertriglyceridemia is the abnormality of most concern.

Therapy with lipid-altering agents should be a component of multiple risk factor intervention in those individuals at significantly increased risk for atherosclerotic vascular disease due to hypercholesterolemia. Treatment should begin and continue with dietary therapy specific for the type of hyperlipoproteinemia determined prior to initiation of drug therapy. Excess body weight may be an important factor and caloric restriction for weight normalization should be addressed prior to drug therapy in the overweight.

Prior to initiating therapy with QUESTRAN secondary causes of hypercholesterolemia (e.g, poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinemias, obstructive liver disease, other drug therapy, alcoholism), should be excluded, and a lipid profile performed to assess Total cholesterol, HDL-C, and triglycerides (TG). For individuals with TG less than 400 mg/dL (<4.5 mmol/L), LDL-C can be estimated using the following equation:-

LDL-C=Total cholesterol - [(TG/5) + HDL-C]

For TG levels >400 mg/dL, this equation is less accurate and LDL-C concentrations should be determined by ultracentrifugation. In hypertriglyceridemic patients, LDL-C may be low or normal despite elevated Total-C. In such cases QUESTRAN may not be indicated.

Serum cholesterol and triglyceride levels should be determined periodically based on NCEP guidelines to confirm initial and adequate long-term response. A favorable trend in cholesterol reduction should occur during the first month of QUESTRAN therapy. The therapy should be continued to sustain cholesterol reduction. If adequate cholesterol reduction is not attained, increasing the dosage of QUESTRAN or adding other lipid-lowering agents in combination with QUESTRAN should be considered.

Since the goal of treatment is to lower LDL-C, the NCEP[4] recommends that LDL-C levels be used to initiate and assess treatment response. If LDL-C levels are not available then Total-C alone may be used to monitor long-term therapy. A lipoprotein analysis (including LDL-C determination) should be carried out once a year. The NCEP treatment guidelines are summarized below.

LDL-Cholesterol mg/dL (mmol/L)

Definite Atherosclerotic Disease*	Two or More Other Risk Factors**	Initiation Level	Goal
NO	NO	≥190 (≥4.9)	<160 (<4.1)
NO	YES	≥160 (≥4.1)	<130 (<3.4)
YES	YES or NO	≥130 (≥3.4)	≤100 (≤2.6)

*Coronary heart disease or peripheral vascular disease (including symptomatic carotid artery disease).

**Other risk factors for coronary heart disease (CHD) include: age (males ≥45 years; females ≥55 years or premature menopause without estrogen replacement therapy); family history of premature CHD; current cigarette smoking; hypertension; confirmed HDL-C <35 mg/dL (<0.91 mmol/L); and diabetes mellitus. Subtract one risk factor if HDL-C is ≥60 mg/dL (≥1.6 mmol/L).

QUESTRAN monotherapy has been demonstrated to retard the rate of progression[2,3] and increase the rate of regression[3] of coronary atherosclerosis.

2) QUESTRAN is indicated for the relief of pruritus associated with partial biliary obstruction. QUESTRAN 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

QUESTRAN 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.

WARNING

PHENYLKETONURICS: QUESTRAN LIGHT CONTAINS 14.0 MG PHENYLALANINE PER 5 GRAM DOSE.

PRECAUTIONS

General

Chronic use of QUESTRAN may be associated with increased bleeding tendency due to hypoprothrombinemia associated with Vitamin K deficiency. This will usually respond promptly to parenteral Vitamin K_1 and recurrences can be prevented by oral administration of Vitamin K_1. Reduction of serum or red cell folate has been reported over long term administration of QUESTRAN. Supplementation with folic acid should be considered in these cases.

There is a possibility that prolonged use of QUESTRAN, since it is a chloride form of anion exchange resin, may produce hyperchloremic acidosis. This would especially be true in younger and smaller patients where the relative dosage may be higher. Caution should also be exercised in patients with renal insufficiency or volume depletion, and in patients receiving concomitant spironolactone.

QUESTRAN may produce or worsen pre-existing constipation. The dosage should be increased gradually in patients to minimize the risk of developing fecal impaction. In patients with pre-existing constipation, the starting dose should be 1 packet or 1 scoop once daily for 5-7 days, increasing to twice daily with monitoring of constipation and of serum lipoproteins, at least twice, 4-6 weeks apart. 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 lipoproteins.

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 symptomatic coronary artery disease. Constipation associated with QUESTRAN may aggravate hemorrhoids.

Information for Patients

Inform your physician if you are pregnant or plan to become pregnant or are breastfeeding. Drink plenty of fluids and mix each 9 gram dose of QUESTRAN Powder in at least 2 to 6 ounces of fluid. Mix each 5 gram dose of QUESTRAN LIGHT in at least 2 to 6 ounces of fluid before taking. Sipping or holding the resin suspension in the mouth for prolonged periods may lead to changes in the surface of the teeth resulting in discoloration, erosion of enamel or decay; good oral hygiene should be maintained.

Laboratory Tests

Serum cholesterol levels should be determined frequently during the first few months of therapy and periodically thereafter. Serum triglyceride levels should be measured periodically to detect whether significant changes have occurred.

The LRC-CPPT showed a dose-related increase in serum triglycerides of 10.7%-17.1% in the cholestyramine-treated group, compared with an increase of 7.9%-11.7% in the placebo group. Based on the mean values and adjusting for the placebo group, the cholestyramine-treated group showed an increase of 5% over pre-entry levels the first year of the study and an increase of 4.3% the seventh year.

Drug Interactions

QUESTRAN (Cholestyramine for Oral Suspension USP) may delay or reduce the absorption of concomitant oral medication such as phenylbutazone, warfarin, thiazide diuretics (acidic), or propranolol (basic), as well as tetracycline, penicillin G, phenobarbital, thyroid and thyroxine preparations, estrogens and progestins, and digitalis. Interference with the absorption of oral phosphate supplements has been observed with another positively-charged bile acid sequestrant. QUESTRAN may interfere with the pharmacokinetics of drugs that undergo enterohepatic circulation. The discontinuance of QUESTRAN could pose a hazard to health if a potentially toxic drug such as digitalis has been titrated to a maintenance level while the patient was taking QUESTRAN.

Because cholestyramine binds bile acids, QUESTRAN may interfere with normal fat digestion and absorption and thus may prevent absorption of fat-soluble vitamins such as A, D, E and K. When QUESTRAN is given for long periods of time, concomitant supplementation with water-miscible (or parenteral) forms of fat-soluble vitamins should be considered.

SINCE QUESTRAN MAY BIND OTHER DRUGS GIVEN CONCURRENTLY, IT IS RECOMMENDED THAT PATIENTS TAKE OTHER DRUGS AT LEAST ONE HOUR BEFORE OR 4 TO 6 HOURS AFTER QUESTRAN (OR AT AS GREAT AN INTERVAL AS POSSIBLE) TO AVOID IMPEDING THEIR ABSORPTION.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In studies conducted in rats in which cholestyramine resin 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 tumors induced by potent carcinogens, the incidence of such tumors was observed to be greater in cholestyramine resin-treated rats than in control rats.

The relevance of this laboratory observation from studies in rats to the clinical use of QUESTRAN is not known. In the LRC-CPPT 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 system 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 confined to the GI tract and not absorbed, and in light of the animal experiments referred to above, a six-year post-trial follow-up of the LRC-CPPT[5] patient population has been completed (a total of 13.4 years of in-trial plus post-trial follow-up) and revealed no significant difference in the incidence of cause-specific mortality or cancer morbidity between cholestyramine and placebo treated patients.

Pregnancy

Pregnancy Category C

There are no adequate and well controlled studies in pregnant women. The use of QUESTRAN in pregnancy or lactation or by women of childbearing age requires that the potential benefits of drug therapy be weighed against the possible hazards to the mother and child. QUESTRAN is not absorbed systemically, however, it is known to interfere with absorption of fat-soluble vitamins; accordingly, regular prenatal supplementation may not be adequate (see **PRECAUTIONS: Drug Interactions**).

Nursing Mothers

Caution should be exercised when QUESTRAN is administered to a nursing mother. The possible lack of proper vitamin absorption described in the **"Pregnancy"** section may have an effect on nursing infants.

Pediatric Use

Although an optimal dosage schedule has not been established, standard texts[6,7] list a usual pediatric dose of 240 mg/kg/day of anhydrous cholestyramine resin in two to three divided doses, normally not to exceed 8 gm/day with dose titration based on response and tolerance.

In calculating pediatric dosages, 44.4 mg of anhydrous cholestyramine resin are contained in 100 mg of QUESTRAN powder and 80 mg of anhydrous cholestyramine resin are contained in 100 mg of QUESTRAN LIGHT.

The effects of long-term administration, as well as its effect in maintaining lowered cholesterol levels in pediatric patients, are unknown. (Also see **ADVERSE REACTIONS**.)

ADVERSE REACTIONS

The most common adverse reaction is constipation. When used as a cholesterol-lowering agent predisposing factors for most complaints of constipation 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.

Less Frequent Adverse Reactions: Abdominal discomfort and/or pain, flatulence, nausea, vomiting, diarrhea, eructation, anorexia, 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. Rare reports of intestinal obstruction, including two deaths, have been reported in pediatric patients.

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

One patient experienced biliary colic on each of three occasions on which he took QUESTRAN. One patient diagnosed as acute abdominal symptom complex was found to have a "pasty mass" in the transverse colon on x-ray.

Other events (not necessarily drug related) reported in patients taking QUESTRAN include:

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

Laboratory test changes-Liver function abnormalities.

Hematologic-Prolonged prothrombin time, ecchymosis, anemia.

Hypersensitivity-Urticaria, asthma, wheezing, shortness of breath.

Musculoskeletal-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 to urine, diuresis.

Miscellaneous-Weight loss, weight gain, increased libido, swollen glands, edema, dental bleeding, dental caries, erosion of tooth enamel, tooth discoloration.

OVERDOSAGE

Overdosage with QUESTRAN 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 overdosage occur, the chief potential harm would be obstruction 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.

DOSAGE AND ADMINISTRATION

The recommended starting adult dose for all QUESTRAN powdered products (QUESTRAN Powder and QUESTRAN LIGHT) is one packet or one level scoopful once or twice a day. The recommended maintenance dose for all QUESTRAN powdered products is 2 to 4 packets or scoopfuls daily (8-16 grams anhydrous cholestyramine resin) divided into two doses. Four grams of anhydrous cholestyramine resin is contained in each measured dose of QUESTRAN as follows:

QUESTRAN Powder	9 grams
QUESTRAN LIGHT	5 grams

It is recommended that increases in dose be gradual with periodic assessment of lipid/lipoprotein levels at intervals of not less than 4 weeks. The maximum recommended daily dose is six packets or scoopfuls of QUESTRAN (24 grams of anhydrous cholestyramine resin). The suggested time of administration is at mealtime but may be modified to avoid interference with absorption of other medications. Although the recommended dosing schedule is twice daily, QUESTRAN may be administered in 1-6 doses per day.

QUESTRAN should not be taken in its dry form. Always mix QUESTRAN with water or other fluids before ingesting. See Preparation Instructions.

Concomitant Therapy

Preliminary evidence suggests that the lipid-lowering effects of QUESTRAN on total and LDL-cholesterol are enhanced when combined with a HMG-CoA reductase inhibitor, e.g., pravastatin, lovastatin, simvastatin, and fluvastatin. Additive effects on LDL-cholesterol are also seen with combined nicotinic acid /QUESTRAN therapy. See the **Drug Interactions** subsection of the **PRECAUTIONS** section for recommendations on administering concomitant therapy.

PREPARATION

The color of QUESTRAN 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 QUESTRAN in a glass or cup. Add an amount of water or other non-carbonated beverage of your choice depending on the product being used:

Product Formula	Amount of Water or other Non-Carbonated Liquid
QUESTRAN Powder	2-6 ounces per dose
QUESTRAN LIGHT	2-6 ounces per dose

Stir to a uniform consistency and drink.

QUESTRAN may also be mixed with highly fluid soups or pulpy fruits with a high moisture content such as applesauce or crushed pineapple.

HOW SUPPLIED

QUESTRAN® Powder (Cholestyramine for Oral Suspension USP) is available in cans containing 378 grams and in cartons of sixty 9 gram packets. Four grams of anhydrous cholestyramine resin are contained in 9 grams of QUESTRAN Powder. The 378 g can includes a 15 cc scoop. The scoop is not interchangeable with scoops from other products.

NDC-49884-936-66	**Can, 378 g**
NDC-49884-936-65	**Carton of 60, 9 g packets**

QUESTRAN® LIGHT (Cholestyramine for Oral Suspension USP) is available in cans containing 210 grams and in cartons of sixty 5 gram packets. Four grams of anhydrous cholestyramine resin are contained in 5 grams of QUESTRAN LIGHT. The 210 g can includes a 9 cc scoop. The scoop is not interchangeable with scoops from other products.

NDC-49884-937-67	**Can, 210 g**
NDC-49884-937-65	**Carton of 60, 5 g packets**

Storage

Store between 20º-25ºC (68º-77ºF). [See USP Controlled Room Temperature]. Excursions permitted to 15º-30ºC (59º-86ºF).

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REFERENCES

1. The Lipid Research Clinics Coronary Primary Prevention Trials Results: (I) Reduction in Incidence of Coronary Heart Disease; (II) The Relationship of Reduction in Incidence of Coronary Heart Disease to Cholesterol Lowering. *JAMA* 1984; 251:351-374.
2. Brensike JF, Levy RI, Kelsey SF, et al. Effects of therapy with cholestyramine on progression of coronary arteriosclerosis: results of the NHLBI type II coronary intervention study. *Circulation* 1984;69:313-24.
3. Watts, GF, Lewis B, Brunt JNH Lewis ES, et al. Effects on coronary artery disease of lipid-lowering diet, or diet plus cholestyramine. In the St. Thomas Atherosclerosis Regression Study (STARS).*Lancet* 1992;339:563-69.
4. National Cholesterol Education Program. Second Report of the Expert Panel Detection. Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II). *Circulation* 1994 Mar; 89(3):1333-445.
5. The Lipid Research Clinics Investigators. The Lipid Research Clinics Coronary Primary Prevention Trial: Results of 6 Years of Post-Trial Follow-up. *Arch Intern Med* 1992;152:1399-1410.
6. Behrman RE et al (eds): *Nelson, Textbook of Pediatrics*, ed 15. Philadelphia, PA WB Saunders Company, 1996.
7. Takemoto CK et Al (eds): *Pediatric Dosage Handbook*, ed 3. Cleveland/Akron, OH, Lexi-Comp, Inc., 1996-1997.

Manufactured by:
PAR PHARMACEUTICAL, INC.
Spring Valley, NY 10977

Issued 02/05 OS936-65-1-01

NDC 49884-937-63

QUESTRAN® LIGHT

(Cholestyramine for Oral Suspension USP)

POWDER

Rx only

SINGLE DOSE

Sugar Free Orange Flavor*

*Contains the artificial sweetener Aspartame

Preparation: Place the contents of one packet in a glass or cup. Add at least 2-6 ounces of water, milk or the noncarbonated beverage of your choice. Stir to a uniform consistancy and drink.

PHENYLKETONURICS: CONTAINS PHENYLALANINE, 14.0 mg per 5 g DOSE.

KEEP THIS AND ALL DRUGS OUT OF REACH OF CHILDREN.

This packet is not child-resistant.

This packet contains 4 grams of anhydrous cholestyramine in 5 grams of Questran Light.

®Registered trademark of Par Pharmaceutical, Inc.

Mfd by:
Par Pharmaceutical, Inc.
Spring Valley, NY 10977

I01/05
PO937-63-1-01

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 77-203

LABELING REVIEWS

REVIEW OF PROFESSIONAL LABELING #1
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

FAXed 1-12-05

ANDA Number: **77-203** (light) **and 77-204**
Date of Submission: July 2, 2004
Applicant's Name: Par Pharmaceutical Inc.
Established Names:
Cholestyramine For Oral Suspension USP, Light (Sugar Free) and
Cholestyramine For Oral Suspension USP, (Sugar Free), in single dose packets and bulk cans

Labeling Deficiencies: Firm submitted CD-ROM for labels and labeling.

1. CONTAINER (5 g or 9 g per packet and 210 g or 378 g can)

   a. Include the following statement "This packet is not child-resistant"
   b. Indicate "scoop is not interchangeable with scoops from other products.
   c. Revise [(b) (4)] to read "Usual Dosage":
   d. Revise "4 grams cholestyramine resin USP, per scoopful" [note: relocated the comma]
   e. Name should read Cholestyramine for Oral Suspension USP, Light [note: position of the comma]
   f. If your stability supports the following, please revise your storage statement to store between 20-25C(68-77F).[See USP Controlled Room Temperature}. Excursion permitted to 15-30C(59-86F).
   g. Add "Rx Only" to your labels and labeling. In addition add the word "powder" so that it appears some where on the main panel. However, it is not part of the established name.

2. CARTON (60 x 5 g or 9 g packets)

   a. See comments under CONTAINER.
   b. Revise "60 single dose" to read "60 X 5 g or 9 g single dose packets".
   c. Revise item 2 and 3 under beverages so that they read the same as the reference listed drug labeling.
   d. Under Healthful Hints - Deleted '[(b) (4)]' from the third billet. Revise the 4th billet to be the same as the reference listed drug.

3. INSERT

   a. General Comment
      Please comment on the submission of the trade name labels and labeling that are still being marketed and manufacturer by the innovator. Your manufacturing statement reflects that you would manufacturer the branded product Questran. Will the innovator discontinue manufacturing or marketing their product and therefore allow you to use their trade name? Please comment.
   b. Delete "powder" from the established name.
   c. Add "Rx Only" as required.
   d. CONTRAINDICATIONS, DOSAGE AND ADMINISTRATION, and INDICATIONS AND USAGE, item 2 - Use "cholestyramine for oral suspension" rather than cholestyramine.
   e. PRECAUTIONS and ADVERSE REACTIONS sections - Use "cholestyramine resin" rather than "Cholestyramine"
   f. HOW SUPPLIED
      i. Indicate that the can is provided with a scoop.
      ii. Indicate "scoop is not interchangeable with scoops from other products".
      iii. Revise the storage statement.

Please prepare and submit final printed labels and labeling in accord with the electronic labeling rule published December 11, 2003, (68 FR 69009) requiring submission of labeling content in electronic format effective June 8, 2004. For additional information, consult the following guidance for industry regarding electronic submissions: Providing Regulatory Submissions in Electronic Format — ANDAs (Issued 6/2002) (http://www.fda.gov/cder/guidance/5004fnl.htm). The guidance specifies labeling to be submitted in pdf format. To assist in our review, we request that labeling also be submitted in MS Word format.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes - http://www.fda.gov/cder/cdernew/listserv.html or http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with the previous labeling with all differences annotated and explained.

Wm. Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number	77-203 and 77-204
Date of Submission	
Applicant	Par Pharmeutical, Inc.
Drug Name	Cholestyramine for Oral Suspension USP (light) or Regular
Strength(s)	5 g or 9 g packets and 210 g or 318 g can

Approval Summary		
Container Labels	**XXXXXXXX**	**Submitted vol XX**
Package Insert Labeling	#XXXXRev.	**vol XX**

BASIS OF APPROVAL:

Patent Data For NDA 16-640

Patent No	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
None	None			PI	

Exclusivity Data For NDA 16-640

Code/sup	Expiration	Description	Labeling impact

Reference Listed Drug

RLD on the 356(h) form	Questran and Questran Light
NDA Number	16-640/S-073 and 19-669/S-022
RLD established name	Cholestryamine for Oral Suspension USP, 9 g Regular and 5 g Light
Firm	BMS
Currently approved PI	S-022
AP Date	Sept. 22, 2002

Note.

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23	X		
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?			X
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			X

Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			X
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		x	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			X
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.		X	

NOTES/QUESTIONS TO THE CHEMIST: Please confirm list of inactive ingredients. The innovator revised labels and labeling for the light product. labels packets are 4 resin grams in 6.4 grams product. The generic has 4 gram resin in 5 grams of product. Does this affect our application in any way.

FOR THE RECORD:

1. This review was based on the labeling of the listed drug (Questran s-074 and Questran Light s-022; Approved September 23, 2002; Revised March 2000).
2. Storage/Dispensing Recommendations
   USP: Tight container.
   NDA: Store at room temperature.
   ANDA: (b) (4) Requested firm revise to read store at 20-25C(...seee USP CRT..excursion...)".

4. All inactives are listed in the DESCRIPTION section of the package insert. Will be confirmed by chemist. C&C not available to labeling reviewer.
5. Product Line

   The innovator markets cartons of 60 single dose packets and cans containing 210 g and 398 g. This generic firm intends to market the same package sizes as the reference listed drug.

6. All manufacturing will be completed by Par. All outside firms are utilized for testing.

Date of Review: Dec. 8, 2004 Date of Submission: July 2, 2004

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cc:

ANDA 77-203 and 77-204
UP/DIVISION FILE
HFD-613/APayne/JGrace (no cc)
V:\FIRMSNZ\PAR\LTRS&REV\77203 and 77204NA1.Lab.doc
Review

ED: draft.- See printed copies with review:

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\\CDSESUBOGD1\N77204\N_000\2004-07-02\labeling\container\proposed\cholestcnt.pdf

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\\CDSESUBOGD1\N77204\N_000\2004-07-02\labeling\packet\proposed\cholestpkt.pdf

and

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12-13-04

12/2/04

APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number	77-203 (Light) and 77-204 (reg.)
Date of Submission	March 3, 2005
Applicant	Par Pharmeutical, Inc.
Drug Name	Cholestyramine for Oral Suspension USP (Light) or Regular and QUESTRAN Light and Regular
Strength(s)	5 g or 9 g packets and 210 g or 378 g can

Container Labels	**Submitted e-FPL**
77-203 (light)	
5 g packet-Chol- light	\\Cdsesubogd1\n77203\N_000\2005-03-03\labeling\proposed\cholepack.pdf
5 g packet- Quest - light	\\Cdsesubogd1\n77203\N_000\2005-03-03\labeling\proposed\questpack.pdf
210 gram can-Chol- light	\\Cdsesubogd1\n77203\N_000\2005-03-03\labeling\proposed\cholescont.pdf
210 gram can- Quest - light	\\Cdsesubogd1\n77203\N_000\2005-03-03\labeling\proposed\questcont.pdf
77- 204 (reg)	
9 gram packet - Chol	\\Cdsesubogd1\n77204\N_000\2005-03-03\labeling\proposed\cholpack.pdf
9 gram packet - Quest	\\Cdsesubogd1\n77204\N_000\2005-03-03\labeling\proposed\questpack.pdf
378 gram can - Chol	\\Cdsesubogd1\n77204\N_000\2005-03-03\labeling\proposed\cholecont.pdf
378 gram can - Quest	\\Cdsesubogd1\n77204\N_000\2005-03-03\labeling\proposed\questcont.pdf
Carton Labeling	
60s (5 g packets)-Chol- light	\\Cdsesubogd1\n77203\N_000\2005-03-03\labeling\proposed\cholescart.pdf
60s (5 g packets)-Quest-light	\\Cdsesubogd1\n77203\N_000\2005-03-03\labeling\proposed\questcart.pdf
60s (9 g packets) - Chol	\\Cdsesubogd1\n77204\N_000\2005-03-03\labeling\proposed\cholcart.pdf
60s (9 g packet) - Quest	\\Cdsesubogd1\n77204\N_000\2005-03-03\labeling\proposed\questcart.pdf
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BASIS OF APPROVAL:

Patent Data For NDA 16-640

Patent No	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
None	None			PI	

Exclusivity Data For NDA 16-640

Code/sup	Expiration	Description	Labeling impact

Reference Listed Drug

RLD on the 356(h) form	Questran and Questran Light
NDA Number	16-640/S-073 and 19-669/S-022
RLD established name	Cholestryamine for Oral Suspension USP, 9 g Regular and 5 g Light
Firm	BMS
Currently approved PI	S-022
AP Date	Sept. 22, 2002

Note. Applicant has acquired the RLD (BMS) marketing, and patent rights for QUESTRAN. Firm plans to market and manufacture both the generic and branded product. Hence 4 labels and labeling are included.

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23	X		
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?			X
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			X

Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			X
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		x	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			X
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.		X	

NOTES/QUESTIONS TO THE CHEMIST: Please confirm list of inactive ingredients. The innovator revised labels and labeling for the light product. labels packets are 4 resin grams in 6.4 grams product. The generic has 4 gram resin in 5 grams of product. Does this affect our application in any way.

FOR THE RECORD:

1. This review was based on the labeling of the listed drug (Questran s-074 and Questran Light s-022; Approved September 23, 2002; Revised March 2000).
2. Storage/Dispensing Recommendations
   USP: Tight container.
   NDA: Store at room temperature.
   ANDA: [redacted] (b) (4) Requested firm revise to read store at 20-25C(...seee USP CRT..excursion...)".

3. All inactives are listed in the DESCRIPTION section of the package insert. Will be confirmed by chemist. C&C not available to labeling reviewer.
4. Product Line

   The innovator markets cartons of 60 single dose packets and cans containing 210 g and 398 g. This generic firm intends to market the same package sizes as the reference listed drug.

5. All manufacturing will be completed by Par. All outside firms are utilized for testing.
6. Par is currently distrubeting the RLD product. In March 2005 the RLD will solely be owned and manufactured by Par. That is way this ANDA has two inserts one for a branded and the other is generic.

Date of Review: April 5, 2005 Date of Submission: March 3, 2005

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cc:

ANDA 77-203 and 77-204
UP/DIVISION FILE
HFD-613/APayne/JGrace (no cc)
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Review

4-5-05
4/13/2005

ED: FPL.-

Container

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Container

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Cartons

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Inserts

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 77-203

CHEMISTRY REVIEWS

ANDA 77-203

Cholestyramine for Oral Suspension USP (Light) (4g / 5 g)

and

ANDA 77-204

Cholestyramine for Oral Suspension USP (4 g / 9 g)

Par Pharmaceutical, Inc

Kenneth Furnkranz
Division of Chemistry 1
Office of Generic Drugs

Chemistry Review #1

Table of Contents

Chemistry Review Data Sheet

1. ANDA 77-203 and 77-204

2. REVIEW #: 1

3. REVIEW DATE: 24-November-2004

4. REVIEWER: Kenneth J. Furnkranz

5. PREVIOUS DOCUMENTS: N/A

Previous Documents	Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
ANDA Original Submissions	02-July-2004

7. NAME & ADDRESS OF APPLICANT:

Name:	Par Pharmaceutical, Inc.
Address:	One Ram Ridge Road Spring Valley, NY 10977
Representative:	Michelle Bonomi-Huvala
Telephone:	845-425-7100
Fax:	845-425-7907

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Cholestyramine

9. LEGAL BASIS FOR SUBMISSION:

The reference listed drugs are:

- Questran® (Cholestyramine for Oral Suspension, USP) Light; Bristol Myers Squibb Co.; NDA #16-640
- Questran® (Cholestyramine for Oral Suspension, USP); Bristol Myers Squibb Co. NDA #16-640

Patent Certification has been provided.

The, active ingredient, route of administration, dosage form, strength and labeling (with the exception of specific changes noted in the comparative labeling) is the same as the listed drug product.

10. PHARMACOL. CATEGORY: Adjunctive therapy to diet for the reduction of elevated serum cholesterol in patients with primary hypercholesterolemia who do not respond adequately to diet.

11. DOSAGE FORM: Powder for Suspension CODE: 834

12. STRENGTH/POTENCY:

Cholestyramine for Oral Suspension USP Light: 4 g resin/5 g powder
Cholestyramine for Oral Suspension USP: 4 g resin/9 g powder

13. ROUTE OF ADMINISTRATION: Oral CODE: 001

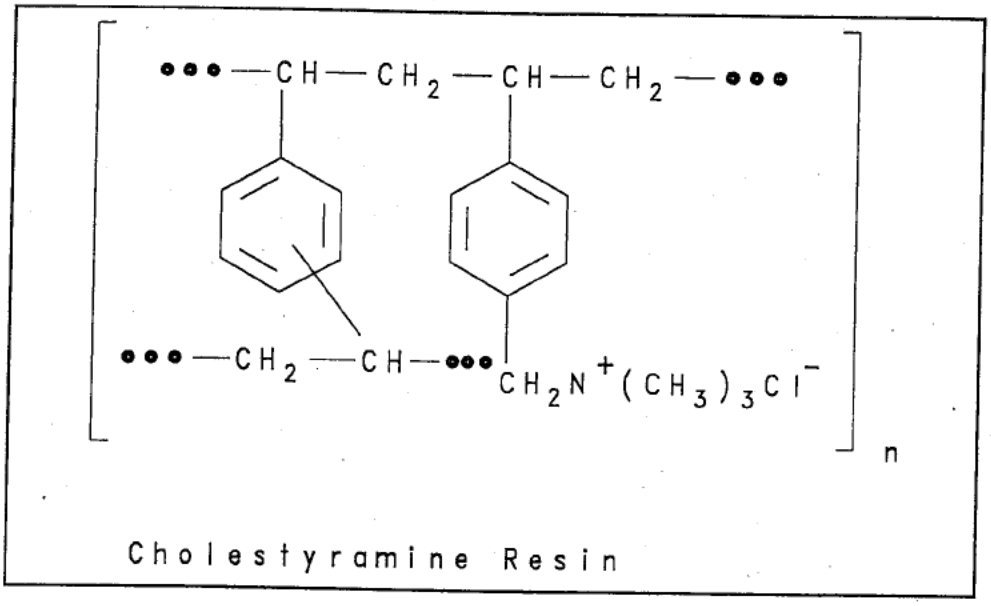
14. Rx/OTC DISPENSED: _X_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

__X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Cholestyramine Resin



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	**II**		(b) (4)	**1**	**Inadequate**	**11/19/04**	
	III			4			

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: None

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

OGD:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Pending		
Methods Validation	Not Necessary	11/5/04	K.J. Furnkranz
Labeling	Pending		
Bioequivalence	Pending		
EA	Satisfactory	11/05/04	K.J. Furnkranz
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW The application submission(s) covered by this review was taken in the date order of receipt. __X__ Yes ____ No If no, explain reason(s) below:

CHEMISTRY REVIEW

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability:
Not Approvable MINOR Amendment

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable:
None identified at this time.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)
The drug substance is a strongly basic anion exchange resin, dried and ground, consisting of a hydrocarbon matrix of a 2% crosslinked copolymer of styrene and divinylbenzene, incorporating quaternary ammonium-type structure, wherein the substituents on each nitrogen atom are on polymeric vinylbenzyl and three methyl groups.

The drug product is a dry powder consisting of cholestyramine in combination with a flavoring, sweetener, and other pharmaceutical ingredients. The dry powder is diluted with water or other fluids to form an oral suspension.

B. Description of How the Drug Product is Intended to be Used
Cholestyramine for Oral Suspension is to be ingested in suspension with water or other fluids. Cholestyramine is not absorbed from the digestive tract. The maximum daily dose (MDD) of Cholestyramine is 24 g/day (6 packets).

C. Basis for Approvability or Not-Approval Recommendation:
These ANDAs are currently not approvable pending resolution of CMC issues, and bioequivalence, EER and labeling review.

III. Administrative

A. Reviewer's Signature Kenneth J. Furnkranz

REVIEWER:
Kenneth J. Furnkranz

DATE COMPLETED:
November 24, 2004

B. Endorsement Block
HFD-625 /K. Furnkranz, Review Chemist/12/1/04 12kb by
HFD-625 /M. Smela , Team Leader12/2/04
HFD-6 17 / P.Chen, Project Manager
V:\FIRMSNZ\Par\LTRS&REV\77203rev01kjf.doc
NOT APPROVABLE – MINOR Amendment

Following this page, 22 pages withheld in full - (b)(4)

a. (b) (4)

b.

c.

d.

In addition, please report the results of these tests at your next stability test station for both drug products.

12. Regarding the (b) (4)

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. All facilities referenced in the ANDA should have a satisfactory compliance evaluation at the time of approval. We have requested an evaluation from the Office of Compliance.

2. Please submit additional long-term stability data on the exhibit lots manufactured to support the ANDA, if available.

3. Your bioequivalence information is pending review.

4. Your labeling information is also pending review.

Sincerely yours,

M Smela for 12/7/04

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

CHEMISTRY REVIEW TEMPLATE

Chemistry Assessment Section

cc: ANDA 77-203; 77-204
ANDA DUP
DIV FILE
Field Copy

Endorsements:
HFD-625/K.Furnkranz, Review Chemist/12/1/04 12/6/04
HFD-625/M.Smela, Team Leader/12/2/04 12/7/04
HFD-617/P.Chen, Project Manager/12/2/04 12/6/04
F/T by: ard/12/3/04

V:\FIRMSNZ\PAR\LTRS&REV\77203Rev01kjf.doc
TYPE OF LETTER: Not Approvable (MINOR)

ANDA 77-203

Cholestyramine for Oral Suspension USP (Light) (4g / 5 g)

and

ANDA 77-204

Cholestyramine for Oral Suspension USP (4 g / 9 g)

Par Pharmaceutical, Inc

Kenneth Furnkranz
Division of Chemistry 1
Office of Generic Drugs

Chemistry Review #2

Table of Contents

Chemistry Review Data Sheet

1. ANDA 77-203 and 77-204

2. REVIEW #: 2

3. REVIEW DATE: 11-April-2004

4. REVIEWER: Kenneth J. Furnkranz

5. PREVIOUS DOCUMENTS: N/A

Previous Documents	Document Date
ANDA Original Submission	02-July-2004
New Correspondence	17-August-2004

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
ANDA MINOR Amendment	21-March-2005
Labeling Amendment	03-March-2005

7. NAME & ADDRESS OF APPLICANT:

Name:	Par Pharmaceutical, Inc.
Address:	One Ram Ridge Road Spring Valley, NY 10977
Representative:	Julie Szozda
Telephone:	845-425-7100
Fax:	845-639-5201

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Cholestyramine

9. LEGAL BASIS FOR SUBMISSION:

The reference listed drugs are:

- Questran® (Cholestyramine for Oral Suspension, USP) Light; Bristol Myers Squibb Co.; NDA #16-640
- Questran® (Cholestyramine for Oral Suspension, USP); Bristol Myers Squibb Co. NDA #16-640

Patent Certification has been provided.

The, active ingredient, route of administration, dosage form, strength and labeling (with the exception of specific changes noted in the comparative labeling) is the same as the listed drug product.

10. PHARMACOL. CATEGORY: Adjunctive therapy to diet for the reduction of elevated serum cholesterol in patients with primary hypercholesterolemia who do not respond adequately to diet.

11. DOSAGE FORM: Powder for Suspension CODE: 834

12. STRENGTH/POTENCY:

Cholestyramine for Oral Suspension USP Light: 4 g resin/5 g powder
Cholestyramine for Oral Suspension USP: 4 g resin/9 g powder

13. ROUTE OF ADMINISTRATION: Oral CODE: 001

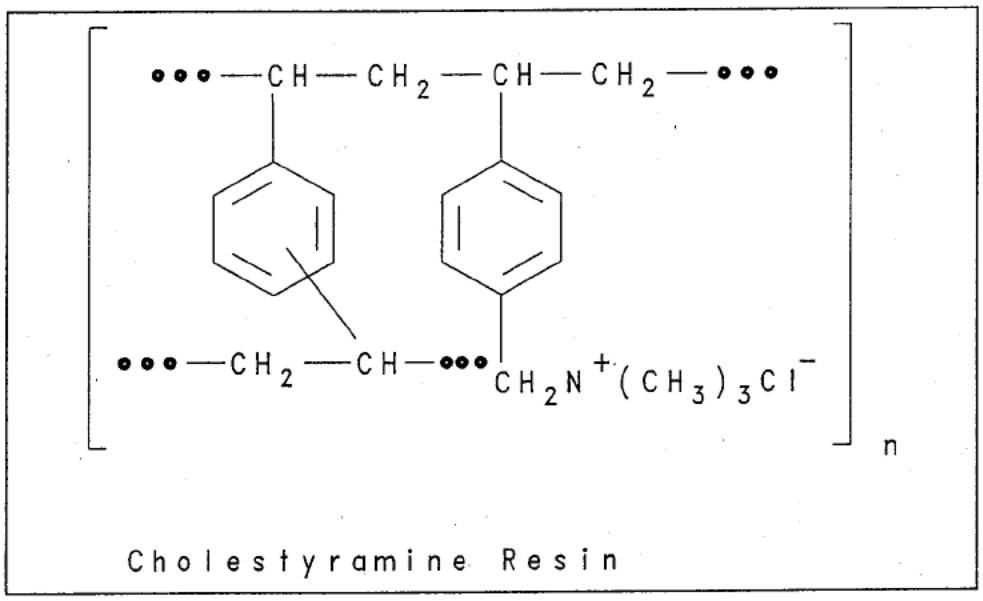
14. Rx/OTC DISPENSED: _X_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

___X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Cholestyramine Resin



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	**II**		(b) (4)	**3**	**Inadequate**	**5/13/05**	
	III			4			

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: None

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

OGD:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Pending		
Methods Validation	Not Necessary	11/5/04	K.J. Furnkranz
Labeling	Satisfactory	4/13/05	A.Payne/J.Grace
Bioequivalence	Pending		
EA	Satisfactory	11/05/04	K.J. Furnkranz
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes __X__ No If no, explain reason(s) below:

MINOR Amendment

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability:
Not Approvable MINOR Amendment

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable:
None identified at this time.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)
The drug substance is a strongly basic anion exchange resin, dried and ground, consisting of a hydrocarbon matrix of a 2% crosslinked copolymer of styrene and divinylbenzene, incorporating quaternary ammonium-type structure, wherein the substituents on each nitrogen atom are on polymeric vinylbenzyl and three methyl groups.

The drug product is a dry powder consisting of cholestyramine in combination with a flavoring, sweetener, and other pharmaceutical ingredients. The dry powder is diluted with water or other fluids to form an oral suspension.

B. Description of How the Drug Product is Intended to be Used
Cholestyramine for Oral Suspension is to be ingested in suspension with water or other fluids. Cholestyramine is not absorbed from the digestive tract. The maximum daily dose (MDD) of Cholestyramine is 24 g/day (6 packets).

C. Basis for Approvability or Not-Approval Recommendation:
These ANDAs are currently not approvable pending resolution of CMC issues, bioequivalence and EER.

III. Administrative

A. Reviewer's Signature Kenneth J. Furnkranz

REVIEWER: Kenneth J. Furnkranz

DATE COMPLETED: April 15, 2005
DATE REVISED: May 9, 2005

B. Endorsement Block
HFD-625 /K. Furnkranz, Review Chemist
HFD-625 /M. Smela , Team Leader
5/16/05
V:\FIRMSNZ\Par\LTRS&REV\77203rev02kjf.doc
NOT APPROVABLE – MINOR Amendment

Following this page, 18 pages withheld in full - (b)(4)

[redacted] (b) (4) (contract packager of pouches)

34. BIOEQUIVALENCE : PENDING REVIEW.
Par Pharmaceutical Inc., has requested a waiver from performing an *in-vivo* bio study for the referenced drug product. The Bioequivalence review is pending at this time.

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION: SATISFACTORY per the C.R. #1. Par has claimed a categorical exclusion under 21 CFR 25.31(a) from performing and Environmental Assessment. Categorical exclusion is granted.

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 77-203 and 77-204 APPLICANT: Par Pharmaceutical Inc.

DRUG PRODUCTS:

Cholestyramine for Oral Suspension USP (Light)
Cholestyramine for Oral Suspension USP

The deficiencies presented below represent MINOR deficiencies.

1. DMF # (b) (4) was most recently reviewed and found inadequate on 5/13/05. (b) (4) has been informed. Please ensure a response prior to submitting your ANDA Amendment.

2. Regarding the (b) (4) Your previous response was too vague.

3. Regarding the (b) (4) of Cholestyramine for Oral Suspension Regular:

   a. Please explain the (b) (4)

   b. Please provide an updated (b) (4)

4. (b) (4)

   a. (b) (4)

   b.

5. Please provide (b) (4)

B. In addition to responding to the deficiencies presented above, please note and

acknowledge the following comments in your response:

1. All facilities referenced in the ANDA should have a satisfactory compliance evaluation at the time of approval. We have requested an evaluation from the Office of Compliance.

2. Your bioequivalence information is pending review.

Sincerely yours,

M Smela for 5/16/05

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 77-203; 77-204
ANDA DUP
DIV FILE
Field Copy

Endorsements:
HFD-625/K.Furnkranz, Review Chemist 5/16/05
HFD-625/M.Smela, Team Leader 5/16/05
HFD-617/P.Chen, Project Manager 5/16/05
F/T by:

V:\FIRMSNZ\PAR\LTRS&REV\77203Rev02kjf.doc
TYPE OF LETTER: Not Approvable (MINOR)

ANDA 77-203

Cholestyramine for Oral Suspension USP (Light) (4g / 5 g)

and

ANDA 77-204

Cholestyramine for Oral Suspension USP (4 g / 9 g)

Par Pharmaceutical, Inc

Kenneth Furnkranz
Division of Chemistry 1
Office of Generic Drugs

Chemistry Review #3

Table of Contents

Chemistry Review Data Sheet

1. ANDA 77-203 and 77-204

2. REVIEW #: 3

3. REVIEW DATE: 15-July-2004

4. REVIEWER: Kenneth J. Furnkranz

5. PREVIOUS DOCUMENTS: N/A

Previous Documents	Document Date
ANDA Original Submission	02-July-2004
Telephone Amendment (Filing Issues)	17-August-2004
Labeling Amendment	3-March-2005
ANDA MINOR Amendment	21-March-2005

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
*ANDA MINOR Amendment	6-June-2005
*Telephone Amendment	14-July-2005
*New Correspondence	15-July-2005

7. NAME & ADDRESS OF APPLICANT:

Name:	Par Pharmaceutical, Inc.
Address:	One Ram Ridge Road Spring Valley, NY 10977
Representative:	Michelle Bonomi-Huvala
Telephone:	845-425-7100
Fax:	845-425-7907

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Cholestyramine

9. LEGAL BASIS FOR SUBMISSION:

The reference listed drugs are:

- Questran® (Cholestyramine for Oral Suspension, USP) Light; Bristol Myers Squibb Co.; NDA #16-640
- Questran® (Cholestyramine for Oral Suspension, USP); Bristol Myers Squibb Co. NDA #16-640

Patent Certification has been provided.

The active ingredient, route of administration, dosage form, strength and labeling (with the exception of specific changes noted in the comparative labeling) is the same as the listed drug product.

10. PHARMACOL. CATEGORY: Adjunctive therapy to diet for the reduction of elevated serum cholesterol in patients with primary hypercholesterolemia who do not respond adequately to diet.

11. DOSAGE FORM: Powder for Suspension CODE: 834

12. STRENGTH/POTENCY:

Cholestyramine for Oral Suspension USP Light: 4 g resin/5 g powder
Cholestyramine for Oral Suspension USP: 4 g resin/9 g powder

13. ROUTE OF ADMINISTRATION: Oral CODE: 001

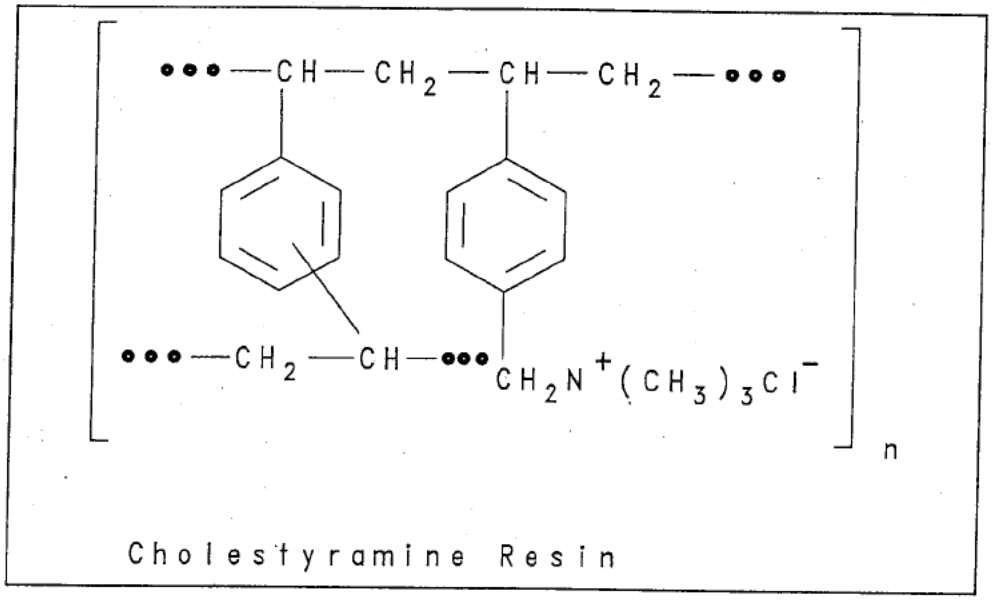
14. Rx/OTC DISPENSED: _X_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

___X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Cholestyramine Resin



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)		1	Adequate	6/24/05	
	III			4			

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

→ No submission since then.
ES for MS
8/25/05

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: None

18. STATUS:

OGD:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Pending		
Methods Validation	Not Necessary	11/5/04	K.J. Furnkranz
Labeling	Satisfactory	4/9/05	A.Payne/J.Grace
Bioequivalence	~~Pending~~ Acceptable 8/11/05		J. Osterhout, Ph.D.
EA	Satisfactory	11/05/04	K.J. Furnkranz
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes __X__ No

If no, explain reason(s): MINOR Amendment.

ES for MS
8/25/05

CHEMISTRY REVIEW TEMPLATE

Chemistry Assessment Section

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability:
Approvable for CMC Issues. Bioequivalence Review and EER are ~~Pending~~ acceptable.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable:
None identified at this time.

ES for MS
8/25/05

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)
The drug substance is a strongly basic anion exchange resin, dried and ground, consisting of a hydrocarbon matrix of a 2% crosslinked copolymer of styrene and divinylbenzene, incorporating quaternary ammonium-type structure, wherein the substituents on each nitrogen atom are on polymeric vinylbenzyl and three methyl groups.

The drug product is a dry powder consisting of cholestyramine in combination with a flavoring, sweetener, and other pharmaceutical ingredients. The dry powder is diluted with water or other fluids to form an oral suspension.

B. Description of How the Drug Product is Intended to be Used
Cholestyramine for Oral Suspension is to be ingested in suspension with water or other fluids. Cholestyramine is not absorbed from the digestive tract. The maximum daily dose (MDD) of Cholestyramine is 24 g/day (6 packets).

C. Basis for Approvability or Not-Approval Recommendation:
These ANDAs are Approvable for CMC. Bioequivalence review and EER are ~~pending.~~ acceptable ES for MS 8/25/05

III. Administrative

A. Reviewer's Signature Kenneth J. Furnkranz

REVIEWER:
Kenneth J. Furnkranz

DATE COMPLETED:
July 15, 2005

B. Endorsement Block
HFD-625 /K. Furnkranz, Review Chemist 7/18/05
HFD-625 /M. Smela , Team Leader M Smela 7/18/05
V:\FIRMSNZ\Par\LTRS&REV\77203rev03kjf.doc
CHEMISTRY COMPLETED. Pending Bioequivalence review and EER

Following this page, 14 pages withheld in full - (b)(4)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 77-203

BIOEQUIVALENCE REVIEWS

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	77203
Drug Product Name	Cholestyramine for Oral Suspension USP, Light
Strength	4g resin/5g powder (sugar free)
Applicant Name	Par Pharmaceutical, Inc.
Address	One Ram Ridge Road, Spring valley, NY 10977
Submission Date(s)	02 July 2004
Amendment Date(s)	NA
Reviewer	James L. Osterhout
First Generic	No
File Location	V:\firmsnz\par\ltrs&rev\77203N0704

I. Executive Summary

The application contains the results of two in vitro equilibrium (without acid pretreatment and with acid pretreatment) bile acid salt binding studies and two in vitro kinetic (0.3mM and 3mM) bile acid salt binding studies. Par submitted these studies in accordance with the Agency's interim guidance on cholestyramine powder (issued 15 July 1993).

The comparative binding studies were conducted on 10 mg of resin from Cholestyramine 4g resin/5g powder for Oral Suspension USP, Light from Par Pharmaceutical, Inc. and the reference product, Questran® Light from Bristol-Myers Squibb. Based on the data from various ANDAs, the DBE has determined that only the equilibrium binding study without acid pretreatment is the **pivotal study** and in the pivotal study, k2 (capacity constant) is the **pivotal parameter**. In the pivotal study, the 90% confidence interval for the k2 (capacity constant) was within the acceptance range of 80-120 (94.65 - 109.41). The application is acceptable.

NOTE: All data presented is calculated by the DBE unless otherwise noted.

II. Table of Contents

III. Submission Summary

A. Drug Product Information

Test Product	Cholestyramine for Oral Suspension USP Light
Reference Product	Questran® Light
RLD Manufacturer	Bristol-Myers Squibb
NDA No.	N16640 & N19669
RLD Approval Date	Prior to Jan 1, 1982 for RLD Questran® (4g resin/9g powder) 05 December 1988 (4g resin/5g powder)
Indication	Indicated s an adjunct to dietary therapy to reduce elevated serum total and LDL cholesterol levels in patients with primary hypercholesterolemia when diet alone is not adequately effective.

B. PK/PD Information

Bioavailability	Not absorbed systemically
Food Effect	Not Applicable.
Tmax	Not Applicable.
Metabolism	None
Excretion	Cholestyramine is excreted unchanged in the feces.
Half-life	Not Applicable.
Relevant OGD or DBE History	The DBE has received the following ANDAs regarding this drug product: Recent ANDA's: 74557, 74558 & 74561, 74562 (EON); 74771(IVAX); 74347 & 74348 (TEVA); 74554 & 74555 (TEVA PHARMS; 73263 (UPSHER SMITH) Note: [redacted] (b) (4) submitted ANDA [redacted] (b) (4) & [redacted] (b) (4) which failed to meet the BE criteria, and were unacceptable.
Agency Guidance	In vivo studies are not necessary to document the bioequivalence of cholestyramine resin formulations. (See Interim Guidance - Cholestyramine Powder In Vitro Bioequivalence, 15 July 1993). Equilibrium and kinetic in vitro bile acid salt binding studies are recommended to document BE between generic and innovator formulations of cholestyramine.
Drug Specific Issues	Because the drug is not absorbed into the systemic circulation, pharmacokinetics information is not available.

C. Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	No	
Single-dose fed	No	
Steady-state	No	
In vitro dissolution	No	
Waiver requests	No	
BCS Waivers	No	
In Vitro Studies	Yes	4
Amendments	No	

D. In Vitro Studies

1. Study Design

a) Equilibrium Binding Studies

Equilibrium binding studies were conducted under conditions of constant time and varying concentrations of bile acid salts. Cholestyramine resin aliquots (10mg) were soaked in 2mL of simulated intestinal fluid (SIF) overnight. In a set, eight incubation tubes of the test product and eight of the reference product, each containing 10mg of resin in a 10mL volume of incubation mixture, were incubated for 24 hours at 37°C. The incubation mixture contained bile acid salts in total concentrations ranging from 0.1mM to 30mM (0.1, 0.3, 1.0, 3.0, 7.0, 10.0, 20.0, and 30.0mM). The bile acid salts solution was a 3:3:1 mixture of the three bile acids, glycocholic acid (GCA), glycochenodeoxycholic acid (GCDA), and taurodeoxycholic acid (TDCA). Solutions containing the same concentrations of bile acid salts were also incubated simultaneously to provide standards.

The equilibrium binding studies were conducted with and without acid pretreatment of the resin product. The acid pretreatment involved soaking 10mg of cholestyramine resin in 10mL of 0.1N hydrochloric acid at 37°C for at least one hour, after which the resin was separated from the acid by centrifugation and repeatedly washed with SIF until the pH of the SIF was maintained by the supernatant solution. The acid treated resin was then subjected to equilibrium binding studies as described above. Each set of equilibrium binding study was repeated six times.

b) Kinetic Binding Studies

Kinetic binding studies were conducted under constant concentration of bile acid salts with varying duration of incubation. Cholestyramine resin aliquots (10mg) were soaked in 2mL of 0.1M sodium chloride overnight. In a set, eight incubation tubes of the test product and eight tubes of the reference product, each containing the equivalent of 10mg of resin, were incubated at 37°C for varying incubation times (0.25, 0.50, 1, 2, 4, 8, 16,

and 24 hours). These incubations were done in a 10mL volume of saline incubation mixture containing total bile acid salt concentration of 0.3mM and 3.0mM. The three bile acid salts were present in a 3:3:1 mixture of GCA, GCDA, and TDCA. Standard solutions containing from 0.05mM to 0.45 (0.3mM bile acid study)and 0.01 to 3.0mM (3mM bile acid study) total bile acid salts were incubated for 24 hours. Each set of kinetic binding study was repeated 6 times.

c) Data Analysis

Means were calculated for amount of adsorption, equilibrium concentration of total bile salts, and percent binding. Langmuir adsorption constants, k1 (affinity constant) and k2 (capacity constant), were calculated. The 90% CI were calculated for k2. Test to reference ratios were calculated for k1.

2. Assay Method Validation

a) Pre-study Validation

Location	Vol 1.1, pages 106-168
Method	HPLC method was used to determine the sodium salts of GCA, TDCA and GDCA in both SIF (pH 6.8) and 0.1M sodium chloride solution.
Specificity	No interfering peaks were detected at the retention times of GCA, TDCA and GDCA.
Linearity	Linear over the total concentration range of 0.05 to 30 mM. The three bile acid salts were present in a 3:3:1 mixture.
Precision & Accuracy	The interday precision and intraday precision ranged from 0.46%-6.78% for each bile salt. The interday accuracy and intraday accuracy ranged from 91.6%-110.6.0% for each bile salt. LLOQ was 0.01mM for total bile acid salts.
Stability	Two standards, 3 mM and 20 mM, were incubated in the absence of cholestyramine at 37°C for 24 hours. All three bile salts after the incubation were within ±4% of their original concentrations.
Auto-sampler stability	All three bile salts after 80 hours on the auto-sampler were within ±5.29% of their original concentrations ranging from 0.05 mM to 25 mM.

b) Within-study Validation

Bile Acid Salt		**Equilibrium Study**	**Kinetic Study**
GCA	**QC Precision (%)**	0.34-2.53	0.49-3.53
	QC Accuracy (%)	97.6-103.2	98.5-100.8
GDCA	**QC Precision (%)**	0.30-2.92	0.63-2.35
	QC Accuracy (%)	97.0-102.6	99.6-102.3

TDCA	**QC Precision (%)**	0.32-9.39	1.14-3.07
	QC Accuracy (%)	96.7-103.0	98.9-102.0

3. Bile Acid Salt Binding

Study Summary	
Study No.	77203
Study Design	Bile-acid salt binding
Test product	Cholestyramine for Oral Suspension USP Light, Lot # 38946
Reference product	Questran® Light, Lot# 3A63681
Strength tested	4g resin/5g powder
Dose	4g resin/5g powder
Analytical Site	(b) (4)
Analytical Director	(b) (4) Ph.D.

a) Equilibrium Binding Studies

Langmuir's Equation(s) Used	k1*k2*Ceq / (1+k1*Ceq)
Bile acid salts concentration range (mM)	0.1, 0.3, 1.0, 3.0, 7.0, 10.0, 20.0, 30.0
Number of replicates?	6
With and without Acid pretreatment? (Y/N)	Yes
Type of Curve Fit used to calculate k1 & k2	Linear regression (firm)

Table 1: Bile Acid Salt Binding Capacity - Pivotal Study (No Acid Pretreatment)

Target (mmole/L)	Test		Reference		T/R Ratio
	Nominal	%	Nominal	%	
TOTAL					
0.10	0.78	78.4	0.82	82.2	0.954
0.30	2.16	72.1	2.29	76.4	0.944
1.00	6.85	68.5	7.22	72.2	0.950
3.00	20.93	69.8	21.21	70.7	0.987
7.00	40.82	58.3	40.32	57.6	1.012
10.00	42.99	43.0	42.78	42.8	1.005
20.00	43.90	22.0	43.55	21.8	1.008
30.00	44.79	14.9	44.02	14.7	1.017
GCA					
0.10	0.22	51.4	0.25	58.5	0.878
0.30	0.61	47.3	0.71	54.9	0.861
1.00	1.78	41.6	2.04	47.7	0.872
3.00	5.49	42.7	5.71	44.4	0.961
7.00	8.01	26.7	7.86	26.2	1.019
10.00	6.31	14.7	6.26	14.6	1.009
20.00	6.93	8.1	7.07	8.3	0.980
30.00	8.36	6.5	8.43	6.6	0.992
GCDCA					
0.10	0.42	98.3	0.43	100.0	0.983
0.30	1.16	90.0	1.18	91.7	0.981
1.00	3.75	87.5	3.83	89.4	0.979
3.00	11.39	88.6	11.43	88.9	0.996
7.00	23.73	79.1	23.41	78.0	1.013
10.00	25.37	59.2	25.29	59.0	1.003
20.00	23.50	27.4	23.36	27.3	1.006
30.00	22.43	17.4	22.21	17.3	1.010
TDCA					
0.10	0.14	100.0	0.14	100.0	1.000
0.30	0.40	93.2	0.41	94.8	0.983
1.00	1.32	92.6	1.34	94.1	0.984
3.00	4.06	94.6	4.07	95.0	0.996
7.00	9.09	90.9	9.05	90.5	1.004
10.00	11.30	79.1	11.24	78.7	1.005
20.00	13.48	47.2	13.12	45.9	1.027
30.00	14.00	32.7	13.38	31.2	1.046

Table 2: Bile Acid Salt Binding Capacity (With Acid Pretreatment)

Target (mmole/L)	Test		Reference		T/R Ratio
	Nominal	%	Nominal	%	
TOTAL					
0.10	0.77	77.3	0.81	81.3	0.951
0.30	2.16	71.9	2.30	76.7	0.937
1.00	6.73	67.3	7.12	71.2	0.945
3.00	20.54	68.5	20.89	69.6	0.983
7.00	39.57	56.5	39.70	56.7	0.997
10.00	38.66	38.7	38.43	38.4	1.006
20.00	34.33	17.2	38.24	19.1	0.898
30.00	30.81	10.3	29.33	9.8	1.050
GCA					
0.10	0.21	49.0	0.24	56.4	0.869
0.30	0.60	46.7	0.71	55.2	0.847
1.00	1.66	38.8	1.94	45.2	0.859
3.00	5.12	39.8	5.36	41.7	0.955
7.00	7.12	23.7	7.23	24.1	0.985
10.00	4.22	9.9	4.46	10.4	0.947
20.00	2.86	3.3	4.50	5.3	0.635
30.00	4.36	3.4	2.86	2.2	1.525
GCDCA					
0.10	0.42	98.1	0.43	100.0	0.981
0.30	1.16	90.0	1.19	92.3	0.976
1.00	3.74	87.3	3.84	89.5	0.975
3.00	11.37	88.4	11.46	89.2	0.992
7.00	23.41	78.0	23.45	78.2	0.998
10.00	23.56	55.0	23.29	54.3	1.012
20.00	19.29	22.5	21.29	24.8	0.906
30.00	15.14	11.8	15.21	11.8	0.995
TDCA					
0.10	0.14	100.0	0.14	100.0	1.000
0.30	0.40	93.2	0.41	94.9	0.982
1.00	1.32	92.6	1.34	94.1	0.984
3.00	4.06	94.6	4.07	94.9	0.997
7.00	9.04	90.4	9.02	90.2	1.003
10.00	10.87	76.1	10.68	74.8	1.018
20.00	12.19	42.7	12.45	43.6	0.979
30.00	11.31	26.4	11.26	26.3	1.004

Comments on Bile Acid Salt Binding Equilibrium Studies:

Mean amount of adsorption of total bile salts per 10 mg resin was calculated at each level of total bile salts input ranging from 0.1 mmole/L to 30 mmole/L as shown in Table 1. The mean amount of adsorption was comparable between the test and reference products as indicated by the test/reference ratio (0.944-1.017). In addition, the mean percent binding decreased with increasing amounts of bile acid salts input, as expected. The standard deviation of nominal binding (uM) ranged from 0.1 to 2.6 for the test product and 0.012 to 2.9 for the reference product in the pivotal study. The highest SD values for both test and reference were at the higher bile acid salt concentrations of 20 and 30mM. The binding capacity data are acceptable.

Table 3: Equilibrium Binding Constants (No Acid Pretreatment)

Replicate	Test		Reference		T/R Ratio	
	k1	k2	k1	k2	k1	k2
Firm Calculated (linear)						
1					0.91	1.07
2					0.98	0.98
3					1.09	0.97
4					0.93	0.99
5					0.86	1.04
6					0.75	1.08
AVG	**0.91**	**4.90**	**1.00**	**4.81**	**0.92**	**1.02**
DBE Calculated (nonlinear)						
1					1.01	1.12
2					1.00	0.95
3					0.99	0.90
4					1.00	0.98
5					1.01	1.08
6					1.01	1.09
AVG	**0.50**	**4.83**	**0.50**	**4.75**	**1.00**	**1.02**

(b) (4)

Table 4: Equilibrium Binding Constants (Acid Pretreatment)

Replicate	Test		Reference		T/R Ratio	
	k1	k2	k1	k2	k1	k2
Firm Calculated (linear)						
1					1.13	0.88
2					1.09	0.95
3					0.88	1.06
4					0.89	1.04
5					0.79	1.00
6					0.87	0.99
AVG	**1.38**	**3.84**	**1.47**	**3.89**	**0.94**	**0.99**

(b) (4)

DBE Calculated (nonlinear)						
1	[redacted] (b) (4)				0.80	1.05
2					0.87	1.04
3					0.96	0.98
4					0.73	1.01
5					0.73	1.03
6					0.69	1.02
AVG	**0.30**	**3.03**	**0.38**	**2.96**	**0.80**	**1.02**

Table 5: 90% Confidence Intervals for K1 and K2

Summary of Statistical Analysis		
Pivotal Study (No Acid Pretreatment)		
Parameter	**Point Estimate**	**90% Confidence Interval**
K1 (pivotal parameter)	0.997	98.99 - 100.34
K2	1.018	94.65 - 109.41
Acid Pretreatment		
Parameter	**Point Estimate**	**90% Confidence Interval**
K1	0.797	71.86 - 88.50
K2	1.021	100.23 - 104.02

Comments on Bile Acid Salt Binding Affinity and Capacity:

The firm determined the binding constants k1 and k2 using a linear regression of the Langmuir equation data, calculating k1 by slope/intercept and k2 by 1/slope. The DBE calculated k1 and k2 directly from the data using Excel Solver (nonlinear regression). The data indicate the test product passes the 90% CI criteria of 80-120 for the constants k1 and k2 in the pivotal study. The data indicate the test product passes the 90% CI criteria of 80-120 for k2 in the acid pretreated study, but the k1 parameter is outside the 90% CI range (see above). However, this finding does not affect the acceptable outcome as the acid pretreatment study is not pivotal. The binding studies are acceptable.

b) Kinetic Binding Studies

Table 6: Bile Acid Salt Binding Kinetics - 0.3mM

Time (hours)	Test		Reference		T/R Ratio
	Nominal	%	Nominal	%	
TOTAL					
0.25	2.35	78.2	2.36	78.7	0.995
0.5	2.35	78.2	2.34	78.1	1.001
1	2.34	78.1	2.34	78.0	1.002
2	2.36	78.5	2.37	78.8	0.996
4	2.38	79.4	2.38	79.2	1.003
8	2.39	79.7	2.39	79.5	1.002
16	2.38	79.5	2.38	79.4	1.002
24	2.37	79.0	2.38	79.3	0.996
GCA					
0.25	0.63	49.2	0.65	50.2	0.980
0.5	0.63	49.2	0.63	49.0	1.003
1	0.63	48.9	0.63	48.7	1.006
2	0.64	49.8	0.65	50.6	0.985
4	0.67	52.0	0.66	51.5	1.010
8	0.68	52.7	0.67	52.3	1.009
16	0.67	52.1	0.67	51.8	1.005
24	0.66	51.1	0.66	51.7	0.987
GCDCA					
0.25	1.29	100.0	1.29	100.0	1.000
0.5	1.29	100.0	1.29	100.0	1.000
1	1.29	100.0	1.29	100.0	1.000
2	1.29	100.0	1.29	100.0	1.000
4	1.29	100.0	1.29	100.0	1.000
8	1.29	100.0	1.29	100.0	1.000
16	1.29	100.0	1.29	100.0	1.000
24	1.29	100.0	1.29	100.0	1.000
TDCA					
0.25	0.43	100.0	0.43	100.0	1.000
0.5	0.43	100.0	0.43	100.0	1.000
1	0.43	100.0	0.43	100.0	1.000
2	0.43	100.0	0.43	100.0	1.000
4	0.43	100.0	0.43	100.0	1.000
8	0.43	100.0	0.43	100.0	1.000
16	0.43	100.0	0.43	100.0	1.000
24	0.43	100.0	0.43	100.0	1.000

Table 7: Bile Acid Salt Binding Kinetics - 3mM

Time (hours)	Test		Reference		T/R Ratio
	Nominal	%	Nominal	%	
TOTAL					
0.25	18.33	61.1	18.68	62.3	0.981
0.5	19.01	63.4	19.12	63.7	0.995
1	19.19	64.0	19.36	64.5	0.991
2	19.04	63.5	19.32	64.4	0.986
4	19.07	63.6	19.35	64.5	0.985
8	19.33	64.4	19.22	64.1	1.006
16	19.36	64.5	19.42	64.7	0.997
24	19.04	63.5	19.30	64.3	0.987
GCA					
0.25	4.52	35.2	4.54	35.3	0.997
0.5	4.57	35.6	4.54	35.3	1.008
1	4.54	35.3	4.66	36.3	0.974
2	4.41	34.3	4.63	36.0	0.954
4	4.64	36.1	4.73	36.8	0.982
8	4.67	36.3	4.60	35.8	1.016
16	4.67	36.3	4.74	36.8	0.986
24	4.44	34.6	4.63	36.0	0.960
GCDCA					
0.25	10.02	77.9	10.31	80.2	0.972
0.5	10.55	82.1	10.67	83.0	0.989
1	10.72	83.4	10.76	83.7	0.996
2	10.69	83.2	10.75	83.6	0.995
4	10.53	81.9	10.70	83.2	0.984
8	10.72	83.4	10.69	83.1	1.003
16	10.75	83.6	10.75	83.6	1.000
24	10.66	82.9	10.72	83.4	0.994
TDCA					
0.25	3.79	88.5	3.84	89.6	0.987
0.5	3.89	90.7	3.91	91.3	0.993
1	3.93	91.7	3.93	91.8	0.999
2	3.93	91.7	3.94	91.9	0.998
4	3.90	90.9	3.93	91.7	0.991
8	3.94	91.9	3.93	91.8	1.001
16	3.94	92.0	3.94	92.0	1.000
24	3.93	91.8	3.94	92.0	0.997

Comments on Kinetic Binding Studies:

Both test and reference products at the low (0.3mM) and high (3.0mM) concentrations of bile acid salts demonstrated maximal binding at the first time point, which corresponds with data for other approved generic products (see DBE History, Page 3). The kinetic

binding studies demonstrate comparable results between test and reference, and are acceptable.

E. Formulation

Location in appendix	Section IV.A, Page 15
Are inactive ingredients within IIG limits?	Yes
If no, list ingredients outside of limits	
If a tablet, is the product scored?	Not Applicable
If yes, which strengths are scored?	
Is scoring of RLD the same as test?	Not Applicable
Is the formulation acceptable?	Yes
If not acceptable, why?	

F. Waiver Request(s)

Strengths for which waivers are requested	None
Regulation cited	
Proportional to strength tested in vivo?	
Is dissolution acceptable?	
Waivers granted?	
If not then why?	

G. Deficiency Comments

None.

H. Recommendations

1. The in vitro equilibrium binding studies conducted by Par on the test product, Cholestyramine for Oral Suspension USP, Light (4g resin/5g powder) Lot # 38946, comparing it with the reference product, Questran® Light, Lot # 3A63681are acceptable.

2. The in vitro kinetic binding studies conducted by Par on the test product, Cholestyramine for Oral Suspension USP, Light (4g resin/5g powder) Lot # 38946, comparing it with the reference product, Questran® Light, Lot # 3A63681are acceptable.

James L. Osterhout, Team 1 — 11 AUG 2005 — Date Signed

Shriniwas G. Nerurkar, Team 1 — 8/12/2005 — Date Signed

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs — 8/18/05 — Date Signed

IV. Appendix

A. Formulation Data

Cholestyramine for Oral Suspension USP, Light - 4g resin/5g powder

Component	Amt (g)/ 5 grams	Amt (%)
(b) (4)		
TOTAL	**5.00**	**100.0**

	Test	Reference
Batch / Lot #	38946	3A63681
Assay	97.8%	Not Given
Content Uniformity	98.0%-100.7%	Not Given
Manufacture Date	July 2, 29-30	NA
Expiration Date	NA	January 2006

B. SAS Output

Study	Output		Program
Equilibrium Binding 90% CI	Acid Treat	Pivotal	90CI.txt

CC: ANDA 77203
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-652/ Reviewer J.L. Osterhout
HFD-652/ Project manager A.W. Sigler
HFD-652/ Team Leader S.G. Nerurkar

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Endorsements: (Final with Dates)
HFD-652/ J.L. Osterhout 4/20 11 AUG 2005
HFD-652/ S.G. Nerurkar 8/12/05
HFD-650/ D.P. Conner 8/15/05

BIOEQUIVALENCY - INCOMPLETE Submission date: 02 July 2004

1.	Other (OTH) (pivotal equilibrium binding)	✓	Strengths: 4g resin/5g powder Outcome: AC
2.	Other (OTH) (acid pretreated equilibrium binding)	✓	Strengths: 4g resin/5g powder Outcome: AC
3.	Other (OTH) (untreated in vitro kinetic binding)	✓	Strengths: 4g resin/5g powder Outcome: AC
4.	Other (OTH) (acid pretreated in vitro kinetic binding)	✓	Strengths: 4g resin/5g powder Outcome: AC

Outcome Decisions: AC - Acceptable
IC - Incomplete

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA #:	77203 **SPONSOR:** Par Pharmaceutical, Inc.
DRUG & DOSAGE FORM:	Cholestyramine for Oral Suspension, Light
STRENGTH(S):	4g resin/5g powder
TYPES OF STUDIES:	in vitro bile acid salt binding
CLINICAL STUDY SITE(S):	Not Applicable
ANALYTICAL SITE(S):	(b) (4)

STUDY SUMMARY: The in-vitro binding studies are acceptable

DISSOLUTION: Not Applicable

DSI INSPECTION STATUS

Inspection needed:	NO	**Inspection status:**	**Inspection results:**
First Generic			
New facility			
For cause			
Other			

Proposed Dissolution Method and Specifications from Original Submission Acceptable?
Yes N/A No N/A (If no, project Manager should verify and sign below when acknowledgement amendment is received)

DBE Dissolution Method and Specifications acknowledged by firm? Yes ___ No ___

AMENDMENT DATE: _____

PROJECT MANAGER: _____ **DATE:** _____

PRIMARY REVIEWER: James Osterhout, Ph.D. **BRANCH:** 1
INITIAL: _____ DATE: 11 Aug 2005

TEAM LEADER: Shriniwas Nerurkar, Ph.D. **BRANCH:** 1
INITIAL: _____ DATE: 8/12/2005

DIRECTOR, DIVISION OF BIOEQUIVALENCE: Dale P. Conner, Pharm.D.
INITIAL: _____ DATE: 8/15/05

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 77203 APPLICANT: Par Pharmaceutical Inc.

DRUG PRODUCT: Cholestyramine for Oral Suspension USP Light, 4g resin/5g powder

The Division of Bioequivalence has completed its review and has no further questions at this time.

Since this is a USP product, the all testing should be conducted as specified in USP 28.

Please note that the bioequivalence comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA 77203
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-652/ Reviewer J.L. Osterhout
HFD-652/ Project manager A.W. Sigler
HFD-652/ Team Leader S.G. Nerurkar

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Endorsements: (Final with Dates)
HFD-652/ J.L. Osterhout 11 AUG 2005
HFD-652/ S.G. Nerurkar 8/12/05
HFD-650/ D.P. Conner 8/15/05

BIOEQUIVALENCY - INCOMPLETE Submission date: 02 July 2004

1. Other (OTH)
(pivotal equilibrium binding)
Strengths: 4g resin/5g powder
Outcome: AC

2. Other (OTH)
(acid pretreated equilibrium binding)
Strengths: 4g resin/5g powder
Outcome: AC

3. Other (OTH)
(untreated in vitro kinetic binding)
Strengths: 4g resin/5g powder
Outcome: AC

4. Other (OTH)
(acid pretreated in vitro kinetic binding)
Strengths: 4g resin/5g powder
Outcome: AC

Outcome Decisions: AC - Acceptable
IC - Incomplete

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 77-203

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Par
Pharmaceutical,
Inc.

One Ram Ridge Road, Spring Valley, NY 10977
(845) 425-7100 • Fax (845) 425-7907

July 2, 2004

Copy 1
Copy 2
Copy 3 (field)*

Food and Drug Administration
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2
7500 Standish Place, Room 150
Rockville, Maryland 20855

RE: Cholestyramine for Oral Suspension, USP Light (4g resin/5g powder)

Dear Sir or Madam:

We herewith submit, in duplicate, an abbreviated new drug application for Cholestyramine for Oral Suspension, USP Light. The application is submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

The official name of the drug relied upon as the basis upon which this application may be filed is Cholestyramine for Oral Suspension, USP Light. The proprietary name of said drug is Questran®. A copy of the appropriate pages from the Electronic Orange Book is enclosed to show that the proposed drug is the same as the listed drug.

The certification concerning the patent is set forth under SECTION III. The approved insert labeling for the listed drug, SECTION V, is provided electronically on the enclosed CD ROM. The third (field) copy certification is provided in SECTION XXI.

In the interim guidance for Cholestyramine Powder *In-Vitro* Bioequivalence, the Division of Bioequivalence has concluded that *in-vivo* studies are not necessary to document the bioequivalence of cholestyramine resin formulations. Based on the interim guidance, an *in-vitro* bioequivalence study of cholestyramine resin was conducted comparing Par's Cholestyramine for Oral Suspension, USP Light to Bristol-Myers Squibb Co., Questran® (Cholestyramine for Oral Suspension, USP) Light. Our *in-vitro* bioequivalence study and relevant formulation data are provided in SECTION VI.

The content of our labeling, SECTION IV and SECTION V, is provided in electronic format (PDF and Word Files) as dictated by the FDA's Electronic Labeling Rule, made effective June 8, 2004. Please note that under

the Asset Purchase Agreement, Par Pharmaceutical, Inc. has acquired the trademark for Questran and Questran Light from Bristol-Myers Squibb. Applicable labeling is incorporated on the enclosed CD ROM.

Please contact us if we may offer any assistance in your review of this application.

Very truly yours,
PAR PHARMACEUTICAL, INC.

Michelle Bonomi-Huvala

Michelle Bonomi-Huvala 845-639-5120
Senior Director, Regulatory Affairs/R&D
Enclosures

* Jerome G. Woyshner
District Director
Food and Drug Administration
New York District Office
158-15 Liberty Avenue
Jamaica, New York 11433

Par
Pharmaceutical,
Inc.

One Ram Ridge Road, Spring Valley, NY 10977
(845) 425-7100 • Fax (845) 425-7907

August 17, 2004

Copy 1 ✓
Copy 2
Copy 3 (field)*

N/mc

Food and Drug Administration
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2
7500 Standish Place, Room 150
Rockville, Maryland 20855

Telephone Amendment

RE: ANDA #77-203 Cholestyramine for Oral Suspension, USP Light (4 g resin/5 g powder)

Dear Sir or Madam:

Reference is made to the Agency's telephone call of August 13, 2004 regarding our pending abbreviated new drug application dated July 2, 2004 for Cholestyramine for Oral Suspension, USP, Light.

In accordance with our August 13, 2004 telephone conversation with Paras Patel from the Agency, we provide the following updated information in support of this telephone amendment.

1. Revised FDA 356h form

Section I

2. Updated Establishment Information to incorporate a contact person for [redacted] (b) (4) the contract manufacturer of the active drug substance and to include the contract packager and labeler, [redacted] (b) (4)

Section II

3. Updated Basis for ANDA Submission statement to reference Questran Light

Section III

4. Updated Paragraph I Certification and Exclusivity Statement to reference Questran Light

Section VIII

5. The breakdown of the [redacted] (b) (4), from the manufacturer, [redacted] (b) (4) is provided.

In addition, for ease of review, the Summary of Container/Closure System pages, **Section XIII** have been updated to incorporate the addresses for the different manufacturers of the containers and closures used for the packaging of the finished product.

We certify that the field copy is a true copy of the technical information contained in the archival and review copies of this telephone amendment and was submitted to the New York District Office.

Please contact us if we may offer any additional assistance in your review of this application.

Very truly yours,
PAR PHARMACEUTICAL, INC.

Julie Szozda

Julie Szozda
Senior Associate, Regulatory Affairs/R&D
Enclosures

* Jerome G. Woyshner
District Director
Food and Drug Administration
New York District Office
158-15 Liberty Avenue
Jamaica, New York 11433

ANDA 77-203

Par Pharmaceutical, Inc.
Attention: Michelle Bonomi-Huvala
One Ram Ridge Road
Spring Valley, NY 10977

SEP - 1 2004

Dear Madam:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is made to the telephone conversations dated August 13, 2004 and August 17, 2004 and your correspondence dated August 17, 2004 and August 30, 2004.

NAME OF DRUG: Cholestyramine for Oral Suspension USP, 4 g/packet

DATE OF APPLICATION: July 2, 2004

DATE (RECEIVED) ACCEPTABLE FOR FILING: July 6, 2004

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Peter Chen
Project Manager
(301) 827-5848

Sincerely yours,

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 77-203
cc: DUP/Jackets
HFD-600/Division File
Field Copy
HFD-610
HFD-92
Endorsement:
HFD-615/MShimer, Chief, RSB _____ date 31 Aug 2004
HFD-615/PPatel, CSO _____ date 8/30/04
Word File V:\Firmsnz\Par\ltrs&rev\77203.ack
F/T PMP 08/30/04
ANDA Acknowledgment Letter!

RECORD OF TELEPHONE CONVERSATION
Office of Generic Drugs
Division of Chemistry 1
Branch 2 HFD-625

FROM: Kenneth Furnkranz, Review Chemist DATE: Dec. 22, 2004

NAME/TITLE OF INDIVIDUAL(S):
FDA: Kenneth Furnkranz
Mike Smela
Peter Chen
Par: (b) (6)
Julie Szozda

FIRM: Par Pharmaceutical
ANDA #'s: 77-203 and 77-204
PRODUCT NAME: Cholestyramine for O.S. (4g/9g) and O.S. Light (4g/5g).
TEL #: (b) (4) passcode (b) (4)
Reference: Call initiated by firm. Re: 12/7/04 ANDA MINOR Amendment deficiency

Notes of Conversation: We contacted Par at their request to discuss several issues regarding our 12/7/04 Deficiency Letter to them. Specifically, Items 5, 7, 8.c., 9, and 11.c.:

5. **Regarding the packaging, please provide information to demonstrate that** (b) (4)

We indicated that they should be able to (b) (4)
USP. It should meet the USP criteria.

7.a. (b) (4)

Following this page, 1 page withheld in full - (b)(4)

(b) (4)

We indicated that this approach would be acceptable.

Summary: The participants were satisfied with the results of the discussions, and parted with appropriate holiday wishes for all.

SIGNATURE OF OGD REPRESENTATIVES:

Kenneth Furnkranz, Review Chemist 12/22/04

Michael Smela, Team Leader 12/23/04

Peter Chen, Project Manager 12/22/04

V:\firmsnz\Par\telecons\77203TC122204kjf.doc

PAR PHARMACEUTICAL

Par Pharmaceutical, Inc.
One Ram Ridge Road
Spring Valley, NY 10977
tel 845 425 7100
fax 845 425 7907
www.parpharm.com

Copy 1
Copy 2

March 3, 2005

Food and Drug Administration
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2
7500 Standish Place, Room 150
Rockville, Maryland 20855

ORIG AMENDMENT
N/AF

Labeling Amendment

RE: ANDA #77-204 Cholestyramine for Oral Suspension USP (4 g resin/9 g)
ANDA #77-203 Cholestyramine for Oral Suspension USP, Light (4 g resin/5 g) ✓

Dear Sir or Madam:

Reference is made to the Agency's correspondence of January 12, 2005 regarding our abbreviated new drug applications dated July 2, 2004 for Cholestyramine for Oral Suspension USP (4 g resin/9 g powder) and Cholestyramine for Oral Suspension USP, Light (4 g resin/5 g powder). A copy of the Agency's January 12, 2005 correspondence is appended in Attachment 1.

Par's labeling has been updated in accordance with the Agency's recommendations noted in the January 12, 2005 correspondence. Final printed labeling is provided electronically on the enclosed CD ROM.

Our response to the Agency's general comment is listed below.

Comment

a. General Comment

Please comment on the submission of the trade name labels and labeling that are still being marketed and manufactured by the innovator. Your manufacturing statement reflects that you would manufacturer the branded product Questran. Will the innovator discontinue manufacturing or marketing their product and therefore allow you to use their trade name? Please comment.

Response

Please be advised that in March 2002 Par acquired sole marketing rights to Questran and Questran Light in the United States, as well as ownership rights to the respective trademarks. Bristol Myers Squib retained ownership of the NDA applications. Par has marketed the brand Questran and Questran Light since 2002. The innovator has supplied the product to Par under our manufacture and supply agreement. The innovator will cease to manufacture the product for Par upon the expiration of this agreement in March 2005. Upon approval of our applications, Par will be the manufacturer and marketer of the Questran and Questran Light brand products."

PAR
PHARMACEUTICAL

The trademark assignment information from the United States Patent and Trademark Office website is provided for your convenience in Attachment 2.

Please contact us if we may offer any additional assistance in your review of this application.

Very truly yours,
PAR PHARMACEUTICAL, INC.

Julie Szozda

Julie Szozda
Senior Associate, Regulatory Affairs/R&D
Enclosures

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 77-203 and 77-204 APPLICANT: Par Pharmaceutical Inc.

DRUG PRODUCTS:

Cholestyramine for Oral Suspension USP (Light)
Cholestyramine for Oral Suspension USP

The deficiencies presented below represent MINOR deficiencies.

1. Regarding the Components and Composition Statements:

   a. (b) (4)

   b.

2. DMF # (b) (4) which was referenced for the manufacture of (b) (4) (b) (4) is inadequate. Please ensure a response.

3. Regarding the (b) (4)

4. (b) (4)

5. Regarding the (b) (4)

6. Regarding the (b) (4) utilized:

Following this page, 1 page withheld in full - (b)(4)

b. (b) (4)

c.

d.

In addition, please report the results of these tests at your next stability test station for both drug products.

12. (b) (4)

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. All facilities referenced in the ANDA should have a satisfactory compliance evaluation at the time of approval. We have requested an evaluation from the Office of Compliance.

2. Please submit additional long-term stability data on the exhibit lots manufactured to support the ANDA, if available.

3. Your bioequivalence information is pending review.

4. Your labeling information is also pending review.

Sincerely yours,

M Smela for

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

PAR PHARMACEUTICAL

Par Pharmaceutical, Inc.
One Ram Ridge Road
Spring Valley, NY 10977
tel 845 425 7100
fax 845 425 7907
www.parpharm.com

March 21, 2005

ORIG AMENDMENT

N/AM

Copy 1 ✓
Copy 2
Copy 3 (field)*

Food and Drug Administration
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2
7500 Standish Place, Room 150
Rockville, Maryland 20855

Minor Amendment

RE: ANDA #77-204 Cholestyramine for Oral Suspension USP (4 g resin/9 g)
ANDA #77-203 Cholestyramine for Oral Suspension USP, Light (4 g resin/5 g) ✓

Dear Sir or Madam:

Reference is made to the Agency's correspondence of December 10, 2004 regarding our abbreviated new drug applications dated July 2, 2004 for Cholestyramine for Oral Suspension, USP (4 g resin/9 g powder) and Cholestyramine for Oral Suspension, USP Light (4 g resin/5 g powder). A copy of the Agency's December 10, 2004 correspondence is appended in Attachment 1. Reference is also made to our December 22, 2004 teleconference with Peter Chen, Mike Smela and Ken Furnkranz from the Office of Generic Drugs, pertaining thereto.

Par Pharmaceutical is addressing the Agency's deficiencies with this minor amendment to ANDA 77-204 and 77-203. The Agency's comments and our responses follow.

Comment 1

Regarding the Components and Composition Statements:

(b) (4)

[redacted]

Following this page, 4 pages withheld in full - (b)(4)

All facilities referenced in the ANDA should have a satisfactory compliance evaluation at the time of approval.
We have requested an evaluation from the Office of Compliance.
Please submit additional long-term stability data on the exhibit lots manufactured to support the ANDA, if available.
Your bioequivalence information is pending review.
Your labeling information is also pending review.

Response
In addition to responding to the deficiencies presented above, we note and acknowledge the following:

All facilities referenced in the ANDA should have a satisfactory compliance evaluation at the time of approval.
Additional long-term stability data on the exhibit lots manufactured to support the ANDA is appended in Attachment 10.
Our bioequivalence information is pending review.
Our labeling information is also pending review.

We certify that the field copy is a true copy of the technical information contained in the archival and review copies of this minor amendment submitted to the Office of Generic Drugs.

Please contact us if we may offer any additional assistance in your review of this application.

Very truly yours,
PAR PHARMACEUTICAL, INC.

Julie Szozda

Julie Szozda
Senior Associate, Regulatory Affairs/R&D
Enclosures

* Jerome G. Woyshner
District Director
Food and Drug Administration
New York District Office
158-15 Liberty Avenue
Jamaica, New York 11433

MAY 18 2005

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 77-203 and 77-204 APPLICANT: Par Pharmaceutical Inc.

DRUG PRODUCTS:

Cholestyramine for Oral Suspension USP (Light)
Cholestyramine for Oral Suspension USP

The deficiencies presented below represent MINOR deficiencies.

1. DMF # (b) (4) was most recently reviewed and found inadequate on 5/13/05. (b) (4) (b) (4) has been informed. Please ensure a response prior to submitting your ANDA Amendment.

2. Regarding the (b) (4) Your previous response was too vague.

3. Regarding the (b) (4) of Cholestyramine for Oral Suspension Regular:

   a. Please explain the (b) (4) .

   b. Please provide an updated (b) (4)

4. (b) (4) :

   a. (b) (4)

   b.

5. Please provide (b) (4)

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. All facilities referenced in the ANDA should have a satisfactory compliance evaluation at the time of approval. We have requested an evaluation from the Office of Compliance.

2. Your bioequivalence information is pending review.

Sincerely yours,

M Smela for

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

Par Pharmaceutical, Inc.
One Ram Ridge Road
Spring Valley, NY 10977
tel 845 425 7100
fax 845 425 7907
www.parpharm.com

Copy 1
Copy 2 ✓
Copy 3 (field)*

June 6, 2005

Food and Drug Administration
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2
7500 Standish Place, Room 150
Rockville, Maryland 20855

ORIG AMENDMENT
N- AM

Minor Amendment

RE: ANDA #77-204 Cholestyramine for Oral Suspension USP (4 g resin/9 g)
ANDA #77-203 Cholestyramine for Oral Suspension USP, Light (4 g resin/5 g) ✓

Dear Sir or Madam:

Reference is made to the Agency's correspondence of May 18, 2005 regarding our abbreviated new drug applications dated July 2, 2004 and all subsequent amendments relative to the Cholestyramine for Oral Suspension, USP (4 g resin/9 g powder) and Cholestyramine for Oral Suspension, USP Light (4 g resin/5 g powder) products. A copy of the Agency's May 18, 2005 correspondence is appended in Attachment 1.

Par Pharmaceutical is addressing the Agency's deficiencies with this minor amendment to ANDA 77-204 and 77-203. The Agency's comments and our responses follow.

Comment
1. DMF # (b) (4) was most recently reviewed and found inadequate on 5/13/05. (b) (4) has been informed. Please ensure a response prior to submitting your ANDA Amendment.

Response
We have been informed by the (b) (4) manufacturer, (b) (4), that they have responded to their outstanding deficiencies in reference to DMF # (b) (4) A copy of (b) (4) cover letter is provided in Attachment 2.

Comment
2. Regarding the (b) (4) . Your previous response was too vague.

Response
(b) (4)

Comment
3. Regarding the (b) (4) of Cholestyramine for Oral Suspension Regular:

RECEIVED
JUN 0 7 2005
OGD / CDER

Following this page, 1 page withheld in full - (b)(4)

Response
4. [redacted] (b) (4)

Comment
Please provide [redacted] (b) (4)

Response
To demonstrate [redacted] (b) (4)
Attachment 5. Please refer to

Comment
B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. All facilities referenced in the ANDA should have a satisfactory compliance evaluation at the time of approval. We have requested an evaluation from the office of Compliance.

2. Your bioequivalence information is pending review.

Response
B. We note and acknowledge the following:

1. All facilities referenced in the ANDA should have a satisfactory compliance evaluation at the time of approval. An evaluation from the office of Compliance has been requested by the Agency.

2. Our bioequivalence information is pending review.

We certify that the field copy is a true copy of the technical information contained in the archival and review copies of this minor amendment submitted to the Office of Generic Drugs.

Please contact us if we may offer any additional assistance in your review of this application.

Very truly yours,
PAR PHARMACEUTICAL, INC.

Julie Szozda
Senior Associate, Regulatory Affairs, R&D
Enclosures

* Jerome G. Woyshner
District Director
Food and Drug Administration
New York District Office
158-15 Liberty Avenue
Jamaica, New York 11433

RECORD OF TELEPHONE CONVERSATION

We contacted Par regarding outstanding issues regarding these ANDA's:

1. We indicated that Par has added a [redacted] (b) (4)

We indicated that the [redacted] (b) (4)

They agreed.

2. We indicated that their response to FDA Deficiency #4.b. of the 5/15/05 deficiency letter was not adequate. The acceptance [redacted] (b) (4)

Dr. [redacted] (b) (6) asked if the [redacted] (b) (4) appropriate.

They agreed to revise the [redacted] (b) (4) accordingly.

The Par representatives indicated that they would prepare a response and submit as a telephone amendment. They weren't sure that they could get back within 10 days (due to the 4th of July

DATE
June 29, 2005

ANDA NUMBER
77-203
77-204

TELECON

INITIATED BY:
OGD

PRODUCT NAME
Cholestyramine for O.S. and Cholestyramine for O.S. Light
4 g/dose

FIRM:
Par Pharmaceuticals, Inc.

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Julie Szozda
[redacted] (b) (6)

TELEPHONE NUMBER
(845) 639-5121

holiday) however, we indicated that they could call and let us know if there would be a delay and we would await their response.

Julie Szozda asked if there were any other outstanding issues, and Peter indicated that the Bioequivalence was currently in the review queue, and the Compliance evaluation was in progress at this time. Julie indicated that she thought the inspection of [redacted] (b) (4) had been completed, however Peter indicated that that does not mean that Compliance has completed their report.

The firm agreed to provide all the requested information, and thanked us for the communication. We wished them a Happy 4th!!

SIGNATURE

6/30/05

Kenneth Furnkranz

6/30/05

Peter Chen

CC: ANDA 77-203 ; 77-204

V:\FIRMSNZ\PAR\TELECONS\77203tc062905kjf.doc

PAR PHARMACEUTICAL

Par Pharmaceutical, Inc.
One Ram Ridge Road
Spring Valley, NY 10977
tel 845 425 7100
fax 845 425 7907
www.parpharm.com

Copy 1 ✓
Copy 2
Copy 3 (field)*

ORIG AMENDMENT
N/000
Am

July 14, 2005

Food and Drug Administration
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2
7500 Standish Place, Room 150
Rockville, Maryland 20855

Telephone Amendment

RE: ANDA #77-204 Cholestyramine for Oral Suspension USP (4 g resin/9 g)
ANDA #77-203 Cholestyramine for Oral Suspension USP, Light (4 g resin/5 g) ✓

Dear Sir or Madam:

Reference is made to the Agency's telephone call of June 29, 2005 regarding our pending abbreviated new drug applications dated July 2, 2004 and all subsequent amendments relative to the Cholestyramine for Oral Suspension, USP (4 g resin/9 g powder) and Cholestyramine for Oral Suspension, USP Light (4 g resin/5 g powder) products.

In accordance with our June 29, 2005 telephone conversation with Ken Furnkranz and Peter Chen from the Agency as well as Par's associated email of July 11, 2005 and subsequent telephone call, we provide the following updated information in support of this telephone amendment.

Comment

1. The Agency requested that a statement be incorporated into the [redacted] (b) (4)

In addition, please provide a copy of the [redacted] (b) (4).

Response

In accordance with the Agency's request the [redacted] (b) (4)
Attachment 1.

A copy of the [redacted] (b) (4) is also provided in Attachment 1.

Comment

2. Revise the [redacted] (b) (4) for both, Cholestyramine for Oral Suspension, USP (4 g resin/9 g powder) and Cholestyramine for Oral Suspension, USP Light (4 g resin/5 g powder) products.

RECEIVED
JUL 15 2005
OGD/CDER

Response

(b) (4)

[redacted]

We certify that the field copy is a true copy of the technical information contained in the archival and review copies of this telephone amendment submitted to the Office of Generic Drugs.

Please contact us if we may offer any additional assistance in your review of this application.

Very truly yours,
PAR PHARMACEUTICAL, INC.

Julie Szozda

Julie Szozda
Senior Associate, Regulatory Affairs, R&D
Enclosures

* Jerome G. Woyshner
District Director
Food and Drug Administration
New York District Office
158-15 Liberty Avenue
Jamaica, New York 11433

PAR PHARMACEUTICAL

Par Pharmaceutical, Inc.
One Ram Ridge Road
Spring Valley, NY 10977
tel 845 425 7100
fax 845 425 7907
www.parpharm.com

Copy 1 ✓
Copy 2
Copy 3 (field)*

July 18, 2005

ORIG AMENDMENT
N/AM

Food and Drug Administration
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2
7500 Standish Place, Room 150
Rockville, Maryland 20855

Telephone Amendment

RE: ANDA #77-204 Cholestyramine for Oral Suspension USP (4 g resin/9 g)
ANDA #77-203 Cholestyramine for Oral Suspension USP, Light (4 g resin/5 g) ✓

Dear Sir or Madam:

Reference is made to our telephone amendment of July 14, 2005 submitted in response to the Agency's teleconference of June 29, 2005 regarding our pending abbreviated new drug applications dated July 2, 2004 for Cholestyramine for Oral Suspension, USP (4 g resin/9 g powder) and Cholestyramine for Oral Suspension, USP Light (4 g resin/5 g powder) products.

Please be advised that the [redacted] (b) (4) (pages 26-30) submitted in the July 14, 2005 telephone amendment, has subsequently been superseded for Cholestyramine for Oral Suspension, UPS 4g/9g. We wish to amend our July 14, 2005 submission and provide the updated [redacted] (b) (4) Please note that a copy of the updated [redacted] (b) (4) was faxed to Peter Chen, Project Manager on July 15, 2005.

We certify that the field copy is a true copy of the technical information contained in the archival and review copies of this telephone amendment submitted to the Office of Generic Drugs.

We apologize for any inconvenience incurred. Please contact us if we may offer any additional assistance in your review of these applications.

Very truly yours,
PAR PHARMACEUTICAL, INC.

Julie Szozda
Julie Szozda
Senior Associate, Regulatory Affairs
Enclosures

* Jerome G. Woyshner
District Director
Food and Drug Administration
New York District Office
158-15 Liberty Avenue
Jamaica, New York 11433

RECEIVED
JUL 19 2005
OGD/CDER

PAR PHARMACEUTICAL

Par Pharmaceutical, Inc.
One Ram Ridge Road
Spring Valley, NY 10977
tel 845 425 7100
fax 845 425 7907
www.parpharm.com

Copy 1 ✓
Copy 2

ORIG AMENDMENT
N/AB

August 9, 2005

Food and Drug Administration
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2
7500 Standish Place, Room 150
Rockville, Maryland 20855

Telephone Amendment

RE: ANDA #77-204 Cholestyramine for Oral Suspension USP (4 g resin/9 g)
ANDA #77-203 Cholestyramine for Oral Suspension USP, Light (4 g resin/5 g) ✓

Dear Sir or Madam:

Reference is made to the Agency's telephone call of July 29, 2005 regarding our pending abbreviated new drug applications dated July 2, 2004 and all subsequent amendments relative to the Cholestyramine for Oral Suspension, USP (4 g resin/9 g powder) and Cholestyramine for Oral Suspension, USP Light (4 g resin/5 g powder) products.

In accordance with our July 29, 2005 telephone conversation with Aaron Sigler from the Division of Bioequivalence, we provide the following information in support of this telephone amendment.

Comment
Aaron Sigler, from the Division of Bioequivalence requested that we provide the assay and content uniformity data for the test and reference products used in the *in-vitro* binding studies for the above referenced applications.

Response
Assay and content uniformity data for the test and reference products used in the *in-vitro* binding studies for Cholestyramine for Oral Suspension USP (4 g resin/9g) and Cholestyramine for Oral Suspension USP, Light (4 g resin/5 g) is provided.

Please contact us if we may offer any additional assistance in your review of this application.

Very truly yours,
PAR PHARMACEUTICAL

Julie Szozda

Julie Szozda
Senior Associate, Regulatory Affairs
Enclosures

Chen, Peter

From: Grace, John F
Sent: Thursday, August 25, 2005 11:08 AM
To: Payne, Angela; Chen, Peter
Subject: RE: Labeling signoff for 77-203 and 77-204 ap letters

concur

-----Original Message-----
From: Payne, Angela
Sent: Wednesday, August 24, 2005 10:44 AM
To: Chen, Peter; Grace, John F
Subject: RE: Labeling signoff for 77-203 and 77-204 ap letters

John/Peter,

The attached approval summary signed by Apayne on 4/5/05 and John Grace remains satisfactory for approval. Checked the OB, Comis and USP/NF no changes to the RLD.

Apayne

-----Original Message-----
From: Chen, Peter
Sent: Wednesday, August 24, 2005 9:43 AM
To: Payne, Angela; Grace, John F
Subject: Labeling signoff for 77-203 and 77-204 ap letters

Angela/John:

Please check the attached and confirm if they are acceptable for labeling signoff.

Thanks,
Peter
<< File: 77203 and 7720 labeling ap.pdf >> << File: 77203ap.ltr.doc >> << File: 77204ap.ltr.doc >>

OGD APPROVAL ROUTING SUMMARY

ANDA # 77-203 Applicant Par Pharmaceuticals
Drug Cholestyramine for Oral Suspension USP, Light Strength(s) 4 g resin/5 g

APPROVAL ☑ **TENTATIVE APPROVAL** ☐ **SUPPLEMENTAL APPROVAL (NEW STRENGTH)** ☐ **OTHER** ☐

REVIEWER: **DRAFT Package** **FINAL Package**

1. Martin Shimer
Chief, Reg. Support Branch

Date 24 Aug 05 Date 8/26/05 for
Initials MS Initials RAW

Contains GDEA certification: Yes ☑ No ☐ (required if sub after 6/1/92)
Determ. of Involvement? Yes ☐ No ☒
Pediatric Exclusivity System
RLD = NDA# 19-669
Patent/Exclusivity Certification: Yes ☑ No ☐ Date Checked N/A
If Para. IV Certification- did applicant
Notify patent holder/NDA holder Yes ☐ No ☐ Nothing Submitted ☐
Was applicant sued w/in 45 days: Yes ☐ No ☐ Written request issued ☐
Has case been settled: Yes ☐ No ☐ Date settled: Study Submitted ☐
Is applicant eligible for 180 day
Generic Drugs Exclusivity for each strength: Yes ☐ No ☑
Date of latest Labeling Review/Approval Summary 4/13/05
Any filing status changes requiring addition Labeling Review Yes ☐ No ☑
Type of Letter:
Comments: No patents/exclusivities ∴ eligible for full Approval

2. Project Manager, Peter Chen Team 2
Review Support Branch

Date 8/24/05 Date 8/24/05
Initials PC Initials PC

Original Rec'd date 7/6/04
Date Acceptable for Filing 7/6/04
Patent Certification (type) I
Date Patent/Exclus.expires N.A.
Citizens' Petition/Legal Case Yes ☐ No ☑
(If YES, attach email from PM to CP coord)
First Generic Yes ☐ No ☑

EER Status Pending ☐ Acceptable ☑ OAI ☐
Date of EER Status 7/18/05
Date of Office Bio Review 8/15/05
Date of Labeling Approv. Sum 4/13/05
Labeling Acceptable Email Rec'd Yes ☑ No ☐
Labeling Acceptable Email filed Yes ☑ No ☐
Date of Sterility Assur. App. N.A.
Methods Val. Samples Pending Yes ☐ No ☑
MV Commitment Rcd. from Firm Yes ☐ No ☐

Acceptable Bio reviews tabbed Yes ☑ No ☐
Suitability Petition/Pediatric Waiver
Pediatric Waiver Request Accepted ☐ Rejected ☐ Pending ☐
Previously reviewed and tentatively approved ☐ Date
Previously reviewed and CGMP def. /NA Minor issued ☐ Date
Comments:

Modified-release dosage form: Yes ☐ No ☑
Interim Dissol. Specs in AP Ltr: Yes ☐

3. David Read **(PP IVs Only)** Pre-MMA Language included ☐ Date
OGD Regulatory Counsel, Post-MMA Language Included ☐ Initials
Comments:
N/A

4. Div. Dir./Deputy Dir.
Chemistry Div. I II OR III
Comments:

Date 8/24/05
Initials RM

The CMC section is satisfactory.

REVIEWER: **FINAL ACTION**

5. Frank Holcombe **First Generics Only**
Assoc. Dir. For Chemistry
Comments: (First generic drug review)
Date_____
Initials_____

N/A. there are multiple ANDAs approved for this drug product.

6. Vacant
Deputy Dir., DLPS
RLD= Questran Light for Oral Suspension
Bristol Myers Co. powder 4gresin/5g powder
NDA 19-669
Date_____
Initials_____

7. Peter Rickman
Director, DLPS
Date 8/26/05
Initials for
Para.IV Patent Cert: Yes ☐ No ☐; Pending Legal Action: Yes ☐ No ☐; Petition: Yes ☐ No ☐
Comments: Acceptable LEES dated 7/18/05 (Verified 8/26/05). No O.I. Letter for FPL found acceptable for approval 8/18/05 (endorsed 8/25/05). CMC found satisfactory 7/18/05. Methods validation was not requested OR Bioequivalence studies (2 in vitro bile acid binding studies) and two in vitro kinetic bile acid binding studies (2° 7/93 Guidance) found acceptable 8/12/05 Office-level bio endorsed 8/15/05.

8. Robert L. West
Deputy Director, OGD
Date 8/26/2005
Initials for
Para.IV Patent Cert: Yes ☐ No ☒; Pending Legal Action: Yes ☐ No ☒; Petition: Yes ☐ No ☐
Comments: there are no unexpired patents or exclusivity listed on the current "Orange Book" for this drug product.
This ANDA is recommended for approval.

9. Gary Buehler
Director, OGD
Comments:
Date 8/26/05
Initials for
First Generic Approval ☐ PD or Clinical for BE ☐ Special Scientific or Reg. Issue ☐

10. Project Manager, Peter Chen, Team 2
Review Support Branch
Date 8/26/05
Initials
N/A Date PETS checked for first generic drug (just prior to notification to firm)
Applicant notification:
11:10A Time notified of approval by phone 11:12A Time approval letter faxed
FDA Notification:
8/26/05 Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
8/26/05 Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

Approval Letter Faxed to Orange Book Staff @ 301-827-7337: Date/Time: _____

File V:/division/dlps/approvrou9.doc