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
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APPLICATION NUMBER:
ANDA 77-203

APPROVAL LETTER
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

8/26/2005
Approved Electronic Labeling Located at:
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Endorsements:

HFD-625/K.Furnkranz/ for

HFD-625/M.Smela/

HFD-617/P.Chen/

HFD-613/A.Payne/

HFD-613/J.Grace/ SEE ATTACHED EMAIL

V:\FIRMSNZ\PAR\LTRS\REV\77203ap.ltr.doc

F/T by

APPROVAL
Cholestryramine for Oral Suspension USP, Light

POWDER
Rx only
SINGLE DOSE

*Contains the artificial sweetener Aspartame

Preparation: Place the contents of one packet in a glass or cup. Add at least 2 1/2 ounces of water, milk or the noncarbonated beverage of your choice. Stir to a uniform consistency 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 cholesyramine in 5 grams of Cholestryramine Light.

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

101/05
PO466-63-1-61
**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.

**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.


Contains the artificial sweetener Aspartame.

Rx only

Sugar Free Orange Flavor

62 MEASURED DOSES
CONTAINS 210 G (58 G ANHYDROUS CHOLESTYRAMINE)

Let
Exp.

LA466-67-1-01

Par Pharmaceutical, Inc.
Spring Valley, NY 10977
**DESCRIPTION**

Cholestryramine for Oral Suspension USP, the chloride salt of a basic anion exchange resin, is a cholesteryl lowering agent, is intended for oral administration. Cholestryramine resin is a quaternary, hydrophilic, and insoluble in water. The cholesterylamine resin in Cholestryramine is not absorbed from the digestive tract. Four grams of cholesterylamine resin are contained in 5 grams of Cholestryramine for Oral Suspension USP. Four grams of atorvastatin cholesterylamine resin is contained in 5 grams of Cholestrylamine for Oral Suspension USP Light. It is represented by the following structural formula:

![Structural formula of Cholestryramine](image)

**APPLICATIONS CLINICAL PHARMACOLOGY**

Cholesterylamine is probably the sole precursor of bile acids. During normal digestion, bile acids are secreted into the intestine. A major portion of the bile acids is absorbed from the intestinal tract and recycled back to the liver via the enterohepatic circulation. Only very small amounts of bile acids are found in normal serum.

Cholesterylamine resins adsorb and combine 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 thereby preventing their absorption.

The increased fecal loss of bile acids due to cholesterylamine administration leads to an increased oxidation of cholesteryl to bile acids, a decrease in liver lipoprotein and free cholesterol plasma levels and a decrease in serum cholesterol levels. Although in man, cholesterylamine produces an increase in hepatic synthesis of cholesterol, plasma cholesterol levels fall.

In patients with partial bile acid obstruction, the reduction of serum bile acid levels by cholesterylamine reduces excess bile acids deposited in the dietary residual with resultant decrease in production.

**CLINICAL STUDIES**

In a large, placebo-controlled, multicentric trial, LSC-CPTP, hypercholesterolemic subjects treated with Cholesterylamine had a mean reduction in total and low-density lipoprotein cholesterol (LDL-C) which was observed to be 10% and 16%, respectively. Over the first year of this study, the placebo group experienced a 30% reduction in the incidence of coronary coronary heart disease death plus non-fatal myocardial infarction (cumulative incidence of 7% in the Cholesterylamine group and 8% in both the placebo group in the combined total coronary heart disease death plus non-fatal myocardial infarction) and a 30% increase in the mean body weight of patients receiving placebo.

Cholesterylamine resin has been demonstrated to retard the rate of progression* and increase the rate of regression of coronary athrosclerosis.

Because of the open-label nature of the study, Cholesterylamine treat patients may be considered in patients with complete bile acid obstruction where bile is not secreted into the intestine and in those individuals who have been hypervitaminosis A to any of its components.

**WARNINGS**

**PRECAUTIONS:** CHOLESTYRAMINE FOR ORAL SUSPENSION USP LIGHT CONTAINS 14.9 mg PHENYLALANINE PER 5 GRAMS DOSE.

**PRECAUTIONS**

Cholesterylamine for oral suspension is contraindicated in patients with complete bile acid obstruction where bile is not secreted into the intestine and in those individuals who have been hypervitaminosis A to any of its components.

**INDICATIONS AND USAGE**

1) Cholesterylamine for Oral Suspension USP is indicated as an adjunctive therapy to diet for the reduction of elevated serum cholesterol in patients with primary hypercholesterolemia (i.e., low density lipoprotein (LDL-C) levels greater than 160 mg/dL). Cholesterylamine for Oral Suspension USP may be used in patients who also have hypertriglyceridemia, but it is not indicated where hyperglycemia is the abnormality of most concern.

2) Therapy with lipophilic agents should be a component of multiple risk factor intervention in those individuals at significantly increased risk for atherosclerotic vascular disease due to hypercholesterolemia.

This agent should begin and continue with dietary therapy specific for the type of hypercholesterolemia. In this determination prior to initiation of therapy. Low body weight may be an important factor in reducing nutrition and should be addressed prior to drug therapy in the overweight.

Cholestryramine has been reported to cause liver damage and malignant hyperthermia. Although not recommended for patients with impaired liver function, a significant reduction in cholesterol lowering efficacy may be observed in patients with mild to moderate liver disease.

**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 LSC-CPTP showed a dose-related increase in serum triglycerides of 10.7% to 17.1% in the cholesterylamine-treated group, compared with an increase of 7.3% to 11% in the placebo group. Based on the mean values and on the placebo group, the cholesterylamine-treated group showed an increase of 3% over the placebo group. The mean serum triglycerides of patients who received the active drug were significantly higher than the mean serum triglycerides of patients in the placebo group. This increase was not associated with a change in the mean serum cholesterol concentrations.

Cholesterylamine may interact with the pharmacodynamics of drugs that do not influence the enterohepatic circulation. The discontinuance of Cholesterylamine for Oral Suspension USP Light may be necessary if a potentially toxic drug such as digoxin has been titrated to a maintenance level while the patient was taking Cholesterylamine for Oral Suspension USP Light.

Because cholesterylamine binds bile acids, cholesterylamine 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 cholesterylamine is given for long periods of time, concomitant supplementation with water-soluble (or parenteral) forms of fat-soluble vitamins should be maintained.
Since cholestyramine may bind other drugs given concurrently, it is recommended that patients take other drugs at least one hour before or one to four hours after cholestyramine or at as great an interval as possible to avoid interfering with their absorption.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In studies conducted in rats in which cholestyramine was administered as a single oral dose or an oral suspension, various adverse effects on reproduction were noted. In two of the studies, increased litters were noted in the treated groups with a lower proportion of females becoming pregnant. In one study, there was a significant decrease in the number of live births. In other studies, cholestyramine did not affect reproductive performance at the given doses. The relevance of these findings to the clinical use of cholestyramine is unknown. In the LRC-CPPT study referred to above, the total incidence of fatal and nonfatal neoplasms was similar in both treatment groups. The incidence of various types of cancer was reported to be lower in one treatment group than in the other. It is not known whether this difference was due to the use of cholestyramine or to other factors.

OVERDOSAGE

Overdosage with cholestyramine has been reported in a patient taking 150% of the maximum recommended daily dosage. No ill effects were reported. Should an overdosage occur, the patient should be managed symptomatically.

DOSAGE AND ADMINISTRATION

The recommended adult dose for oral suspension is 30 grams of anhydrous cholestyramine resin in two to three divided doses, normally not to exceed 8 grams/day. Store at 20º-25ºC (68º-77ºF). [See USP Controlled Room Temperature]. Excursions permitted to 15º-30ºC (59º-86ºF).

Concomitant Therapy

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

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:

<table>
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<th>Amount of Water or other</th>
<th>Scoops from Other Products</th>
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<tr>
<td>8 ounces per dose</td>
<td>Scoops from other products</td>
</tr>
<tr>
<td>2-6 ounces per dose</td>
<td>Scoops from other products</td>
</tr>
</tbody>
</table>

Cholestyramine may also be mixed with highly fluid soups or puffy foods with a high moisture content such as an apple sauce or crushed pineapple.

NOTICE TO CLINICIANS

PREPARATION

OR 4 TO 6 HOURS AFTER

CHOLESTYRAMINE

Circulation

section for rec-

Nelson, Textbook of Pediatrics

Arch Intern Med

Lancet


section may have an effect on nursing infants.

DOSAGE AND ADMINISTRATION

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 6 grams/day. See dosage and tolerability 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 include:

- Anorexia, flatulence, bloating, nausea, vomiting, diarrhea, abdominal discomfort, and pain.
- Rash, pruritus, urticaria, alopecia, acne, alopecia, and pruritus.
- Hypertension.
- Syncope, dizziness, malaise, weight change, and sexual dysfunction.
- Increased bleeding tendency.
- OCULAR: Photophobia, diplopia, visual disturbance.
- GI: Bleeding, hematemesis, melena, epigastric pain, anorexia, nausea, vomiting, regurgitation, dyspepsia, diarrhea, abdominal pain, diarrhea, and distention.
- Nervous System: Headache, dizziness, vertigo, ataxia, mood changes, depression, and anxiety.
- Skin: Rashes, pruritus, urticaria, eczema, alopecia, pruritus, and acniform eruptions.
- Respiratory: Cough, dyspnea, pharyngitis, tonsillitis, and epistaxis.
- Hematologic: Neutropenia, leukopenia, anemia, agranulocytosis, and toxic epidermal necrolysis.
- Other: Fatigue, asthenia, anxiety, weight loss, weight gain, pyrexia, and fever.

ADVERSE EFFECTS

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 include:

- Anorexia, flatulence, bloating, nausea, vomiting, diarrhea, abdominal discomfort, and pain.
- Rash, pruritus, urticaria, alopecia, acne, alopecia, and pruritus.
- Hypertension.
- Syncope, dizziness, malaise, weight change, and sexual dysfunction.
- Increased bleeding tendency.
- OCULAR: Photophobia, diplopia, visual disturbance.
- GI: Bleeding, hematemesis, melena, epigastric pain, anorexia, nausea, vomiting, regurgitation, dyspepsia, diarrhea, abdominal pain, diarrhea, and distention.
- Nervous System: Headache, dizziness, vertigo, ataxia, mood changes, depression, and anxiety.
- Skin: Rashes, pruritus, urticaria, eczema, alopecia, pruritus, and acniform eruptions.
- Respiratory: Cough, dyspnea, pharyngitis, tonsillitis, and epistaxis.
- Hematologic: Neutropenia, leukopenia, anemia, agranulocytosis, and toxic epidermal necrolysis.
- Other: Fatigue, asthenia, anxiety, weight loss, weight gain, pyrexia, and fever.

REFERENCES


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

Issued: 02/95
05496-65-1-01
QUESTRAN® LIGHT
(Cholestyramine for Oral Suspension USP)
Powder

4 GRAMS CHOLESTYRAMINE RESIN USP, PER SCOOPFUL

Rx only
Sugar Free Orange Flavor

62 MEASURED DOSES
CONTAINS 210 G (98 G ANHYDROUS CHOLESTYRAMINE)

NDC 49864-937-67

WARNINGS:
PHENYLKETONURCS: 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.
*Contains the artificial sweetener Aspartame.
®Registered trademark of Par Pharmaceutical, Inc.
Mfr by: Par Pharmaceutical, Inc.
Spring Valley, NY 10977

User's 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.
DESCRIPTION

QUESTRA® (Cholestryramine for Oral Suspension USP), the cholestyramine ion-exchange resin, is a cholesteryl lowering agent, is intended for use in adults. Cholestryramine resin is quite hydrophilic, but insoluble in water. The cholestryramine resin in QUESTRA® is not absorbed from the digestive tract. Four grams of anhydrous cholestryramine resin is contained in 1 gram of QUESTRA® powder. Four pieces of anhydrous cholestryramine resin are contained in 1 gram of QUESTRA® LIGHT. It is represented by the following structural formula:

\[
\begin{array}{c}
\text{C}17\text{H}_{16}\text{O}_{2}\text{Na}_{2}\text{Si}_{4}\text{O}_{16}\text{N}_{2}\text{P}_{2}\\
\text{Si(OC}2\text{H})_{4}\text{O}^{-}\text{Na}^{+}
\end{array}
\]

QUESTRA® powder contains the following inactive ingredients: saccharin, citric acid, D&C Yellow No. 10, FD&C Red No. 40, hydroxypropyl cellulose, polyethylene glycol, saccharin sodium, and sodium bicarbonate. QUESTRA® LIGHT contains the following inactive ingredients: aspartame, citric acid, cellulose microcrystals, D&C Yellow No. 10, FD&C Red No. 40, flavor (natural and artificial Orange), polyethylene glycol 400, and sodium bicarbonate.

ACTION/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.

At least 75% of the bile acids in the intestine is converted to an insoluble complex which is absorbed in the feces. This results in a partial removal of bile acids from the enterohepatic circulation by preventing their absorption.

The increased faecal loss of bile acids due to QUESTRA® administration leads to an increased oxidation of cholesterol to bile acids. This increase is seen in the biliary and small intestine and in serum cholesterol levels and in patients with partial biliary obstruction, the reduction of serum bile acid levels by QUESTRA® reduces excess bile acids deposited in the normal tissue with resultant decrease in pruritus.

Clinical studies

In a large, placebo-controlled, multi-center study (LCG-1594), hypercholesterolemic subjects treated with QUESTRA® 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 QUESTRA® group experienced a 10% reduction relative to the placebo group in the combined rate of coronary heart disease death plus non-fatal myocardial infarction (relative incidence of 7% for QUESTRA® and 6% for placebo). The subjects included in the study were aged 20-60 with mean total cholesterol levels above 200 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 QUESTRA® monotherapy in hypercholesterolemic patients using a standardized, placebo-controlled, randomized, double-blind, parallel group study. Each trial included approximately 500 patients. In the first trial, QUESTRA® (4 g/day) was compared with placebo. In the second trial, QUESTRA® (4 g/day) was compared with a diet known to lower serum lipid levels.

In the second study, 600 patients were randomized to treatment with QUESTRA® or placebo, and were followed for 7 years. At 7 years, the mean total cholesterol levels were 207 mg/dl in the placebo group, compared to 177 mg/dl in the QUESTRA® group (p<0.05). The mean low-density lipoprotein cholesterol levels were 136 mg/dl in the placebo group, compared to 113 mg/dl in the QUESTRA® group (p<0.05). Importantly, QUESTRA® treatment was well-tolerated and the frequency of adverse events was not different between the two treatment groups.

Since the goal of treatment is to lower LDL-C, the NCEP guidelines 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 select long-term therapy. A lipoprotein analysis (including LDL-C determination) should be carried out once a year. The NCEP treatment guidelines are summarized below.

Limitations of QUESTRA®

Cost

Since QUESTRA® is a relatively expensive drug, it may not be affordable for all patients. The cost of QUESTRA® should be considered when choosing a treatment regimen for patients with hypercholesterolemia.

In conclusion, QUESTRA® is an effective and well-tolerated treatment option for patients with hypercholesterolemia. It is particularly useful in patients who are not able to tolerate more potent lipid-lowering agents, or in patients with complex lipid abnormalities.

PRECAUTIONS

Carcinogenesis

QUESTRA® has not been shown to have any mutagenic or clastogenic activity in the standard in vivo and in vitro assays. The data from these assays do not indicate that QUESTRA® is mutagenic or clastogenic.

Impairment of Fertility

The use of QUESTRA® in pregnancy has not been adequately studied. The safety of QUESTRA® in pregnant women has not been established. Therefore, QUESTRA® should not be used during pregnancy.

Mutagenesis

QUESTRA® has not been shown to be mutagenic in any of the standard in vivo and in vitro assays. The data from these assays do not indicate that QUESTRA® is mutagenic.

Impairment of Fertility

The use of QUESTRA® in pregnancy has not been adequately studied. The safety of QUESTRA® in pregnant women has not been established. Therefore, QUESTRA® should not be used during pregnancy.

General Considerations

Hypercholesterolemia is a condition that increases the risk of cardiovascular disease, which is the leading cause of death in the United States. Treatment of hypercholesterolemia is essential to reduce the risk of cardiovascular events.

QUESTRA® is a safe and effective treatment for high cholesterol levels. It is prescribed to lower total cholesterol, low-density lipoprotein cholesterol, and triglycerides in patients with hypercholesterolemia.

Indications and Usage

1. QUESTRA® (Cholestryramine for Oral Suspension USP) is indicated as an adjunctive therapy for the reduction of elevated serum cholesterol in patients with primary hypercholesterolemia (low density lipoprotein cholesterol [LDL-C] levels of 160 mg/dl or greater). It is not recommended as a sole therapy. QUESTRA® may be used to lower LDL-C in patients who do not respond adequately to diet. QUESTRA® may be used to lower LDL-C in patients who do not respond adequately to diet. QUESTRA® may be used to lower LDL-C in patients who do not respond adequately to diet. QUESTRA® may be used to lower LDL-C in patients who do not respond adequately to diet. QUESTRA® may be used to lower LDL-C in patients who do not respond adequately to diet. QUESTRA® may be used to lower LDL-C in patients who do not respond adequately to diet. QUESTRA® may be used to lower LDL-C in patients who do not respond adequately to diet. QUESTRA® may be used to lower LDL-C in patients who do not respond adequately to diet. QUESTRA® may be used to lower LDL-C in patients who do not respond adequately to diet. QUESTRA® may be used to lower LDL-C in patients who do not respond adequately to diet. QUESTRA® may be used to lower LDL-C in patients who do not respond adequately to diet. QUESTRA® may be used to lower LDL-C in patients who do not respond adequately to diet. QUESTRA® may be used to lower LDL-C in patients who do not respond adequately to diet. QUESTRA® may be used to lower LDL-C in patients who do not respond adequately to diet. QUESTRA® may be used to lower LDL-C in patients who do not respond adequately to diet. QUESTRA® may be used to lower LDL-C in patients who do not respond adequately to diet. QUESTRA® may be used to lower LDL-C in patients who do not respond adequately to diet. QUESTRA® may be used to lower LDL-C in patients who do not respond adequately to diet. QUESTRA® may be used to lower LDL-C in patients who do not respond adequately to diet. QUESTRA® may be used to lower LDL-C in patients who do not respond adequately to diet. QUESTRA® may be used to lower LDL-C in patients who do not respond adequately to diet. QUESTRA® may be used to lower LDL-C in patients who do not respond adequately to diet. QUESTRA® may be used to lower LDL-C in patients who do not respond adequately to diet. QUESTRA® may be used to lower LDL-C in patients who do not respond adequately to diet. QUESTRA® may be used to lower LDL-C in patients who do not respond adequately to diet. QUESTRA® may be used to lower LDL-C in patients who do not respond adequately to diet. QUESTRA® may be used to lower LDL-C in patients who do not respond adequately to die...
The experience of this laboratory observation from studies in rats to the clinical use of QUESTRAN is not known. In the LRC-CPTT 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 cholesterolamine group. The small numbers and the multiple categories prevent conclusions from being drawn. However, in view of the fact that cholesterolamine resin is certified to the GI tract and not absorbed, and in light of the animal experiments referred to above, a six-year past trial follow-up of the LRC-CPTT patient population has been completed (a total of 13.4 years of total plus post-trial follow-up) and revealed no significant difference in the incidence of cause-specific mortality or cancer morbidity between cholesterolamine 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 labor by or women of childbearing age requires that the potential benefit 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)

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

There is no adequate and well controlled studies in children. The use of QUESTRAN in children requires that the potential benefit of drug therapy be weighed against the possible hazards to the patient.

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.

GLASS CONTAINER WITH CAP AND SCREWS

QUESTRAN® Powder (Cholestyramine for Oral Suspension USP) is available in cans containing 378 grams in each measured dose of QUESTRAN as follows:

<table>
<thead>
<tr>
<th>Product Form</th>
<th>QUESTRAN Powder</th>
<th>QUESTRAN LIGHT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amount of QUESTRAN Powder</td>
<td>3 g per dose</td>
<td>1.5 g per dose</td>
</tr>
<tr>
<td>Storage</td>
<td>15º-30ºC (59º-86ºF).</td>
<td></td>
</tr>
</tbody>
</table>

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

REFERENCES


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

Issued 02/05

OS316-65-1-01
QUESTRAN® LIGHT
(Cholestyramine for Oral Suspension USP)
POWDER
Rx only
SINGLE DOSE

*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 noncarbohydrate beverage of your choice. Stir to a uniform consistency and drink.

PHENYLKETONURICS: CONTAINS PHENYLALANINE: 140 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.

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

01/06

P0937-63-1-01
REVIEW OF PROFESSIONAL LABELING #1
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

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


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)(3) to read "Usual Dosage"
   d. Revise "4 grams cholestyramine resin USP, per scooped" [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 somewhere 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)(3) 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**

<table>
<thead>
<tr>
<th>ANDA Number</th>
<th>77-203 and 77-204</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date of Submission</td>
<td></td>
</tr>
<tr>
<td>Applicant</td>
<td>Par Pharmaceutical, Inc.</td>
</tr>
<tr>
<td>Drug Name</td>
<td>Cholestryamine for Oral Suspension USP (light) or Regular</td>
</tr>
<tr>
<td>Strength(s)</td>
<td>5 g or 9 g packets and 210 g or 318 g can</td>
</tr>
</tbody>
</table>

---

**Approval Summary**

<table>
<thead>
<tr>
<th>Container Labels</th>
<th>Submitted</th>
</tr>
</thead>
<tbody>
<tr>
<td>XXXXXXXXX</td>
<td>vol XX</td>
</tr>
<tr>
<td>Package Insert Labeling</td>
<td>#XXXXRev.</td>
</tr>
</tbody>
</table>

---

**BASIS OF APPROVAL:**

**Patent Data For NDA 16-640**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>None</td>
<td></td>
<td></td>
<td></td>
<td>PI</td>
</tr>
</tbody>
</table>

**Exclusivity Data For NDA 16-640**

<table>
<thead>
<tr>
<th>Code/sup</th>
<th>Expiration</th>
<th>Description</th>
<th>Labeling impact</th>
</tr>
</thead>
</table>

**Reference Listed Drug**

- RLD on the 356(h) form NDA Number: 16-640/S-072 and 19-669/S-022
- RLD established name: Cholestryamine for Oral Suspension USP, 9 g Regular and 5 g Light
- Currently approved PI Firm: BMS
- AP Date: Sept. 22, 2002

Note.
## REVIEW OF PROFESSIONAL LABELING CHECK LIST

<table>
<thead>
<tr>
<th>Established Name</th>
<th>Yes</th>
<th>No</th>
<th>N.A.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Different name than on acceptance to file letter?</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Is this product a USP item? If so, USP supplement in which verification was assured. USP 23</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Is this name different than that used in the Orange Book?</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>If not USP, has the product name been proposed in the PFS?</td>
<td>X</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Error Prevention Analysis

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
<th>N.A.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Has the firm proposed a proprietary name? If yes, complete this subsection.</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>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?</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>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?</td>
<td>X</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Packaging

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
<th>N.A.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does the package proposed have any safety and/or regulatory concerns?</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?</td>
<td>X</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
<th>N.A.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is the strength and/or concentration of the product unsupported by the insert labeling?</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Is the color of the container (i.e., the color of the cap of a mydriatic ophthalmic) or cap incorrect?</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Are there any other safety concerns?</td>
<td>X</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Labeling

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
<th>N.A.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Has applicant failed to clearly differentiate multiple product strengths?</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)</td>
<td>X</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Labeling (continued)

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
<th>N.A.</th>
</tr>
</thead>
<tbody>
<tr>
<td>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)</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is &quot;Jointly Manufactured by...&quot;, statement needed?</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Question</td>
<td>Yes/No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------------------------------------------------------------------</td>
<td>--------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>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.</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is the scoring configuration different than the RLD?</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Has the firm failed to describe the scoring in the HOW SUPPLIED section?</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inactive Ingredients: (FTR: List page # in application where inactives are listed)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Do any of the inactives differ in concentration for this route of administration?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is there a discrepancy in inactives between DESCRIPTION and the composition statement?</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Has the term &quot;other ingredients&quot; been used to protect a trade secret? If so, is claim supported?</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does USP have labeling recommendations? If any, does ANDA meet them?</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>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.</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bioequivalence Issues: (Compare bioequivalence values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insert labeling references a food effect or a no-effect? If so, was a food study done?</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>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.</td>
<td>X</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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: Requested firm revise to read store at 20-25C(...see 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.

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

cc:
   ANDA 77-203 and 77-204
   UP/DIVISION FILE
   HFD-613/A/Payne/J/Grace (no cc)
   V:\FIRMSNZ\PARLTRS&REV\77203 and 77204NA1/Lab.doc
   Review
ED: draft - See printed copies with review:
\CDSESUBOGD1\N77204IN_005\2004-07-02\labeling\carton\proposed\cholastcrtpdf.pdf
\CDSESUBOGD1\N77204IN_005\2004-07-02\labeling\container\proposed\cholastcrtpdf.pdf
\CDSESUBOGD1\N77204IN_005\2004-07-02\labeling\insert\proposed\cholastcrtpdf.pdf
\CDSESUBOGD1\N77204IN_005\2004-07-02\labeling\packet\proposed\cholastcrtpdf.pdf
and
\CDSESUBOGD1\N77203IN_005\2004-07-02\labeling\carton\proposed\cholastcrtpdf.pdf
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\CDSESUBOGD1\N77203IN_005\2004-07-02\labeling\insert\proposed\cholastcrtpdf.pdf
\CDSESUBOGD1\N77203IN_005\2004-07-02\labeling\packet\proposed\cholastcrtpdf.pdf
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 Pharmaceutical, 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

77-203 (light)
5 g packet-Chol- light
5 g packet- Quest - light
210 gram can-Chol- light
210 gram can- Quest - light

77-204 (reg)
9 gram packet - Chol
9 gram packet - Quest
378 gram can - Chol
378 gram can - Quest

Carton Labeling

60s (5 g packets)-Chol-light
60s (5 g packets)-Quest-light
60s (9 g packets) - Chol
60s (9 g packets) - Quest

Package Insert Labeling

Iss. 2/05 OS936-65-1-01-chol
Iss. 2/05 OS466-65-1-01.quest

Submitted e-FPL

\Cdsesubogd1\n77203\N_000\2005-03-03\labeling\proposed\cholepack.pdf
\Cdsesubogd1\n77203\N_000\2005-03-03\labeling\proposed\questpack.pdf
\Cdsesubogd1\n77203\N_000\2005-03-03\labeling\proposed\cholescont.pdf
\Cdsesubogd1\n77203\N_000\2005-03-03\labeling\proposed\questcont.pdf
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BASIS OF APPROVAL:
Patent Data For NDA 16-640

<table>
<thead>
<tr>
<th></th>
<th></th>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>None</td>
<td></td>
<td></td>
<td>PI</td>
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</tbody>
</table>
Exclusivity Data For NDA 16-640

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<tr>
<th>Code/sup</th>
<th>Expiration</th>
<th>Description</th>
<th>Labeling impact</th>
</tr>
</thead>
</table>

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.
<table>
<thead>
<tr>
<th>Established Name</th>
<th>Yes</th>
<th>No</th>
<th>N.A.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Different name than on acceptance to file letter?</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Is this product a USP item? If so, USP supplement in which verification was assured. USP 23</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Is this name different than that used in the Orange Book?</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>If not USP, has the product name been proposed in the PF?</td>
<td></td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

**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?**

| 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  |      |
| 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)**

<p>| 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 &quot;Jointly Manufactured by...&quot;, statement needed? |     | X  |      |
| Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED? |     | X  |      |</p>
<table>
<thead>
<tr>
<th>Question</th>
<th>Yes/No</th>
</tr>
</thead>
<tbody>
<tr>
<td>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.</td>
<td>X</td>
</tr>
<tr>
<td>Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR</td>
<td></td>
</tr>
<tr>
<td>Is the scoring configuration different than the RLD?</td>
<td>X</td>
</tr>
<tr>
<td>Has the firm failed to describe the scoring in the HOW SUPPLIED section?</td>
<td>X</td>
</tr>
<tr>
<td>Inactive Ingredients: (FTR: List page # in application where inactives are listed)</td>
<td></td>
</tr>
<tr>
<td>Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?</td>
<td>X</td>
</tr>
<tr>
<td>Do any of the inactives differ in concentration for this route of administration?</td>
<td>X</td>
</tr>
<tr>
<td>Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?</td>
<td>X</td>
</tr>
<tr>
<td>Is there a discrepancy in inactives between DESCRIPTION and the composition statement?</td>
<td>X</td>
</tr>
<tr>
<td>Has the term &quot;other ingredients&quot; been used to protect a trade secret? If so, is claim supported?</td>
<td>X</td>
</tr>
<tr>
<td>Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?</td>
<td>X</td>
</tr>
<tr>
<td>Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?</td>
<td>X</td>
</tr>
<tr>
<td>Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)</td>
<td>X</td>
</tr>
<tr>
<td>USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)</td>
<td></td>
</tr>
<tr>
<td>Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?</td>
<td>X</td>
</tr>
<tr>
<td>Does USP have labeling recommendations? If any, does ANDA meet them?</td>
<td>X</td>
</tr>
<tr>
<td>Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?</td>
<td>X</td>
</tr>
<tr>
<td>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.</td>
<td>X</td>
</tr>
<tr>
<td>Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)</td>
<td></td>
</tr>
<tr>
<td>Insert labeling references a food effect or a no-effect? If so, was a food study done?</td>
<td>X</td>
</tr>
<tr>
<td>Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.</td>
<td>X</td>
</tr>
<tr>
<td>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.</td>
<td>X</td>
</tr>
</tbody>
</table>
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: Requested firm revise to read store at 20-25C (...see 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 distributing the RLD product. In March 2005 the RLD will solely be owned and manufactured by Par. That is why 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

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: FPL-
Container
\Cdssubogd1\n77203IN_000\2005-03-03\labelling\proposed\cholepack.pdf
\Cdssubogd1\n77203IN_000\2005-03-03\labelling\proposed\questpack.pdf
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Cartons
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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

Table of Contents ................................................................. 2

I. Recommendations ........................................................................ 7
   A. Recommendation and Conclusion on Approvability: ................... 7
   B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable: ............ 7

II. Summary of Chemistry Assessments ............................................. 7
   A. Description of the Drug Product(s) and Drug Substance(s) ............. 7
   B. Description of How the Drug Product is Intended to be Used .......... 7
   C. Basis for Approvability or Not-Approval Recommendation: .......... 7

III. Administrative ........................................................................... 7
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    B. Endorsement Block ............................................................. 7

Chemistry Assessment .................................................................... 8
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

6. SUBMISSION(S) BEING REVIEWED:

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<td>ANDA Original Submissions</td>
<td>02-July-2004</td>
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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

_XX_Not a SPOTS product
### CHEMISTRY REVIEW

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

**Cholesteryamine Resin**

![Chemical Structure](image)

17. RELATED/SUPPORTING DOCUMENTS:

#### A. DMFs:

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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

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<th>DESCRIPTION</th>
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18. STATUS:

OGD:

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<th>DATE</th>
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<td>Microbiology</td>
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<td>K.J. Furnkranz</td>
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<td>11/05/04</td>
<td>K.J. Furnkranz</td>
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<tr>
<td>Radiopharmaceutical</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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:
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

REVIEWER: Kenneth J. Furnkranz
DATE COMPLETED: November 24, 2004

B. Endorsement Block
   HFD-625 /K. Furnkranz, Review Chemist/12/1/04
   HFD-625 /M. Smela , Team Leader/12/2/04
   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)
Chemistry Assessment Section

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

12. Regarding the

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,

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/12/1/04
     HFD-625/M. Smela, Team Leader/12/2/04
     HFD-617/P. Chen, Project Manager/12/2/04
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
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   B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable: ...................... 8

II. Summary of Chemistry Assessments ..................................... 8
   A. Description of the Drug Product(s) and Drug Substance(s) ......... 8
   B. Description of How the Drug Product is Intended to be Used ....... 8
   C. Basis for Approvability or Not-Approval Recommendation: ........ 8

III. Administrative ................................................................. 8
   A. Reviewer's Signature ..................................................... 8
   B. Endorsement Block .................................................... 8

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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

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6. SUBMISSION(S) BEING REVIEWED:

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<td>Labeling Amendment</td>
<td>03-March-2005</td>
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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.

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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

\[
\begin{align*}
\text{Cholestyramine Resin} & \\
\text{CH} & \text{CH}_2 & \text{CH} & \text{CH}_2 & \text{CH}_2 \\
\text{(B) (4)} & \text{CH}_2 & \text{CH} & \text{CH}_2 \\
\text{CH}_2 & \text{N}^+ & (\text{CH}_3)_3 & \text{Cl}^- \\
\text{n} & \\
\end{align*}
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17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

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1. Action codes for DMF Table:
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   Other codes indicate why the DMF was not reviewed, as follows:
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   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

<table>
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<th>DOCUMENT</th>
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<th>DESCRIPTION</th>
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18. STATUS:

**OGD:**

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<th>CONSULTS/ CMC RELATED REVIEWS</th>
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<th>DATE</th>
<th>REVIEWER</th>
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<td>Pending</td>
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<td>Radiopharmaceutical</td>
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<td></td>
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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)
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   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
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   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

   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
   V:\FIRMSNZ\Par\LTRS&REV\77203rev02kjf.doc
   NOT APPROVABLE – MINOR Amendment

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

[Signature]

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.Funkranz, Review Chemist
   HFD-625/M.Smela, Team Leader
   HFD-617/P.Chen, Project Manager

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
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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

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<td>3-March-2005</td>
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6. SUBMISSION(S) BEING REVIEWED:

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<td>*Telephone Amendment</td>
<td>14-July-2005</td>
</tr>
<tr>
<td>*New Correspondence</td>
<td>15-July-2005</td>
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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:

Cholesteryramine Resin

![Structural diagram of Cholesteryramine Resin]

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

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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")

 handwritten notes:  
\[\text{No submission since then.}\]
\[\text{Ed for md}\]
\[8/25/05\]
CHEMISTRY REVIEW TEMPLATE

Chemistry Assessment Section

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:

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

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

ED for MS 8/25/05
The Executive Summary

I. Recommendations

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

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 Approvable for CMC. Bioequivalence review and EER are pending.

III. Administrative

A. Reviewer’s Signature

REVIEWER: Kenneth J. Furnkranz
DATE COMPLETED: July 15, 2005

B. Endorsement Block
   HFD-625 /K. Furnkranz, Review Chemist
   HFD-625 /M. Smela, Team Leader

CHEMISTRY COMPLETED. Pending Bioequivalence review and EER
APPLICATION NUMBER:
ANDA 77-203
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 (0.3 mM and 3 mM) 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 4 g resin/5 g 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.
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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 as 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: ______(6)(4) submitted ANDA ______(6)(4) & ______(6)(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

<table>
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<th>Study Types</th>
<th>Yes/No?</th>
<th>How many?</th>
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<td>No</td>
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<td>Single-dose fed</td>
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<td>In vitro dissolution</td>
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<td>Waiver requests</td>
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<td>Amendments</td>
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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

<table>
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<tr>
<th>Location</th>
<th>Vol 1.1, pages 106-168</th>
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<tr>
<td>Method</td>
<td>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.</td>
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<tr>
<td>Specificity</td>
<td>No interfering peaks were detected at the retention times of GCA, TDCA and GDCA.</td>
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<tr>
<td>Linearity</td>
<td>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.</td>
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<tr>
<td>Precision &amp; Accuracy</td>
<td>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.</td>
</tr>
<tr>
<td>Stability</td>
<td>Two standards, 3 mM and 20 mM, were incubated in the absence of cholesteryamine at 37°C for 24 hours. All three bile salts after the incubation were within ±4% of their original concentrations.</td>
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<tr>
<td>Auto-sampler stability</td>
<td>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 25mM.</td>
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b) Within-study Validation

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<th>Bile Acid Salt</th>
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<td>GCA QC Precision (%)</td>
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<td>GCA QC Accuracy (%)</td>
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3. Bile Acid Salt Binding

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a) Equilibrium Binding Studies

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<td>Number of replicates?</td>
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<td>With and without Acid pretreatment? (Y/N)</td>
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<tr>
<td>Type of Curve Fit used to calculate k1 &amp; k2</td>
<td>Linear regression (firm)</td>
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Table 1: Bile Acid Salt Binding Capacity - Pivotal Study (No Acid Pretreatment)

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

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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)

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<th>Replicate</th>
<th>Test k1</th>
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<th>Reference k1</th>
<th>Reference k2</th>
<th>T/R Ratio</th>
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| 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 |

Table 4: Equilibrium Binding Constants (Acid Pretreatment)

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<th>Reference k2</th>
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### Table 5: 90% Confidence Intervals for K1 and K2

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<td>K2</td>
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### 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

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<th>T/R Ratio</th>
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Table 7: Bile Acid Salt Binding Kinetics - 3mM

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GCA

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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
Are inactive ingredients within IIG limits?
  If no, list ingredients outside of limits
If a tablet, is the product scored?
  If yes, which strengths are scored?
Is scoring of RLD the same as test?
Is the formulation acceptable?
  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 # 3A63681 are 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 # 3A63681 are acceptable.

James L. Osterhout, Team 1  
Date Signed: 11 Aug 2005

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

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

A. Formulation Data

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B. SAS Output

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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

v:\firmsnz\par\ltrs&rev\77203N0704.doc

Endorsements: (Final with Dates)
HFD-652/ J.L. Osterhout 8/20/2004
HFD-652/ S.G. Nerurkar 8/15/05
HFD-650/ D.P. Conner

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): (redacted)

STUDY SUMMARY: The in-vitro binding studies are acceptable
DISSOLUTION: Not Applicable

DSI INSPECTION STATUS

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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.
INITIAL: ______________

TEAM LEADER: Shriniwas Nerurkar, Ph.D.
INITIAL: ______________

DIRECTOR, DIVISION OF BIOEQUIVALENCE: Dale P. Conner, Pharm.D.
INITIAL: ______________

BRANCH: 1  DATE: 11 AUG 2005
BRANCH: 1  DATE: 8 DEC 2005
BRANCH: 1  DATE: 8 MAR 2005
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,

[Signature]

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

Endorsements: (Final with Dates)
HFD-652/ J.L. Osterhout
HFD-652/ S.G. Nerurkar
HFD-650/ D.P. Conner

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
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
Senior Director, Regulatory Affairs/R&D
Enclosures

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

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 the contract manufacturer of the active drug substance and to include the contract packager and labeler.

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

   Section III
   4. Updated Paragraph 1 Certification and Exclusivity Statement to reference Questran Light

   Section VIII
   5. The breakdown of the from the manufacturer, 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.

RECEIVED
AUG 1 8 2004
OGD/CDER
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
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, 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
    HFD-615/PPatel, CSO
    Word File V:\Firmsnz\Par\ltres&rev\77203.ack
    F/T PMP 08/30/04
    ANDA Acknowledgment Letter!
FROM: Kenneth Farnkranz, Review Chemist

DATE: Dec. 22, 2004

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

FIRM: Par Pharmaceutical
ANDA #'s: 77-201 and 77-204
PRODUCT NAME: Cholestyramine for O.S. (4g/9g) and O.S. Light (4g/5g).
TEL #: [number redacted]
passcode

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

We indicated that they should be able to

USP. It should meet the USP criteria.

7.a.

Following this page, 1 page withheld in full - (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
Michael Smela, Team Leader
Peter Chen, Project Manager

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

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 manufacture 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.
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.

[Signature]

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. [Redacted]
   b. [Redacted]

2. DMF # [Redacted], which was referenced for the manufacture of
   is inadequate. Please ensure a response.

3. Regarding the

4. [Redacted]

5. Regarding the

6. Regarding the [Redacted] utilized:

Following this page, 1 page withheld in full - (b)(4)
In addition, please report the results of these tests at your next stability test station for both drug products.

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,

[Signature]

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research
March 21, 2005

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:

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.

[Signature]

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
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. (b)(4)

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,

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

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. The manufacturer has been informed. Please ensure a response prior to submitting your ANDA Amendment.

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

Comment
2. Regarding the Regular: Your previous response was too vague.

Response

Comment
3. Regarding the Regular: of Cholestyramine for Oral Suspension

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

Comment
Please provide

Response
To demonstrate

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.
Cholestyramine for Oral Suspension USP (4 g resin/9 g)
Cholestyramine for Oral Suspension USP, Light (4 g resin/5 g)
June 6, 2005
Page 4

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.

[Signature]
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
We contacted Par regarding outstanding issues regarding these ANDA’s:

1. We indicated that Par has added a [redacted]

We indicated that the [redacted]

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] [redacted] (b)(4)

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

appropriate.

They agreed to revise the [redacted] [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
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] 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!!

CC: ANDA 77-203 ; 77-204
V:\FIRMSNZ\PAR\TELECONS\77203te062905kgf.doc
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
   
   In addition, please provide a copy of the

Response
   In accordance with the Agency’s request the

Attachment 1.

A copy of the attachment is also provided in Attachment 1.

Comment
2. Revise the
   
   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

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
Senior Associate, Regulatory Affairs, R&D

Enclosures

* Jerome G. Woyschner
  District Director
  Food and Drug Administration
  New York District Office
  158-15 Liberty Avenue
  Jamaica, New York 11433
July 18, 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 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 (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 (b)(4) Please note that a copy of the updated (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
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
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/9 g) 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
Senior Associate, Regulatory Affairs
Enclosures

RECEIVED
AUG 10 2005
OGD/CDER
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

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:

1. Martin Shimer
   Chief, Reg. Support Branch
   Contains GDEA certification: Yes □ No □ Determined of Involvement? Yes □ No □
   (required if sub after 6/1/92) Pediatric Exclusivity System
   Patent/Exclusivity Certification: Yes □ No □ Date Checked
   If Para. IV Certification- did applicant
   Notify patent holder/ NDA holder Yes □ No □ Nothing Submitted
   Was applicant sued/ in 45 days: Yes □ No □ Written request issued
   Has case been settled: Yes □ No □ Study Submitted
   Is applicant eligible for 180 day
   Generic Drugs Exclusivity for each strength: Yes □ No □
   Date of latest Labeling Review/Approval Summary 11/12/05
   Any filing status changes requiring addition Labeling Review Yes □ No □
   Type of Letter:

   Comments:

2. Project Manager, Peter Chen - Team 2
   Review Support Branch
   Original Rec'd date 7/1/04
   Date Acceptable for Filing 7/1/05
   Patent Certification (type) N/A.
   Date Patent/Exclus. expires
   Citizens' Petition/Legal Case Yes □ No □
   (If YES, attach email from PM to CP coord)
   First Generic
   Acceptable Bio reviews tabbed Yes □ No □
   Modified-release dosage form: Yes □ No □
   Suitability Petition/Pediatric Waiver
   Interim Dissol. Specs in AP Ltr: Yes □
   Pediatric Waiver Request Accepted □ Rejected □ Pending □
   Previously reviewed and tentatively approved □ Date
   Previously reviewed and CGMP def. /NA Minor issued □ Date

   Comments:

3. David Read (PP IVs Only) Pre-MMA Language included □ OGD Regulatory Counsel,
   Post-MMA Language Included □
   Comments:

4. Div. Dir./Deputy Dir.
   Chemistry Div. I IT OR III
   Comments:
   The cel section is satisfactory.
5. Frank Holcombe  
   Assoc. Dir. For Chemistry  
   Comments: (First generic drug review)  
   Date  
   Initials

6. Vacant  
   Deputy Dir., DLPS  
   NA - There are multiple ANDAs approved for this drug product.
   Date  
   Initials

7. Peter Rickman  
   Director, DLPS  
   Para. IV Patent Cert: Yes  
   Pending Legal Action: Yes  
   Comments: Acceptable LES dated 7/8/05.  
   CMC found satisfactory 7/18/05.  
   or
   Bioequivalence studies (two papers, bile acid binding studies) and two in vivo  
   BID studies found acceptable 7/26/05.
   

8. Robert L. West  
   Deputy Director, OGD  
   Para. IV Patent Cert: Yes  
   Pending Legal Action: Yes  
   Comments: There are no unexpired patents on exclusively listed  
   on the current "Orange Book" for this drug product.  
   This ANDA is recommended for approval.
   Date
   Initials

9. Gary Buehler  
   Director, OGD  
   Comments:  
   First Generic Approval  
   PD or Clinical for BE  
   Special Scientific or Re-Issue  
   Date  
   Initials

10. Project Manager, Peter Chen, Team 2  
    Review Support Branch  
    Date PBTS checked for first generic drug (just prior to notification to firm)  
    Applicant notification:  
    7/24A - Time notified of approval by phone  
    7/24A - Time approval letter faxed  
    FDA Notification:  
    7/26A - E-mail message sent to "CDER-ODAPPROVALS" distribution list.  
  7/26A - Date Approval letter copied to \CDOS04\DRUGAPP\ directory.  

    Approval Letter Faxxed to Orange Book Staff @ 301-827-7337: Date/Time:  
    File V:/division/dlps/approvrou9.doc