CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40-322

APPROVAL LETTER

ANDA 40-322

JAN 19 2000

Copley Pharmaceutical, Inc.
Attention: Isidoro Nudelman
25 John Road
Canton, MA 02021

Dear Sir:

This is in reference to your abbreviated new drug application dated June 30, 1998, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Prednisolone Syrup USP, 15 mg/5 mL.

Reference is also made to your amendments dated March 16, September 14, September 29, and November 15, 1999; and January 7, 2000.

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 Prednisolone Syrup USP, 15 mg/5 mL, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Prelone® Syrup, 15 mg/5 mL, of Muro Pharmaceutical Inc.).

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.

Post-marketing 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.

We request that you submit, in duplicate, any proposed advertising or promotional copy that you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

Douglas L. Sporn 1/19/00
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40-322

APPROVED DRAFT LABELING

NDC 38245-129-19

Prednisolone Syrup, USP

15 mg per 5 mL

℞ Only

240 mL

Copley Pharmaceutical, Inc.
Canton, MA 02021

DESCRIPTION: Prednisolone syrup contains 15 mg of Prednisolone in each 5 mL (teaspoonful).
Benzoic acid 0.1% added as a preservative.
Also alcohol, 5%.

USUAL DOSAGE: See accompanying circular.

STORE AT CONTROLLED ROOM TEMPERATURE 15°-30°C (59°-86°F). DO NOT REFRIGERATE.

Dispense in tight, light-resistant and child-resistant containers as defined in USP.

PHARMACIST: Dispense with a suitable Calibrated Measuring Device.

3 38245-129-19 5

LAB725201

LOT:
EXP:

LOT:
EXP:

NDC 38245-129-07

DESCRIPTION: Prednisolone syrup contains 15 mg of Prednisolone in each 5 mL (teaspoonful).
Benzoic acid 0.1% added as a preservative.
Also alcohol, 5%.

USUAL DOSAGE: See accompanying circular.

STORE AT CONTROLLED ROOM TEMPERATURE 15°-30°C (59°-86°F). DO NOT REFRIGERATE.

Dispense in tight, light-resistant and child-resistant containers as defined in USP.

PHARMACIST: Dispense with a suitable Calibrated Measuring Device.

3 38245-129-07 2

Prednisolone Syrup, USP

15 mg per 5 mL

℞ Only

480 mL

Copley Pharmaceutical, Inc.
Canton, MA 02021

LAB725301

Prednisolone Syrup, USP
15 mg per 5 mL

508201

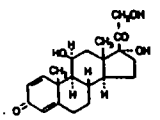
LEA508201
Revised: September 1999

℞ Only

508201

DESCRIPTION: Prednisolone syrup contains prednisolone which is a glucocorticoid. Glucocorticoids are adrenocortical steroids, both naturally occurring and synthetic, which are readily absorbed from the gastrointestinal tract. Prednisolone is a white to practically white, odorless, crystalline powder. It is very slightly soluble in water, soluble in methanol and in dioxane; sparingly soluble in acetone and in alcohol, slightly soluble in chloroform.

The chemical name for Prednisolone is Pregna-1,4-diene-3,20-dione,11,17, 21-trihydroxy-,(11β)-. Its molecular weight is 360.45. The molecular formula is $C_{21}H_{28}O_5$, and the structural formula is:



Prednisolone Syrup, for oral administration, contains 15 mg of prednisolone in each 5 mL and alcohol 5%. Benzoic acid 0.1% is added as a preservative. In addition, it contains the following inactive ingredients: citric acid, dl-menthol, edetate disodium, fructose, glycerin, pharmasweet flavor, propylene glycol, purified water, sodium saccharin, artificial cherry flavor, FD&C blue #1 and red #40.

CLINICAL PHARMACOLOGY: Naturally occurring glucocorticoids (hydrocortisone and cortisone), which also have salt-retaining properties, are used as replacement therapy in adrenocortical deficiency states. Their synthetic analogs such as prednisolone are primarily used for their potent anti-inflammatory effects in disorders of many organ systems.

Glucocorticoids such as prednisolone cause profound and varied metabolic effects. In addition, they modify the body's immune responses to diverse stimuli.

INDICATIONS AND USAGE: Prednisolone syrup is indicated in the following conditions:

1. **Endocrine Disorders**
   - Primary or secondary adrenocortical insufficiency (hydrocortisone or cortisone is the first choice; synthetic analogs may be used in conjunction with mineralocorticoids where applicable; in infancy mineralocorticoid supplementation is of particular importance).
   - Congenital adrenal hyperplasia
   - Nonsuppurative thyroiditis
   - Hypercalcemia associated with cancer
2. **Rheumatic Disorders**
   - As adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in:
   - Psoriatic arthritis
   - Rheumatoid arthritis, including juvenile rheumatoid arthritis (selected cases may require low-dose maintenance therapy)
   - Ankylosing spondylitis
   - Acute and subacute bursitis
   - Acute nonspecific tenosynovitis
   - Acute gouty arthritis
   - Post-traumatic osteoarthritis
   - Synovitis of osteoarthritis
   - Epicondylitis
3. **Collagen Diseases**
   - During an exacerbation or as maintenance therapy in selected cases of:
   - Systemic lupus erythematosus
   - Acute rheumatic carditis
4. **Dermatologic Diseases**
   - Pemphigus
   - Bullous dermatitis herpetiformis
   - Severe erythema multiforme (Stevens-Johnson syndrome)
   - Exfoliative dermatitis
   - Mycosis fungoides
   - Severe psoriasis
   - Severe seborrheic dermatitis
5. **Allergic States**
   - Control of severe or incapacitating allergic conditions intractable to adequate trials of conventional treatment:
   - Seasonal or perennial allergic rhinitis
   - Bronchial asthma
   - Contact dermatitis
   - Atopic dermatitis
   - Serum sickness
   - Drug hypersensitivity reactions
6. **Ophthalmic Diseases**
   - Severe acute and chronic allergic and inflammatory processes involving the eye and its adnexa such as:
   - Allergic corneal marginal ulcers
   - Herpes zoster ophthalmicus
   - Anterior segment inflammation
   - Diffuse posterior uveitis and choroiditis
   - Sympathetic ophthalmia
   - Allergic conjunctivitis
   - Keratitis
   - Chorioretinitis
   - Optic neuritis
   - Iritis and iridocyclitis
7. **Respiratory Diseases**
   - Symptomatic sarcoidosis
   - Loeffler's syndrome not manageable by other means
   - Berylliosis
   - Fulminating or disseminated pulmonary tuberculosis when used concurrently with appropriate chemotherapy
   - Aspiration pneumonitis
8. **Hematologic Disorders**
   - Idiopathic thrombocytopenic purpura in adults
   - Secondary thrombocytopenia in adults
   - Acquired (autoimmune) hemolytic anemia
   - Erythroblastopenia (RBC anemia)
   - Congenital (erythroid) hypoplastic anemia
9. **Neoplastic Diseases**
   - For palliative management of:
   - Leukemias and lymphomas in adults
   - Acute leukemia of childhood
10. **Edematous States**
    - To induce a diuresis or remission of proteinuria in the nephrotic syndrome, without uremia, of the idiopathic type or that due to lupus erythematosus.
11. **Gastrointestinal Diseases**
    - To tide the patient over a critical period of the disease in:
    - Ulcerative colitis
    - Regional enteritis
12. **Miscellaneous**
    - Tuberculous meningitis with subarachnoid block or impending block used concurrently with appropriate antituberculous chemotherapy. Trichinosis with neurologic or myocardial involvement.

In addition to the above indications prednisolone syrup is indicated for systemic dermatomyositis (polymyositis).

CONTRAINDICATIONS: Systemic fungal infections.

WARNINGS: In patients on corticosteroid therapy subjected to unusual stress, increased dosage of rapidly acting corticosteroids before, during, and after the stressful situation is indicated.

Corticosteroids may mask some signs of infection, and new infections may appear during

their use. There may be decreased resistance and inability to localize infection when corticosteroids are used.

Prolonged use of corticosteroids may produce posterior subcapsular cataracts, glaucoma with possible damage to the optic nerves, and may enhance the establishment of secondary ocular infections due to fungi or viruses.

Average and large doses of hydrocortisone or cortisone can cause elevation of blood pressure, salt and water retention, and increased excretion of potassium. These effects are less likely to occur with the synthetic derivatives except when used in large doses. Dietary salt restriction and potassium supplementation may be necessary. All corticosteroids increase calcium excretion.

While on corticosteroid therapy, patients should not be vaccinated against smallpox. Other immunization procedures should not be undertaken in patients who are on corticosteroids, especially on high dose, because of possible hazards of neurological complications and a lack of antibody response.

Persons who are on drugs which suppress the immune system are more susceptible to infections than healthy individuals. Chickenpox and measles, for example, can have a more serious or even fatal course in non-immune children or adults on corticosteroids. In such children or adults who have not had these diseases, particular care should be taken to avoid exposure. How the dose, route and duration of corticosteroid administration affects the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing information). If chickenpox develops, treatment with antiviral agents may be considered.

The use of prednisolone syrup in active tuberculosis should be restricted to those cases of fulminating or disseminated tuberculosis in which the corticosteroid is used for the management of the disease in conjunction with an appropriate antituberculous regimen.

If corticosteroids are indicated in patients with latent tuberculosis or tuberculin reactivity, close observation is necessary as reactivation of the disease may occur. During prolonged corticosteroid therapy, these patients should receive chemoprophylaxis.

Use in pregnancy: Since adequate human reproduction studies have not been done with corticosteroids, the use of these drugs in pregnancy, nursing mothers or women of childbearing potential requires that the possible benefits of the drug be weighed against the potential hazards to the mother and embryo or fetus. Infants born of mothers who have received substantial doses of corticosteroids during pregnancy should be carefully observed for signs of hypoadrenalism.

PRECAUTIONS:

General: Drug-induced secondary adrenocortical insufficiency may be minimized by gradual reduction of dosage. This type of relative insufficiency may persist for months after discontinuation of therapy; therefore, in any situation of stress occurring during that period, hormone therapy should be reinstituted. Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently.

There is an enhanced effect of corticosteroids on patients with hypothyroidism and in those with cirrhosis.

Corticosteroids should be used cautiously in patients with ocular herpes simplex because of possible corneal perforation.

The lowest possible dose of corticosteroid should be used to control the condition under treatment, and when reduction in dosage is possible, the reduction should be gradual.

Psychic derangements may appear when corticosteroids are used, ranging from euphoria, insomnia, mood swings, personality changes, and severe depression, to frank psychotic manifestations. Also, existing emotional instability or psychotic tendencies may be aggravated by corticosteroids.

Aspirin should be used cautiously in conjunction with corticosteroids in hypoprothrombinemia.

Steroids should be used with caution in nonspecific ulcerative colitis, if there is a probability of impending perforation, abscess or other pyogenic infections; diverticulitis; fresh intestinal anastomoses; active or latent peptic ulcer; renal insufficiency; hypertension; osteoporosis; and myasthenia gravis.

Growth and development of infants and children on prolonged corticosteroid therapy should be carefully observed.

Information for Patients: Patients who are on immunosuppressant doses of corticosteroids should be warned to avoid exposure to chickenpox or measles. Patients should also be advised that if they are exposed, medical advice should be sought without delay.

ADVERSE REACTIONS:

Fluid and Electrolyte Disturbances

- Sodium retention
- Fluid retention
- Congestive heart failure in susceptible patients
- Potassium loss
- Hypokalemic alkalosis
- Hypertension

Musculoskeletal

- Muscle weakness
- Steroid myopathy
- Loss of muscle mass
- Osteoporosis
- Vertebral compression fractures
- Aseptic necrosis of femoral and humeral heads
- Pathologic fracture of long bones

Gastrointestinal

- Peptic ulcer with possible perforation and hemorrhage
- Pancreatitis
- Abdominal distention
- Ulcerative esophagitis

Dermatologic

- Impaired wound healing
- Thin fragile skin
- Petechiae and ecchymoses
- Facial erythema
- Increased sweating
- May suppress reactions to skin tests

Neurological

- Convulsions
- Increased intracranial pressure with papilledema (pseudo-tumor cerebri) usually after treatment
- Vertigo
- Headache

Endocrine

- Menstrual irregularities
- Development of Cushingoid state
- Suppression of growth in pediatric patients
- Secondary adrenocortical and pituitary unresponsiveness, particularly in times of stress, as in trauma, surgery or illness
- Decreased carbohydrate tolerance
- Manifestations of latent diabetes mellitus
- Increased requirements for insulin or oral hypoglycemic agents in diabetics

Ophthalmic

- Posterior subcapsular cataracts
- Increased intraocular pressure
- Glaucoma
- Exophthalmos

Metabolic

- Negative nitrogen balance due to protein catabolism

DOSAGE AND ADMINISTRATION: Dosage of prednisolone syrup should be individualized according to the severity of the disease and the response of the patient. For infants and children, the recommended dosage should be governed by the same considerations rather than strict adherence to the ratio indicated by age or body weight.

Hormone therapy is an adjunct to and not a replacement for conventional therapy.

Dosage should be decreased or discontinued gradually when the drug has been administered for more than a few days.

The severity, prognosis, expected duration of the disease, and the reaction of the patient to medication are primary factors in determining dosage.

If a period of spontaneous remission occurs in a chronic condition, treatment should be discontinued.

Blood pressure, body weight, routine laboratory studies, including two-hour postprandial blood glucose and serum potassium, and a chest X-ray should be obtained at regular intervals during prolonged therapy. Upper GI X-rays are desirable in patients with known or suspected peptic ulcer disease.

The initial dosage of prednisolone syrup may vary from 5 mg to 60 mg per day depending on the specific disease entity being treated. In situations of less severity lower doses will generally suffice while in selected patients higher initial doses may be required. The initial dosage should be maintained or adjusted until a satisfactory response is noted. If after a reasonable period of time there is a lack of satisfactory clinical response, prednisolone syrup should be discontinued and the patient transferred to other appropriate therapy. **IT SHOULD BE EMPHASIZED THAT DOSAGE REQUIREMENTS ARE VARIABLE AND MUST BE INDIVIDUALIZED ON THE BASIS OF THE DISEASE UNDER TREATMENT AND THE RESPONSE OF THE PATIENT.**

After a favorable response is noted, the proper maintenance dosage should be determined by decreasing the initial drug dosage in small decrements at appropriate time intervals until the lowest dosage which will maintain an adequate clinical response is reached. It should be kept in mind that constant monitoring is needed in regard to drug dosage. Included in the situations which may make dosage adjustments necessary are changes in clinical status secondary to remissions or exacerbations in the disease process, the patient's individual drug responsiveness, and the effect of patient exposure to stressful situations not directly related to the disease entity under treatment. In this latter situation it may be necessary to increase the dosage of prednisolone syrup for a period of time consistent with the patient's condition. If after long-term therapy the drug is to be stopped, it is recommended that it be withdrawn gradually rather than abruptly.

HOW SUPPLIED: Prednisolone syrup is a cherry flavored red liquid containing 15 mg of Prednisolone in each 5 mL (teaspoonful) and is supplied in 240 mL bottles (NDC 38245-129-19) and 480 mL bottles (NDC 38245-129-07).

Pharmacist: Dispense with a suitable calibrated measuring device to assure proper measuring of dose.

Dose/Volume Chart

15 mg prednisolone = 1 teaspoon

10 mg prednisolone = 2/3 teaspoon

7.5 mg prednisolone = 1/2 teaspoon

5 mg prednisolone = 1/3 teaspoon

Dispense in tight, light-resistant and child-resistant containers as defined in USP/NF.

Store at controlled room temperature 15°-30°C (59°-86°F). Do Not Refrigerate.

Copley Pharmaceutical, Inc.
Canton, MA
LEA508201
Revised: September 1999

LOT:
EXP:

Prednisolone Syrup, USP

NDC 38245-129-19

Prednisolone Syrup, USP

15 mg per 5 mL

℞ Only

240 mL

Copley Pharmaceutical, Inc.
Canton, MA 02021

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Benzoic acid 0.1% added as a preservative.
Also alcohol, 5%.

NDC 38245-129-19

Prednisolone Syrup, USP

15 mg per 5 mL

℞ Only

240 mL

Copley Pharmaceutical, Inc.
Canton, MA 02021

USUAL DOSAGE: See accompanying circular.

Dispense in tight, light-resistant and child-resistant containers as defined in USP.

STORE AT CONTROLLED ROOM TEMPERATURE 15°-30°C (59°-86°F). DO NOT REFRIGERATE.

PHARMACIST: Dispense with a suitable Calibrated Measuring Device.

For your convenience, calibrated teaspoons are enclosed.

EXP:
LOT:

Prednisolone Syrup, USP

NDC 38245-129-07

Prednisolone Syrup, USP

15 mg per 5 mL

℞ Only

480 mL

Copley Pharmaceutical, Inc.
Canton, MA 02021

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Canton, MA 02021

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PHARMACIST: Dispense with a suitable Calibrated Measuring Device.

For your convenience, calibrated teaspoons are enclosed.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40-322

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO. 2

2. ANDA # 40-322

3. NAME AND ADDRESS OF APPLICANT

Copley Pharmaceutical, Inc.
25 John Road
Canton, MA 02021

4. LEGAL BASIS FOR SUBMISSION

In Copley's opinion and to the best of their knowledge, there are no United States patents that claim the listed drug referred to in this application or which claims a use or formulation for the listed drug for which Copley is seeking approval.

5. SUPPLEMENT(s)

Original 6/30/98

6. PROPRIETARY NAME

7. NONPROPRIETARY NAME

Prednisolone

8. SUPPLEMENT(s) PROVIDE(s) FOR:

N/A

9. AMENDMENTS AND OTHER DATES:

Amendment 8/11/98
Amendment 3/16/99
Amendment 9/14/99
Amendment 9/29/99
Amendment 11/15/99
Amendment 1/7/00

10. PHARMACOLOGICAL CATEGORY

Steroid

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

DMF's

13. DOSAGE FORM

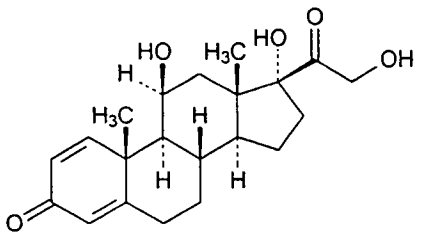
Syrup

14. POTENCY

15 mg/5 mL

15. CHEMICAL NAME AND STRUCTURE

Prednisolone. Pregna-1,4-diene-3,20-dione, 11,17,21-trihydroxy-, (11β)-. $C_{21}H_{28}O_5$. 360.45. 50-24-8. Glucocorticoid.



16. RECORDS AND REPORTS

17. COMMENTS

18. CONCLUSIONS AND RECOMMENDATIONS

The application is approvable.

19. REVIEWER: DATE COMPLETED:

Nashed E. Nashed, Ph.D. 1/10/00

Supervisor: Paul Schwartz, Ph.D.

Page(s) 10

Contain Trade Secret, Commercial/Confidential Information and are not releasable.

clem Rev 2

1/10/00

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40-322

Bioequivalence Review(s)

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 40-322 APPLICANT: Copley Pharmaceutical, Inc.

DRUG PRODUCT: Prednisolone Syrup, 15 mg/5 ml

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

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to 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 bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

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

Prednisolone Syrup
15 mg/5 ml
ANDA #40-322
Reviewer: Carol Y. Kim
v:\firmsam\copley\ltrs&rev\40322w.399

Copley Pharmaceutical, Inc.
Canton, MA
Submission Date:
March 16, 1999

REVIEW OF A WAIVER REQUEST

I. Background

1. The firm has requested a waiver of an in vivo bioequivalence study requirement for its proposed product, Prednisolone Syrup, 15 mg/5 ml, manufactured by Copley Pharmaceutical, Inc. The reference listed product is Prelone^{R} (prednisolone syrup, USP) Syrup, 15 mg/5 ml, manufactured by Muro Pharmaceutical, Inc.

2. In a letter dated July 20, 1999, OGD stated a refusal to file the firm's ANDA under 21 CDF 314.101 (d) (2) due to the presence of inactive ingredients, Cherry Concentrated Flavor and ı Sweet Flavor Natural in the proposed formulation. These inactive ingredients have not been approved in a drug product for human use by the same route of administration [21 CDF 314.127 (a) (8) (ii)].

3. In response to OGD's Refusal to File letter, the firm contacted the manufacturer and supplier of the two inactive ingredients, ' n, and was informed that all flavor components contained in these inactive ingredients are either approved for use in a FDA regulated food product, or are generally recognized as safe (FDMA GRAS). Also, the firm was informed that the Cherry Concentrate Flavor is generally sold to the food industry for the manufacture of hard candy at a concentration of 0.1 % to 0.2 %. (see attachment for quantitative composition and safety information)

4. On May 5th and 10th of 1999, Dr. Robert Osterberg, Team Leader, Pharm/Tox, ODE-IV DAIDP forwarded his reviews of these flavoring components to OGD via electronic mail. Dr. Osterberg concluded that Cherry Concentrate Flavor nd Sweet Flavor Natural ı in this syrup formulation have little risk to patients due to low levels of the components in the final formulation of the Prednisolone Oral Syrup. (see attachments)

5. Prednisolone is a glucocorticoid primarily used for its potent anti-inflammatory effects in disorders of many organ systems as well as replacement therapy in adrenocortical deficiency states.

6. The test and the reference listed product are both oral syrups to be administered by mouth.

II. Formulation Comparison

The test and reference formulations are compared as shown below:

Prednisolone Syrup		Prelone[R] Syrup*	
Ingredients	Mg/ 5 ml	Ingredients	Mg/ 5 ml
Prednisolone, Anhydrous,	15.00	Prednisolone	15.00
Disodium Edetate,			
Sodium Saccharin,			
Citric Acid,			
FD&C Red #40			
FD&C Blue #1			
Fructose,			
Glycerin,			
Flavor, Artificial Cherry Conc.			
Flavor, Pharmasweet			
DL-menthol,			
Alcohol,			
Propylene Glycol,			
Benzoic Acid,			
Purified Water,			
Theoretical net weight			

* From COMIS database

III. Comments

1. The test product, Prednisolone Syrup, 15 mg/5 ml, contains the same active ingredient in the same concentration and dosage form as the reference product, Prelone[R] (prednisolone syrup, USP) Syrup, 15 mg/5 ml. The test formulation does not contain any inactive ingredients known to significantly affect absorption of the active ingredient or drug moieties.

2. Although fructose in this syrup preparation is not listed in the interim inactive ingredient guide, it can be accepted since fructose has been in a dosage form that has been previously approved, and it does not affect the safety and efficacy of the proposed product. (21 CFR 314.94 (a) (9) (ii)) The concentration of fructose in the proposed

syrup is within the potency limit listed under oral solution preparation. (see attached memo from Mr. Don Hare, dated May 13, 1999)

3. A waiver is granted under 21 CFR 320.22 (b) (3), which states that the drug product is (i) a syrup and (ii) contains an active drug ingredient or therapeutic moiety in the same dosage form as a drug product that is the subject of an approved full NDA.

IV. Recommendation

The Division of Bioequivalence agrees that the information submitted by Copley Pharmaceutical, Inc. on its drug product, Prednisolone Syrup, 15 mg/ 5ml, falls under 21 CFR section 320.22 (b) (3) of the Bioavailability/Bioequivalence Regulations. The waiver of an in vivo bioequivalence study for the drug is granted. The Division of Bioequivalence deems the test product, Prednisolone Syrup, 15 mg/5 ml, bioequivalent to the reference product, Prelone[R] (prednisolone syrup, USP) Syrup, 15 mg/5 ml, manufactured by Muro Pharmaceutical, Inc.

The firm should be informed of the recommendation.

Carol Y. Kim, Pharm.D.
Division of Bioequivalence
Review Branch III

RD INITIALLED BY BDAVIT BMD 5/18/99
FT INITIALLED BY BDAVIT Barbara M Davit Date: 5/20/99

Concur: _____ Date: 5/26/99
for Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40-322

ADMINISTRATIVE DOCUMENTS

APPROVAL PACKAGE SUMMARY FOR 40-322

ANDA: 40-322

FIRM: Copley Pharmaceutical, Inc.

DRUG: Prednisolone

DOSAGE: Syrup

STRENGTH: 15 mg/5 mL

CGMP STATEMENT/EIR UPDATE STATUS: EER is acceptable 3/30/99

BIO STUDY/BIOEQUIVALENCE STATUS: Bio is satisfactory 5/26/99

METHODS VALIDATION: The drug product is compendial

STABILITY: The firm has provided satisfactory 3 months accelerated stability data at 40°C upright/inverted and 18 months room temperature stability data at 25°C/60%RH inverted/upright for both packaging sizes. The expiry date is 18 months.

LABELING REVIEW STATUS: Labeling is satisfactory 10/8/99

STERILIZATION VALIDATION: N/A

BATCH SIZES: The firm has submitted blank batch record for maximum intended batch size and a copy of the exhibit batch for The firm will be using the same drug substance manufacture, same process and same equipment.

COMMENTS: The application is Approvable.

REVIEWER: Nashed E. Nashed, Ph.D. DATE: 1/10/00

SUPERVISOR: Paul Schwartz, Ph.D.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40-322

CORRESPONDENCE

COPLEY PHARMACEUTICAL, INC.
25 John Road
Canton, MA 02021

Fax to Number: 1-301-594-0180	From: Vincent Andolina
Recipient's Phone Number: 1-301-827-5848	Date: January 7, 2000
Sender's Phone Number: 781-575-7318	Pages: 12 (including cover)
To: **Ms. Elaine Hu, Project Manager** Division of Chemistry I, Team 3	

RE: Prednisolone Syrup USP, 15 mg / 5 mL
ANDA 40-322
Telephone Amendment to a Pending Application

Dear Ms. Hu:

Reference is made to Copley's ANDA for Prednisolone Syrup USP, 15 mg / 5 mL submitted June 30, 1998, and to the Agency's telephone deficiencies communicated on December 9, 1999 by yourself and Paul Schwartz, Ph.D., Team Leader, Division of Chemistry I, Team 3.

Following is our Telephone Amendment responding to all the deficiencies outlined in the Agency's December 9, 1999 telephone communication.

We are submitting a hard copy via Federal Express, as well as this facsimile transmission.

Please contact the undersigned at 781-575-7318, should you require any additional information.

Sincerely,

Vincent Andolina

Vincent Andolina, RAC
Sr. Manager, Product Registration

Copley Pharmaceutical Inc.

25 John Road
Canton, Massachusetts 02021
(781) 821-6111
Mailroom Fax: (781) 821-4068

Direct Tel: (781) 575-7318
Fax: (781) 575-7362

January 7, 2000

Mr. Douglas Sporn
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855-2773

RE: Prednisolone Syrup USP, 15 mg / 5 mL
ANDA 40-322
Telephone Amendment to a Pending Application

Dear Mr. Sporn:

Reference is made to Copley's ANDA for Prednisolone Syrup USP, 15 mg / 5 mL submitted June 30, 1998, and to the Agency's telephone deficiencies communicated on December 9, 1999 by Paul Schwartz, Ph.D., Team Leader, and Ms. Elaine Hu, Project Manager, Division of Chemistry I, Team 3. The Agency's comments have been restated and our responses follow.

1. **Submit revised Finished Product Specifications (Document No. , and Stability Specifications (Document No.) section, including Microbial Limit specifications for Total Colony Forming Units (cfu/mL) and Total Yeast and Mold (TYM/mL).**

Please refer to Attachment 1 for revised Finished Product Specifications (Document No. dated 1/6/00) and Stability Specifications (Document No. ated 1/6/00) for Prednisolone Syrup, USP, 15 mg / 5 mL, including Microbial Limit specifications for Total Colony Forming Units (CFU/mL) and Total Yeast and Mold (TYM/mL).

The specifications of not more than . (or per gram) Aerobic Plate Count, Yeast Count, and Mold Count have been added to these specifications.

2. **Submit a revised Raw Material Specification for Prednisolone, USP (Document No.) and a revised Certificate of Analysis for the drug substance including the "Other Impurities" test and specification from *USP 23* Supplement 9.**

USP 23 Supplement 9 added a heading for "Other Impurities," but neglected to add any test for it. *USP 24* (now in effect) does not include the Other Impurities heading. Therefore, we have not added this test to our specifications.

3. **Submit revised Stability Specifications (Document No. ']) with a reduced limit for Individual Related Substances. The proposed limit of ' for Individual Related Substances is not acceptable.**

Please refer to Attachment 1 for revised Stability Specifications for Prednisolone Syrup, USP, 15 mg / 5 mL, (Document No dated 1/6/00) including tighter specifications for Individual Related Substances.

The Individual Related Substances limits have been revised from:

and

quest approval of this application.

Please contact Gail Shamsi, RAC, Senior Regulatory Associate at 781-575-7828 or the undersigned at 781-575-7318, should you require any additional information.

Sincerely,

Vincent Andolina

Vincent Andolina, RAC
Sr. Manager, Product Registration

VA:va
Enclosure

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Copley Pharmaceutical Inc.

25 John Road
Canton, Massachusetts 02021
(781) 821-6111
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Direct Tel: (781) 575-7695
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November 15, 1999

Mr. Douglas Sporn
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855-2773

NDA ORIG AMENDMENT
N/A

RE: Prednisolone Syrup USP, 15 mg / 5 mL
ANDA # 40-322
Telephone Amendment to a Pending Application

Dear Mr. Sporn:

Reference is made to Copley's ANDA for Prednisolone Syrup USP, 15 mg / 5 mL submitted June 30, 1998, and to the Agency's telephone deficiencies communicated on October 21, 1999 by Paul Schwartz, Ph.D., Team Leader, and Mr. Joseph Buccine, Project Manager, Division of Chemistry I, Team 3. The Agency's comments have been restated and our responses follow.

1. **Add the USP IR Identification test for the release testing of the drug product. Submit revised Finished Product Specifications as well as a revised Certificate of Analysis including the IR Identification results.**

Please refer to Attachment 1 for revised Finished Product Specifications for Prednisolone Syrup, USP, 15 mg / 5 mL (Document No. 9 dated 11/2/99) including the USP IR <197K> test for Identification.

Please refer to Attachment 2 for a revised Certificate of Analysis for the exhibit batch, Lot No. 129Z01 (Finished Product Stage Release, Document No. dated 11/2/99) including the IR identification results.

2. **Reduce the individual and total Related Substances limits for release only (not stability).**

Please refer to Attachment 1 for revised Finished Product Specifications for Prednisolone Syrup, USP, 15 mg / 5 mL (Document dated 11/2/99) including tighter limits for individual and total Related Substances. The Related Substances limits have been revised from:

3. **The accelerated stability data submitted with the original ANDA (pages 000757-000758) are not appropriate to support the requested 24-month expiration dating because the data show significant decreases in potency and significant increases in Related Substances. Since Copley has submitted acceptable 18-month room temperature data (pages 000005-000008 of the Sept. 14, 1999 Facsimile Amendment), the firm should reduce the proposed expiration dating to 18-months.**

We acknowledge the Agency's comment, and commit to 18-month expiration dating for our Prednisolone Syrup, USP, 15 mg / 5 mL at this time. As additional room temperature stability data, for three production lots beyond 18 months, becomes available, the expiration date may be extended as warranted. The extension will be filed in the annual report in accordance with 21 CFR § 314.70(d)(5).

We believe this information satisfactorily addresses the Agency's concerns, and request approval of this application.

Please contact Vincent Andolina RAC, Sr. Manager of Product Registration at 781-575-7318 or the undersigned at 781-575-7695, should you require any additional information.

Sincerely,

Vincent Andolina for

I. Nudelman, RAC
Director, Regulatory Affairs

IN:va
Enclosure

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Copley Pharmaceutical Inc.

25 John Road
Canton, Massachusetts 02021
(781) 821-6111
Mailroom Fax: (781) 821-4068

September 29, 1999

FPL
Urug AMENDMENT
FA

Mr. Douglas Sporn
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855-2773

RE: Prednisolone Syrup USP, 15 mg / 5 mL
ANDA # 40-322
Facsimile Amendment to a Pending Application

Dear Mr. Sporn:

Reference is made to Copley's ANDA for Prednisolone Syrup USP, 15 mg / 5 mL submitted June 30, 1998, to our facsimile amendment of September 14, 1999, and to your facsimile transmission dated September 23, 1999 (attached), which requested additional revisions of our container and insert labeling.

Accordingly, we have revised our labeling and have enclosed 12 final printed container and insert labeling (6 copies in the Archival folder and 6 copies in the Review folder).

A side-by-side comparison of our proposed labeling with our previous submission with all differences annotated and explained is provided to facilitate review of the requested changes.

Please contact the undersigned at 781-575-7695, or Bozena Wasil, Regulatory Associate at 781-575-7369, should you require any additional information.

Sincerely,

I. Nudelman, RAC
Director, Regulatory Affairs

Enclosure

Copley Pharmaceutical Inc.

25 John Road
Canton, Massachusetts 02021
(781) 821-6111
Mailroom Fax: (781) 821-4068

September 14, 1999

FPL
ORIG AMENDMENT
FA

Mr. Douglas Sporn
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855-2773

RE: Prednisolone Syrup USP, 15 mg / 5 mL
ANDA # 40-322
Facsimile Amendment to a Pending Application

Dear Mr. Sporn:

Reference is made to Copley's ANDA for Prednisolone Syrup USP, 15 mg / 5 mL submitted June 30, 1998, and to your facsimile transmission dated August 20, 1999 (attached). The Agency's comments have been restated and our responses follow.

Chemistry Comments to be Provided to the Applicant

A. Deficiencies:

1. Please tighten your limits for related substances for the finished drug product and stability based on your data.

Stability Sample	Storage	Period	Largest Individual Rel n	Total

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Please revise your dru

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important.

4. Please provide all available room temperature stability data.

Please refer to Attachment 1 for 18 months' room temperature stability data for Prednisolone Syrup, 15 mg / 5 mL, Lot 129Z01, in 8 oz. and 16 oz. packages (document lated 8/31/99).

5. Please revise your specifications for the finished drug product to include a volume specification per USP <698>.

Please refer to Attachment 4 for revised finished product specifications (document dated 9/2/99), including USP <698> "Deliverable Volume" for the 8 oz. (240 mL) package.

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

1. The firms referenced in your ANDA application should be in compliance with CGMP at the time of approval.

2. USP methods are the regulatory methods and will prevail in the event of a dispute.

We acknowledge these comments and agree that

1. The firms referenced in our ANDA should be in compliance with CGMP at the time of approval.
2. USP methods are the regulatory methods and will prevail in the event of a dispute.

Labeling Deficiencies

Please refer to Attachment 5 for final printed container labeling and revised package insert labeling, including a side-by-side comparison of our proposed labeling with our previous submission, with all differences annotated and explained.

We believe this information satisfactorily addresses the Administration's concerns, and request Agency approval of this application.

Please contact Vincent Andolina RAC, Sr. Manager of Product Registration at 781-575-7318 or the undersigned at 781-575-7695, should you require any additional information.

Sincerely,

I. Nudelman, RAC
Director, Regulatory Affairs

IN:va
Enclosure

h:\predniso\faxamend.doc

Copley Pharmaceutical Inc.

25 John Road
Canton, Massachusetts 02021
(781) 821-6111
Mailroom Fax: (781) 821-4068

March 16, 1999

N/AC

Mr. Douglas Sporn
Director, Office of Generic Drugs
CDER (HFD600)
Food and Drug Administration
7500 Standish Place
Rockville, MD 20855

Prednisolone Syrup USP, 15 mg / 5 mL, ANDA # 40-322
New Correspondence
Refusal to File Letters
July 20 and September 2, 1998

Dear Mr. Sporn:

Reference is made to the pending application for Prednisolone Syrup USP, 15 mg / 5 mL, ANDA # 40-322 and to today's telephone discussion between Ms. Saundra Middleton, Project Manager, Office of Generic Drugs and myself.

This will serve to confirm that , will be forwarding the information requested following the telephone conference of January 26, 1999, between representatives of the Food and Drug Administration and of Copley Pharmaceutical Inc. During this telephone conference, the participants discussed FDA's "Refusal to File" letters of July 20 and September 2, 1998.

Please contact the undersigned at 1-781-575-7695 (Fax: 1-781-575-7362), should you have any question regarding the above information.

Sincerely,

I. Nudelman, RAC
Director, Regulatory Affairs
Copley Pharmaceutical, Inc.

Copley Pharmaceutical Inc.

25 John Road
Canton, Massachusetts 02021
(617) 821-6111
Mailroom Fax: (617) 821-4068

N/AC

August 11, 1998

Mr. Douglas Sporn
Director, Office of Generic Drugs
Center For Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855-2773

RESPONSE TO A REFUSAL TO FILE
Prednisolone Syrup USP, 15 mg / 5 mL
ANDA No. 40-322

Dear Mr. Sporn:

Reference is made to our Abbreviated New Drug Application No. 40-322 for Prednisolone Syrup USP, 15 mg / 5 mL dated June 30, 1998.

Further reference is made to FDA's letter dated July 20, 1998, and received by Copley Pharmaceutical Inc. on July 23, 1998. Based on a preliminary review, the Agency has refused to file ANDA No. 40-322. The Agency based this decision on the fact that Copley's proposed formulation for Prednisolone Syrup USP, 15 mg / 5 mL appears to contain inactive ingredients (namely Cherry Concentrate Flavor and Pharma Sweet Flavor Natural) that have not been approved in a drug product for human use by the same route of administration. The Agency has requested that Copley provide additional information to support the safe use of these inactive ingredients in Copley's Prednisolone Syrup USP drug product. The Agency has given Copley Pharmaceutical, Inc. thirty (30) days to address this issue.

Our records indicate that the inactive ingredients, Cherry Concentrate Flavor Pharma Sweet Flavor Natural, were manufactured and supplied by a subsidiary of Copley Pharmaceutical, Inc. has been informed by that all flavor components contained in these inactive ingredients are either approved for use in a FDA regulation, or are generally recognized as safe on a reliable published association list (FEMA GRAS). We were additionally informed that the Cherry Concentrate Flavor is generally sold to the food industry for the manufacture of hard candy at a concentration of 0.1% to 0.2% (2 oz. per 100 lbs).

The Expert Panel of the Flavor and Extract Manufacturers Association (FEMA) has served the flavor industry, the U.S. Food and Drug Administration, and the public for more than 30 years as the primary body for the evaluation of the safety of food flavors through its assessment of the "generally recognized as safe" (GRAS) by the FEMA Expert Panel pursuant to the authority granted in Section 201(s) of the U.S. Federal Food, Drug, and Cosmetic Act which is administered by FDA.

AUG 13 1998

The purpose of this submission is to respond to the Agency's refusal to file letter of July 20, 1998. In support of this submission, we provide, a quantitative composition and safety information for Cherry Concentrate Flavor and Pharma Sweet Flavor Natural :h references to each component as either GRAS and/or FEMA approved. We have also provided test specifications for the inactive ingredients. A "Certificate of Compliance" from has also been provided.

We remind you that an authorization letter has already been provided by authorizing the FDA to refer to the enclosed data in Drug Master :onnection with this application. For the convenience of the reviewer, we have included another copy of this letter.

We trust that the information provided in this amendment is satisfactory, and provides assurance that the inactive ingredients contained in the formulation for Prednisolone Syrup USP, 15 mg/ 5 mL are safe.

Should you have any questions regarding this submission, please contact the undersigned at (781) 575-7695 or Mr. Gary Lewis, Manager Regulatory Affairs at (781) 575-7363.

Sincerely,

COPLEY PHARMACEUTICAL, INC.

I. Nudelman, RAC
Director, Regulatory Affairs

Enclosures:

Archival Copy (blue folder): 1 copy
Chemistry, Manufacturing, Controls Copy (red folder): 1 copy