# CENTER FOR DRUG EVALUATION AND RESEARCH

**Approval Package for:**

***APPLICATION NUMBER:***

# 19-157

***Trade Name:*** Pediapred

***Generic Name:*** (prednisolone sodium phosphate)

***Sponsor:*** Fisons Corporation

***Approval Date:*** May 26, 1986

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

# 19-157

## CONTENTS

## Reviews / Information Included in this NDA Review.

| | |
|---|---|
| **Approval Letter** | X |
| **Approvable Letter(s)** | **X** |
| **Final Printed Labeling** | **X** |
| **Medical Review(s)** | **X** |
| **Chemistry Review(s)** | **X** |
| **EA/FONSI** | |
| **Pharmacology Review(s)** | **X** |
| **Statistical Review(s)** | |
| **Microbiology Review(s)** | |
| **Clinical Pharmacology/ Biopharmaceutics Review(s)** | **X** |
| **Administrative and Correspondence Document(s)** | **X** |

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

# 19-157

# APPROVAL LETTER

NDA 19-157

[redacted]

Fisons Corporation
Two Preston Court
Bedford, Massachusetts 01730

Attention: Patricia J. Richards
Associate Director
Regulatory Affairs

Dear Ms. Richards:

Reference is made to your new drug application dated November 1, 1983 submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Pediapred (prednisolone sodium phosphate) Oral Liquid.

We also acknowledge receipt of your amendment of January 16, 1986 which responded to our letter of January 3, 1986. We note your commitment to perform a Phase IV literature search for

Additionally, validation of the analytical methodology has been requested, and this Administration expects your cooperation to resolve any problems which may be encountered in the methods validation.

We have completed our review of this application and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the final printed labeling submitted on January 16, 1986. Accordingly, the application is approved, effective on the date of this letter.

Please submit one market package when available.

We remind you that you must comply with the requirements set forth under 21 CFR 314.80 and 314.81 for an approved NDA.

Sincerely yours,

Palmer 5-27-86

John F. Palmer, M.D.
Director
Division of Oncology and
Radiopharmaceutical Drug Products
Office of Drug Research and Review
Center for Drug and Biologics

cc: Orig. NDA 19-157
HFN-150
HFN-150/DPease/4-22-86
HFN-150/RHuckins
HFN-232 (w/FPL)
HFN-83 (w/FPL)
HFN-730 (w/FPL)
HFN-100 (w/FPL)
D/T:tw:4/23/86: R/D init. by RHHuckins 4/24/86
J Hester 4/28/86 EBSheinin 4/25/86 EBSheinin 5-16-86
SStolzenberg 4/28/86
DJRichman 4/28/86 apmurray 5/16/86
F/T:dwp:4/28/86: rev. by dwp per RAJerussi 5/16/86 5/16/86
Wang #05370 5/23/86
APPROVAL

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

# 19-157

## APPROVABLE LETTER(S)

PEASE
COPY

NDA 19-157

JAN 3 1986

Fisons Corporation
Two Preston Court
Bedford, Massachusetts 01730

Attention: Patricia J. Richards
Associate Director
Regulatory Affairs

Dear Ms. Richards:

Please refer to your new drug application dated November 1, 1983 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Pediapred (prednisolone sodium phosphate) Oral Liquid.

We also refer to your amendment of May 1, 1985 which responded to our letter of July 6, 1984.

We have completed our review of this application and it is approvable. Before the application may be approved, however, we request that you respond to the following:

1. The specifications for Pediapred Liquid should include an assay for

2. The Pediapred Liquid stability study should contain an assay for

3. The amount of prednisolone and other degradation products at each stability station should be monitored and reported as none, trace or actual amount found.

4. We request the following paragraph be substituted for the third paragraph under Clinical Pharmacology in the labeling:

   Prednisolone is rapidly and well absorbed from the gastrointestinal tract following oral administration. Pediapred produces a 20% higher peak plasma level of prednisolone which occurs approximately 15 minutes earlier than the peak seen with tablet formulations. Prednisolone is 70-90% protein-bound in the plasma and it is eliminated from the plasma with a half-life of 2 to 4 hours. It is metabolized mainly in the liver and excreted in the urine as sulphate and glucuronide conjugates.

5. [redacted]

Please submit, in duplicate, the advertising copy which you intend to use in your proposed introductory promotional and/or advertising campaign. Please submit one copy to the Division of Oncology and Radiopharmaceutical Drug Products, and the second copy to the Division of Drug Advertising and Labeling, HFN-240, Room 10B-04, 5600 Fishers Lane, Rockville, Maryland 20857. Please submit all proposed materials in draft or mock-up form, not final print. Also, please do not use form FD-2253 for this submission; this form is for routine use, not proposed materials.

Within 10 days after the date of this letter, you are required to amend the application, or notify us of your intent to file an amendment, or follow one of the other actions under 21 CFR 314.110. In the absence of such action FDA may take action to withdraw the application.

The drug may not be legally marketed until you have been notified in writing that the application is approved.

Sincerely yours,

John F. Palmer, M.D.
Director
Division of Oncology and
Radiopharmaceutical Drug Products
Office of Drug Research and Review
Center for Drugs and Biologics

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

# 19-157

## NOT APPROVABLE LETTER(S)

JUL 6 1984

NDA #19-157

Fisons Corporation
Attention: Patricia J. Richards
Associate Director, Regulatory Affairs
Two Preston Court
Bedford, Massachusetts 01730

Dear Ms. Richards:

Please refer to your new drug application dated November 1, 1983 submitted pursuant to section 505(b) of The Federal Food, Drug and Cosmetic Act for Pediapred Oral Liquid (prednisolone sodium phosphate).

Your endorsed 356H form lists the name of the drug as that shown above. However, in other parts of the application, including the labeling, the drug is referred to as Pediapred ——— Please advise us.

We have completed our review of the chemistry and pharmacology portions of your submission and find the information presented is inadequate and the application is not approvable. The deficiencies may be summarized as follows:

Chemistry:

The application is deficient under section 505(b)(4) of the Act as follows:

1.

a. The physical dimension specifications for the ——— containers.

b.

6. The

7.

9. We have reservations as to the adequacy of the stability tests described for the drug. Specifically:

a. Some stability samples should be stored under temperature cycling stress conditions.

b. Some samples should be inverted.

c. The methylparaben and all degradation products should be incorporated into the stability specifications and tested at regular intervals.

d. The stability commitment should be revised to read as follows:

(1). [redacted]

(2). [redacted]

10. [redacted]

11. [redacted]

12. [redacted]

13. [redacted]

We will forward the results of the biopharmaceutics review when it is completed. In addition, we will provide comments on proposed labeling as the other portions of your application are nearing completion.

This file is now closed. If you wish to reopen it, the submission should be in the form of an amendment to this application, adequately organized, that represents the information necessary to remove all deficiencies we have outlined.

If you do not agree with our conclusions, you may make a written request to file the application over protest, as authorized by 21 CFR 314.110(d). If you do so, the application shall be reevaluated, and within 90 days of the date of receipt of such request (or such additional period as you and we may agree upon), the application shall be approved or you shall be given a written notice of opportunity for a hearing on the question of whether the application is approvable.

Sincerely yours,

Robert Temple, M.D.
Acting Director
Office of Drug Research and Review
Center for Drugs and Biologics

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

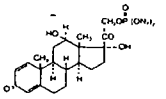
# 19-157

## APPROVED LABELING

# PEDIAPRED™
## (prednisolone sodium phosphate, USP)
## ORAL LIQUID

**DESCRIPTION:** PEDIAPRED Oral Liquid is a dye free, colorless to light straw colored, raspberry flavored solution. Each 5 ml (teaspoonful) of PEDIAPRED contains 6.70 mg prednisolone sodium phosphate (5.00 mg prednisolone base) in a palatable, aqueous vehicle.

Prednisolone sodium phosphate occurs as white or slightly yellow, friable granules or powder. It is freely soluble in water; soluble in methanol; slightly soluble in alcohol and in chloroform; and very slightly soluble in acetone and in dioxane. The chemical name of prednisolone sodium phosphate is pregna-1,4-diene-3,20-dione,11,17-dihydroxy-21-(phosphonooxy)-, disodium salt, (11β)-. Its chemical structure is:



Pharmacological Category: Glucocorticoid

**CLINICAL PHARMACOLOGY:** Prednisolone is a synthetic adrenocortical steroid drug with predominantly glucocorticoid properties. Some of these properties reproduce the physiological actions of endogenous glucocorticosteroids, but others do not necessarily reflect any of the adrenal hormones' normal functions; they are seen only after administration of large therapeutic doses of the drug. The pharmacological effects of prednisolone which are due to its glucocorticoid properties include: promotion of gluconeogenesis; increased deposition of glycogen in the liver; inhibition of the utilization of glucose; anti-insulin activity; increased catabolism of protein; increased lipolysis; stimulation of fat synthesis and storage; increased glomerular filtration rate and resulting increase in urinary excretion of urate (creatinine excretion remains unchanged); and increased calcium excretion.

Depressed production of eosinophils and lymphocytes occurs, but erythropoiesis and production of polymorphonuclear leukocytes are stimulated. Anti-inflammatory processes (edema, fibrin deposition, capillary dilatation, migration of leukocytes and phagocytosis) and the later stages of wound healing (capillary proliferation, deposition of collagen, cicatrization) are inhibited. Prednisolone can stimulate secretion of various components of gastric juice. Stimulation of the production of corticotropin may lead to suppression of endogenous corticosteroids. Prednisolone has slight mineralocorticoid activity, whereby entry of sodium into cells and loss of intracellular potassium is stimulated. This is particularly evident in the kidney, where rapid ion exchange leads to sodium retention and hypertension.

Prednisolone is rapidly and well absorbed from the gastrointestinal tract following oral administration. PEDIAPRED Oral Liquid produces a 20% higher peak plasma level of prednisolone which occurs approximately 15 minutes earlier than the peak seen with tablet formulations. Prednisolone is 70-90% protein-bound in the plasma and it is eliminated from the plasma with a half-life of 2 to 4 hours. It is metabolized mainly in the liver and excreted in the urine as sulfate and glucuronide conjugates.

**INDICATIONS AND USAGE:** PEDIAPRED Oral Liquid 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; hypercalcemia associated with cancer; nonsuppurative thyroiditis

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; systemic dermatomyositis (polymyositis); acute rheumatic carditis

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; hypercalcemia associated with cancer; nonsuppurative thyroiditis

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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; systemic dermatomyositis (polymyositis); 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 in: 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 conjunctivitis; keratitis; allergic corneal marginal ulcers; herpes zoster ophthalmicus; iritis and iridocyclitis; chorioretinitis; anterior segment inflammation; diffuse posterior uveitis and choroiditis; optic neuritis; sympathetic ophthalmia

7. **Respiratory Diseases**
Symptomatic sarcoidosis; Loeffler's syndrome not manageable by other means; berylliosis; fulminating or disseminated pulmonary tuberculosis when used concurrently with appropriate antituberculous 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. **Nervous System**
Acute exacerbations of multiple sclerosis

13. **Miscellaneous**
Tuberculous meningitis with subarachnoid block or impending block when used concurrently with appropriate antituberculous chemotherapy; trichinosis with neurologic or myocardial involvement

**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 doses, because of possible hazards of neurological complications and a lack of antibody response.**

The use of prednisolone 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.

**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 in 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 infection; 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.

Although controlled clinical trials have shown corticosteroids to be effective in speeding the resolution of acute exacerbations of multiple sclerosis, they do not show that they affect the ultimate outcome or natural history of the disease. The studies do show that relatively high doses of corticosteroids are necessary to demonstrate a significant effect. (See DOSAGE AND ADMINISTRATION.)

Since complications of treatment with glucocorticoids are dependent on the size of the dose and the duration of treatment, a risk/benefit decision must be made in each individual case as to dose and duration of treatment and as to whether daily or intermittent therapy should be used.

**Information for Patients:** Patients should be warned not to discontinue the use of PEDIAPRED abruptly or without medical supervision; to advise any medical attendants that they are taking PEDIAPRED and to seek medical advice at once should they develop fever or other signs of infection.

**Drug Interactions:** Drugs such as barbiturates which induce hepatic microsomal drug metabolizing enzyme activity may enhance metabolism of prednisolone and require that the dosage of PEDIAPRED be increased.

**Pregnancy:** Pregnancy Category C - Prednisolone has been shown to be teratogenic in many species when given in doses equivalent to the human dose. There are no adequate and well controlled studies in pregnant women. PEDIAPRED should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Animal studies in which prednisolone has been given to pregnant mice, rats and rabbits have yielded an increased incidence of cleft palate in the offspring.

**Nursing Mothers:** Prednisolone is excreted in breast milk, but only to a small (less than 1% of the administered dose) and probably clinically insignificant extent. Caution should be exercised when PEDIAPRED is administered to a nursing woman.

**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; osteopo. sis; 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

**Metabolic**
Negative nitrogen balance due to protein catabolism

**Neurological**
Convulsions; increased intracranial pressure with papilledema (pseudotumor cerebri) usually after treatment; vertigo; headache

**Endocrine**

Menstrual irregularities, development of cushingoid state; secondary adrenocortical and pituitary unresponsiveness, particularly in times of stress, as in trauma, surgery or illness; suppression of growth in children; decreased carbohydrate tolerance; manifestations of

**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

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Convulsions; increased intracranial pressure with papilledema (pseudotumor cerebri) usually after treatment; vertigo; headache

**Endocrine**

Menstrual irregularities; development of cushingoid state; secondary adrenocortical and pituitary unresponsiveness, particularly in times of stress, as in trauma, surgery or illness; suppression of growth in children; decreased carbohydrate tolerance; manifestations of latent diabetes mellitus; increased requirements for insulin or oral hypoglycemic agents in diabetes

**Ophthalmic**
Posterior subcapsular cataracts; increased intraocular pressure; glaucoma; exophthalmos

**OVERDOSAGE:** The effects of accidental ingestion of large quantities of prednisolone over a very short period of time have not been reported, but prolonged use of the drug can produce mental symptoms, moon face, abnormal fat deposits, fluid retention, excessive appetite, weight gain, hypertrichosis, acne, striae, ecchymosis, increased sweating, pigmentation, dry scaly skin, thinning scalp hair, increased blood pressure, tachycardia, thrombophlebitis, decreased resistance to infection, negative nitrogen balance with delayed bone and wound healing, headache, weakness, menstrual disorders, accentuated menopausal symptoms, neuropathy, fractures, osteoporosis, peptic ulcer, decreased glucose tolerance, hypokalemia, and adrenal insufficiency. Hepatomegaly and abdominal distention have been observed in children.

Treatment of acute overdosage is by immediate gastric lavage or emesis. For chronic overdosage in the face of severe disease requiring continuous steroid therapy the dosage of prednisolone may be reduced only temporarily, or alternate day treatment may be introduced.

**DOSAGE AND ADMINISTRATION:** The initial dosage of PEDIAPRED may vary from 5 ml to 60 ml (5 to 60 mg prednisolone base) 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, PEDIAPRED 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 PEDIAPRED 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.

In the treatment of acute exacerbations of multiple sclerosis daily doses of 200 mg of prednisolone for a week followed by 80 mg every other day or 4 to 8 mg dexamethasone every other day for one month have been shown to be effective.

For the purpose of comparison, the following is the equivalent milligram dosage of the various glucocorticoids: cortisone, 25; hydrocortisone, 20; prednisolone, 5; prednisone, 5; methylprednisolone, 4; triamcinolone, 4; paramethasone, 2; betamethasone, 0.75; dexamethasone, 0.75. These dose relationships apply only to oral or intravenous administration of these compounds. When these substances or their derivatives are injected intramuscularly or into joint spaces, their relative properties may be greatly altered.

**HOW SUPPLIED:** PEDIAPRED Oral Liquid is a colorless to light straw colored solution containing 6.70 mg prednisolone sodium phosphate (5.00 mg prednisolone base) per 5 ml (teaspoonful).

NDC 0585-2250-01 4 Fl. oz bottle

Store at room temperature. Do not refrigerate. Keep tightly closed and out of the reach of children.

**CAUTION:** Federal law prohibits dispensing without prescription.

**FISONS**

**FISONS CORPORATION**
**BEDFORD, MA 01730 U.S.A.**



Revised 1/86

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

# 19-157

## MEDICAL REVIEW

CONFIDENTIAL

# Medical Review

CONFIDENTIAL

Department of Health and Human Services
Public Health Service
Food and Drug Administration

Memorandum

To: Dr. Palmer/HFN-150
Dr. Harter/HFN-150

JUL 9 1984

From: Acting Director
Office of Drug Research and Review/HFN-100

Subject: Pediapred, NDA 19-157

The basis for approving the clinical portions of this application without clinical trials or a literature search should be explicit. I believe a sound basis for considering further data unnecessary lies in the DESI review and our own subsequent reviews of labeling and claims for corticosteroids and the fact that prednisolone products were among the subjects of that review; it is the prednisolone moiety that circulates, not the salt, so that clinical conclusions regarding effectiveness of one salt should be applicable to the others. There could, of course, be clinical questions that might arise from the bioavailability data, but these can be considered without a review of the literature designed to show that prednisolone is effective.

Unless you disagree with the above, we can consider it as providing reasons for dispensing with a literature search in this case.

Robert Temple

Robert Temple, M.D.

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

# 19-157

## CHEMISTRY REVIEW(S)

CONFIDENTIAL

# Chemistry Review #1

CONFIDENTIAL

Pedsc

APR 18 1984

# REVIEW OF CHEMISTRY AND MANUFACTURING CONTROLS

NDA #19157

Applicant: Fisons Corporation

Sponsor: Two Preston Court

Address: Bedford, Massachusetts, 01730

Division: HFN-150

Chemist Review #1

Reviewing Chemist:
Robert N. Huckins
Date Completed: 4/2/84

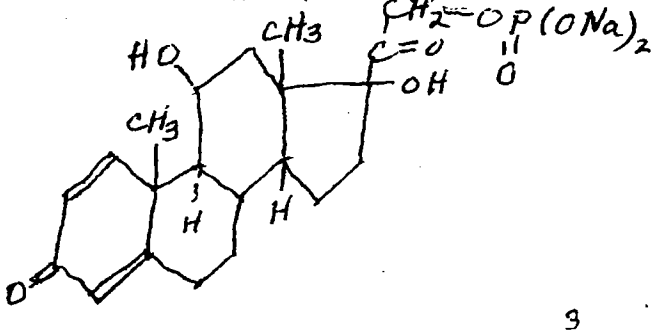
Product Name(s):

Proprietary: Pediapred
Non-proprietary: prednisolone sodium phosphate
Compendium:
USAN:
Code name/number:

Dosage Form (s) and Route (s) of Administration: oral, liquid, 5mg (base)/5ml

Pharmacological Category and/or Principal Indication: anti-inflammatory agent

Structural Formula & Chemical Name: pregna- 1,4-diene-3, 20-diene, 11, 17-dehydroxy- 21-(phosphonooxy)- disodium salt, (11 β)




Initial Submission: November 1, 1983 (BD date 11/8/83 received by me 11/22/83)

Amendment (s):

Related Documents: DMF ; ———

Remarks: The following deficiences in the submission are as follows:

1. The environmental impact statetment is not adequate
2. Need composition for ———
3. Statement on immediate label and package insert as " ——— should be deleted
4. Not clear if same formulation for —— used in stability, clinical and bioavailability studies
5. Need information on control numbers
6. Validation of method —— will not suffice as a substitute for the validation of method ——

7. Method — does not specify what column packing will be used
8. Need letter of authorization from _____ so FDA may refer to their Drug Master File for information on their _____
9. Stability statement needs revision

Conclusions and Recommendations: Chemical controls are non-approvable -see draft of chemist's portion of NDA letter.

Robert N. Huckins
Chemist

cc:
Orig. NDA #19157
HFN-102
HFN-150/Div. File
HFN-150/Pease/Behrens
HFN-150/Robert N. Huckins
R/D Endorsed by: RHWood 4/10/84
F/T by; dj 4/11/84
Wang # 2093P

RHWood
4/13/84

4/16/84

**WITHHOLD 18 PAGE(S)**

B4

Chemistry Review 1

CONFIDENTIAL

# Chemistry Review #2

CONFIDENTIAL

DWP

Division of Oncology and Radiopharmaceutical Drug Products

Chemist Review #2

NDA: 19-157

Applicant/Sponsor: Fisons Corporation
Two Preston Court
Bedford, Massachusettes 01730

Date Completed: July 12, 1985

Product Names:

Proprietary: Pediapred
Non-proprietary: Prednisolone sodium phosphate

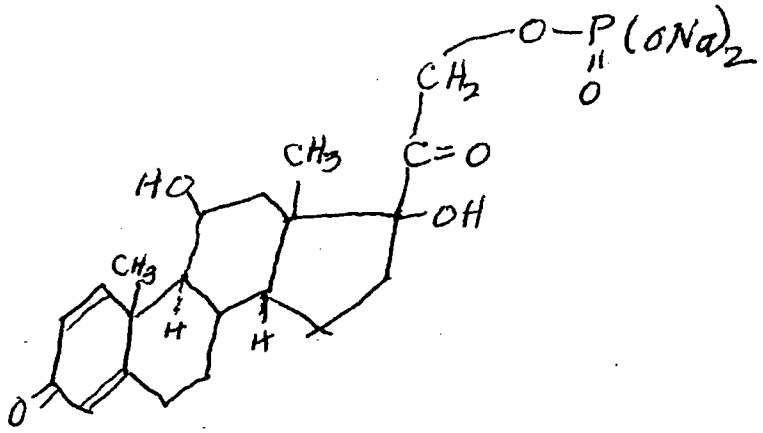
Dosage Form and Route of Administration:

oral, liquid, 5 mg (base)/5 ml

Pharmacological Category: anti-inflammatory

Structural Formula and Chemical Name:

pregna-1, 4-diene-3, 20-diene, 11, 17-dehydroxy-21-(phosphen ooxy)-disodium salt (11, β)




Initial Submission: November 1, 1983

Amendments: May 1, 1985

Related Documents: ———————

Remarks:

The submission is still deficient due to the following: -

1. [redacted]
2.
3.
4.

Conclusions and Recommendations:

The submission is still non-approvable - see draft.

Robert N. Huckins
Robert N. Huckins
July 12, 1985

cc:
Orig NDA 19-157
HFN-150/Div File
HFN-102/CKumkumian
HFN-150/RNHuckins/7-12-85
HFN-150/DWPease
R/D Init by: RHWood/7-12-85
F/T: tl/7-16-85
Wang # 0062J

RHWood 7/23/85
RA Jenner 8/28/85

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B4

Chemistry Review 2

# Chemistry Review #3

DWP

MAY 28 1986

# DIVISION OF ONCOLOGY AND RADIOPHARMACEUTICAL DRUG PRODUCTS

NDA: 19-157

Division: HFN-150

Chemist Review #: 3

Date Completed: 4/11/86

Applicant/Sponsor:

Fisons Corporation
Two Preston Court
Bedford, Massachusetts 01730

Product Name(s):

Proprietary: Pediapred
Non-proprietary: Prednisolone Sodium Phosphate

Compendium:
USAN:
Code name/number:

Dosage Form(s) and Route(s) of Administration:

Oral; liquid; 5 mg(base)/5ml

Pharmacological Category and/or Principal Indication:

Anti-inflammatory agent

Structural Formula and Chemical Name:

Initial Submission:

November 1, 1983

Amendment(s):

January 16, 1986

Related Documents:

DMF

Remarks:

CSO has requested that methods validation data be prepared so FDA may validate methods in NDA. Letter from Hercules (received 4/9/86) states that all ingredients in

are on GRAS List. They (Fizons) have agreed to adding an _____ on the release specifications and also the stability data will contain an _____ Also degradation products will be monitored during the stability studies.

Conclusions and Recommendations:

The application is approvable in respect to chemical controls. When final printed label is submitted it should contain expiration dating.

Robert N. Huckins
Robert Huckins
April 11, 1986

GPB 4/25/86

Ra Jenner 5/28/86

cc:
Orig NDA 19-157
HFN-150
HFN-150/RHuckins
HFN-150/DPease
R/D Init.by: ESheinin/4-22-86
D/T:tw:4/22/86
Wang #05330
F/T:tw:4/23/86

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B4

Chemistry Review #3

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

# 19-157

# PHARMACOLOGY REVIEW

# Pharmacology Review



CONFIDENTIAL

PHARMACOLOGY REVIEW

NDA 19-157

APR 5- 1984

Fisons Corporation
Bedford, MA

Date of Submission: 11/1/83
Date Received by NCDB: 11/8/83
Drug: Pediapred Oral Liquid (prednisolone sodium phosphate; 6.7 mg/5 ml, of which 5.0 mg is the free prednisolone base).

Category: Corticosteroid, glucocorticoid.
Related: DESI 7750; 35 FR 16424 and 42 FR 11888.

Preclinical Studies: None are submitted and there is no reference to an IND or NDA for pharmacology and animal safety studies to support this ANDA. However, the sponsor was not requested to do so in the FDA communications described below.

Formulation:

| Ingredient | Amount per 5 ml (Unit Dose) |
|---|---|
| [redacted] | [redacted] |

Summary and Evaluation:

The drug is another prednisolone preparation formulated as a liquid for oral administration. The excipients in the formulatin are GRAS.

Although the sponsor was repeatedly advised to submit this application as a NDA and not as an ANDA (see Memorandum of Meeting of 10/28/83 and Memorandum of Telephone Conversation of 10/31/83), this application was submitted as an ANDA. They claim the dosage form "is sufficiently related or similar to those products reviewed under the DESI notice to warrant submission of an ANDA". In other respects, the firm appears to have complied with FDA recommendations.

Labeling:

This generally appears similar to that seen for other corticosteroid preparations and appears adequate. However, under PRECAUTIONS, it may be [redacted]

Recommendation

1. There are no objections from Pharmacology for approval of this ANDA.

2. [ ]

Sidney Stolzenberg, Ph.D.

cc:Orig NDA 19-157
HFN-150
HFN-150/Stolzenbert
HFN-150/Pease
~~HFN-102/(1st chem/rev only)Dr. Kumkumian~~
R/D init by:DJRichman/1/25/84
F/T by:Amanda Velich 3/12/84
Wang #1686

3-27-84

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

# 19-157

# CLINICAL PHARMACOLOGY/ BIOPHARMACEUTICS REVIEW(S)

CONFIDENTIAL

# Biopharmaceutics Review

CONFIDENTIAL

Prednisolone Sodium Phosphate
(Pediapred)
6.7 mg/5 ml Syrup (= 5.0 mg base/5 ml)
NDA 19-157
Reviewer: T.E. Mary Ong-Chen
Wang #5147x
1S, 10

Fisons Corporation
Two Preston Court
Bedford, MA 01730
Submission Dated
November 8, 1983

DEC 30 1985

# REVIEW OF A BIOEQUIVALENCY STUDY AND LABELING

## I. BACKGROUND

Prednisolone sodium phosphate is the monobasic phosphate ester of the glucocorticosteroid prednisolone. It is freely soluble in water and slightly hygroscopic.

To be pharmacologically active, oral prednisolone sodium phosphate (prodrug) has to be converted to prednisolone in-vivo. Prednisolone is widely prescribed as anti-inflammatory and immunosuppressant drug for a wide variety of disorders. The metabolic interconversion between prednisolone and prednisone is well documented; prednisolone is biotransformed, at a lesser extent, to prednisone.

Prednisolone sodium phosphate is currently available on the U.S. market as topical, ophthalmic, and parenteral preparations but not as an oral preparation. Intravenous doses of prednisolone sodium phosphate can range from 4 to 60 mg. For Pediapred, the package insert recommends initial dosage to be between 5 and 60 mg base per day, depending on the specific disease being treated.

The firm has claimed that prednisolone sodium phosphate is pharmaceutically and therapeutically equivalent to its degradation product, prednisolone; and that the pharmacologically active moiety prednisolone is DESI effective. The firm intends to market the oral syrup formulation of the sodium phosphate ester of prednisolone in a palatable aqueous vehicle (raspberry flavored) for the following reasons:

- That oral liquid is more soluble and, hence, more rapidly, evenly and completely absorbed than tablet forms which may have bioavailability problems;
- That individual patient dosage may be easily titrated on oral syrup;
- That the availability of a convenient ___ will be of benefit to special populations (e.g., pediatric or elderly ) for whom the product is indicated.

On November 11, 1982 the firm filed the Abbreviated New Drug Application (ANDA) for the oral syrup form of Prednisolone Sodium Phosphate to the Division of Generic Drug Products (then HFN-530). On January 7, 1983, the firm was advised by the Division of Generic Drug Products that the test product 'Pediapred' would have to be reclassified as a "New Drug" rather than a "Generic" and that the safety and efficacy of this product in an oral dosage form should be reviewed by the Division of Oncology and Radiopharmaceutical Drug Products (HFN-150). On March 4, 1983, the firm asked the Agency to reconsider the resubmission of an ANDA for Pediapred; however, that request was denied by FDA and same application was later transferred from HFN-530 to HFN-150.

This submission (dated November 8, 1983) is the official application for Pediapred filed as NDA 19-157 which contains chemistry information and a bioequivalency study comparing the test [redacted] to a marketed tablet.

II. OBJECTIVE: The objective of this study was to determine the relative bioavailability of prednisolone sodium phosphate syrup against standard prednisolone tablets. The products studied were 10 ml prednisolone sodium phosphate (=10 mg prednisolone) test solution. manufactured by Fisons Corporation and two tablets of 5 mg [redacted] brand of prednisolone).

III. TEST FORMULATION : The composition for unit dose of the test [redacted] formulation of prednisolone sodium phosphate is outlined below.

| INGREDIENT | AMOUNT (MG PER 5 ML) |
|---|---|
| [redacted] | [redacted] |

IV. STUDY PROTOCOL & PROCEDURE

Principal Investigator & Site: [redacted] of the Division of Clinical Pharmacology, School of Medicine, [redacted]

Design: Open label, single-dose, randomized, two-legged crossover study.

Subjects: Twelve (n.b., three additional subjects were reserved in case of dropouts) healthy male volunteers with mean age of 35 y (20-51 y) and weighed within +/- 10% of the ideal body weight (of the [redacted] entered the bioequivalence study. They were judged normal and healthy on the basis of medical history, complete physical examination , and laboratory tests (viz., hematology, blood chemistry, & urinalysis). The selection of the study population was based on the inclusion and exclusion criteria as described in the protocol. Excluded were alcohol/drug abusers, those who took concomitant medications or those who had known history of drug allergies, diseased states (e.g., GI, CV, hepatic, pulmonary, renal, diabetic).

Treatment: Subjects were divided into 2 equal groups of 6 subjects each. They fasted overnight for at least 8 hours. Each received the following medications with 240 ml of water according to a two-way crossover design.

Treatment A: 10 ml of Test Syrup [Fisons Lot #EX24118],
Treatment B: Two 5 mg of [redacted] Tablets Lot # 893HK].

Water was allowed up to 2 h before administration of test drug. At 1, 2, 3, & 4 h postdosing, subject swallowed 100 ml of water to ensure adequate urine output.

The alternate medication was given in a single dose with a 3-day washout period between treatments.

Specimens: Collected test specimens were analyzed for corticosteroids (i.e., prednisolone, prednisone, and/or hydrocortisone).

- BLOOD: Samples (5 ml) were collected in heparinized tubes at the following time points after dosing: 0, 0.083, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, & 24 hours. Following centrifugation, plasma sample was separated and kept frozen until analyzed.

- URINE: On test days, subjects completely emptied his bladder immediately before dosing and at the following postdose intervals: 0-1, 1-2, 2-3, 3-4, 4-6, 6-12, and 12-24 hours. The volume of collected urine was recorded and two aliquots from each sample were taken for analysis.

Analytical Methodology

[redacted]

Pharmacokinetic & Statistical Analysis

Prednisolone plasma concentration profiles were obtained and major derived PK parameters were estimated. Data generated (plasma & urine) were fitted to the appropriate model as described by Wagner. The AUC (0-t h) was calculated by using trapezoidal rule via a computer program STEPAREA and the residual area (AUC t-oo) was extrapolated and estimated as $C_t/\overline{B}$. The apparent elimination half-life for prednisolone was calculated by $T_{0.5} = 0.693/\overline{B}$. Total AUC was used to calculate the plasma clearance of prednisolone where total $CL_{pl}/F$ = Dose/AUC (0-oo). The $V_{d,area}$ was based on $CL_{pl}/\overline{B}$. The bioavailability of sodium phosphate solution (A) relative to ——— tablets (B) was calculated as F or $[AUC_T]_A/[AUC_T]_B$.

Analysis of variance (ANOVA) testing for the effects (sequence, formulation, subject, etc.) was performed on three PK parameters; namely, AUC (0-oo h), Cmax, and Tmax.

V. RESULTS:

1. The results of ANOVA tests (Table I) indicated that there were no statistically significant differences between the predisolone sodium phosphate —— and the prednisolone tablet for three major prednisolone PK parameters. However, based upon the ANOVA analyses, the power of the study to detect a 20% difference between treatment means was only about 68% for $AUC_{0-\infty}$ and 39% for Cmax. Two One-Sided Tests (i.e., Confidence Interval Method) did however indicate the test —— and the reference tablet to be EQUIVALENT in their EXTENTS of drug absorption (see Appendix I). Using $AUC_{0-\infty}$ and the 75/75-125 Rule, 92% of subjects had percent relative bioavailability (RBA= $AUC_{Test}/AUC_{Ref}$) between 75% and 125% with an overall mean value of 106%.

   Table II summarizes the mean blood profiles data and the derived pK parameters of the three corticosteroids. The individual subject's blood profile data following administration of test ——and reference tablet are shown in Tables VIII, IX, and X for prednisolone, prednisone, and hydrocortisone, respectively.

- For Cmax, the mean concentration (Table IV) was higher following the syrup (238 ng/ml), as compared to that following the reference tablet (209 ng/ml).

  Using both the Two One-Sided Test approach (Confidence Interval Method) and the 75/75-125 Rule, this study demonstrated the —— Cmax to be NOT EQUIVALENT to the tablet Cmax, which is not necessarily unexpected. Using the Two One-Sided Test approach, one of the tests indicated the treatment mean Cmax difference to be greater than +20%. The 75/75-125 Rule demonstrated that only 67% of the subjects had Cmax RBA between 75 to 125% with 25% of the subjects having relative Cmax greater than 125%. The mean Cmax RBA valve was 121%.

2. The mean Tmax was reached 15 minutes sooner with the —— than with the reference (Table IV).

3. Following the administration of the —— and tablet treatments, the mean $T_{0.5}$ values were similar; 2.5 h & 2.6 h, respectively. Mean values for $CL_T$ were 9.9 & 11.2 L/h; mean $Vd_{area}$ values were 35.0 & 41.7 L, respectively (Table V).

4. The urinary recovery data (Table VI) for both prednisolone (3.4% for Drug A & 6.8% for Drug B) and prednisone (2.7 & 2.3% for Drugs A & B, respectively) were low. The urinary data in this study were however, unreliable due to analytical error. The firm failed to measure the initial urine volume at the sampling time 0-1 h for some subjects (cf., Tables XI & XII).

5. For the assay's calibaration curves (Table VII), it was shown that the variability (both interday and intraday) for hydrocortisone was somewhat greater than those for either prednisolone or prednisone.

## VI. COMMENTS

1. In a meeting on December 17, 1985 between Dr. Harter (the reviewing medical officer in HFN-150) and Mr. Hunt, it was indicated that the extents of prednisolone absorption for the —— and the reference tablet were equivalent but the rates of drug absorption were not. It was felt by the medical officer that the increased rate of prednisolone absorption should not have clinical consequences but that the demonstrated difference in rate of absorption between Pediapred and the prednisolone tablets should be indicated in the package insert for Pediapred.

2. The mean Vd values following the two different treatments were 35 and 41.7 L. Since the firm did not perform any statistical analyses on this PK parameter, there appears to be no statistical basis for claiming no difference in $V_d$ between the two treatments.

3. The pharmacokinetic information that appears in the Clinical Pharmacology Section of Pediapred's package insert should be expanded to reflect both the firm's pharmacokinetic research findings (i.e., a 21% higher mean Cmax and a mean Tmax that occurs about 15 minutes sooner for the —— when compared to the tablet under fasting conditions) and information available in the literature. The drug labeling, as currently presented, lacks comprehensive characterization of prednisolone pharmacokinetics in different disease states, etc. for which information is available (e.g. Goodman and Gilman), etc.

4. Due to the nature of this new oral —— formulation, it will probably be often prescribed to children and to the elderly. Knowing this, the firm should survey the literature to determine if prednisolone pharmacokinetic information is available for these two aged groups. The package insert should then be updated accordingly to provide pertinent pharmacokinetic information for these two patient populations.

5. Supplied by the sponsor were plasma level results (Tables VIII-X) for prednisolone, prednisone, and hydrocortisone for this study. However, no rigorous pharmacokinetic data analyses were provided for either prednisone or hydrocortisone. In the process of reviewing the current literature for the purpose of updating the package insert, pharmacokinetic data analyses of the prednisone or hydrocortisone levels might be warranted; either to support or refute any relevant literature findings.

6. There seemed to be some problems with the analytical methodology used for assaying prednisolone (Table XI) or prednisone (Table XII) in urine (i.e., existence of many interfering peaks). Moreover, the firm indicated that they had duplicate sets of urine samples but they failed to measure some urine volumes for some of the collected urine samples (0-1 h). This has resulted in inaccurate calculations of percent prednisolone excreted in urine and little confidence can therefore be given to the overall urinary excretion results.

VII. RECOMMENDATION:

- Bioavailability Study: Acceptable
- Package Insert: Needs Additional Changes
- Application: Approvable for Meeting the Bio-Regs.

1. The Division of Biopharmaceutics has reviewed the sponsor's bioavailability study that was submitted on November 8, 1983 under NDA 19-157 and has found it to be acceptable.

2. Review of the sponsor's Package Insert for Pediapred however requires revision and the inclusion of additional information from the firm's study along with information found in the literature, as outlined in Comment Nos. 3 and 4. The sponsor should submit all obtained literature information that is used to support FDA's recommended package-insert labeling changes for FDA review when final printed labeling is filed.

The above recommendations, as well as Comments #3, 4 and 5, should be forwarded to the firm.

Tsuj Eng Ong

T.E. Mary Ong-Chen, Biochemist
Pharmacokinetics Evaluation Branch

RD Initialed by John P. Hunt
FT Initialed by C.T. Viswanathan, Ph.D. CTV 12/24/85

cc: NDA 19-157 orig., HFN-810(2), HFN-226(Ong-Chen), Chron, Drug, FOI Files

TEOC/dea/kek(12/19/85)

Figure 1: Average Plasma Concentrations of Prednisolone vs. Time Following Two Treatments.

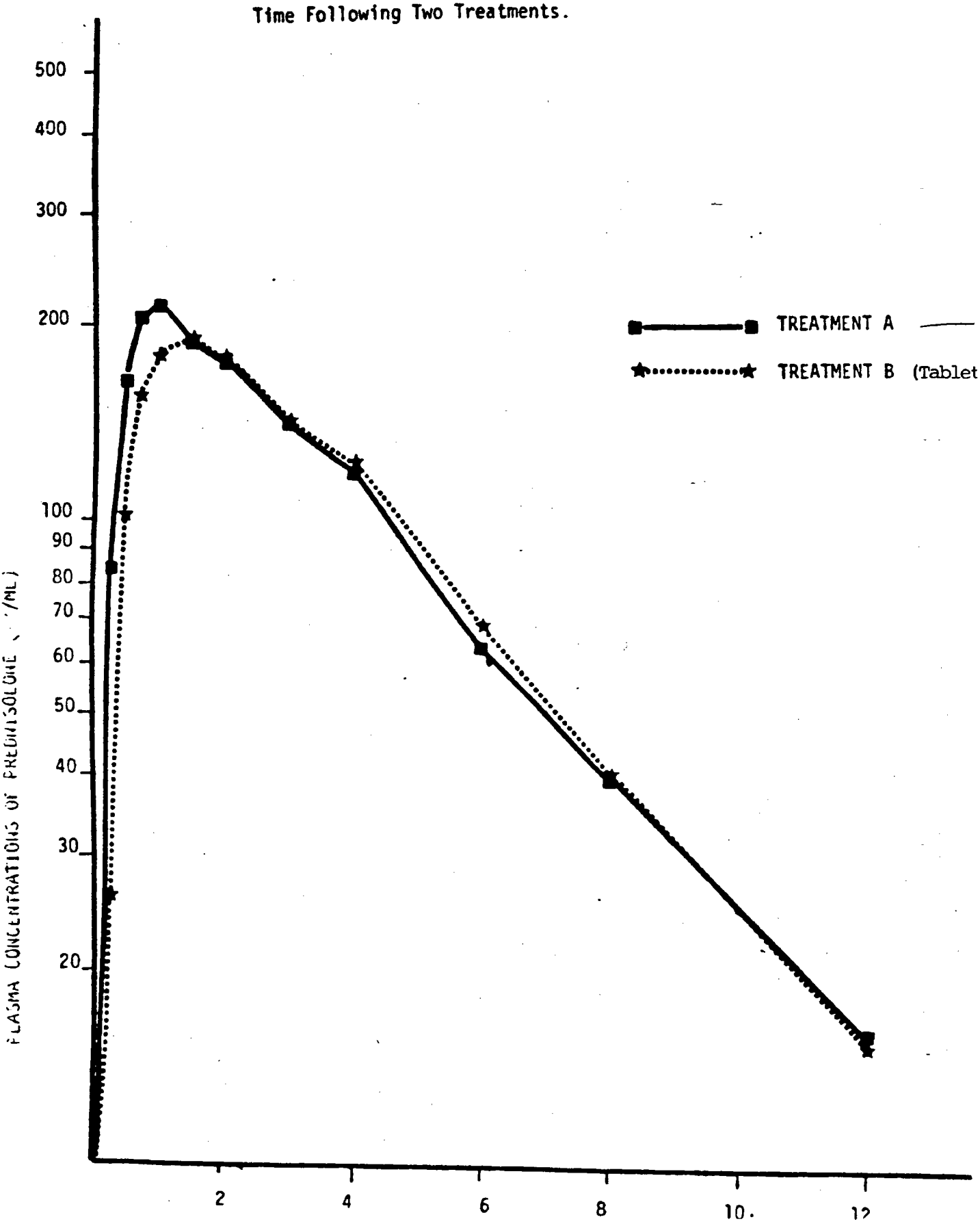


Table I

ANOVA Table for Pharmcokinetic Parameters of Prednisolone
Following Administration of Two Different Treatments

| SOURCE OF VARIATION | DF | SS | MS | F | Significance Level |
|---|---|---|---|---|---|
| | | | TOTAL AUC (0-oo) | | |
| Total | 23 | 1008815 | -- | -- | -- |
| Subjects | 11 | 632173 | 57470 | 1.68 | N.S. |
| Groups | 1 | 179920 | 179920 | 5.25 | p = 0.05 |
| Subj/Group | 10 | 452252 | 45225 | 1.32 | N.S. |
| Weeks | 1 | 33153 | 33153 | 0.97 | N.S. |
| Treatments | 1 | 963 | 963 | 0.028 | N.S. |
| Residual | 10 | 342527 | 34253 | -- | -- |
| | | | PEAK CONCENTRATION | | |
| Total | 23 | 49255.3 | -- | -- | -- |
| Subjects | 11 | 15185.3 | 1380.5 | 0.48 | N.S. |
| Groups | 1 | 3650.6 | 3650.6 | 1.26 | N.S. |
| Sub/group | 10 | 11535.0 | 1153.5 | 0.4 | N.S. |
| Weeks | 1 | 1441.5 | 1441.5 | 0.5 | N.S. |
| Treatments | 1 | 3700.2 | 3700.2 | 1.28 | N.S. |
| Residual | 10 | 28928.3 | 2892.8 | -- | -- |
| | | | TIME TO REACH PEAK CONCENTRATION | | |
| Total | 23 | 4.25 | -- | -- | -- |
| Subjects | 11 | 1.4375 | 0.1307 | 0.633 | N.S. |
| Groups | 1 | 0.0417 | 0.0417 | 0.202 | N.S. |
| Subj/Group | 10 | 1.3958 | 0.1396 | 0.677 | N.S. |
| Weeks | 1 | 0.375 | 0.375 | 1.82 | N.S. |
| Treatments | 1 | 0.375 | 0.375 | 1.82 | N.S. |
| Residual | 10 | 2.063 | 0.2063 | -- | -- |

N.S.= not statistically significantly different

Table II

Pharmacokinetic Parameters for Steroid Hormones (n= 12 subjects)

| | MEAN VALUE (C.V., %) | | | | | |
|---|---|---|---|---|---|---|
| | Prednisolone | | Prednisone | | Hydrocortisone | |
| PARAMETER | A | B | A | B | A | B |
| Time (h) | Concentration Profile (ng/ml) | | | | | |
| 0.0 | 0 | 0 | 0 | 0 | 156 (31) | 138 (39) |
| 0.083 | 4 | 0 | 0 | 0 | 94 (30) | 91 (44) |
| 0.25 | 83 (87) | 26 (62) | 0.7(345) | --- | 71 (39) | 89 (67) |
| 0.50 | 163 (50) | 102 (53) | 6.7 (96) | 2.8(133) | 52 (45) | 64(112) |
| 0.75 | 203 (29) | 155 (43) | 16.3 (75) | 8.5 (54) | 45 (68) | 46(117) |
| 1.0 | 215 (18) | 180 (38) | 18.4 (57) | 14.2 (44) | 41 (60) | 34(136) |
| 1.5 | 188 (13) | 190 (22) | 21.1 (50) | 22.4 (47 | 35(103) | 19(119) |
| 2.0 | 175 (14) | 177 (21) | 24.2 (56) | 21.9 (42) | 25(132) | 12(154) |
| 3.0 | 140 (16) | 156 (31) | 21 (41) | 24.5 (51) | 14(146) | 7(152) |
| 4.0 | 118 (17) | 124 (24) | 19 (37) | 21.4 (52) | 8(150) | 3(176) |
| 6.0 | 63 (22) | 69 (30) | 10.5 (59) | 13.4 (73) | 0.5(340) | 0.9(233) |
| 8.0 | 40 (10) | 40 (29) | 4.2 (98) | 5.4 (80) | --- | 24(253) |
| 12.0 | 16 (34) | 15 (56) | --- | 1.0(270) | 2.1(353) | 19(346) |
| 24.0 | --- | --- | --- | 0.7(333) | 97.3 (57) | 111 (49) |
| AUC [0-oo] (ng.h/ml) | 1034 (16) | 1021 (25) | | | | |
| Cmax (ng/ml) | 238 (17) | 209 (24) | | | | |
| Tmax (h) | 1 (45) | 1.2(31) | | | | |
| $T_{0.5}$ (h) | 2.5(26) | 2.6(21) | | | | |
| $CL_{pl}$ (L/h) | 9.9(18) | 11.2(27) | | | | |
| $V_{d,area}$ (L) | 35 (18) | 41.7(45) | | | | |

A= 10 ml Prednisolone sodium phosphate solution (10 mg prednisolone);

B= Two Delta-Cortef Tablets, 5 mg (10 mg Prednisolone, Upjohn's).

TABLE III

**Relative Bioavailability of Prednisolone Sodium Phosphate Solution**

| SUBJECT | AUC (0-oo h) [ng/ml x hr] A | B | (A/B) x 100% |
|---|---|---|---|
| 1 | 1134 | 1396 | 81 |
| 2 | 733 | 866 | 85 |
| 3 | 994 | 850 | 117 |
| 4 | 766 | 966 | 79 |
| 5 | 1166 | 597 | 195+ |
| 6 | 1164 | 952 | 122 |
| 7 | 1116 | 1032 | 108 |
| 8 | 1179 | 1037 | 114 |
| 9 | 881 | 1031 | 85 |
| 10 | 1123 | 964 | 116 |
| 11 | 960 | 970 | 99 |
| 12 | 1186 | 1590 | 75 |
| MEAN | 1034 | 1021 | 106 |
| S.D. | 164 | 254 | 33 |
| CV(%) | 15.9 | 24.9 | 30.8 |
| MIN. | 733 | 597 | 75 |
| MAX. | 1166 | 1590 | 195 |
| % Population with AUC Ratio w/i 75-125% Range | | | 92 |

A= Test ——— B= Commercial Tablets ———

TABLE IV

**Peak Concentrations & Time to reach Peak Concentration for Prednisolone Following Two Different Formulations**

| SUBJECT NO. | Cmax [ ng / ml ] A | B | A/B | Tmax [ Hour ] A | B | A/B | A-B |
|---|---|---|---|---|---|---|---|
| 1 | 266 | 239 | 1.11 | 0.5 | 0.75 | 0.67 | -0.25 |
| 2 | 203 | 192 | 1.06 | 1.0 | 1.5 | 0.67 | -0.50 |
| 3 | 204 | 187 | 1.09 | 1.5 | 0.75 | 2.00 | +0.75 |
| 4 | 173 | 300 | 0.58 | 1.5 | 1.0 | 1.50 | +0.50 |
| 5 | 300 | 118 | 2.54 | 1.0 | 2.0 | 0.50 | -1.00 |
| 6 | 213 | 192 | 1.11 | 0.5 | 1.0 | 0.50 | -0.50 |
| 7 | 242 | 183 | 1.32 | 0.75 | 1.5 | 0.50 | -0.75 |
| 8 | 271 | 231 | 1.17 | 0.75 | 1.5 | 0.50 | -0.75 |
| 9 | 170 | 222 | 0.76 | 2.00 | 1.0 | 2.00 | +1.00 |
| 10 | 248 | 233 | 1.06 | 1.00 | 1.0 | 1.00 | 0 |
| 11 | 244 | 148 | 1.65 | 0.75 | 1.5 | 0.50 | -0.75 |
| 12 | 271 | 262 | 1.03 | 0.75 | 1.5 | 0.50 | -0.75 |
| Mean | 238 | 209 | 1.21 | 1.0 | 1.25 | 0.90 | -0.25 |
| S.D. | 41.1 | 49.5 | 0.49 | 0.45 | 0.38 | 0.59 | +0.67 |
| C.V.(%) | 17.3 | 23.7 | 40.9 | 45.0 | 30.7 | 65.6 | 266.3 |
| % Population with Ratio | | | | | | | |
| LE 0.70 | | | 8.3 | | | 66.7 | |
| w/i 0.75-1.25 | | | 66.7 | | | 8.3 | |
| ME 1.30 | | | 25.0 | | | 25.0 | |

TABLE V

Pharmacokinetic Parameters for Prednisolone

| | PHARMACOKINETIC PARAMETER | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | $T_{0.5}$ (Hours) | | | $CL_{pl}$ (L/h) | | | $V_d$ area (Liter) | | |
| Subject | A | B | A/B | A | B | A/B | A | B | A/B |
| 1 | 2.0 | 2.1 | 0.95 | 8.8 | 7.4 | 1.19 | 25.1 | 22.0 | 1.13 |
| 2 | 1.5 | 1.9 | 0.79 | 13.6 | 12.5 | 1.09 | 29.7 | 34.0 | 0.87 |
| 3 | 2.5 | 2.3 | 1.09 | 10.1 | 12.2 | 0.83 | 35.9 | 40.0 | 0.88 |
| 4 | 1.8 | 2.4 | 0.75 | 13.1 | 10.7 | 1.22 | 33.7 | 37.0 | 0.91 |
| 5 | 2.4 | 3.5 | 0.68 | 8.6 | 19.3 | 0.44 | 30.2 | 97.0 | 0.31 |
| 6 | 2.9 | 3.1 | 0.93 | 8.6 | 11.3 | 0.76 | 36.0 | 51.0 | 0.70 |
| 7 | 2.8 | 2.5 | 1.12 | 9.0 | 10.3 | 0.87 | 36.1 | 37.7 | 0.96 |
| 8 | 4.1 | 2.1 | 1.95 | 8.5 | 10.7 | 0.79 | 49.7 | 32.3 | 1.54 |
| 9 | 2.4 | 2.5 | 0.96 | 11.4 | 11.2 | 1.02 | 39.4 | 39.6 | 0.99 |
| 10 | 2.9 | 2.2 | 1.32 | 8.9 | 10.7 | 0.83 | 37.4 | 33.1 | 1.13 |
| 11 | 2.5 | 2.6 | 0.96 | 10.4 | 10.9 | 0.95 | 37.7 | 40.7 | 0.93 |
| 12 | 2.4 | 3.5 | 0.68 | 8.4 | 7.0 | 1.20 | 29.6 | 35.2 | 0.84 |
| MEAN | 2.5 | 2.6 | 1.02 | 9.9 | 11.2 | 0.93 | 35.0 | 41.7 | |
| S.D. | 0.7 | 0.5 | 0.35 | 1.8 | 3.0 | 0.23 | 6.3 | 18.7 | |
| CV (%) | 26.2 | 20.6 | 34.4 | 18.4 | 27.2 | 24.2 | 17.9 | 44.8 | 3. |
| MIN. | 1.5 | 1.9 | 0.68 | 8.4 | 7.0 | 0.44 | 25.1 | 22.0 | 0. |
| MAX. | 4.1 | 3.5 | 1.95 | 13.6 | 19.3 | 1.22 | 49.7 | 97.0 | 1. |
| % Population with Ratio | | | | | | | | | |
| LE 0.70 | | | 16.7 | | | 8.3 | | | 16. |
| w/i 0.75-1.25 | | | 66.7 | | | 91.7 | | | 75. |
| ME 1.30 | | | 16.7 | | | 0 | | | 8. |

**WITHHOLD 7 PAGE(S)**

Bioequivalence Review.

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

# 19-157

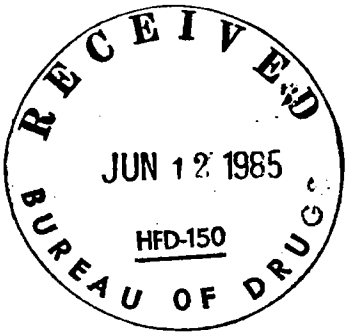
## ADMINISTRATIVE DOCUMENTS AND CORRESPONDENCE

Certified 164/85

FISONS

**Fisons Corporation**
Two Preston Court
Bedford, Massachusetts 01730
Telephone (617) 275-1000
Telex 200066 FISN UR
Cables Fisons Bedfordmass

June 10, 1985




John Palmer, M.D.
Division of Oncology and
Radiopharmaceutical Drug Products, HFN 150
Center for Drugs & Biologics
Attn: Document Control Room 17B-34
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 19-157
Pediapred® Oral Liquid (prednisolone sodium phosphate)

Dear Dr. Palmer:

Reference is made to the Drug Price Competition and Patent Term Restoration Act of 1984, section 102(a)(1) and to the above-referenced NDA. Fisons Corporation submits the accompanying patent information for inclusion in the NDA file.

A copy of this information is also provided to Mr. Thomas McGinnis, Division of Information Resources (HFN 84).

If you have any questions, please contact Ms. Patricia J. Richards or the undersigned.

Sincerely,

Aaron M. Taub, Ph.D.
Senior Regulatory Affairs
Scientist

AMT:tac
Attachment

| | | | |
|---|---|---|---|
| 1) | Active Ingredient(s) | Prednisolone Sodium Phosphate | |
| 2) | Strength(s) | 6.70 mg/5 ml (5.0 mg Prednisolone Base/5 ml) | |
| 3) | Trade Name | Pediapred™ Oral Liquid | |
| 4) | (Dosage Form, Route of Administration) | Oral | |
| 5) | Applicant Firm Name | Fisons Corporation | |
| 6) | NDA Number | 19-157 | |
| 7) | Approval Date | Pending | |
| 8) | Exclusivity - Date first ANDA could be approved and length of exclusivity period | | |
| 9) | Applicable patent numbers and expiration date of each | 4448774 | May 15, 2001 |

M E M O R A N D U M

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
National Center for Drugs and Biologics

TO : Acting Director, HFN-100
Office of New Drug Evaluation

DATE: Nov. 23, 1982

FROM : Associate Director for Drug Monographs (HFN-500)

SUBJECT: Request for ANDA Status for Prednisolone Sodium Phosphate Oral Liquid, 6.70 mg/5 ml

By a submission of November 1, 1982, Fisons Corporation has requested a determination as to whether a Prednisolone Sodium Phosphate Oral Liquid, 6.70 mg/5 ml would be acceptable as an ANDA.

Background

The most relevant DESI notice is 7750 (see 35 FR 16424, October 21, 1970; and 42 FR 11888, March 1, 1977). In this notice, the following are included in the acceptable products list:

Hydrocortisone Suspension
Triamcinolone Diacetate Syrup
Dexamethasone Elixir
Prednisolone Tablets

For the Hydrocortisone Suspension and the Dexamethasone Elixir, the active ingredients are the same chemical form as the tablet. The Triamcinolone Diacetate Syrup is not the same as the tablet (Triamcinolone), however, the diacetate is the salt which is available in injectable products.

Recently, a Prednisone Syrup was determined to be acceptably similar and related to prednisone tablets for purposes of accepting an ANDA, and was subsequently approved as an ANDA.

The firm has provided a bioequivalence study in support of their request to allow their product to be processed as an ANDA. This study compares their orally administered prednisolone sodium phosphate product to prednisolone tablets. The firm alleges that the study demonstrates bioequivalence between the two products.

The proposed product incorporates a soluble salt (sodium phosphate) of a glucocorticoid. There is no precedent for a soluble salt in any marketed product intended for oral use, although prednisolone sodium phosphate is the active entity in certain ANDA acceptable products for ophthalmic and parenteral use.

Past policy involving new salts of DESI active ingredients is to require NDAs for initial submissions. Also, we generally feel reluctant to allow ANDAs for different salts or esters of DESI drugs so as to undermine the current agency policy limiting propoxyphene napsylate to a full NDA as a post-1962 product.

We have not called for review of the bioequivalence study at this point in time, on the basis that you may find that consideration as subordinate to the "new salt" issue. If however, you believe that the new oral salt dosage form would be acceptable if bioequivalent to prednisolone tablets, we will arrange for a review.

We would appreciate your review on this matter.

Gene Knapp

cc: Mr. Rosen/HFN-532
Dr. Bryan/HFN-501
Mr. Hare/HFD-503
Chron File/HFN-500
ANDA Acceptable File/HFN-500
KJohnson/cjl/11-23-82

NDA 19-157

APR 8 1986

Fisons Corporation
Two Preston Court
Bedford, Massachusetts 01730

Attention: Patricia J. Richards
Associate Director
Regulatory Affairs

Dear Ms. Richards:

Reference is made to the amendment to your new drug application received by FDA on January 22, 1986.

We consider your amendment a major amendment under 21 CFR 314.60 and we have determined that sixty additional days will be required for its review. The new due date is March 22, 1986.

Sincerely yours,

John F. Palmer, M.D.
Director
Division of Oncology and
Radiopharmaceutical Drug Products
Office of Drug Research and Review
Center for Drugs and Biologics

cc:
Orig. NDA 19-157
HFN-150
HFN-150/DPease/3-13-86
HFN-150/ESheinin
HFN-150/RHuckins
D/T:tw:3/13/86
F/T:tw:3/18/86
Wang #04630

NDA 19-157

Fisons Corporation
Attention: Patricia J. Richards
Two Preston Court
Bedford, Mass. 01730

Dear Sirs:

We are pleased to acknowledge your new drug application submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug: PEDIAPRED Oral Liquid

Date of Application: November 1, 1983

Date of Receipt: November 6, 1983

Our Reference Number: NDA 19-157

We will correspond with you further after we have had the opportunity to study the application. Should you have any questions prior to our contacting you, please call:

Ms. Dotti Pease
Consumer Safety Officer
(301) 443-5197

All future communications concerning this NDA should be addressed as follows:

National Center for Drugs and Biologics, HFN-150
Attention: DOCUMENT CONTROL ROOM #17B-28
5600 Fishers Lane
Rockville, Maryland 20852

Sincerely yours,

John F. Palmer, M.D.
Acting Director
Division of Oncology and
Radiopharmaceutical Drug Products
Office of Drug Research and Review
National Center for Drugs and Biologics

cc: BOS-DD
Orig NDA 19-157
HFN-150/Div File
HFN-150
HFN-150/McCullen/
HFN-150/Pease
F/T by P. Amoss/12/9/83
Wang #0794P

ACKNOWLEDGE

May 26, 1983

Fisons Corporation
Attention: James M. Parker, J.D., Ph.D.
Two Preston Court
Bedford, MA 01730

Dear Dr. Parker:

This is in response to your letter dated March 4, 1983, wherein you requested a reconsideration of the decision that Pediapred (Prednisolone Sodium Phosphate) 6.70 mg/5 ml oral liquid, is not a candidate for submission as an abbreviated new drug application.

You are advised that Dr. Temple, the Acting Director, Office of New Drug Evaluation has re-evaluated the material submitted and has determined that this product is not an acceptable candidate for submission as an abbreviated new drug application.

You may contact the Division of Oncology and Radiopharmaceutical Drug Products (HFN-150), National Center for Drugs and Biologics, Office of New Drug Evaluation, 5500 Fishers Lane, Rockville, MD 20857 for information regarding application requirements for the product prednisolone sodium phosphate 6.70 mg/5 ml oral liquid.

The material submitted is being retained in our files. Please advise us if you would like the material returned to you or forwarded to the Division of Oncology and Radiopharmaceutical Drug Products.

Sincerely yours,

Marvin Seife 5/26/83

Marvin Seife, M. D.
Director
Division of Generic Drug Monographs
Office of the Associate Director
for Drug Monographs
Office of Drugs
National Center for Drugs and Biologics

JAN 7 1983

Fisons Corporation
Attention: Ms. Patricia J. Richards
Two Preston Court
Bedford, MA 01730

Dear Ms. Richards;

Reference is made to your application dated November 1, 1982 submitted pursuant to Section 505(b) of the Federal Food, Drug and Cosmetic Act for Pediapred (Prednisolone Sodium Phosphate) 6.70 mg./5 ml. oral liquid.

The application was submitted in the form of an abbreviated new drug application.

You are advised that this product has been determined not to be an acceptable candidate for submission as an abbreviated new drug application. Although prednisolone sodium phosphate has been determined to be effective and thus ANDA eligible for certain opthalmic and parenteral drug products, the firm must submit clinical studies to demonstrate the safety and efficacy of prednisolone sodium phosphate in an oral dosage form.

Please contact the Division of Oncology and Radiopharmaceutical Drug Products (HFN-150), National Center for Drugs and Biologics, Office of New Drug Evaluations, 5600 Fishers Lane, Rockville, MD 20857 for information regarding application requirements for the product prednisolone sodium phosphate 6.70 mg./5 ml oral liquid.

The material submited is being returned to you.

Sincerely yours,

Marvin Seife 1/7/83

Marvin Seife, M.D.
Director
Division of Generic Drug Monographs
Office of the Associate Director
for Drug Monographs
National Center for Drugs and Biologics

Fisons File
DRosen

Certified 206/83

FISONS

**Fisons Corporation**
Two Preston Court
Bedford, Massachusetts 01730
Telephone (617)275-1000
Telex 92-3400. Cables Fisons Bedfordmass

October 19, 1983

Ms. Mary DuValle
Division of New Drug Evaluation
National Center for Drugs
& Biologics
Room 14B-45
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: Pediapred™ (prednisolone sodium phosphate) Syrup

Dear Mrs. DuValle:

Thank you for your telephone call of October 17, 1983, confirming the meeting to be held on October 28, 1983, at 10:00 AM in Dr. Temple's office with Dr. Temple, Dr. Palmer, Dr. Harter, Dr. Wood, and Miss Moore. The subject of the meeting will be Pediapred (prednisolone sodium phosphate) Syrup.

We now plan to have the following persons from Fisons Corporation attend:

| | |
|---|---|
| Roger Menendez, M.D. | Director of Medical Affairs |
| James M. Parker, Ph.D., J.D. | Vice President, Legal, Regulatory & Medical Affairs & Export Operations |
| Patricia J. Richards | Associate Director, Regulatory Affairs |
| Aaron M. Taub, Ph.D. | Senior Regulatory Affairs Scientist |

Please find attached to this letter six (6) copies of the proposed labeling which you requested for the participants at this meeting.

Thank you for your cooperation.

Sincerely,

Aaron M. Taub, Ph.D.
Senior Regulatory Affairs Scientist

AMT:lmd
Attachments

**WITHHOLD 28 PAGE(S)**

Draft Labeling