CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-959

MEDICAL REVIEW(S)

CLINICAL REVIEW

DATE: May 15, 2006
TO: File, NDA 21-959
FROM: Joel Schiffenbauer, M.D.
Medical Team Leader, DAARP
RE: Supervisory Review of NDA 21-959; Orapred ODT

Background:

The sponsor has submitted a 505(b)(2) Application for Orapred ODT 10, 15 and 30 mg tablets. The submission relies on the FDA's findings of safety and efficacy of the reference listed product Pediapred oral solution (prednisolone base 5 mg/5 ml) via cross reference to NDA 19-157. Two bioequivalence trials are submitted that compare Orapred with Pediapred. No additional efficacy trials are submitted. Safety from the 2 bioequivalence trials and a literature review is also submitted.

This document serves as the secondary medical review of NDA 21-959. Dr. J Castle is the primary medical reviewer and Dr. D. Lee is the primary biopharmaceutics reviewer.

Medicis intends to rely on the FDA's previous findings of the safety and effectiveness of Pediapred oral solution via cross–reference to NDA 19–157.

Medicis met with the Division April 11, 2005 for a Pre-NDA meeting. They proposed a label [redacted]

The following summarizes some of the points that were noted during a teleconference held on July 11, 2005:
1. The sponsor clarified that although they own Orapred Solution, they chose Pediapred Solution (NDA 19-157) as the reference listed product (RLD) because this application contained the data supporting approval upon which the Orapred Solution ANDA was based.
2. The integrated summary of efficacy (ISE) is a necessary component of the NDA. In the case of a 505(b)(2) application that will not contain clinical efficacy studies, the ISE would consist of the data describing why it is appropriate to rely on prior findings of efficacy for the RLD, such as bioequivalence.
3. The integrated summary of safety (ISS) should include results from a literature review and safety reports of the active moiety, prednisolone sodium phosphate. As a similar review was performed for the Orapred Solution generic application, the information from that application along with the any new information in the two years subsequent to approval would be adequate. The sponsor will also provide information from safety reports for Orapred Solution. The emphasis will be on safety concerns that differ from

the existing package insert for the reference listed product. Summary tables will be provided.
4. [redacted] and will provide further feedback as information is received from the Office of Generic Drugs.
5. The sponsor confirmed that they are not pursuing a dose less than 10 mg per ODT tablet.
6. The limited dosing flexibility presented by the lowest proposed formulation of 10 mg would be reflected in the labeling, including effects on pediatric dosing indications. The sponsor acknowledged this potential impact on labeling.

In addition, a consult was obtained from the Division of Pediatric Drug Development in regards to the issue of waiving the need for pediatric studies. Their response was as follows:

A bioequivalence study is sufficient to meet PREA requirements, but a lower dosage strength of the ODT formulation must be available to permit dosing across the dosing range recommended in the pediatric population for the reference listed product, Pediapred. An alternative option if the Sponsor does not wish to develop a lower dosage strength of Orapred ODT is to waive pediatric studies because the already marketed formulations permit flexibility on dosing across the dosage range recommended for prednisolone in the pediatric population.

Clinical Pharmacology and Biopharmaceutics

Dr. David Lee, the Clinical Pharmcology and Biopharmaceutics reviewer has determined, based on the review of 2 bioequivalence studies, that Orapred ODT is bioequivalent to the reference listed product, Pediapred. Furthermore, Orapred ODT is bioequivalent to Orapred solution. Orpared ODT can be taken with or without water. No food effect studies were required by the Division.

Dr. Lee also recommends that all references to Pediapred solution be removed and a statement in regards to the fact that Orapred ODT may not be an appropriate formulation for pediatric patients, be added. This is consistent with my recommendations.

Efficacy

No efficacy studies are submitted in this application. The applicant has relied on 2 PK studies to demonstrate bioequivalence with a previously approved product, Pediapred. The conclusion from each study is that the 90% confidence interval derived from the analyses of log-transformed PK parameters AUC, and Cmax for prednisolone were within the 80-125% range, and therefore that Orapred ODT and Pediapred were bioequivalent.

The reader is referred to the OCPB review for more details of the results and analyses of these 2 trials.

Safety

Oral prednisolone sodium phosphate dosage forms have been available in the US to treat a variety of inflammatory conditions in both adults and children for over 20 years, and the adverse event profile of glucocorticoids in general is well established. The adverse event profile is well described in the current package insert for prednisolone sodium phosphate oral solution and other steroid preparations in general.

For the ISS the applicant provided safety data from 3 sources: 1) the PK trials; 2) postmarketing data for the 2 years since the approval of Orapred solution; and 3) a safety review previously provided for Orapred solution (in addition to new information in the 2 years subsequent to that approval). The label of Orapred solution was updated in December of 2004 to reflect current safety information.

Data from post-marketing was provided as follows: There were three 15 day reports. One patient developed urticaria after taking Orapred for asthma. A second patient developed urticaria and dyspnea after taking Orapred for respiratory distress. A third patient who developed urticaria with increased wheezing and coughing after taking Orapred. All were children. There were 7 serious and expected events reported. Three events were the urticaria previously mentioned. The remaining 4 events occurred in one patient treated for pneumonia (depression, headache, abdominal pain and malaise). There were 28 not serious and unexpected cases reported. There were 4 reported cases of hypersensitivity described as rash, swelling itching. There were 15 cases of not serious and expected events.

A literature search was conducted by ——— on behalf of Medicis, for safety concerns regarding prednisolone sodium phosphate over the past 2 years. The search was conducted for adverse effect of Orapred or prednisolone sodium phosphate(see sponsors submission Appendix 3 for a list of terms and Appendix 4 for a list of databases searched; databases such as Medline, Toxline, Embase were searched). No serious or unexpected events were found in the search of the medical literature.

The sponsor performed 2 PK studies; Study OPD-001-01 consisted of 24 healthy adult volunteers and Study OPD-002-01 consisted of 14 healthy adult volunteers. Three subjects reported 6 treatment emergent adverse events during Study 001-01. No severe or serious adverse events were noted. No adverse events were noted during study 002-01.

There were no laboratories listed as AEs in the study report or the ISS. Review of laboratory summary table in Study OPD-002-01 showed leukocyte count as high as 12.4 thousand/uL, normal range 4.5-11.5 thousand/uL. These laboratories were not considered by the investigators to be clinically significant.

Overall, there appear to be no clinically significant laboratory AEs seen with short term use of Orapred ODT as seen in Study OPD-001-01 and OPD-002-01.

The third source of safety information comes from the label for the Orapred solution which was updated 2 years ago.

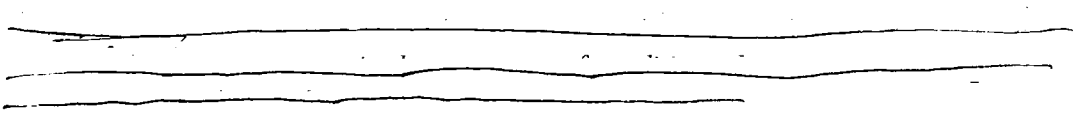
See also Dr. Castle's review for additional details in regards to the safety reports. Overall, in the opinion of this reviewer, the safety profile does not reveal any significant new safety concerns.

Conclusions

Orapred ODT appears to be bioequivalent to Pepdiapred. Furthermore, there are no new safety issues that would prevent approval of this product. However, there are 2 issues with this product both related to the fact that the 10 mg dose is the lowest available dose. The first issue relates to use in the pediatric population, and the second relates to the (in)ability to taper down to levels below 10 mg both for the adult as well as the pediatric population.

First, the applicant has demonstrated that Orapred ODT is bioequivalent to Pediapred (the reference listed product). However, the Pediapred label contains language concerning the use of Pediapred in the pediatric population. Because the lowest dose of Orapred available for use is 10 mg it may be possible that small children will not be able to use this product.

Second, and possibly of greater significance, is that in many instances steroid products require a tapering schedule, that most often necessitates the use of doses at levels less than 10 mg. With this product it will be impossible to taper the drug below the 10 mg level without requiring a change in formulation (to the liquid formulation, for example). This could potentially lead to some confusion with the appropriate dose, resulting in either under or overdosing of the product, at least to some extent (it is difficult to determine if this would be clinically important as small differences in dose may not have a significant clinical effect). The issue of using doses less than 10 mg was discussed with the applicant. It was the decision of the applicant not to pursue a formulation with a dose below the 10 mg dose. It was further determined by Dr. Hertz after discussion with the applicant that this could be adequately addressed with appropriate labeling. The applicant has submitted the following language in their label (under the *Dosage and Administration* section) to address this issue:



This language does not appear to clearly state the problem with using Orapred ODT if tapering to below 10 mg is necessary. In addition, it is not necessary to direct the

physician to use [redacted], but rather, any appropriate formulation would be adequate for therapy. The applicant's language appears to be promotional in a sense. Pending DDMAC's final recomendations alternate wording should be considered, such as the following:

[redacted]

In terms of safety, Dr. Castle, the medical reviewer has also recommended: 1) that a number of adverse events be added to the new label (see her review under the safety section); and 2) that a comment about lack of immunogenicity assessments be added to the label.

First, the AEs listed in her review (AEs suggested for addition include the following: dyspnea, wheezing, facial edema, emesis, diarrhea, tremor, leukocytosis), for the most part come from either post-marketing safety reports for Orapred solution (different formulation), or from an individual subject in the bioequivalence studies, and are essentially already covered in the standard glucocorticoid labeling. Leukocytosis for example, is a well known effect of systemic steroid administration and would not necessarily be considered an AE. Some of the other events also occurred in individuals with concomitant medical illnesses for which steroids are indicated (asthma and wheezing for example). As an additional example, Dr. Castle lists "head banging" as an AE that should be added to the label. This occurred in a patient with a seizure disorder, which makes it difficult to attribute the cause to Orapred. Therefore, in general I do not agree with her assessment. As such, I would not recommend that these additional AEs be added and that the Orapred label that was updated only 2 years ago, be used unchanged (except for the changes related to the issues discussed above).

Second, new immunogenicity studies are not routinely needed for a 505(b)(2) product, but might be needed if there was a specific concern for any product (such as a biologic/protein). Furthermore, steroids are not known per se to be immunogenic but rather immunosuppressive. Lastly, it is possible that if antibodies were to develop to Orapred they would be directed against the excipients rather than the steroid portion itself, and these excipients have been found acceptable by the toxicology and biopharmaceutics reviewers. I do not believe that immunogenicity studies are needed, and furthermore, a statement that they were not performed, is not necessary and does not add useful information to the label.

With agreement on appropriate labeling [redacted]

an NDA (Orapred ODT-505b2), it is recommended that the application be approved.

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/s/

Joel Schiffenbauer
5/22/2006 06:42:25 AM
MEDICAL OFFICER

CLINICAL REVIEW

Application Type	NDA
Submission Number	21-959
Submission Code	N-000
Letter Date	28 JUL 2005
Stamp Date	01 AUG 2005
PDUFA Goal Date	01 JUN 2006
Reviewer Name	Julia Castle, M.D., M.P.H.
Review Completion Date	March, 2006
Established Name	prednisolone sodium phosphate
(Proposed) Trade Name	Orapred ODT®
Therapeutic Class	Glucocorticoid
Applicant	Medicis Pediatrics, Inc.
Priority Designation	S
Formulation	orally disintegrating tablet
Dosing Regimen	10, 15, and 30 mg
Indication	Same as other glucocorticoid preparations, such as Orapred® or Pediapred®
Intended Population	Adults and Pediatric

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

This 505(b)(2) application from Medicis Pediatrics, Inc. is for the same indications as for other glucocorticoid preparations, for Orapred ODT® (prednisolone sodium phosphate) 10, 15, and 30 mg. This application consists of two bioequivalence studies, a summary of periodic adverse events reports (PAERs) for the last two years submitted for Orapred oral solution, and a literature search for the last two years for oral prednisolone sodium phosphate and clinical studies, or serious or unexpected adverse events (AEs). Prednisolone is approved in the U.S. for over forty indications[1,2].

In this submission, efficacy data for Orapred ODT is referenced to the DESI review which showed safety and efficacy for prednisolone in the past. There are no efficacy trials submitted as part of this NDA. Two bioequivalence trials were submitted, Studies OPD-001-01 and OPD-002-01.

Review of safety did not find additional safety concerns other than a list of adverse events which should be added to the label. This reviewer concludes that there is sufficient evidence of efficacy and safety for Orapred ODT at the 10, 15, and 30 mg doses for the glucocorticoid indications, and recommends approval with labeling changes.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

The sponsor did not submit, nor did the FDA request, a risk management plan.

1.2.2 Required Phase 4 Commitments

No Phase 4 commitments will be required of the sponsor.

1.2.3 Other Phase 4 Requests

There were no other Phase 4 requests.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

This is a review of a 505 (b)(2) application submitted by Medicis Pediatrics, Inc. on August 1, 2005 for the glucocorticoid indications. There were no efficacy trials submitted as part of this NDA. The sponsor submitted a safety database which included data from Studies OPD-001-01 and OPD-002-01, as well as information from a summary of PAERs reports for the last two years submitted for Orapred oral solution, and a literature search over the last two years for oral prednisolone sodium phosphate and clinical studies, or serious or unexpected AEs.

1.3.2 Efficacy

Efficacy data for Orapred ODT is referenced to the DESI review which showed safety and efficacy for prednisolone in the past. The FDA and Medicis Pediatrics, Inc. agreed to this in a meeting on April 11, 2005. There are no efficacy trials submitted as part of this NDA. Only two bioequivalence trials were submitted.

1.3.3 Safety

Review of safety found additional safety concerns for AEs which need to be added to the label for Orapred ODT®. The safety data reported in this submission are consistent with the proposed label, except for the following AEs which should be added:

Face edema,

Pharyngolaryngeal pain
Blood in stool
Eye irritation
Eyelid edema

Wheezing

Depression

Emesis

[redacted]

Erythema

[redacted]

1.3.4 Dosing Regimen and Administration

Orapred ODT® 10, 15, and 30 mg doses are effective based on information from other glucocorticoid preparations on the market. The dose should be titrated to the lowest effective dose.

1.3.5 Drug-Drug Interactions

No new information was submitted with this application. The possibility of a change in absorption with concomitant H2 blocker treatment was raised and will be further discussed in the clinical pharmacology review by Srikanth Nallani, PhD.

1.3.6 Special Populations

There are special considerations for both the Pediatric and Geriatric populations. The PRECAUTIONS section of the label gives detailed information regarding these populations. In addition to AEs seen in the adult population, the pediatric population may be at risk for a decrease in growth velocity, which should be monitored. To minimize these effects children should be titrated to the lowest effective dose.

In addition to AEs seen in the adult population, the geriatric population is at higher risk for osteoporosis. This risk may decrease over time and with doses less than 5 mg per day. Doses of prednisolone of 7.5 mg per day or higher have been associated with an increased risk of fractures. Bisphosphonate treatment in addition to using the lowest effective dose has been recommended in the prevention of steroid-induced osteoporosis. Since decreased renal function is seen frequently in the elderly, dosing should be adjusted as needed.

2 INTRODUCTION AND BACKGROUND

Glucocorticoids have been on the market in the U.S. for over forty years. This is a 505(b)(2) application for Orapred ODT® (prednisolone sodium phosphate). Prednisolone has mostly glucocorticoid activity and some mineralocorticoid properties, and is a synthetic adrenocortical steroid. Prednisolone has potent anti-inflammatory effects on many diseases affecting organ systems such as endocrine, rheumatic, hematologic, nervous system, dermatologic, ophthalmic, gastrointestinal, and pulmonary. Prednisolone is indicated also for edematous states and allergies.

Orapred ODT was developed for patients who may have difficulty swallowing tablets, and/or difficulty tolerating large volumes of liquid required for therapeutic doses, particularly in pediatric and geriatric populations. This tablet dissolves in the mouth, and is produced in a 10, 15, and 30 mg tablet. Prednisolone is metabolized by the liver, and excreted by the kidneys.

2.1 Product Information

Orapred ODT® is the trade name for this application's product. The generic name is prednisolone sodium phosphate. Orapred ODT® is a glucocorticoid formulated in an orally disintegrating tablet, with an empirical formula of $C_{21}H_{27}Na_2O_8P$.

2.2 Currently Available Treatment for Indications

Orapred®, Pediapred®

2.3 Availability of Proposed Active Ingredient in the United States

The main active ingredient is prednisolone sodium phosphate for Orapred ODT. The orally disintegrating tablets will be available in tablets equivalent to 10 mg, 15 mg or 30 mg of prednisolone base.

2.4 Important Issues With Pharmacologically Related Products

The sponsors performed a literature search for the last two years for prednisolone sodium phosphate, looking for AEs or clinical trials over the last two years and found none. This NDA also included Periodic Adverse Experience Reports for the last two years submitted for Orapred oral solution. These results were reviewed and presented in section 7.1.17.

2.5 Presubmission Regulatory Activity

A pre-NDA meeting was held with the FDA and the sponsor on April 26, 2005 during which the FDA stated that the Orapred ODT® application could be submitted as a 505(b)(2) application.

The two proposed bioequivalency studies were found acceptable, and the need for a food effect study was stated.

BioMarin submitted CMC information on June 1, 2005, which was discussed during the pre-NDA meeting. BioMarin submitted Clinical information on May 6, 2005, which was discussed during the pre-NDA meeting. On June 20, 2005, BioMarin submitted a summary of published literature regarding the effect of food on the bioavailability of prednisolone, and stated that a food-effect study was not needed.

A teleconference was held July 11, 2005. The FDA expressed a need for a literature review for the last two years of safety information for Orapred® oral solution for this submission.

The sponsor was changed to Medicis Pediatrics, Inc. prior to this submission.

2.6 Other Relevant Background Information

There was no additional relevant background information.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

The chemistry review will be performed by Rao Puttagunta, PhD. The review was not completed at the time of this review.

3.2 Animal Pharmacology/Toxicology

The Pharmacology and Toxicology review will be performed by Steve Leshin, PhD. His review was not available at the time of this review.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The full study reports for studies OPD-001-01 and OPD-002-01 were submitted as part of the electronic and paper submission for this NDA, and were reviewed. The ISS was reviewed along with the patient narratives, and case report forms (CRFs) for all three patients who dropped out of Study OPD-001-01.

Safety data was reviewed and presented in section 7.1.

This NDA also included Periodic Adverse Experience Reports (PAERs) reports and a literature search. The PAERs reports for the last two years submitted for Orapred oral solution were submitted with summaries of 15-day alert reports, serious and expected events, not serious and unexpected events, and not serious and expected events. The PAERs were reviewed and presented in section 7.1.17.

The literature search was performed by [redacted]. for prednisolone sodium phosphate, looking for AEs or clinical trials over the last two years, as the label for Pediapred was two years old and safety was updated then. The literature search was reviewed and described in section 7.

4.2 Tables of Clinical Studies

This NDA included data from two completed relative bioavailability trials. Study OPD-001-01 was a three way crossover study in healthy volunteers, comparing three treatments as follows: Orapred ODT 30 mg tablet, Pediapred oral solution 30 mg, and Orapred oral solution 30 mg all given orally over two weeks. Study OPD-002-01 was a two way crossover study in healthy volunteers comparing Orapred ODT 30 mg tablet with and without 240 mL water, given orally over one week. There was a seven day washout between treatments for both studies. The studies are listed in Table 4.2.1 below.

Table 4.2.1 Bioavailability Studies in Healthy Subjects for Orapred ODT

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Health Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Relative Bioavailability	OPD-001-01	5.3.1.1	Determine relative bioavailability of equivalent doses of Orapred ODT, Pediapred, liquid and Orapred liquid.	3 way crossover relative bioavailability study	A: 30mg Orapred ODT tablet., p.o. B: 30mg dose Pediapred oral solution, p.o. C: 30mg dose Orapred oral solution, p.o.	24 (20/4) 26 y (19-42)	Healthy volunteers	Single dose of each treatment with 7 day washout between periods	Complete; Full Report
Relative Bioavailability	OPD-002-01	5.3.1.2	Determine relative bioavailability of equivalent doses of Orapred ODT given with 240 mL water versus without water.	2 way crossover relative bioavailability study	A: 30mg Orapred ODT Tab with 240mL water, p.o. B: 30mg Orapred ODT Tab without water, p.o	14 (12/2) 30 y (20-45)	Healthy volunteers	Single dose of each treatment with 7 day washout between periods	Complete; Full Report

(from Sponsor's Table 5.2.1 of Module 5, Volume 1 of 16, page 3 of 254)

4.3 Review Strategy

The two bioequivalent studies presented in the table above were reviewed. There were no efficacy studies. The safety review included the two studies above, PAERs reports for the last two years for Orapred solution, and a literature search for the last two years for prednisolone.

4.4 Data Quality and Integrity

There were no significant issues requiring an audit of the clinical safety data.

4.5 Compliance with Good Clinical Practices

The studies were conducted in accordance with acceptable ethical standards. The study reports indicated that informed consent was obtained as well as IRB approval. There were few protocol violations which did not seem to favor any treatment group.

4.6 Financial Disclosures

Financial disclosures were provided for the clinical investigators and did not show a conflict of interest.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

There were two new pharmacokinetics studies. The reader is referred to the review by David Lee, PhD. The biopharmacology review was not available at the time of this review.

5.2 Pharmacodynamics

There were no new pharmacodynamics studies.

5.3 Exposure-Response Relationships

There were no new exposure-response relationship studies.

6 INTEGRATED REVIEW OF EFFICACY

Efficacy data for Orapred ODT is referenced to the DESI review which showed safety and efficacy for prednisolone in the past. The FDA and Medicis Pharmaceutical Corporation agreed to this in a meeting on April 11, 2005. There are no efficacy trials submitted as part of this NDA. Only two bioequivalence trials were submitted.

6.1 Indication

The proposed indications are the same indications as for Orapred and Pediapred listed in the proposed annotated label as seen in the text below.

INDICATIONS AND USAGE: Orapred is indicated in the following conditions:

1. Allergic States

Control of severe or incapacitating allergic conditions intractable to adequate trials of conventional treatment in adult and pediatric populations with: seasonal or perennial allergic rhinitis; asthma; contact dermatitis; atopic dermatitis; serum sickness; drug hypersensitivity reactions.

2. Dermatologic Diseases

Pemphigus; bullous dermatitis herpetiformis; severe erythema multiforme (Stevens-Johnson syndrome); exfoliative erythroderma; mycosis fungoides.

3. Edematous States

To induce diuresis or remission of proteinuria in nephrotic syndrome in adults with lupus erythematosus and in adults and pediatric populations, with idiopathic nephrotic syndrome, without uremia.

4. 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.

5. Gastrointestinal Diseases

To tide the patient over a critical period of the disease in: ulcerative colitis; regional enteritis.

6. Hematologic Disorders

Idiopathic thrombocytopenic purpura in adults; selected cases of secondary thrombocytopenia; acquired (autoimmune) hemolytic anemia; pure red cell aplasia; Diamond-Blackfan anemia.

7. Neoplastic Diseases

For the treatment of acute leukemia and aggressive lymphomas in adults and children.

8. Nervous System

Acute exacerbations of multiple sclerosis.

9. Ophthalmic Diseases

Uveitis and ocular inflammatory conditions unresponsive to topical corticosteroids; temporal arteritis; sympathetic ophthalmia.

10. Respiratory Diseases

Symptomatic sarcoidosis; idiopathic eosinophilic pneumonias; fulminating or disseminated pulmonary tuberculosis when used concurrently with appropriate antituberculous chemotherapy; asthma (as distinct from allergic asthma listed above under "Allergic States"), hypersensitivity pneumonitis, idiopathic pulmonary fibrosis, acute exacerbations of chronic obstructive pulmonary disease (COPD), and Pneumocystis carinii pneumonia (PCP) associated with hypoxemia occurring in an HIV (+) individual who is also under treatment with appropriate anti-PCP antibiotics. Studies support the efficacy of systemic corticosteroids for the treatment of these conditions: allergic bronchopulmonary aspergillosis, idiopathic bronchiolitis obliterans with organizing pneumonia.

11. 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; epicondylitis. For the treatment of systemic lupus erythematosus, dermatomyositis (polymyositis), polymyalgia rheumatica, Sjogren's syndrome, relapsing polychondritis, and certain cases of vasculitis.
12. Miscellaneous
Tuberculous meningitis with subarachnoid block or impending block, tuberculosis with enlarged mediastinal lymph nodes causing respiratory difficulty, and tuberculosis with pleural or pericardial effusion (appropriate antituberculous chemotherapy must be used concurrently when treating any tuberculosis complications); Trichinosis with neurologic or myocardial involvement; acute or chronic solid organ rejection (with or without other agents).
(from Sponsor's Proposed Annotated Label)

6.1.1 Methods

There were no efficacy studies submitted for review.

6.1.2 General Discussion of Endpoints

There were no efficacy studies submitted for review.

6.1.3 Study Design

There were no efficacy studies submitted for review.

6.1.4 Efficacy Findings

There were no efficacy studies submitted for review.

6.1.5 Clinical Microbiology

There were no efficacy studies submitted for review.

6.1.6 Efficacy Conclusions

There were no efficacy studies submitted for review.

7 INTEGRATED REVIEW OF SAFETY

There were no clinical studies for efficacy conducted. Adverse events have been well described in the label for prednisolone sodium phosphate oral solution which includes information from chronic systemic adrenocortical steroid use over the last forty years. Prednisolone affects

exocrine and endocrine function, as well as the immune system. Known side effects include effects on the cardiac, endocrine, gastrointestinal, musculoskeletal, neurologic, ophthalmic, psychiatric, and renal systems.

Overall there were safety data from two bioavailability studies submitted for this NDA. Study OPD-001-01 and Study OPD-002-01 are described below. In these two relative bioavailability studies, subjects who received at least one dose of prednisolone sodium phosphate were included in the safety evaluation. Safety data reported includes subject vital signs, laboratories, physical exams, AEs, and ECGs. AEs were coded using MedDRA version 6.1. The clinical study reports include by-subject adverse event data with verbatim terms, coded terms, severity, and treatment groups.

Additional safety information is presented from the last two years of Periodic Adverse Event Reports (PAER) for Orapred Oral Solution.

In addition, a literature search for serious unlisted adverse events related to oral prednisolone sodium phosphate over the last two years was performed. No clinical studies, and no serious or unexpected AEs were found involving Orapred.

7.1 Methods and Findings

STUDY OPD-001-01
Study OPD-001-01 was a bioavailability study in healthy volunteers, to determine the bioequivalence of Orapred ODT to Pediapred, the reference listed drug, and to Orapred liquid. Study drug exposure was a single 30 mg prednisolone base equivalent dose, in a series of three treatments, given with a seven day washout period as follows: Orapred ODT 30 mg tablet, Pediapred oral solution 30 mg, and Orapred oral solution 30 mg all given orally over two weeks. The subjects received a total of three doses.

There were two protocol violations in this study as follows:

Subject 13 did not have a second aliquot for the hour 16, Day 1, period 1 because there was not enough fluid.

Subject 22 withdrew on March 22, 2005, and received termination vital signs and laboratory tests. The subject returned on March 30, 2005, and the termination vital signs and laboratories were repeated. The results from March 22, 2005, were entered as early termination results. The results from March 30, 2005, were documented in the source documents.

Forty-nine blood draw deviations were reported involving 17 subjects. The duration of the deviations ranged from 32 seconds to 15 minutes and 12 seconds late. One patient took concomitant medications due to an AE which were listed as Visine 1 drop, and ibuprofen 200 mg one dose. None of the deviations appear to be clinically significant.

STUDY OPD-002-01

Study OPD-002-01 was a bioavailability study of Orapred ODT with and without water, in healthy volunteers. The study was a two way crossover study in healthy volunteers comparing Orapred ODT 30 mg tablet with and without 240 mL water, given orally with a seven day washout between treatments. In Study OPD-002-01 subjects received a total of two doses.

There were 10 blood draw time deviations reported involving 8 subjects. The duration of the deviations ranged from 32 seconds to 4 minutes and 9 seconds. No concomitant medications were reported, see Table 7.1.1 below. None of these reported deviations appear to be clinically significant.

Table 7.1.1 Orapred™ ODT (prednisolone sodium phosphate) Orally Disintegrating Tablets
Combined Schedule of Events for Two PK Trials (OPD-001-01 and OPD-002-01)

Study OPD-001-01	Screening*	Period 1 March 14-16, 2005	Period 2 March 21-23, 2005	Period 3 March 28-30, 2005	Study OPD-002-01	Screening*	Period 1 March 21-23, 2005	Period 2 March 28-30, 2005
Inclusion/Exclusion Criteria	X					X		
Check-in Questionnaire		X	X	X			X	X
Medical History and Demographic Data	X					X		
Physical Examination	X					X		
Vital signs**	X	X	X	X		X	X	X
12-lead ECG	X					X		
Hematology	X			X		X		X
Serum Chemistry	X			X		X		X
Urinalysis	X			X		X		X
HIV test	X					X		
HbsAg	X					X		
HCV	X					X		
Urine drug screen	X	X	X	X		X	X	X
Serum Pregnancy Test ***	X	X	X	X		X	X	X
Concomitant Medications	X	X	X	X		X	X	X
Adverse Events	X	X	X	X		X	X	X
Test Compound Administration		X	X	X			X	X
Blood Draw Times (Serum Prednisolone)		X	X	X			X	X
Meal Times		X	X	X			X	X

* Screening date for OPD-001-01 was March 8, 2005. Screening dates for OPD-002-01 were March 8, 11, and 14, 2005.
** Vital signs were obtained once at screening, and also obtained at check-in and check-out for each study period.
*** Serum pregnancy test performed for females only.

(from sponsor's table, emailed 2/13/2006)

Disposition
The individual trial design for Studies OPD-001-01 and OPD-002-01, as well as subject disposition were reviewed above.

Patient Exposure from each study
The extent of exposure in the PK studies was a single 30 mg dose of Orapred ODT for Study OPD-001-01, and two 30 mg doses of Orapred ODT in Study OPD-002-01. Twenty-one patients completed Study OPD-001-01 and received the single dose of Orapred ODT, and of the three subjects who dropped out (CRF states Early Termination occurred prior to Site Visit 3 for all three dropouts), one received Orapred ODT, see Table 7.1.1 below. All 14 subjects completed Study OPD-002-01 and received two doses of Orapred ODT.

Table 7.1.1 Exposure of Subjects who Dropped Out for Study OPD-001-01

Subject number	Treatment Dosed	Further Treatment	Study Completion	Date of Dropout
8	Orapred ODT 40.3 mg	None	Early Termination	4/1/2005
18	Orapred 40.2 mg/5ml	None	Early Termination	4/7/2005
22	Orapred 40.2 mg/5ml	None	Early Termination	3/22/2005

7.1.1 Deaths

There were no deaths reported in the current submission.

7.1.2 Other Serious Adverse Events

There were no serious adverse events reported in the current submission.

7.1.3 Dropouts and Other Significant Adverse Events

In Study OPD-001-01, there were three dropouts, and no missing data reported in the study report and the Integrated Summary of Safety (ISS). The three dropouts were listed as three withdrawals in the study report under disposition of patients. The withdrawals were for personal reasons. The CRFs were reviewed for all three patients and no AEs were listed.

In Study OPD-002-01, there were no dropouts or missing data reported in the study reports or the ISS. There was no mention of dropouts in the safety section of the study reports.

7.1.3.1 Overall profile of dropouts

The three dropouts in Study OPD-001-01 were due to personal reasons. There were no dropouts in Study OPD-002-01.

7.1.3.2 Adverse events associated with dropouts

The CRFs for the three dropouts in Study OPD-001-01 were reviewed. There were no AEs listed in the CRFs for Subjects number 8, 18, and 22 who dropped out for personal reasons. No further detail was listed in the CRF regarding the dropouts.

7.1.3.3 Other significant adverse events

There were no AEs that led to dose reduction, or significant concomitant medications.

7.1.4 Other Search Strategies

No other search strategies were used. Pediapred and Orapred oral solution are products in the same class that are already approved, and have AEs listed in the label.

7.1.5 Common Adverse Events

There were six treatment-emergent adverse events (AEs) reported in Study OPD-001-01, in three subjects. There were no AEs in Study OPD-002-01. The proposed label for Orapred, following the precedent of other glucocorticoids, does not contain a table of AEs. There is a text list of AEs as noted in section 7.1.5.4 below.

The observation of AEs in the study reports are consistent with the proposed label, except for face edema/swelling face, pharyngolaryngeal pain, blood in stool, eye irritation, and eyelid oedema which should be added to the label.

7.1.5.1 Eliciting adverse events data in the development program

Spontaneous reporting of AEs was performed by investigators. AEs were monitored throughout the entire study for both Study OPD-001-01, and Study OPD-002-01.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

The sponsor used the MedDRA dictionary for classifying AEs and applied it in the displays of AEs. Investigators recorded AEs on CRFs in English.

7.1.5.3 Incidence of common adverse events

The sponsor's reporting of AEs was consistent between the study reports and the Integrated Summary of Safety. Tables of AEs summarized AE frequency by treatment and severity for Study OPD-001-01. These presentations were reviewed in depth and are shown in Table 7.1.5.3.1 below. As noted above, there were no AEs reported for Study OPD-002-01.

The sponsor listed the AEs by severity in Study OPD-001-01 as follows: mild events included face oedema, eye irritation, eyelid oedema, and pharyngolaryngeal pain. Moderate events included swelling face, and blood in stool.

Table 7.1.5.3.1 Adverse Event Frequency by Treatment – Number of Subjects Reporting the Event (% of Subjects Dosed)

Adverse Event*	Treatment			
System Organ Class Preferred Term	A	B	C	Total
Number of Subjects Dosed	22 (100%)	21 (100%)	23 (100%)	24 (100%)
Number of Subjects Without Adverse Events	19 (86.4%)	21 (100%)	23 (100%)	23 (97.5%)
Number of Subjects With Adverse Events	3 (13.6%)	0 (0.0%)	0 (0.0%)	3 (12.5%)
Skin and subcutaneous tissue disorders	1 (4.5%)	0 (0.0%)	0 (0.0%)	1 (4.2%)
Face oedema	1 (4.5%)	0 (0.0%)	0 (0.0%)	1 (4.2%)
Swelling face	1 (4.5%)	0 (0.0%)	0 (0.0%)	1 (4.2%)
Respiratory, thoracic and mediastinal disorders	1 (4.5%)	0 (0.0%)	0 (0.0%)	1 (4.2%)
Pharyngolaryngeal pain	1 (4.5%)	0 (0.0%)	0 (0.0%)	1 (4.2%)
Investigations	1 (4.5%)	0 (0.0%)	0 (0.0%)	1 (4.2%)
Blood in stool	1 (4.5%)	0 (0.0%)	0 (0.0%)	1 (4.2%)

Note: * Adverse events are classified according to MedDRA Version 6.1.
Treatment A = Orapred® ODT (prednisolone sodium phosphate) 40.3 mg
Treatment B = Celltech Pediapred® (prednisolone sodium phosphate) oral solution 6.7mg/5ml
Treatment C = Orapred® (prednisolone sodium phosphate) oral solution 20.2 mg/5ml

(from Sponsor's Table 14.3.1.1 on page 69 of 254 of Module 5, Volume 1)

Table 7.1.5.3.1 (continued) Adverse Event Frequency by Treatment – Number of Subjects Reporting the Event (% of Subjects Dosed)

Adverse Event*	Treatment			
System Organ Class Preferred Term	A	B	C	Total
Eye disorders	1 (4.5%)	0 (0.0%)	0 (0.0%)	1 (4.2%)
Eye irritation	1 (4.5%)	0 (0.0%)	0 (0.0%)	1 (4.2%)
Eyelid oedema	1 (4.5%)	0 (0.0%)	0 (0.0%)	1 (4.2%)

Note: * Adverse events are classified according to MedDRA Version 6.1.
Treatment A = Orapred® ODT (prednisolone sodium phosphate) 40.3 mg
Treatment B = Celltech Pediapred® (prednisolone sodium phosphate) oral solution 6.7mg/5ml
Treatment C = Orapred® (prednisolone sodium phosphate) oral solution 20.2 mg/5ml

(from Sponsor's Table 14.3.1.1 on page 70 of 254 of Module 5, Volume 1)

7.1.5.4 Common adverse event tables

The proposed label does not include an adverse events table. The label does include a list of AEs identical to approved products Pediapred and Orapred oral solution, except for the order which was changed to alphabetical. This approach is acceptable and consistent with other glucocorticoid products. Of note, "Fluid and Electrolyte Disturbances" needs to be changed to bold print. The sponsor's proposed label is presented below.

Proposed Label Adverse Reactions section

ADVERSE REACTIONS: (listed alphabetically under each subsection):
Cardiovascular: Hypertrophic cardiomyopathy in premature infants.
Dermatologic: Facial erythema; increased sweating; impaired wound healing; may suppress reactions to skin tests; petechiae and ecchymoses; thin fragile skin; urticaria; edema.
Endocrine: Decreased carbohydrate tolerance; development of cushingoid state; hirsutism; increased requirements for insulin or oral hypoglycemic agents in diabetic patients; manifestations of latent diabetes mellitus; menstrual irregularities; secondary adrenocortical and pituitary unresponsiveness, particularly in times of stress, as in trauma, surgery or illness; suppression of growth in children.
Fluid and Electrolyte Disturbances: Congestive heart failure in susceptible patients; fluid retention; hypertension; hypokalemic alkalosis; potassium loss; sodium retention.
Gastrointestinal: Abdominal distention; elevation in serum liver enzyme levels (usually reversible upon discontinuation); pancreatitis; peptic ulcer with possible perforation and hemorrhage; ulcerative esophagitis.
Metabolic: Negative nitrogen balance due to protein catabolism.
Musculoskeletal: Aseptic necrosis of femoral and humeral heads; loss of muscle mass; muscle weakness; osteoporosis; pathologic fracture of long bones; steroid myopathy; tendon rupture; vertebral compression fractures.
Neurological: Convulsions; headache; increased intracranial pressure with papilledema (pseudotumor cerebri) usually following discontinuation of treatment; psychic disorders; vertigo.
Ophthalmic: Exophthalmos; glaucoma; increased intraocular pressure; posterior subcapsular cataracts.
Other: Increased appetite; malaise; nausea; weight gain.
(from Sponsor's Proposed Annotated Label)

7.1.5.5 Identifying common and drug-related adverse events

The AEs occurred in only three subjects, and in Study OPD-001-01 there were only a total of 24 subjects. Due to the small sample size it is difficult to make any conclusions about the frequency of events and possible relation to drug effect. With this noted, these three subjects were all in the treatment group and received Orapred ODT, thus all six AEs occurred in the Orapred ODT treatment group, within an overall frequency of 13.6%, in comparison to 0% for the Pediapred and Orapred oral solution groups.

Three subjects had six events which were listed as follows: face oedema, swelling face, pharyngolaryngeal pain, blood in stool, eye irritation, and eyelid oedema. Due to the small sample size and design of the protocol, it is difficult to make any conclusion regarding drug-relatedness.

7.1.5.6 Additional analyses and explorations

Due to the small sample size, 24 subjects in Study OPD-001-01, and 14 subjects in Study OPD-002-01, there were no AEs conclusively related to the study drug, Orapred ODT.

7.1.6 Less Common Adverse Events

The proposed label contains no information about less common AEs. Postmarketing monitoring was also reported, see section 7.1.17.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

Laboratory testing for safety in Study OPD-001-01 and OPD-002-01 included PK analysis for plasma concentrations of prednisolone, and hematologic, hepatic, and renal function tests. There were no laboratories listed as AEs in the study report or the ISS.

Review of laboratory summary tables in Study OPD-001-01 showed leukocyte count as low as 3.6 thousand/uL, normal range 4.5-11.5 thousand/uL. Platelet counts were reported as low as 139 thousand/uL, normal range 150-400 thousand/uL. These laboratories were not considered by the investigators to be clinically significant.

Review of laboratory summary table in Study OPD-002-01 showed leukocyte count as high as 12.4 thousand/uL, normal range 4.5-11.5 thousand/uL. Platelet counts were reported as low as 104 thousand/uL, normal range 150-400 thousand/uL. These laboratories were not considered by the investigators to be clinically significant.

Overall, there appear to be no clinically significant laboratory AEs seen with short term use of Orapred ODT as seen in Study OPD-001-01 and OPD-002-01.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

See section 7.1.7.1 above.

7.1.7.3 Standard analyses and explorations of laboratory data

See section 7.1.7.1 above.

7.1.7.4 Additional analyses and explorations

See section 7.1.7.1 above.

7.1.7.5 Special assessments

See section 7.1.7.1 above.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

In Study OPD-001-01 vital signs including heart rate, blood pressure, temperature, and respiratory rate, were recorded at check-in and check-out during screening, and the three study periods. In Study OPD-002-01 vital signs including heart rate, blood pressure, temperature, and respiratory rate, were recorded at check-in and check-out at screening, and the two study periods. The sponsor reported mean, median, and range values for these vital signs. There were no clinically significant differences among the treatment groups for both studies. Given the small sample size the data is limited. No further analysis is indicated.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

See above section 7.1.8.1.

7.1.8.3 Standard analyses and explorations of vital signs data

See above section 7.1.8.1.

7.1.8.4 Additional analyses and explorations

See above section 7.1.8.1.

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

Twelve-lead ECGs were performed at baseline with the physical examination for both Study OPD-001-01 and Study OPD-002-01. Only patients with normal ECGs were included in both studies. No further ECGs were performed which was appropriate for Orapred ODT and the healthy subjects.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

See above section 7.1.9.1.

7.1.9.3 Standard analyses and explorations of ECG data

See above section 7.1.9.1.

7.1.9.4 Additional analyses and explorations

See above section 7.1.9.1.

7.1.10 Immunogenicity

There was no data for immunogenicity submitted for Orapred ODT. The reviewer performed a pubmed search using the term anti-prednisolone antibody on February 10, 2006. The search resulted in one abstract from a Japanese journal[3]. The abstract reported that the author's lab developed an anti-prednisolone antibody to measure prednisolone levels in humans. No other clinical reports of this antibody were found.

A statement should be added to the Clinical Pharmacology section of the label stating that no immunogenicity assessments were performed.

7.1.11 Human Carcinogenicity

Human carcinogenicity was not evaluated due to the brevity of the trials.

7.1.12 Special Safety Studies

No special safety studies were performed.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

A well known withdrawal phenomena with synthetic adrenocortical steroids is adrenocortical insufficiency, which is listed in the label in the Warnings section. The Precautions section also notes this with the comment that these phenomena may be reduced by gradually tapering the dose when discontinuing. There is no abuse potential.

7.1.14 Human Reproduction and Pregnancy Data

New human reproduction and pregnancy data were not submitted with this NDA.

7.1.15 Assessment of Effect on Growth

Due to the brevity of the studies no new data on the effect on growth of prednisolone was submitted.

7.1.16 Overdose Experience

There were no inadvertent overdoses reported in Study OPD-001-01 or Study OPD-002-01.

7.1.17 Postmarketing Experience

The sponsor submitted the last two years of Periodic Adverse Experience Reports (PAERs) for Orapred oral solution. There were three "15-day alert reports" during the last two years, seven "serious and expected" events, 28 "not serious and unexpected events", and 15 "not serious and expected" events.

The first of the three 15-day reports during the last two years was a 6 month old female who was treated with Orapred for asthma and developed urticaria within 5 minutes of receiving the first dose. The patient was treated with diphenhydramine, cetirizine, levosalbutamol and epinephrine by an allergist to prevent an Anaphylactoid reaction.

The second report was a 14 month old male who was treated with Orapred for respiratory distress and developed urticaria and dyspnea. The patient was hospitalized and later diagnosed with a pneumonia. The patient was rechallenged gradually with Orapred 6 months later by an allergist. The boy developed urticaria after taking 3 mL Orapred over one hour and 20 minutes.

The third report was a four year old boy who developed wheezing, coughing, and urticaria. He had a history of asthma and a peanut allergy, and had previously been treated with prednisolone at the age of two years. The boy developed wheezing and coughing and was taken to the pediatrician. After receiving Orapred and ventolin in the pediatrician's office he developed urticaria, increased wheezing and coughing. An ambulance was called which took the patient to the ER. In the ER the boy was treated with albuterol, flovent, epinephrine, and decadron. The boy was hospitalized overnight and respiratory symptoms resolved within twelve hours. The pediatrician noted there were peanuts out in the office which may have contributed to breathing problems.

The seven "serious and expected" events included 3 reports of urticaria also reported as 15-day reports and described above. The other four events were depression, headache, abdominal pain, and malaise, and occurred in one patient. An eleven year old boy with croup and pneumonia was treated with Orapred for 7 days and Zithromax. During his treatment he complained of headache, abdominal pain, and malaise, and the timing is unclear. He had a normal CT scan, which was not specified as to body location. He developed symptoms of depression which persisted at three weeks after the illness and an evaluation by a child psychologist was planned.

The 28 "not serious and unexpected" events included 14 events in one boy. A 7 year old boy with a history of allergies took Orapred for wheezing and congestion. During the first five days of treatment with Orapred the patient had no new symptoms. He then switched to a new bottle and complained of the taste, within two hours he experienced the following: lethargy, confusion, could not stand or hold up his head, back pain, double vision, slurred words, dizziness, and difficulty breathing. The patient was taken to the ER where his heart rate was 125 beats per minute (bpm). He was sent home with no treatment. The following day at the pediatrician's office his heart rate was 132 bpm, and he had dizziness, back, flank, and generalized pain, wheezing, and cough. After treatment with levosalbutamol, ipratropium bromide, and Orapred he had decreased wheezing. Orapred was continued with a new bottle without incident. Another patient developed lethargy. Four of the reports were for hypersensitivity which included rash, swelling, itching, and redness in the mouth, and pain and difficulty in swallowing. The last three events were nausea, emesis, diarrhea, and bulging fontanelle. The patient with the bulging fontanelle was diagnosed with idiopathic intracranial hypertension, and had an episode not associated with Orapred, thus this seems unrelated to Orapred. Other events include hypercholesterolemia, and lack of response to Orapred which appear unrelated to Orapred. Lastly tremor, dysphemia, and head banging occurred in a 24-month old female with a seizure disorder.

The 15 "not serious and expected" events include increased heart rate, eight psychiatric events known to be AEs of Orapred, three reports of urticaria, and one case of erythema, pruritis, and rash. Lastly a 2 year old girl with juvenile rheumatoid arthritis developed transient leukocytosis.

The label for Orapred contains urticaria, headache, malaise, and nausea, however, many other AEs noted above were not found in the label. Since the AEs reported for the seven-year-old boy all occurred with one bottle of Orapred, and resolved with a new bottle, these AEs do not appear to warrant inclusion in the label. The reviewer recommends that the following be added to the label for Orapred ODT:

[redacted]
Wheezing
[redacted]
Depression
[redacted]
Emesis
[redacted]

Erythema (Note: facial erythema was present in label)

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

The two bioequivalence studies were reviewed. For descriptive information for these studies, including study design, number of subjects, and dosing schedule see Table 4.2.1, as well as the study schematic found in Table 7.1.1. For number of subjects reporting events see Table 7.1.5.3.1.

7.2.1.2 Demographics

There were no significant differences in demographics among the treatment groups.

7.2.1.3 Extent of exposure (dose/duration)

The extent of exposure in the PK studies was a single 30 mg dose of Orapred ODT for Study OPD-001-01, and two 30 mg doses of Orapred ODT in Study OPD-002-01. Twenty-one patients completed Study OPD-001-01 and received the single dose of Orapred ODT, and of the three subjects who dropped out (CRF states Early Termination occurred prior to Site Visit 3 for all three dropouts), one received Orapred ODT, see Table 7.1.1 above for further detail. All 14 subjects completed Study OPD-002-01 and received two doses of Orapred ODT.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

The NDA did not include or refer to any other studies for the safety evaluation.

7.2.2.2 Postmarketing experience

Safety information is presented from the last two years of Periodic Adverse Event Reports (PAER) for Orapred Oral Solution, see section 7.1.17 above.

7.2.2.3 Literature

In addition, a literature search for serious unlisted adverse events related to oral prednisolone sodium phosphate over the last two years was performed. No clinical studies, and no serious or unexpected AEs were found involving Orapred.

The reviewer performed a pubmed search using the term anti-prednisolone antibody. The search resulted in one abstract from a Japanese journal. The abstract reported that the author's lab developed an anti-prednisolone antibody to measure prednisolone levels in humans. No other clinical reports of this antibody were found.

7.2.3 Adequacy of Overall Clinical Experience

Adequate information was included in this submission to assess the safety of Orapred ODT®.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

There was no special animal testing. See the clinical pharmacology review regarding any in vitro testing.

7.2.5 Adequacy of Routine Clinical Testing

Routine clinical testing of study subjects for adverse effects was appropriate and satisfactory. Monitoring for safety included laboratories, vital signs, and baseline EKGs.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

See the review by Clinical Pharmacology.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The use of this product with H2 blockers will be further discussed in the clinical pharmacology review, especially regarding the ability for the tablet to dissolve.

7.2.8 Assessment of Quality and Completeness of Data

The CRFs for dropouts were complete, and the overall quality and completeness of the data was adequate.

7.2.9 Additional Submissions, Including Safety Update

Additional submissions to the application relevant to safety were submitted in responses to information requests.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

To summarize the AE profile for Orapred ODT® the generic label for prednisolone must be considered. See Section 7.1.5.4.

In addition to the AEs listed in the proposed prednisolone label the following AEs should be added:

Wheezing

Depression

Emesis

Erythema (Note: facial erythema was present in label)

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

Pooling of data was not used for this review.

7.4.1.2 Combining data

Data were not combined for this review.

7.4.2 Explorations for Predictive Factors

The sample size was not large enough to explore for predictive factors.

7.4.2.1 Explorations for dose dependency for adverse findings

The sample size was not large enough to explore for dose dependency for AEs.

7.4.2.2 Explorations for time dependency for adverse findings

See section 7.4.2 above.

7.4.2.3 Explorations for drug-demographic interactions

The sample size was not large enough to explore drug-demographic interactions.

7.4.2.4 Explorations for drug-disease interactions

The two studies were performed in healthy volunteers; therefore drug-disease interactions were not relevant.

7.4.2.5 Explorations for drug-drug interactions

No new information was submitted with this application. The possibility of a change in absorption with concomitant H2 blocker treatment was raised and will be further discussed in the clinical pharmacology review by Srikanth Nallani, PhD.

7.4.3 Causality Determination

Causality could not be established due to the small sample size.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The dosages and dosing regimens of Orapred ODT® were derived from other glucocorticoid preparations on the market.

8.2 Drug-Drug Interactions

See section 7.4.2.5 above.

8.3 Special Populations

There are special considerations for both the Pediatric and Geriatric populations. The PRECAUTIONS section of the label gives detailed information regarding these populations. In addition to AEs seen in the adult population, the pediatric population may be at risk for a decrease in growth velocity, which should be monitored. To minimize these effects children should be titrated to the lowest effective dose.

In addition to AEs seen in the adult population, the geriatric population is at higher risk for osteoporosis. This risk may decrease over time and with doses less than 5 mg per day. Doses of prednisolone of 7.5 mg per day or higher have been associated with an increased risk of fractures. Bisphosphonate treatment in addition to using the lowest effective dose has been recommended in the prevention of steroid-induced osteoporosis. Since decreased renal function is seen frequently in the elderly, dosing should be adjusted as needed.

8.4 Pediatrics

The requirement for pediatric studies was waived for this application because oral prednisolone solution is available for titrating pediatric doses.

8.5 Advisory Committee Meeting

No Advisory Committee meeting related to this application was held or is planned.

8.6 Literature Review

See section 7.

8.7 Postmarketing Risk Management Plan

The sponsor did not include a risk management plan in the application.

8.8 Other Relevant Materials

A consult was submitted to generics, and the response was not available at the time of this review.

9 OVERALL ASSESSMENT

9.1 Conclusions

In addition to the AEs listed in the proposed prednisolone label the following AEs should be added:

Wheezing

Depression

Emesis

- Erythema (Note: facial erythema was present in label)

Other labeling comments:
There are numerous places where [redacted] is mentioned in the label. [redacted] "
should be replaced by " [redacted] in the Dosage and Administration
section, add the following: " [redacted]

Of note, "Fluid and Electrolyte Disturbances" needs to be changed to bold print.

A statement should be added to the Clinical Pharmacology section of the label stating that [redacted]

9.2 Recommendation on Regulatory Action

Approval with labeling changes.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

The sponsor did not submit a risk management plan with this proposal.

9.3.2 Required Phase 4 Commitments

No Phase 4 commitments will be required of the Applicant.

9.3.3 Other Phase 4 Requests

There were no other Phase 4 requests.

9.4 Labeling Review

The proposed label does not include an adverse events table. The label does include a list of AEs identical to the approved products Pediapred and Orapred oral solution, except for the order which was changed to alphabetical. This approach is acceptable and consistent with other glucocorticoid products.

Based on safety data reported in this submission, the reviewer recommends that the following be added to the label for Orapred ODT:

Face edema,

Pharyngolaryngeal pain
Blood in stool
Eye irritation
Eyelid edema

Wheezing

Depression

Emesis

Erythema (Note: facial erythema was present in label)

Other labeling comments:
There are numerous places where is mentioned in the label. " " should be replaced by " ". In the Dosage and Administration section, add the following: "

Of note, "Fluid and Electrolyte Disturbances" needs to be changed to bold print.

A statement should be added to the Clinical Pharmacology section of the label stating that

9.5 Comments to Applicant

9.5.1 Comments Regarding the Proposed Package Insert.

1. The Adverse Events section needs to include the following for Orapred ODT®:

Face edema,

Pharyngolaryngeal pain
Blood in stool
Eye irritation
Eyelid edema

Wheezing

Depression

Emesis

Erythema (Note: facial erythema was present in label)

2. There are numerous places where [redacted] is mentioned in the label. ' [redacted] should be replaced by "

3. In the Dosage and Administration section, add the following: "

4. In the Fluid and Electrolyte Disturbances section, "Fluid and Electrolyte Disturbances" needs to be changed to bold print.

5. A statement should be added to the Clinical Pharmacology section of the label stating that

10 APPENDICES

10.1 Review of Individual Study Reports

Refer to section 7.1.

10.2 Line-by-Line Labeling Review

Refer to section 9.4.

REFERENCES

1. Food and Drug Administration, current product insert for Orapred®
2. Food and Drug Administration, current product insert for Pediapred®
3. Adachi K. et. al.; Nippon Narbunpi Gakkai Zasshi; 1990 Feb 20; 66(2):113-26.

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/s/

Julia Castle
3/17/2006 07:13:42 PM
MEDICAL OFFICER

Joel Schiffenbauer
3/31/2006 08:26:11 AM
MEDICAL OFFICER
Please see my secondary review for additional comments.