CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-959

PHARMACOLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	**21-959**
SERIAL NUMBER:	**000**
DATE RECEIVED BY CENTER:	**Aug 1, 2005**
PRODUCT:	**Orapred ODT™**
INTENDED CLINICAL POPULATION:	**Prednisolone sodium phosphate is indicated in the following conditions: allergic states, dermatologic diseases, edematous states, endocrine disorders, gastrointestinal diseases, hematologic disorders, neoplastic diseases, nervous system, ophthalmic diseases, respiratory diseases, rheumatic disorders, and other miscellaneous disorders.**
SPONSOR:	**Medicis Pharmaceutical Corp.**
DOCUMENTS REVIEWED:	**Vol. 3**
REVIEW DIVISION:	**Division of Anesthesia, Analgesia and Rheumatology Products (HFD-170)**
PHARM/TOX REVIEWER:	**L.S. Leshin**
PHARM/TOX SUPERVISOR:	**D. Mellon**
DIVISION DIRECTOR:	**B. Rappaport**
PROJECT MANAGER:	**K. Compton**

Date of review submission to Division File System (DFS): **May 22, 2006**

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EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability
Approve

B. Recommendation for nonclinical studies
None

C. Recommendations on labeling
There were no pharmtox-related changes to the proposed labeling. No changes are recommended at this time for this NDA application.

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings
No studies were submitted.

B. Pharmacologic activity
No studies were submitted.

C. Nonclinical safety issues relevant to clinical use
The nonclinical and clinical safety of this drug is similar and well known. This Reviewer concurred with the Sponsor submission that additional nonclinical studies would not provide additional useful safety or efficacy information for the proposed indications.

[Please limit to 1-3 pages]

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 21-959
Review number: 1
Sequence number/date/type of submission: 000/Aug 1, 2005/commercial
Information to sponsor: Yes
Sponsor and/or agent: Medicis Pharmaceutical Corp.

Manufacturer for drug substance: [redacted]

Reviewer name: L. S. Leshin
Division name: Division of Anesthesia, Analgesia, and Rheumatology Products
HFD 170
Review completion date: May 7, 2006

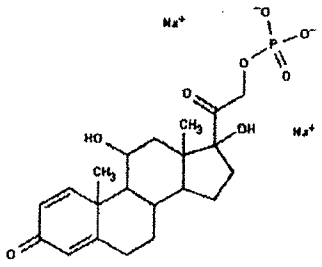
Drug:

Trade name: Orapred ODT™ (Orally Disintegrating Tablets)
Generic name: Prednisolone Sodium Phosphate
Chemical names:

Pregna-l,4-diene-3,20-dione, 11,17- dihydroxy-21-(phosphono oxy)-,disodium salt;
(11-β)-Pregna-l,4-diene-3,20-dione, 11-β,17,21-trihydroxy-, 21-(dihydrogen phosphate), disodium salt;
11-β,17,21-Trihydroxypregna-l,4-diene-3,20-dione 21-(disodium phosphate)

CAS registry number: 125-02-0
Molecular formula: $C_{21}H_{27}Na_2O_8P$
Molecular weight: 484.39
Structure:

Figure 1: Prednisolone Sodium Phosphate



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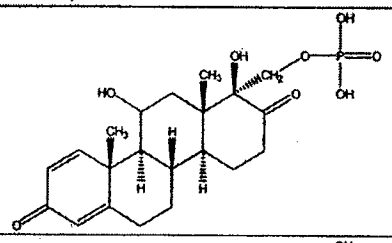
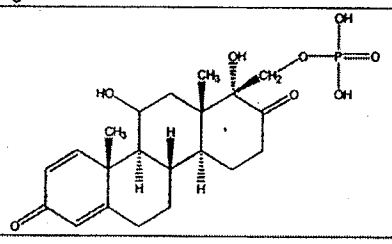
D-homo A derivative	0.58	
D-homo B derivative	0.78	

Relevant INDs/NDAs/DMFs:

NDA 19-157 (Pediapred, Celltech Pharms), **Reference Listed Drug Product**
DMF [redacted] (Prednisolone Sodium Phosphate, [redacted])
IND 70,495 (Orapred ODT)
ANDA 75-117 (Orapred® Oral Solution, prednisolone sodium phosphate)
DESI 7750 (Prednisolone)

Drug class: glucocorticoid

Intended clinical population:

Prednisolone sodium phosphate is indicated in the following conditions: allergic states, dermatologic diseases, edematous states, endocrine disorders, gastrointestinal diseases, hematologic disorders, neoplastic diseases, nervous system, ophthalmic diseases, respiratory diseases, rheumatic disorders, and other miscellaneous disorders.

The proposed indications for Orapred™ ODT are the same as for the Reference Listed Product, Pediapred® Oral Solution (NDA 19-157; prednisolone sodium phosphate) and for Orapred® Oral Solution (ANDA 75-117; prednisolone sodium phosphate).

Clinical formulation:

The proposed Orapred ODT dosage strengths are 10 mg, 15 mg, and 30 mg of prednisolone free base (equivalent to 13.4 mg, 20.2 mg and 40.3 mg prednisolone sodium phosphate). Orapred ODT is an orally disintegrating tablet formulation of the existing liquid formulations that have been approved, Pediapred Oral Solution (NDA 19-157; prednisolone sodium phosphate; eq. 5 mg base/5 mL) and Orapred Oral Solution (ANDA 75-117; prednisolone sodium phosphate; eq. 15 mg base/5 mL). Tablet composition is listed in Table 2, below.

Table 2: Composition of Orapred ODT™ 10mg, 15 mg and 30 mg

Route of administration: Oral

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

Right of Reference and Cross Reference to Other Applications

For (b)(2) applications:
Data Reliance

Except as specifically identified below, all data and information discussed below and necessary for approval of NDA 21-959 are owned by Medicis Pharmaceutical Corp. or are data for which Medicis Pharmaceutical Corp. has obtained a written right of reference. Any information or data necessary for approval of NDA 21-959 that Medicis

Pharmaceutical Corp. does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug's approved labeling. Any data or information described or referenced below from a previously approved application that Medicis Pharmaceutical Corp. does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of NDA 21-959.

Sponsor History

Since November 15, 2001, Medicis Pharmaceutical Corporation, under the name Ascent Pediatrics, Inc., has been the applicant for the Orapred ANDA 75-117. In May 2004, BioMarin licensed the rights to assets held by Ascent Pediatrics, including rights to Orapred® and the name "Ascent Pediatrics," from Medicis Pharmaceutical Corporation (Medicis). In connection with the license, Medicis renamed Ascent Pediatrics, Inc. to Medicis Pediatrics, Inc., and they (Medicis Pharmaceutical Corporation) remain the applicant for this submission for Orapred ODT™, NDA 21-959. BioMarin became the authorized agent for Orapred effective May 27, 2004 via a letter to the Agency from Medicis. This same relationship will apply to the Orapred ODT™ product, i.e., Medicis Pharmaceutical Corporation will be listed as the applicant and BioMarin will be listed as the regulatory agent. CIMA Labs, Inc. in Brooklyn Park, Minnesota, is the developer and manufacturer of the Orapred ODT™ product.

Relevant Submission History

As agreed upon during the April 11, 2005 Pre-NDA meeting, BioMarin will rely on FDA's previous findings of the safety and effectiveness of Pediapred® Oral solution (Reference Listed Drug) via cross-reference to NDA 19-157 (Pediapred® Oral solution, Celltech Pharms). The 505(b)(2) submission consists of two clinical pharmacology studies. No additional nonclinical or clinical studies were submitted.

The reference listed drug, Pedipred® Oral Solution, NDA 19-157, was originally submitted [redacted] It was eventually resubmitted to the Division of Oncology and Radiopharmaceutical Drug Products (HFD-150) as an NDA in Nov 1983, only requiring chemistry and bioequivalence characterization. It was approved in May, 1986.

For this NDA submission, the following sections were judged by the Sponsor as not applicable and no information was submitted.

2.4.2 Pharmacology
2.4.3 Pharmacokinetics
2.4.4 Toxicology

2.4.5 Nonclinical Overview
2.4.6 List of literature citations

The Nonclinical Reviewer concurred that additional nonclinical studies would not provide useful additional safety or efficacy information for the proposed indications. The information discussed in this NDA review was summarized from the published literature and is included for descriptive purposes only.

Studies reviewed within this submission:

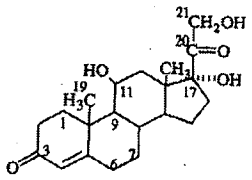
There were no nonclinical studies submitted.

Studies not reviewed within this submission:

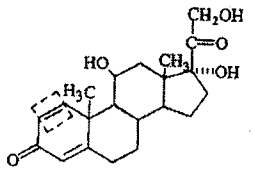
N/A.

2.6.2 PHARMACOLOGY

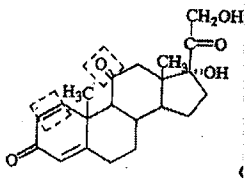
Prednisolone sodium phosphate is the monobasic phosphate ester of the glucocorticosteroid, prednisolone. Pharmacological activity occurs after prednisolone sodium phosphate is converted to prednisolone. In addition, there is some metabolic interconversion between prednisolone and prednisone.



Cortisol (Hydrocortisone)



Prednisolone



Prednisone

The above structures and summary of glucocorticoid activity below is taken from Ferguson, D.C. and M. Hoenig (1995) Glucocorticoids, Mineralcorticoids and Steroid Synthesis Inhibitors, In: Adams, H.R. (editor) Veterinary Pharmacology and Therapeutics, 7th Edition, Iowa State University Press, Ames, Iowa.

Chemistry

Alterations in the steroid base structure influence its affinity for glucocorticoid and mineralcorticoid receptors as well as its protein-binding avidity, side-chain stability, rate of reduction, and metabolic products. Certain structures on the steroid base are essential for glucocorticoid activity. An 11-ketol is essential for glucocorticoid activity, and compounds like cortisone and prednisone must first be reduced in the liver from the 11-carbon ketone to the ketol for full activity. The 1,2 double bond (in prednisolone and prednisone, but not cortisol) provides a fourfold increase in glucocorticoid activity. The C-3 and C-20 ketone groups are also essential for glucocorticoid activity. The 16-α-methyl group enhances antiinflammatory activity. Modifications of the glucocorticoid molecular structure also alter the tendency for the molecule to bind with corticosteroid-binding globulin (CBG) in the plasma. An increase in binding to CBG results in a lower tendency for the hormone to be metabolized. The 11-hydroxyl group tends to inhibit metabolism, since the half-life of 11-deoxycortisol is half that of cortisol. In some cases, the agent administered is a prodrug: prednisone is rapidly reduced to prednisolone, and cortisone is rapidly converted to cortisol by the liver. The synthetic corticosteroids for oral use are in most cases rapidly and completely absorbed when given by mouth.

Esterification of the alcohol at C-21 serves a number of potential purposes. The ester moiety determines to a significant extent the water/lipid solubility ratio and also influences the duration of action of the base compound's release from subcutaneous or intramuscular sites. Tissue esterases cleave the ester, resulting in free base, which then is distributed via the circulation to tissue sites of action. Phosphate moieties provide for greater water solubility for IV or IM use and rapid action and metabolism.

Physiologic Effects

The glucocorticoids have widespread effects because they influence the function of most cells in the body. A principal role of glucocorticoids is the maintenance of fluid homeostasis by regulation of volume and composition of body fluids and by being permissive for essential cellular metabolism. Glucocorticoids in physiological quantities are essential for the dilution of the renal filtrate into the hyposthenuric range. Other physiological roles of glucocorticoids are to increase gluconeogenesis, decrease protein synthesis, and increase lipolysis with the release of glycerol and free fatty acids (an insulin-antagonistic effect). Although many of the effects are dose related, glucocorticoids may also act in a permissive manner to optimize certain cellular reactions such as the gluconeogenesis stimulated by glucagon and catecholamine. The physiological effects of glucocorticoids in the fed state are not very significant; however, during fasting, glucocorticoids contribute to the maintenance of glucose concentrations by increasing the release of glucose by the liver and increasing gluconeogenesis and glycogen deposition by stimulating glycogen synthase. The effect on muscle is catabolic because glucose uptake decreases and amino acid release (gluconeogenesis) increases. Glucocorticoids also are permissive for activity of the hormone-sensitive lipase which is responsible for mobilization of free fatty acids from adipose stores. Lipolysis is stimulated; therefore, when insulin is lacking or being greatly antagonized, ketogenesis may result (Aron and Tyrrell 1994; Feldman and Nelson 1987; Ferguson 1985a; Goldfien 1992; Haynes 1990; Melby 1974; Wilcke and Davis 1982). The effect of glucocorticoids on glucose metabolism is likely to be time and dose dependent. Insulin and glucose concentrations, or glucose tolerance, were not significantly altered by the administration for 28 days of an anti-inflammatory dosage of oral prednisone (Moore and Hoenig1993).

Glucocorticoids also maintain microcirculation, normal vascular permeability, and stability of lysosomal membranes and suppress inflammatory reactions, although these functions are more commonly associated with the pharmacologic effects of glucocorticoids. Glucocorticoids play a physiological role in the development of pulmonary surfactant in the near-term fetus, allowing an adaptation to air breathing (Aron and Tyrrell 1994; Tyrrell et al. 1994).

Pharmacologic Effects

Energy Metabolism: Glucocorticoids have an antagonistic effect to that of insulin, leading to increased glucose production from amino acids (gluconeogenesis) and reduced incorporation of amino acids into protein. Glucocorticoids enhance lipolysis; however, glucocorticoid excess (pharmacological amounts) or spontaneous hyperadrenocorticism may result in redistribution of fat because glucocorticoids stimulate appetite, thereby stimulating hyperinsulinemia, which results in lipogenesis. As a result, diabetes mellitus may result from prolonged glucocorticoid use at high dosages in animals with diminished insulin secretory capacity (prediabetics). Muscle wasting and weakness are not uncommon with glucocorticoid excess; although glucocorticoids stimulate protein and RNA synthesis in the liver, they have catabolic effects in lymphoid and connective tissue, muscle, fat, and skin. While not usually a recognizable clinical problem in domestic

animals, osteoporosis may result in people with Cushing's syndrome or on chronic glucocorticoid administration. The problem likely is most significant in areas of healing bone; glucocorticoids directly inhibit bone formation by inhibiting osteoblast proliferation and the synthesis of bone matrix while stimulating osteoclast activity. In addition, glucocorticoids potentiate the action of parathyroid hormone (PTH) and vitamin D and inhibit the gut absorption of calcium, an effect which can be used to advantage in hypercalcemic states. In the young animal, the catabolic effects of excessive amounts of glucocorticoid reduce growth. In children, this reduced growth is not prevented by growth hormone (Aron and Tyrell 1994; Tyrrell et al. 1994).

Water and Electrolyte Balance: Glucocorticoid use invariably leads to polyuria and polydipsia via inhibition of antidiuretic hormone (ADH) release and action, resulting in increased water intake. No glucocorticoid given in large doses is completely devoid of mineralcorticoid (salt-retaining and K+-losing) activity. Therefore, excessive use may precipitate or exacerbate hypertension and induce hypokalemia. Glucocorticoids increase the glomerular filtration rate, in part by increasing extracellular fluid volume, and are required in physiologic amounts for maximal dilution of urine (Ferguson 1985a; Melby 1974; Nakamoto et al. 1992).

Immune and Hematologic Effects: Often the desired result of a therapeutic application, anti-inflammatory effects of glucocorticoids are primarily seen at pharmacologic doses. Glucocorticoids result in alterations in the concentration, distribution, and function of peripheral leukocytes and in inhibition of phospholipase A_2 activity in the plasma membranes of these cells. In addition to contributing to maintenance of the microcirculation and cell membrane integrity, glucocorticoids interfere with progressive dissolution and disruption of connective tissue and cells, possibly by stabilizing lysosomal membranes (Aron and Tyrrell 1994; Aucoin 1982; Barragry 1994). Although lysosomal stabilization by glucocorticoids has been demonstrated experimentally, it is hard to know what benefit these effects have in clinical situations. Glucocorticoids also decrease formation of induced histamine (histamine produced by cells during injury), an action not blocked by antihistamines. They also antagonize toxins and kinins, reducing the resultant inflammation. It is important to realize, however, that most of their effects are nonspecific; that is, they have profound metabolic effects regardless of the initial insult.

Glucocorticoids are used to advantage to suppress both the number of cells and the actions of the immune system. The suppressive effects on cell mediated immunity predominate over those on humoral immunity. Antibody production is generally unaffected by moderate dosages of glucocorticoids and is inhibited only at high dosages and with long-term therapy. They cause lymphopenia and eosinopenia, an effect secondary to cell redistribution and/or lysis, and lead to increased vascular demargination of neutrophils from the vascular bed to lymphoid tissue. Glucocorticoids inhibit virus-induced interferon synthesis and diminish the functional capacity of monocytes, macrophages, and eosinophils through inhibition of the formation of interleukins (ILs) such as IL-1 (macrophages), IL-2 (lymphocytes), IL-3, and IL-6 and other chemotactic

factors (Barragry 1994; Ehrich et al. 1992; McDonald and Langston 1994; Melby 1974; Tyrrell et al. 1994).

Cardiorespiratory Effects: In addition to indirect effects on electrolyte metabolism, glucocorticoids have direct positive chronotropic and inotropic actions on the heart. They appear to block the increased permeability of capillaries induced by acute inflammation, reducing transport of protein into damaged areas and maintaining microcirculation. Because glucocorticoids are necessary for maximal catecholamine sensitivity, they contribute to maintenance of vascular tone (Ferguson et al.1978; Nakamoto et al. 1992). In shock, production of vasoactive products of lipid peroxidation (arachidonic acid cascade), such as the vasoconstrictor thromboxane A_2, may be decreased by glucocorticoids, but probably only in the early stage of cell disruption. Glucocorticoids cause vasoconstriction when applied directly to vessels. They decrease capillary permeability by inhibiting the activity of kinins and bacterial endotoxins and by reducing the amount of histamine released by basophils.

Glucocorticoids increase the number and affinity of β-adrenergic receptors. Glucocorticoids prevent receptor down-regulation and therefore tachyphylaxis, resulting in potentiation of the effects of β-adrenergic agonists on bronchial smooth muscle, an important effect in the asthmatic patient (Sprung et al. 1984; Tyrrell et al. 1994; Wilcke and Davis 1982).

CNS Effects: Although rarely described in domestic animals, glucocorticoids (or lack of them) have marked effects on the psyche, resulting in a form of mental, as well as physical, dependence (Ferguson 1985a; Metz et al. 1982).

Endocrine Effects: Glucocorticoids, in addition to being diabetogenic, also have marked effects on hypothalamic and pituitary function. Adrenocorticotropic hormone (ACTH), β-lipotropin, thyroid-stimulating hormone (TSH), follicle-stimulating hormone (FSH), and growth hormone (GH) synthesis and secretion are all suppressed; however, β-endorphin levels are unaffected. Glucocorticoids, even at "physiological" dosages (0.22 mg/kg prednisolone once daily orally in the dog), resulted in hypothalamic-pituitary-adrenal-axis (HPAA) suppression, indicated by the reduction in the ACTH-stimulated cortisol concentration and the reduced ratio of the histological width of zonas fasciculata and reticularis to zona glomerulosa in the adrenal gland. Anti-inflammatory dosages of prednisolone (0.5 mg/kg q12h orally) resulted in adrenal suppression within 2 weeks of therapy (Chastain and Graham 1979). In another study in dogs, 1 month of the same dosage prednisolone orally resulted in profound suppression of endogenous plasma ACTH and cortisol concentrations, CRH-stimulated ACTH release, and ACTH-stimulated cortisol release. However, following withdrawal of the prednisolone, the HPAA returned to normal within 2 weeks (Moore and Hoenig 1992). Higher dosages and longer-acting preparations (dexamethasone, triamcinolone, and depot products) may result in more-pronounced and longer-lasting HP suppression (Kemppainen and Sartin 1984; Kemppainen 1986; Kemppainen et al 1982).

Pharmacological doses of glucocorticoids generally reduce serum thyroid hormone concentrations presumably through suppression of pituitary TSH. These effects have been well documented in the dog, are not as significant in the cat, and are not well studied in other domestic species (Ferguson and Peterson 1992; Kaptein et al. 1992; Moore et al 1993). The metabolic consequences of these lowered concentrations of thyroid hormones are not known in the dog; however, a state of hypothyroidism is not believed to be the result (Jennings and Ferguson 1984). In humans, large doses of glucocorticoids stimulate excessive production of acid and pepsin in the stomach and may cause peptic ulcer. They facilitate fat absorption and appear to antagonize the effect of vitamin D on calcium absorption. Therefore, glucocorticoids are employed in chronic hypercalcemic states in an attempt to inhibit gastrointestinal calcium absorption (Aron and Tyrrell 1994; Tyrrell et al. 1994).

Toxicity

The main limiting factors for glucocorticoid administration are the global toxic effects of these agents. Table 32.3 (at the end of this section) lists most of the reported side effects as described in the dog, the nonclinical species in which glucocorticoids are most widely used therapeutically. Of course, there is variability from species to species. The following discussion highlights the basis for some of these effects.

Metabolic and Endocrine Effects: The endocrine manifestations of glucocorticoid administration can be severe. Iatrogenic Cushing's syndrome may develop with adrenal insufficiency on withdrawal of the medication. The gluconeogenic effects may unmask or exacerbate diabetes and polyuric and polydipsic states and may induce hypertension.

CNS Effects: In animals, the effects on mental status are difficult to assess or compare with those in humans; however, glucocorticoids likely induce a state of well-being. Neurologically, there is also evidence that glucocorticoids may decrease the threshold for seizures. Lethargy and panting occasionally develop in dogs and cats. Rapid withdrawal of glucocorticoids can induce depression and irritability (Ferguson 1985a,b; McDonald and Langston 1994).

Gastrointestinal and Hepatic Effects: The gastrointestinal and hepatic effects of glucocorticoids are among the most limiting regarding chronic administration. Glucocorticoids clearly induce form of micronodular cirrhosis and stimulate the steroid-specific isozyme of alkaline phosphatase. In addition to hepatopathy and hepatomegaly, glucocorticoid excess may result in increased gastric acid and possible gastric ulceration, but more commonly high doses of potent glucocorticoids cause colonic perforation in dogs. Glucocorticoids may stimulate appetite, an effect occasionally used to advantage in some therapeutic situations. It has been postulated that glucocorticoids may also cause pancreatitis.

Musculoskeletal Effects: Chronic glucocorticoid administration induces excessive catabolism and muscle atrophy. Animals may become clinically weak and be unable to

exercise optimally. Bone growth may be inhibited and antagonism of vitamin D activity may result in osteoporosis with chronic administration of glucocorticoids.

Dermatologic Effects: Glucocorticoids reduce collagen synthesis and thereby reduce the rate of wound healing. The skin becomes thin and more easily stretched and bruised due to increased capillary fragility. Dogs on large dosages of glucocorticoids often develop bilateral symmetrical alopecia, known as a "Cushingoid" appearance. Cats tend to be less susceptible to these effects. Occasionally, exogenous glucocorticoid administration will induce calcium deposition in the dystrophic epidermis; however, the incidence in dogs appears to be less than with spontaneous hyperadrenocorticism (Scott 1982).

Immunologic Effects: Although immune suppression is often the desired therapeutic effect of glucocorticoids, these agents are notorious for exacerbation of clinical or latent infectious disease processes. Animals on chronic glucocorticoid therapy have a higher incidence of bacterial infections; in one study, 75% of dogs on glucocorticoids for allergic skin disease had clinical or subclinical urinary tract infections. Of course, by inhibiting the cell-mediated immune response to an infection, glucocorticoids slow the function of immune cells that help contain an infection (Aucoin 1982; Fauci 1976; Feldman and Nelson 1987; Ferguson 1985a,b; Siegel 1985).

Reproductive Effects: High doses of glucocorticoids induce parturition during the latter part of pregnancy in ruminants and horses (Barragry 1994). There is also now evidence that dexamethasone can cause abortion in the dog. Glucocorticoids generally have teratogenic effects during early pregnancy and should be avoided in the breeding animal if possible.

Fatal Sequelae in the Dog: As an example of the severe consequences of glucocorticoid excess in the dog, the following clinical case, reported in the veterinary literature (Bellah et al. 1989), is provided.

A dog was given multiple doses of glucocorticoids for treatment of intervertebral "disk disease over a 25-day period: methylprednisolone acetate (Depo-Medrol)-20 mg IM; dexamethasone sodium phosphate-2 mg IM; flumethasone-0.5 mg and 1 mg IM; dexamethasone-0.25 mg q8h orally as needed; triamcinolone diacetate-40 mg IM (60 times the manufacturer's recommended dose). The dog presented to the examining clinician with historical and physical findings of polyuria/polydipsia, fever, murmur, pendulous abdomen, marked hepatomegaly, hindlimb paraparesis, mid-lumbar hyperpathia, and normal pain perception in the hindlimbs. Initial laboratory findings included anemia, leukocytosis, neutrophilia, hyperalbuminemia, increased serum alkaline phosphatase (SAP), alanine aminotransferase (ALT), and glucose, increased bromsulfophthalein (BSP) retention, isosthenuria, bacteriuria (staphylococcus), and low baseline and post-ACTH stimulation plasma cortisol levels.

Subsequently, laboratory findings demonstrated a deteriorating state of anemia, hypoproteinemia, leukocytosis, neutrophilia, thrombocytopenia, hyperglycemia, hyperbilirubinemia, increased SAP and ALT. Radiographic findings included

cardiomegaly, hepatomegaly, and a herniated intervertebral disk at L5-L6. Needle biopsy of the liver revealed a micronodular cirrhosis, changes consistent with glucocorticoid hepatopathy. Despite extensive supportive treatment, the dog succumbed following the development of *Haemobartonella*-induced hemolytic anemia, more vomiting, depression, anorexia, melena, and multiple cutaneous abscesses. The dog was euthanatized and necropsy revealed generalized atrophy, icterus, and thinning of the skin, hepatomegaly, severe adrenocortical atrophy, hepatic vacuolization, and pancreatic fibrosis with foci of necrosis and inflammation. Although this case represents an extreme overdoseage, it illustrates the severe and potentially fatal toxicity which can result from excessive dosage or duration of glucocorticoid administration (Bellah et al. 1989).

TABLE 32.3—Reported side effects of glucocorticoid treatment (with emphasis on dogs)

Blood and blood chemistry
Increases in:
- Neutrophils
- Erythrocytes
- Monocytes
- Platelets
- Alkaline phosphatase*
- Cholesterol
- Glucose
- Alanine aminotransferase

Decreases in:
- Eosinophils*
- Lymphocytes
- Blood urea nitrogen

Central nervous system
Behavioral and mood changes (depression, increased irritability)
Lethargy
Panting

Endocrine
Iatrogenic Cushing's disease, HPAA suppression*, secondary adrenocortical insufficiency
Reduced thyroid hormone (T_4 and T_3) levels
Reduced gonadotropin and sex steroid levels
Anestrus, testicular atrophy, reduced libido
Elevated insulin levels, carbohydrate intolerance
Reduced vitamin D levels
Elevated parathyroid hormone levels

Gastrointestinal
Polyphagia
Anorexia (rare)
Diarrhea (may be bloody)
Increased gastric acid secretion
Hepatomegaly
Hepatopathy
Pancreatitis
Colonic perforation

Renal
Polyuria with secondary polydipsia*
Increased urinary calcium excretion

Musculoskeletal
Muscle atrophy
Weakness, exercise intolerance
Myotonia (rare)
Osteoporosis

Skin
Calcinosis cutis
Thin skin
Bilateral hair loss
Increased bruising

Other
Increased risk of infection
Enhanced spread of infection
Poor wound healing
Redistribution of body fat
Reduced growth

Source: Summarized from Kemppainen 1986.
*Relatively common finding in dogs.

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions:

No additional nonclinical studies were performed in support of this 505(b)(2) application.

Unresolved toxicology issues (if any):

There were no unresolved issues.

Recommendations:

Approval of the application is recommended.

Suggested labeling:

There were no changes to the nonclinical aspects of the label. The label is essential identical to that of the Reference Listed Drug, Pediapred®. For this NDA application, no changes are recommended.

Reviewer Signature _____
L. S. Leshin, D.V.M., Ph.D.

Supervisor Signature_____ **Concurrence** Yes ___ No ___
Dan Mellon, Ph.D

Appendix

References:

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/s/

Lawrence Leshin
5/22/2006 05:31:00 PM
PHARMACOLOGIST

R. Daniel Mellon
5/22/2006 05:35:48 PM
PHARMACOLOGIST
I concur with Dr. Leshin's recommendation that NDA 21-959 may be approved from the nonclinical pharmacology toxicology perspective.