CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-067

PHARMACOLOGY REVIEW(S)

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

DIVISION OF ANESTHESIA, ANALGESIA AND RHEUMATOLOGY PRODUCTS

Supervisory Memo

NDA: 22-067
Drug: **Flo-Pred (prednisolone acetate oral suspension)**
Indication: Multiple (endocrine disorders; rheumatic disorders; [redacted] dermatologic diseases; allergic states; ophthalmic diseases; respiratory diseases; hematologic disorders; neoplastic diseases; [redacted] gastrointestinal diseases; [redacted] b(4)

[redacted] b(4)

Sponsor: Taro Pharmaceuticals
Date of Memo: 6/13/2007

Background

The present NDA was submitted by Taro Pharmaceuticals to support marketing approval for Flo-Pred (prednisolone acetate oral suspension) for use in various inflammatory conditions for which steroids are commonly prescribed. Prednisolone was approved by the Agency first in 1955 (NDA 10-255) and has since been approved in many formulations and products and clinical experience is extensive. Therefore, no nonclinical studies were required of the Sponsor to support the use of prednisolone in the product.

Two issues were considered as part of the review of this NDA, however. The first issue was the drug formulation and in particular the safety of excipients utilized in the drug product. The second issue was the adequacy of nonclinical sections of the proposed label which represents the first prednisolone label to conform to the Physician's Labeling Rule (PLR) format.

The formulation to be used by the Sponsor is shown in the following table:

Strength (Label claim):	0.097% (w/w) equivalent to 5 mg/5 mL		0.293% (w/w) equivalent to 15 mg/5 mL	
Component and Quality Standard	Quantity per unit[1] (mg/5 ml)	%	Quantity per unit[1] (mg/5 ml)	%
Purified water, USP[2]				
EDTA Disodium, USP				
Carbomer 934P				
Sorbitol crystalline, NF				
Glycerin, USP				
Sucralose liquid concentrate[4]				
Masking agent				
Cherry flavor				
Butylparaben, NF				
Sodium hydroxide, NF[7]				
Poloxamer 188, NF				
Propylene glycol, USP				
Prednisolone Acetate, USP[8]				
Total Weight / Volume	--	100	--	100

b(4)

A table listing the justification for allowing excipient levels used in the formulation is presented in the primary pharmacology/toxicology review of Dr. Jerry Cott and will not be reproduced here. With the exception of the preservative butylparaben, all excipients in the formulation are contained in approved oral products at levels (by weight) which exceed that in the proposed product and can be found in the FDA's Inactive Ingredient Guide (IIG). Butylparaben is listed as present at [redacted] This [redacted] the maximum potency (by weight) listed in the IIG (0.04 mg). However, the Sponsor has noted that the IIG lists an approved oral suspension product with a [redacted] of butylparaben [redacted] than in the current product. This may not take into consideration a potentially [redacted] total daily intake of active drug in the present application and the differences in duration of therapeutic use (acute vs. chronic) compared to the product cited for support (which was without identification). However, an equivalent daily dose of butylparaben in the cited product would be approximately 20-fold lower than a 5 mL volume [redacted] which would seem an unlikely volume of administration. Nevertheless, examination of FDA databases identified butylparaben approved in Tagamet HB 200 (NDA 20-951) solution at a [redacted] concentration for OTC use in the treatment of heartburn or prophylactic prevention of heartburn. The full 20 mL is used for an adult dosage therefore daily butylparaben intake in this product exceeds that in the Flo-Pred product and allows the use at levels proposed.

b(4)

In regard to the Flo-Pred label, the Division requested a consult from Dr. Richardae Araojo of the Pediatric and Maternal Health Staff. The consult request was made to obtain recommendations on the pregnancy sections of the proposed label including the Pregnancy Category. The Division received the consult response which contained review of several nonclinical reports along with more extensive evaluation of the clinical literature. A Pregnancy Category D was recommended for the label as well as changes to the Highlights (Warnings and Precautions), Warnings and Precautions, and Use in Specific Populations (8.1 Pregnancy and 8.3 Nursing Mothers).

In the following table, the recommended label from the primary review of Dr. Jerry Cott is compared with the label as written by PMHS and integrated as seems appropriate. Incorporation of PMHS wording is indicated in blue and additional changes to primary pharm/tox or PMHS is indicated in underline.

7 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Pharm/Tox-1

Internal Recommendations
Based on 1) prior agency findings of safety and efficacy with RLDs cited, as well as 2) the extensive clinical experience with prednisolone and corticosteroid use in numerous approved products, and 3) a formulation which appears acceptable, the NDA 22-067 for Flo-Pred (prednisolone acetate oral suspension) may be approved with incorporation of recommended labeling.

External Comments
None

Adam M. Wasserman, Ph.D.

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/s/

Adam Wasserman
6/20/2007 05:40:08 PM
PHARMACOLOGIST

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:	22-067
SERIAL NUMBER:	000
DATE RECEIVED BY CENTER:	8/14/06
DRUG NAME:	FLOPRED (prednisolone acetate oral suspension)
INDICATION:	endocrine disorders; rheumatic disorders; [redacted] dermatologic diseases; allergic states; ophthalmic diseases; respiratory diseases; hematologic disorders; neoplastic diseases; [redacted]; gastrointestinal diseases; [redacted] b(4)
SPONSOR:	Taro Pharmaceuticals
DOCUMENTS REVIEWED:	Vol. 1
REVIEW DIVISION:	Division of Anesthesia, Analgesia and Rheumatology Products (HFD-170)
PHARM/TOX REVIEWER:	Jerry M. Cott, Ph.D.
PHARM/TOX SUPERVISOR:	Adam Wasserman, Ph.D.
DIVISION DIRECTOR:	Bob Rappaport, M.D.
PROJECT MANAGER:	Parinda Jani

Date of review submission to Division File System (DFS): 6/4/07

TABLE OF CONTENTS

EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability
Approve

B. Recommendation for nonclinical studies
None

C. Recommendations on labeling
Recommendations were made for Sections 8.1 Pregnancy, and 13 Nonclinical Toxicology. See suggested labeling in OVERALL CONCLUSIONS AND RECOMMENDATIONS.

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 prednisolone is well known. This reviewer concurred with the Sponsor's rationale that additional nonclinical studies would not provide additional useful safety information for the proposed indications.

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

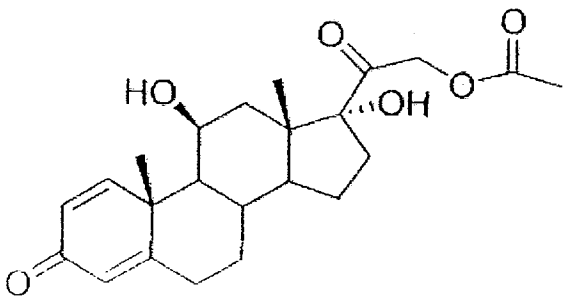
2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number:	22-067
Review number:	1
Sequence number/date/type of submission:	000 / 8/14/06
Information to sponsor:	Yes ( ) No (X)
Sponsor and/or agent:	Taro Pharmaceuticals, Hawthorne, NY 10532
Manufacturer for drug substance:	Taro Pharmaceutical Industries, Ltd., Haifa Israel
Reviewer name:	Jerry M. Cott, Ph.D.
Division name:	Division of Anesthesia, Analgesia, and Rheumatology Products
HFD #:	170
Review completion date:	5-31-07

Drug:

Trade name:	FLOPRED
Generic name:	Prednisolone Acetate Oral Suspension
Code name:	S40216
Chemical name:	(11ß)-11,17,21-Trihydroxypregna-1 ,4-diene-3,20-dione, 21-Acetate Prednisolone 21-Acetate
CAS registry number:	52-21-1
Molecular formula/molecular weight:	$C_{23}H_{30}O_6$ / 402.49

Structure:



Relevant INDs/NDAs/DMFs: DESI reference for prednisolone acetate suspension, NDA 11-896, DESI # 07110
NDA 19-157 (Pediapred; prednisolone sodium phosphate oral solution)
NDA 21-959 (Orapred; prednisolone sodium phosphate oral solution)
ANDA 40-364 (Prednisolone syrup 15 mg/mL)
ANDA 40-423 (Prednisolone syrup 5 mg/mL)
ANDA 80-354 (Prednisolone tablet 5 mg)

Drug class: glucocorticoid

Indication: Endocrine disorders; rheumatic disorders; [redacted]; dermatologic diseases; allergic states; ophthalmic diseases; respiratory diseases; hematologic disorders; neoplastic diseases; [redacted], gastrointestinal diseases; [redacted] b(4)

Clinical formulation: 5 mg/5 mL & 15mg/5 mL bottles of 120 mL (4 oz) [redacted] Active ingredient: Prednisolone (as Prednisolone Acetate). Inactive ingredients: Butylparaben, carbomer 934P, disodium edetate, glycerin, masking agent, poloxamer 188, propylene glycol, purified water, sodium hydroxide, sobitol crystalline, sucralose liquid concentrate, and cherry flavor. Table of excipients used in 15 and 5 mg mg/mL formulations (EBK-P18 and EBK-19, respectively) from Sponsor:

Ingredient	Function	Taro EBK-P18 and EBK-P19 % (w/w)	Max. Potency in IIG web site % (w/w)[1]
Purified Water			
Edetate Disodium			
Carbomer 934P			
[redacted]			
Sorbitol Crystalline			
Glycerin			
Sucralose Liquid Concentrate			
Masking Agent			
Artificial Cherry Flavor			
Poloxamer 188			
Propylene Glycol			
Butylparaben			
Sodium Hydroxide			

[redacted] b(4)

Route of administration: Oral

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

Data reliance: Except as specifically identified below, all data and information discussed below and necessary for approval of NDA 22-067 are owned by Taro Pharmaceuticals or are data for which Taro Pharmaceuticals has obtained a written right of reference. Any information or data necessary for approval of NDA 22-067 that Taro Pharmaceuticals 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 Taro Pharmaceuticals 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 22-067.

Studies reviewed within this submission:

There were no nonclinical studies submitted.

Studies not reviewed within this submission: N/A

2.6.2 PHARMACOLOGY

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

Depressed production of eosinophils and lymphocytes occurs, but erythropoiesis and production of polymorphonuclear leukocytes are stimulated. Inflammatory processes (edema, fibrin deposition, capillary dilatation, migration of leukocytes and phagocytosis) and the later stages of wound healing (capillary proliferation, deposition of collagen, cicatrization) are inhibited.

Prednisolone can stimulate secretion of various components of gastric juice. Suppression of the production of corticotropin may lead to suppression of endogenous corticosteroids. Prednisolone has slight mineralocorticoid activity, whereby entry of sodium into cells and loss of intracellular potassium is stimulated. This is particularly evident in the kidney, where rapid ion exchange leads to sodium retention and hypertension.

2.6.6 TOXICOLOGY

The Sponsor did not perform or sponsor any nonclinical studies to support approval of NDA 22-067. The Sponsor submitted only generally available, published toxicology studies to support the nonclinical sections of the proposed label. The Sponsor stated that they relied on prior Agency findings of safety and efficacy of other prednisolone-containing products. In addition, this reviewer searched the literature for additional published studies. The following is a summary of the studies found:

Mutagenicity:

Mouse lymphoma: The Sponsor found one paper that evaluated prednisolone in a mouse lymphoma thymidine kinase (TK) forward mutation assay by Wangenheim and Bolcsfoldi (1988). The authors judged prednisolone to be positive only after statistical analysis based on the following data from the publication:

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As can be seen, the effect is marginal, especially without metabolic activation. A dose-response is not clear, perhaps because the doses used were so narrowly spaced. An International Workshop on Genotoxicity - Tests Workgroup (IWGTW; Moore et al., 2003) suggests that the Induced Mutation Frequency should be above the background by a "Global Evaluation Factor" of 88 to consider it a significant effect, not just statistically significant. By these standards, the result would be considered negative.

Ames Test: An Ames assay was reported in a study by Otsuka et al. (1992; article in Japanese with English tables and abstract.). It reported negative findings for prednisolone and details of the study were determined to be adequate for consideration. Tables from this study are reproduced below:

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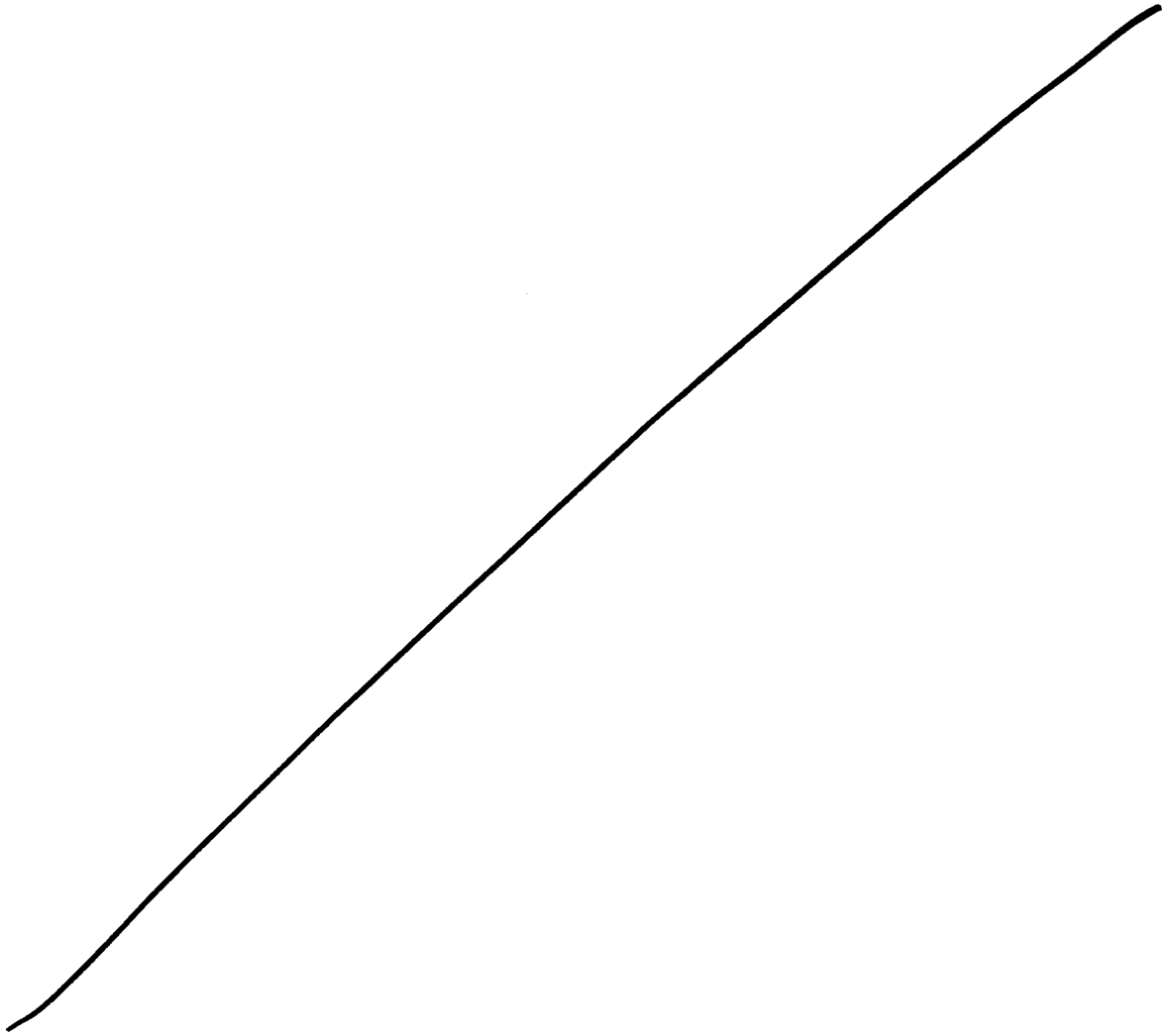


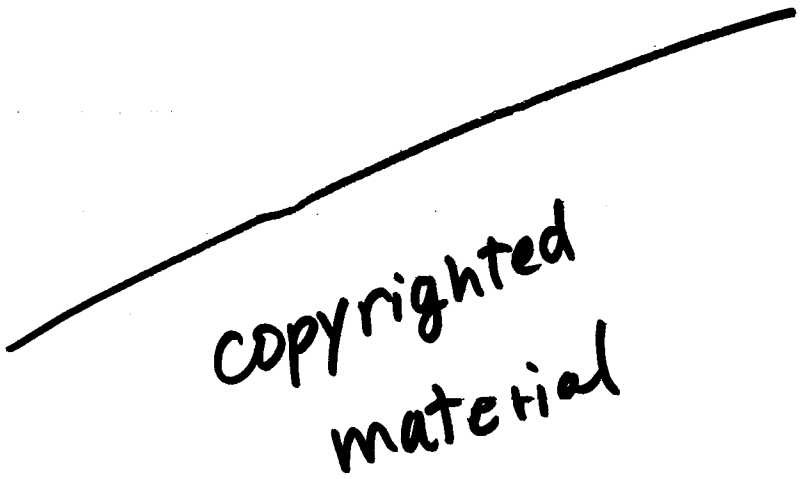
Thus, there appears to be adequate data from the Ames to determine that under the conditions of this study, prednisolone does not induce mutations either with or without metabolic activation at concentrations of 312-5000 µg/plate.

A second Ames test (reported to be negative) was found on Toxnet (Bakshi et al., 1985), but it could not be located in PubMed and thus could not be considered. However, the reported negative results are consistent with those of Otsuka et al. (1992) mentioned above.

Chromosomal aberration test: Also in the Otsuka paper was a chromosomal aberration test in a Chinese hamster fibroblast cell line (CHL). See results from this study in the following tables from the publication:

It is not clear from the tables how the maximum concentration was determined, e.g. by cytotoxicity or solubility. Consultation with reviewer Conrad Chen, Ph.D. (who is fluent in Japanese) confirmed that both maximum solubility and cytotoxicity were reached in preliminary studies described in the methods section. Under the conditions of this study, metabolic activation of prednisolone produced a slight increase in the incidence of structural chromosomal aberrations in CHL cells (primarily in chromatid exchange) at 1,500 µg/mL (Table 3-1). Table 3-2 was apparently a confirmation assay and resulted in no effect at 1500 but a small effect at 750 µg/mL; likewise table 3-3 showed a small effect at 1500 but not at 750 µg/mL. Again, the changes were primarily for chromatid exchange. The authors judged these results to be negative. Due to the weakness of the effect, the non-dose dependence, and the inconsistency of it occurrence, this seems a reasonable interpretation.

Micronucleus test: Finally, the Otsuka et al. (1992) paper contained a micronucleus test with prednisolone farnesylate. A table from the publication is below:



While the conclusion of the authors was negative for the test drug at a single SC dose of up to 2000 mg/kg, they only dosed the animals once, and they harvested only at 24 hours. EPA and OECD guidance suggest either multiple dosing and one harvest at ~ 24 hours, or a single dose with at least two harvests (e.g. 24 & 48 h). These guidance documents also recommend oral or IP administration of the test substance unless there is a justification. Again, consultation with reviewer Conrad Chen, Ph.D. (who is fluent in Japanese) explained that preliminary studies described in the methods section, examined several time points for harvest: 18, 24, 48, and 72 hours. The authors determined that no differences were seen at any of these timepoints, so 24 hours was chosen for the main study. No data from this pilot study was delineated in the publication, therefore the conclusion could not be independently verified by this reviewer. Thus, the current negative result , while being supportive, does not carry the full weight of a study conducted according to current guidelines.

Teratogenicity:

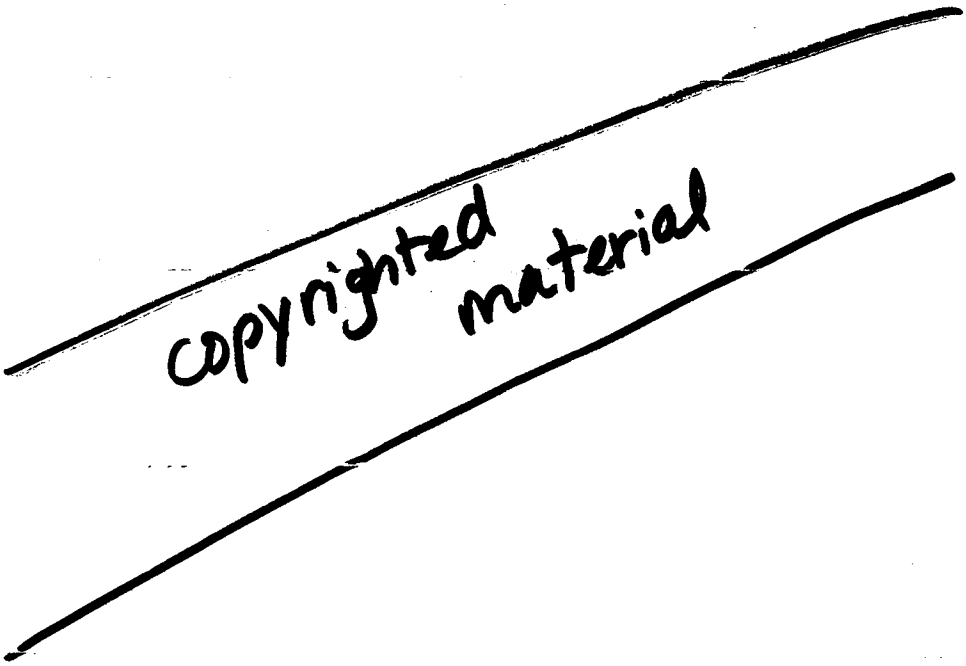
Several published papers were submitted by the sponsor. Prednisolone has been shown to cause developmental toxicity (primarily cleft palate) in several animal species exposed via a variety of routes of administration. While some studies have shown rats to be resistant to the teratogenic effects of prednisolone when dosed between days 6-15 (Walker, 1969 and 1971; Kalter, 1962) if dosed at higher levels between days 12-14, a teratogenic effect (cleft palate) was revealed (Fritz and Giese, 1990). Other species showing cleft palate include mice dosed by the ocular route (Pinsky and DiGeorge, 1965; Hasegawa, et al., 1974; Ballard, et al., 1977; Hearney, et al. 1977), rabbits (Walker, 1967) and hamsters (Shah and Kilistoff, 1976). Cleft palate was the primary

finding in these studies. The most substantiated ones, containing adequate detail for some level of confidence, are summarized below.

Fritz and Giese, 1990: In this study, various categories of chemicals (including salicylate, prednisolone, cyclophosiphamide, 5-hydroxytryptamine, glycinonitrile, and dimethylformamide) were used for the evaluation of experimental procedures to determine dose-related teratogenic potencies. Special consideration was given to whether abnormalities were considered to be related to maternal toxicity, if they were related to the pharmacology, and if they were correlated with effects on growth. A 3-mg/kg dose was without effect under the experimental conditions employed. At 30 and 100 mg/kg, in addition to an increase in the rate of dosage-related embryo and fetolethality, an incidence of marginal teratogenicity, was noted. Against the spontaneous incidence of cleft palate and omphalocele (regarded as a 'retardation-type' malformation) of 0/2207 in a historical control population and the absence of such a malformation in the vehicle control, 'marginal' teratogenicity was assumed for both these doses. A 200 mg/kg dose of prednisolone was severely toxic to the dams. Among the few fetuses surviving from this maternal treatment on days 6-15 post conception, no malformation or anomaly was noted (see table from the publication). However, a higher percentage of malformations occurred following the restriction of dosing to days 12-14 post coital, which suggested a teratogenic potential of prednisolone in the rat.

Two different types of malformation (omphalocele and cleft palate) occurred with a similar incidence.

Walker, 1967: Female rabbits of the New Zealand White or American Dutch strains were treated with varying levels of triamcinolone, dexamethasone or with IM prednisolone 1 – 8 mg, on days 13 – 16 post conception (killed on day 21). The teratogenic range for cleft palate was between 1.5 and 4 mg/day of prednisolone. No cleft palate was observed in rabbit offspring at 1.0 mg/kg/day. The reference compounds were teratogenic at lower doses. The highest dose of prednisolone, 8 mg/day, resulted in complete litter resorption. See table from the publication below:



While there were no untreated controls in this study, the low doses ranges of the teratogenic drugs and all doses of methylprednisolone (even doses resulting in complete litter resorption; not shown in above table) resulted in 240 normal palates. The authors feel (and the reviewer agrees) that while this may not be equivalent to a background rate, the high doses clearly are resulting in a significant increase in cleft palates.

Shah and Kilistoff, 1976: The effect of prenatal administration of different doses of cortisone, corticosterone, dexamethasone, triamcinolone and prednisolone as a single IM dose on the hamster fetus and its palatal development was studied. All the glucocorticoids, except cortisone, produced cleft palate in the fetuses. Both the total frequency and morphologically different types of cleft palate were related to the dose of the teratogen. See table from the publication below:

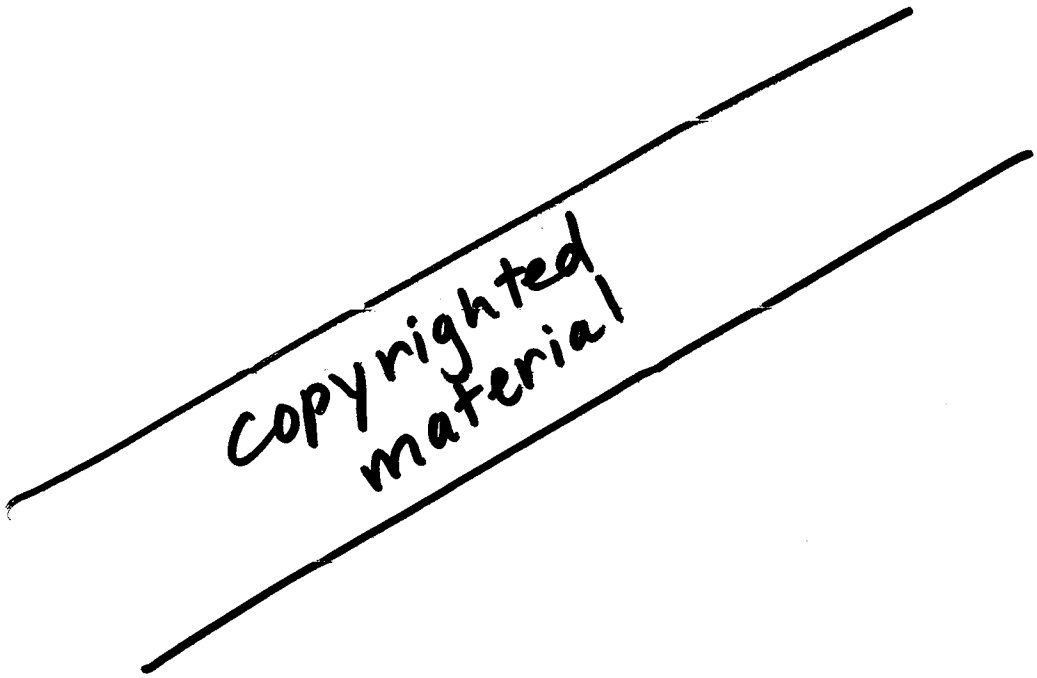
Pinsky and DiGeorge, 1965:
In this study, clinically equivalent IM doses of hydrocortisone, prednisolone, and dexamethasone had progressively increasing teratogenic activity as judged by their ability to induce cleft palate in the offspring of pregnant mice treated with these drugs during days 11-14 of gestation. While there does not appear to be a vehicle control for comparison, the results show an increase of resorptions and in the incidence of cleft palate. (see Table taken from this study)

Carcinogenicity:

Note: the Sponsor was unable to find any carcinogenicity studies from their perusal of the literature. Our own investigation through ToxNet, led to the following two studies, which were reviewed for possible inclusion in the label.

Ryrfeldt et al., 1992:
Male Sprague-Dawley rats were treated with the investigational drug budesonide, with prednisolone (368 µg/kg) or triamcinolone acetonide (4.8 µg/kg) as comparison drugs, in drinking water for up to 104 weeks. Prednisolone-treated rats developed slightly increased incidences of basophilic foci though this was not statistically significant, and significantly increased incidences

of hepatocellular adenoma. While hepatocellular carcinoma was elevated in the prednisolone condition compared with controls this was not statistically significant. However, the combination of hepatocellular adenomas/carcinomas (recommended in McConnell et al., 1986) as compared to controls was statistically significant (see tables below from the publication).



Based upon reduced body weight gains and survivals, the doses administered were considered to be toxic. The authors concluded that the positive findings represented a class effect, probably involving glucocorticoid receptors.

Berger et al., 1986:
Chlorambucil was linked to prednisolone ("prednimustine") to improve the therapeutic and toxic properties of this potent alkylating agent, which is known to induce second tumors in humans. In an industry-sponsored study, the carcinogenic potency of the linked compound with that of the individual agents was compared (see table from the publication below). Prednimustine (12 mg/kg; I), chlorambucil (3 mg/kg; II), prednisolone (3 mg/kg; III), chlorambucil plus prednisolone (3 mg/kg; IV), or vehicle were administered by oral gavage to groups of female Sprague-Dawley rats (n=30/group) for 18 months. Dosing was intermittent, given 1, 2, 4.5, or 9 times per month (designated as a, b, c, or d, respectively, in the table below). After natural death of animals, median survival times were analyzed, and percentages of malignant tumors were recorded. An increased tumor risk was found in the following organs compared with those of vehicle-treated controls: Group I: external auditory canal (EAC); Group II: mammary gland (MG), central and peripheral nervous tissue (CPNT), hematopoietic and lymphatic tissue (HLT), and EAC; Group III: none; and Group IV: MG, CPNT, and EAC.

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions:

Taro Pharmaceuticals did not conduct any pharmacology or toxicology studies to support approval of FLOPRED. However, there is a long clinical history of prednisolone use for numerous indications and by multiple routes of administration (primarily oral and ophthalmic). In addition, there are considerable data from nonclinical studies of prednisolone that have been reported in the literature. The Sponsor summarized these findings and conclusions in the initial application. At the request of FDA, additional published information was made available by the Sponsor in order to complete nonclinical toxicology and pregnancy sections of the FLOPRED labeling. Several published papers regarding teratogenicity were provided by the Sponsor as well as one evaluation of genotoxicity in a mouse lymphoma assay. A review of the literature found two additional studies using the Ames test, one of which also reported results from a chromosome aberration assay and an in vivo micronucleus test. While no carcinogenicity references were found by the Sponsor, a search of the literature by this reviewer did reveal two publications. These publications as well as those provided by the Sponsor were reviewed.

While the mutagenicity studies were generally negative, none of the primary data were available. The mouse lymphoma thymidine kinase forward mutation assay was deemed marginally, statistically positive by the authors, but current standards consider the induced mutation frequency must exceed a "Global Evaluation Factor" beyond that of the background (Moore et al., 2003). By these standards, the result would be considered negative. Two studies were conducted using the Ames assay. The published paper for Bakshi et al. (1985) was not available, and the other was published in Japanese (Otsuka et al., 1992). However, the Otsuka paper contained sufficient detail in the abstract and the tables to determine that results were probably valid for the Ames assay – and the results were negative. Also in the Otsuka paper, was a chromosomal aberration test where a slight increase was seen in the incidence of structural chromosomal aberrations (primarily chromatid exchange) with metabolic activation of prednisolone farnesylate at the highest concentration tested, 1,500 µg/mL. The authors determined the results were negative for prednisolone. To this reviewer, they would appear to be equivocal. Finally, the Otsuka paper contained a micronucleus test. While there was no increase of micronucleated polychromatic erythrocytes after a single SC dose (250-2000 mg/kg) of prednisolone, the study was deemed inadequate since the harvest was performed only at 24 hours. Current guidelines suggest harvesting at two timepoints, e.g. 24 and 48 hours after single administration and also recommends use of the intraperitoneal or oral route unless justified. A consulting Japanese-speaking reviewer determined that a preliminary time course study was performed at 18, 24, 48, and 72 hours and found no effects at any time. The main study was performed only at 24 hours.

Published studies in the literature, primarily those using prednisolone as a comparison drug, have revealed prednisolone to be teratogenic in rats, rabbits, and hamsters, after oral administration and in mice after ocular administration in doses equivalent to the human dose. These effects are manifested primarily as cleft palate in all species.

Published carcinogenicity studies which evaluated prednisolone (primarily as a comparison drug), were found during the review process. In a 104 week study in male Sprague-Dawley rats,

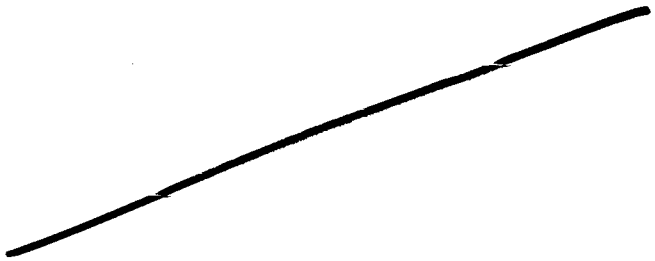
prednisolone was reported to significantly increase incidences of hepatocellular adenomas and the combination of hepatocellular adenomas/carcinomas as compared to controls when added to the drinking water at 368 µg/kg. This corresponds to a human equivalent dose of ~ 3.5 mg/day, a rather small clinical dose. No lower doses were tested, thus, the NOAEL dose is not known. In an 18 month study in female Sprague-Dawley rats using intermittent dosing of 3 mg/kg (human equivalent dose ~ 30 mg) given 1, 2, 4.5, or 9 times per month, no increase in tumors was reported.

Unresolved toxicology issues: None

Recommendations: Approval

Suggested labeling:
The Sponsor's proposed label was not sufficient as it did not contain several of the published nonclinical toxicology studies. A section on pharmacological effects in a single dog was removed.

8.1 Pregnancy



b(4)

13 Nonclinical Toxicology
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

FLOPRED was not formally evaluated in carcinogenicity studies. Review of the published literature identified carcinogenicity studies of prednisolone at doses which are less than the typical clinical dose. In a 2-year study, male Sprague-Dawley rats administered prednisolone in drinking water at a dose of 368 mcg/kg/day (equivalent to 3.5 mg/day in a 60 kg individual based on mg/m^2 body surface area comparison) increased the incidence of hepatic adenomas. Lower doses were not studied and therefore a no effect level could not be identified. In an 18-month study intermittent oral gavage administration of prednisolone did not induce tumors in female Sprague-Dawley rats when given 1, 2, 4.5, or 9 times per month at 3 mg/kg (equivalent to 29 mg in a 60 kg individual based on mg/m^2 comparison).

FLOPRED was not formally evaluated for genotoxicity. However, in published studies prednisolone was not mutagenic with or without metabolic activation in the Ames bacterial reverse mutation assay using *S. typhimurium* and *E. coli*, or in a mammalian cell gene mutation assay using mouse lymphoma L5178Y cells, according to current evaluation standards. In a published chromosomal aberration study in Chinese Hamster Lung (CHL) cells, a slight increase was seen in the incidence of structural chromosomal aberrations with metabolic activation at the highest concentration tested, however, the effect appeared to be equivocal. Prednisolone was not genotoxic in an *in vivo* micronucleus assay in the mouse though the study design did not meet current criteria.

FLOPRED was not formally evaluated in fertility studies. However menstrual irregularities have been described with clinical use (see ADVERSE REACTIONS).

Reviewer Signature Jerry M. Cott, Ph.D., Pharmacologist

Supervisor Signature_____Adam M. Wasserman, Ph.D._____ Concurrence Yes _X__ No ___

References:

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I concur with Dr. Cott's review and recommended labeling.