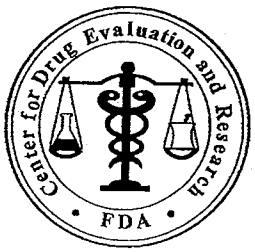
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-067

OTHER REVIEW(S)



Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	December 27, 2007
To:	Bob Rappaport, MD, Director Division of Anesthesia, Analgesia, and Rheumatology Products
Thru:	Kellie Taylor, PharmD, MPH, Team Leader Denise Toyer, PharmD, Deputy Director Carol Holquist, RPh, Director Division of Medication Errors and Technical Support
From:	Felicia Duffy, RN, BSN, Safety Evaluator Division of Medication Errors and Technical Support
Subject:	Labeling Review for Flo-Pred
Drug Name(s):	Flo-Pred (Prednisolone Acetate Oral Suspension)
Application Type/Number:	NDA 22-067
Submission Number:	Not Applicable
Applicant/sponsor:	Taro Pharmaceuticals
OSE RCM #:	2007-2453

1 INTRODUCTION

This memorandum is in response to a November 28, 2007, request from the Division of Anesthesia, Analgesia, and Rheumatology Products for a review of the revised container labels, carton and insert labeling for Flo-Pred. The Sponsor submitted a labeling amendment in response to comments provided in an Approvable Letter dated September 14, 2007, and email correspondence from the Agency dated November 5, 2007 and November 8, 2007.

2 MATERIAL REVIEWED

Revised container labels, carton and insert labeling submitted on November 19, 2007.

3 DISCUSSION

DMETS acknowledges that the sponsor has deleted the [redacted] from the proposed trade name. Additionally, we acknowledge the removal of [redacted] from the new flag. b(4)

The Sponsor also indicates that the dosing spoons will be attached at the end of the handles in a stacked position, and colors of the spoons are accurately reflected on the labeling. Furthermore, the Attention statement on all panels was revised as the Agency requested.

Upon review of the revised labeling, DMETS notes that [redacted] comparison to the established name. It is important for t

b(4)

[redacted]

4 CONCLUSIONS AND RECOMMENDATIONS

To minimize the potential for errors, and to improve readability, we recommend implementation of the container label and carton labeling revisions outlined below.

4.1 Increase the size of the product strength (5.6 mg/5 mL, 16.7 mg/5 mL) and the equivalency strength (5 mg/5 mL, 15 mg/5 mL) to at least the same size and boldness of the established name.

4.2 Revise the fading effect of the colored stripe containing the established name, product strength, and equivalency statement so that each stripe is one solid color without any fading.

DMETS would appreciate feedback on the final outcome of this review. We would be willing to meet with the Division for further discussion, if needed. Please copy DMETS on any communication to the Sponsor with regard to this review. If you have further questions or need clarifications, please contact Cheryl Wiseman, Project Manager, at 301-796-0567.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Felicia Duffy
12/27/2007 12:05:59 PM
DRUG SAFETY OFFICE REVIEWER

Kellie Taylor
12/27/2007 12:30:14 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
12/27/2007 04:23:26 PM
DRUG SAFETY OFFICE REVIEWER

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	August 1, 2007
To:	Bob Rappaport, MD, Director, Division of Anesthesia, Analgesia, and Rheumatology Products
Through:	Kellie Taylor, PharmD, Acting Team Leader, DMETS Denise Toyer, PharmD, Deputy Director, DMETS Carol Holquist, RPh, Division Director, DMETS
From:	Felicia Duffy, RN, BSN, MSEd, Safety Evaluator, DMETS
Subject:	Labeling Review for Flo-Pred
Drug Name(s):	Flo-Pred (Prednisolone Acetate Oral Suspension)
Application Type/Number:	NDA#: 22-067
Submission Number:	Not Applicable
Applicant/sponsor:	Taro Pharmaceuticals
OSE RCM #:	2007-1479

1 INTRODUCTION

This memorandum is in response to a July 3, 2007 request from the Division of Anesthesia, Analgesia, and Rheumatology Products for a review of the revised container labels, carton and insert labeling for Flo-Pred.

2 MATERIAL REVIEWED

Revised container labels, carton and insert labeling submitted on June 26, 2007.

3 DISCUSSION

DMETS has concerns with the design and layout of the container, carton, and teaspoon for this product. We believe these factors could lead to medication errors based on our postmarketing experiences. We are primarily concerned with the expression of the product strength as this may be confusing to pharmacists and prescribers which can potentially lead to dosing calculation errors. The Chemist provided clarification to DMETS that the product strength is based on the prednisolone acetate ester (e.g., 5.6 mg/5 mL) and not the prednisolone component (e.g., 5 mg/5 mL). [redacted] prednisolone equivalency statement (e.g., equivalent to 5 mg/5 mL) should be deleted from the carton, container, and from the insert labeling. b(4)

Additionally, we are concerned that providing two teaspoons with the drug product may confuse consumers which may lead to dosing errors. Furthermore, the calibrated dosing teaspoon is difficult to read because the labeling on the teaspoon does not provide adequate contrast for easy readability which may contribute to dosing errors.

We acknowledge that the Sponsor has removed the term [redacted] from the proximity of the established name, and that the term appears as part of the Sponsor's registered trademark for [redacted] on the upper left side on the carton and container labels. DMETS' labeling comments in OSE review 2006-926 (section IIIA7) indicated that b(4)

[redacted] b(4)

4 CONCLUSIONS AND RECOMMENDATIONS

To minimize the potential for dosing errors, we recommend implementation of the container label and carton labeling revisions outlined below.

[redacted] b(4)

2 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Administrative- 7

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Kellie Taylor
8/1/2007 11:44:09 AM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
8/1/2007 11:53:33 AM
DRUG SAFETY OFFICE REVIEWER

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Pediatric and Maternal Health Staff
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-0700
FAX 301-796-9744

M E M O R A N D U M

Date: June 4, 2007 **Date Consulted:** May 1, 2007

From: Richardae Araojo, Pharm.D.
Pediatric and Maternal Health Staff

Through: Sandra Kweder, MD
Deputy Director, Office of New Drugs

Lisa Mathis, MD
Associate Director, Pediatric and Maternal Health Staff

Karen Feibus, MD
Team Leader, Pediatric and Maternal Health Staff

To: Division of Anesthesia, Analgesia and Rheumatology Products (DAARP)

Drug: Flo-Pred (prednisolone) Oral Suspension [5mg/5ml and 15mg/5ml]; NDA 22-067

Subject: Lack of pregnancy category for prednisolone labeling.

Materials Reviewed: Reprotox, TERIS-The Teratogen Information System, Shepard's Catalog of Teratogenic Agents, and the National Library of Medicine's Drug and Lactation Database on prednisolone. Other published reports and references as cited.

Consult Question: The current steroid labels have inadequate information in the pregnancy subsection of labeling: Please review the Flo-Pred (prednisolone) oral suspension proposed pregnancy labeling and determine if there are other human data that bear on the issue of pregnancy category? Does a pregnancy category C seem reasonable based on the available information?

EXECUTIVE SUMMARY

Taro Pharmaceuticals submitted a literature-based 505(b)(2) new drug application for Flo-Pred (prednisolone) oral suspension on April 11, 2006. DAARP consulted the Maternal Health Team (MHT) to review the appropriateness of the sponsors proposed labeling in the *Use in Specific Populations, Pregnancy* subsection of labeling. Since current labeling for prednisolone products lack a pregnancy category, DAARP proposed a pregnancy category C based on literature reports in animals showing developmental toxicity and cleft palate. In addition, the MHT was asked to determine if there are any additional human data that should influence the pregnancy category chosen.

Prednisolone is a glucocorticoid and the active metabolite of prednisone. The principle therapeutic uses of prednisolone are as an anti-inflammatory or immunosuppressive agent for certain allergic, dermatologic, gastrointestinal, hematologic, severe or chronic allergic and inflammatory processes involving the eye, renal, respiratory, or rheumatologic diseases or conditions. Prednisolone may also be used in the treatment of antiphospholipid antibodies during pregnancy.

Animal reproductive toxicology studies in rats, mice, rabbits, and hamsters all showed an increased rate of cleft palate in offspring following maternal exposure to prednisolone or other corticosteroids. In these studies, first trimester exposure to corticosteroids was also associated with an increased risk of intrauterine growth restriction and decreased birth weight. Multiple cohort and case control studies in humans suggest a three to five-fold increased risk of cleft lip with or without cleft palate with maternal use of corticosteroids during the first trimester of pregnancy. Two prospective case control studies in humans also showed a decrease in birth weight. This risk appears to be dose related and can be minimized by administering lower dosages. It is likely that underlying maternal conditions contribute to intrauterine growth restriction and decreased birth weight, but it is unclear to what extent these maternal conditions contribute to the increased risk of orofacial clefts.

The risk of infant exposure to prednisolone during pregnancy should be weighed against the benefits of maternal treatment for the mother and fetus. If prednisolone must be prescribed, the mother should be informed of this risk so that she can actively participate in the decision regarding corticosteroid use during her pregnancy. In addition, infants born to mothers who have received corticosteroids during pregnancy should be carefully observed for signs of hypoadrenalism.

With regard to breastfeeding, prednisolone crosses into breast milk, and breast milk concentrations range from 5 to 25% of maternal serum levels.[6] Based on the literature, the expert clinical community considers maternal doses of prednisolone of 20 mg/day safe for use

during breastfeeding.[9] When doses larger than 20 mg/day are needed, some clinicians advise mothers to wait at least four hours before nursing their baby.[8,9] However, there is no data to support this recommendation. *Even at 80 mg/day the amount of prednisolone secreted in breast milk would be equivalent to less than 10% of a nursing infant's endogenous cortisol production, and it is unlikely that such a dose would produce clinically significant effects.*[3] There have been no adverse events reported in infants from exposure to prednisolone via breast milk in the literature. While there are no data to support this assumption, it is possible that infant exposure to higher maternal doses of steroids (> 40 mg/day) via breast milk for extended periods of time could produce effects on infant growth and development.[9] The American Academy of Pediatrics (AAP) considers prednisolone and prednisone compatible with breastfeeding.[1]

The risk of infant exposure to prednisolone in breast milk should be weighed against the known benefits of breastfeeding for both the mother and baby. If prednisolone must be used in a breastfeeding mother, the lowest dose should be prescribed to achieve the desired clinical effect.

Maternal Health Team Response:

1. The Office of Surveillance and Epidemiology (OSE) should be consulted and asked to conduct an AERS database search for reports of teratogenic effects in infants exposed to prednisone or prednisolone during pregnancy. This information may be useful in providing further guidance to prescribing practitioners caring for pregnant women.

2. The Office of Surveillance and Epidemiology should be consulted and asked to conduct an AERS database search for reports of adverse events in infants associated with exposure to prednisone or prednisolone via breast milk. This information may be useful in providing further guidance to prescribing practitioners and breastfeeding women.

3. The MHT recommends a Pregnancy Category D for Flo-Pred (prednisolone) Oral Solution. This recommendation is based on both available human data suggesting an increased risk of orofacial clefts and the benefits of treatment for pregnant women (and their fetuses) with underlying conditions requiring corticosteroid treatment. The MHT's recommended revisions to the sponsors proposed labeling are provided on pages 22-24 of this review. These labeling recommendations should be considered for all oral corticosteroid labeling.

BACKGROUND

Taro Pharmaceuticals submitted a literature-based 505(b)(2) new drug application for Flo-Pred (prednisolone) oral suspension on April 11, 2006. DAARP consulted the Maternal Health Team (MHT) to review the appropriateness of the sponsors proposed labeling in the *Use in Specific Populations, Pregnancy* subsection of labeling. Since current labeling for prednisolone products lacks a pregnancy category, DAARP proposed pregnancy category C based on literature reports in animals showing developmental toxicity and cleft palate. In addition, DAARP asked MHT to determine if there are any additional human data that should influence the pregnancy category chosen.

Prednisolone is a glucocorticoid that is also the active metabolite of prednisone. The principle therapeutic uses of prednisolone are as an anti-inflammatory or immunosuppressive agent for certain allergic, dermatologic, gastrointestinal, hematologic, severe or chronic allergic and inflammatory processes involving the eye, renal, respiratory, or rheumatologic diseases or conditions. Prednisolone may also be used in the treatment of pregnant women with antiphospholipid antibodies.

Published reports suggest that use of prednisolone and other glucocorticoids during pregnancy is associated with an increased risk of cleft palate and impaired fetal growth in both animals and humans. During lactation, prednisolone enters human breast milk in small amounts. The American Academy of Pediatrics (AAP) considers prednisolone and prednisone compatible with breastfeeding.[1]

REVIEW OF DATA

Submitted Materials

Animal Reproductive and Developmental Toxicity Data:

The sponsor provided the following information regarding prednisolone animal reproductive and developmental toxicity:

"Prednisolone has been shown to cause developmental toxicity in a number of animal species exposed via a variety of routes including to the cornea:

- Rats - Hasegawa, et al., 1974; Fritz and Giese, 1990; Taniguchi, H. et al., 1992; Walker, 1969 and 1971
- Mice - Pinsky and DiGeorge, 1965; Hasegawa, et al., 1974; Ballard, et al., 1977; Hearney, et al.,1977
- Rabbits - Walker, 1967
- Hamsters - Shah and Kilistoff, 1976

Cleft palate was the primary finding in these studies. This teratogenic effect has been reported for other glucocorticoids as well, except for hydrocortisone. Additionally, some elevation of fetal resorptions frequency was observed.

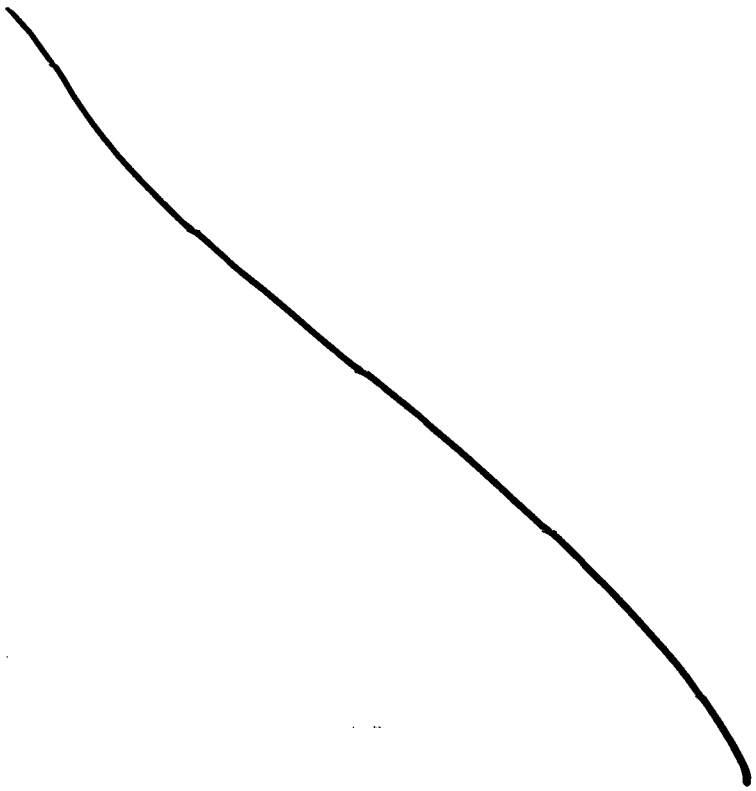
The rat results were the least consistent with respect to prednisolone-induced cleft palate. Some of the rat studies reported above failed to exhibit the effect, most likely due to the fact that the dosing was not sufficient in the organogenesis phase to induce the effect (Tanaguchi, et al., 1992). Prednisolone was found to have minimal to moderate ability to induce cleft palates in most species compared to drugs such as betamethasone and dexamethasone, potent glucocorticoids."

[1] The American Academy of Pediatrics, Committee on Drugs, The transfer of drugs and other chemicals into human milk. Pediatrics. 2001; 108(3):776-789.

Reviewer comment:
This difference in the ability of different corticosteroids to induce orofacial clefts may be related to the higher relative potencies of betamethasone and dexamethasone compared to prednisolone. If so, hydrocortisone would be expected to exhibit an even smaller effect.

Based on the data presented above, Taro Pharmaceuticals proposes the following language for labeling:

b(4)



b(4)

Additional studies reviewed
This reviewer conducted a Pub Med search of the literature to identify other published sources of information about the use of prednisolone and corticosteroids during pregnancy and lactation in animals and humans. Information from this search is presented below.

Animal data

Published reproductive toxicology studies in animals show an association between maternal corticosteroid exposure and constriction of the ductus arteriosus, low birth weight, and intrauterine growth restriction. A summary of these findings are described below.

1. **Momma K, Nishihara S, Ota Y: Constriction of the fetal ductus arteriosus by glucocorticoid hormones. Pediatr Res. 15:19-21, 1981.**

   In 1981 Momma, Nirshihara, and Ota observed constriction of the ductus arteriosus in offspring of pregnant rats near term injected with prednisolone at doses 10 to 1000 times the doses used in humans.[2,3]

   To determine intrauterine ductus size in the rat, hydrocortisone (10 mg/kg), prednisolone (10 mg/kg), or betamethasone (0.2 mg/kg) was injected into the dorsum of the thorax of 17 pregnant rats on the 21st day of gestation. Animals were sacrificed 1, 2, 4, 8, and 24 hr after the injection. After animals were sacrificed, fetal ductus arteriosus was studied using a rapid whole-body freezing technique.

   On the 21st day of gestation, doses of hydrocortisone (1 to 1000 mg/kg), prednisolone (0.1 to 1000 mg/kg), and betamethasone (0.001 to 100 mg/ kg) were injected into 27 pregnant rats and fetal ductus size was determined at four hours after injection.

   Influence of gestational age on the effect of glucocorticoids on intrauterine ductus size was assessed by injecting four pregnant rats on the 19th day with hydrocortisone (10 mg/kg), prednisolone, or betamethasone. Fetal ductus size was determined at four hours after injection and compared with those in the experiment on 21st day of gestation. Control values were obtained by determining fetal ductal size on the 19th and 21st day of gestation in two rats who did not receive any medication. Six pregnant rats were allowed to deliver spontaneously on the 21st or 22nd day of pregnancy to obtain normal birth weight in the rat.

   Fetal ductus constriction began in the first hour after injection in all glucocorticoids ($P < 0.05$). Maximum fetal ductus constriction occurred at one to four hours after injection of hydrocortisone, at two hours after injection of prednisolone, and at four hours after injection of betamethasone. Ductus constriction persisted at 24 hours after injection of each glucocorticoid ($P < 0.05$). Massive doses of each glucocorticoid resulted in complete constriction of the fetal ductus arteriosus. Relative potency of the ductus constricting effect of hydrocortisone, prednisolone, and betamethasone was estimated to be 1:2:20. Vital signs, behavior, and activity of the rat and fetus were unchanged after injection of each glucocorticoid except for one rat which became dyspneic and collapsed at four hours after injection of prednisolone (1000 mg/kg). Three of 15 litter mates from this rat showed failing vital signs, and the remaining litter mates showed completely

[2] Momma K, Nishihara S, Ota Y: Constriction of the fetal ductus arteriosus by glucocorticoid hormones. Pediatr Res. 15:19-21, 1981.

[3] Reprotox database on prednisolone; available through Micromedex - http://csi.micromedex.com/DATA/RX/RX1359.HTM

closed ductus. No increased mortality of fetuses was observed in other procedures. Each glucocorticoid showed stronger ductus constriction in premature fetuses of the 19th day of gestation than in mature fetuses ($P < 0.05$).

The authors concluded that glucocorticoids have a dose dependent effect on the constriction of the ductus arteriosus of the rat fetus.

2. **Reinisch JM et al.: Prenatal exposure to prednisone in humans and animals retards intrauterine growth. Science. 202:436-8, 1978.**

Reinisch et al., studied animals treated with prednisone at doses proportional to human therapeutic doses. Male and female Rockland-Swiss mice were assigned to one of four groups on day 13 of pregnancy. Group one received no treatment, group two received 100 mcg of prednisone (this dose was calculated to be proportional to the 10 mg dose received by the women enrolled in the study), the third group received 400 mcg of prednisone, and the fourth group received vehicle only. No significant difference was found in offspring between the two control groups and no significant differences in weight between males and females in treatment groups were observed. However, 16 day-old fetuses exposed to prednisone (either 100 or 400 mcg) for four days weighed significantly less than controls ($P < 0.00001$). Both the 18 day-old fetuses and the full-term pups exposed to either the 100 or 400 mcg dose of prednisone also weighed less than did offspring of controls ($P < 0.00001$). Duncan's test was conducted and revealed that on days 16, 18, and at term animals exposed to 100 mcg of prednisone weighed significantly less than did controls ($P < 0.05$). In addition, on day 18 and at term the fetuses and pups exposed to 400 mcg of prednisone weighed significantly less than those exposed to 100 mcg ($P < 0.001$).[4]

The authors concluded that prenatal exposure to prednisone may retard fetal growth and be associated with low birth weight.

Human data

1. **Reinisch JM et al.: Prenatal exposure to prednisone in humans and animals retards intrauterine growth. Science. 202:436-8, 1978.**

In 1978, Reinisch et al., studied human and animal offspring exposed to low doses of corticosteroids throughout gestation. The full-term offspring of 119 women who were treated with prednisone 10 mg/day for infertility and throughout pregnancy at a private Southern California infertility clinic between 1955 and 1975 were enrolled. A comparison group of offspring of 67 women from the same clinical population who did not require prednisone therapy or any other hormonal therapy during pregnancy were enrolled as a control group. The results of the study indicated that offspring exposed

prenatally to prednisone weighed significantly less than control offspring ($p < 0.0001$). No difference between the birth weight of male and female offspring was observed.[4]

The authors concluded that prenatal exposure to prednisone may retard fetal growth and be associated with low birth weight.

2. **Fraser FC, Sajoo A. Teratogenic potential of corticosteroids in humans. Teratology. 1995; 51:45-46.**

Fraser and Sajoo surveyed the literature from 1952-1994 for reports of maternal treatment with corticosteroids (cortisone, cortisol, prednisone, prednisolone, or dexamethasone) during the first 70 days after conception. The indications for use of these medications were mainly systemic lupus erythematous, asthma, and infertility.

Eighteen single case reports were identified in which the mother was exposed to corticosteroids during the first trimester of pregnancy. Among these 18 cases, there were 26 pregnancies exposed to corticosteroids. Seven of these pregnancies (27%) resulted in malformed offspring. This was considered higher than the reported population frequency of about 3%. Four of these malformations were cleft palate (15%) which could signify a teratogenic effect or simply be due to reporting bias. Other malformations observed were bilateral nuclear cataract, gastroschisis, and hydrocephalus.

Seventeen case series reports of patients exposed to corticosteroids were identified. Of these, 457 patients were included in the series and 16 (3.5%) were malformed. This malformation rate was the same as that for the general population. There were two offspring (0.4%) with cleft palate. Based on the low rate of cleft palate seen in the case series reports, the authors suggest that the high rate see in the single case reports may be due to reporting bias. However since the expected number of cleft palate cases would be about 0.2 and the population frequency of cleft palate is 1/2500, the authors stated that the possibility of the two cleft palate cases being real cannot be overlooked.

Other malformations reported were anencephaly (2), clubfoot (3), dislocated hip, coarctation of the aorta (2; 1 with a positive family history), transposition of the great vessels (with a positive family history), cataract (2; 1 with a family history), hypospadias (2), and undescended testis.

The frequency of adverse pregnancy outcome such as stillbirth, neonatal death, prematurity, and low birth weight in treated women was 21%. The incidence of these poor pregnancy outcomes was difficult to interpret due to confounding factors such as the contribution from the maternal disorder requiring corticosteroid treatment. The authors stated that *although the data are scanty and subject to bias, they suggest that, in humans, treatment with corticosteroids during pregnancy presents little, if any, teratogenic risk to the fetus.*

[4] Reinisch JM et al.: Prenatal exposure to prednisone in humans and animals retards intrauterine growth. Science. 202:436-8, 1978.

3. **Czeizel AE, Rockenbauer M. Population-based case-control study of teratogenic potential of corticosteroids. Teratology. 1997; 56:335-340.**

Czeizel and Rockenbauer retrospectively evaluated the teratogenic potential of oral and topical corticosteroid treatment during pregnancy using the Hungarian Case Control Surveillance of Congenital Abnormalities dataset (based on the Hungarian Congenital Abnormality Registry) from 1980-1994. Cases with isolated congenital abnormalities and unidentified multiple abnormalities were identified and included. Newborn infants without controls were matched to each case. A reply-paid questionnaire was sent to the parents of each identified case and control. If a response was not received, the parents were visited in person.

The total number of cases and controls were 20,830 and 35,727, respectively. Table 1 below illustrates the absolute risk of maternal oral and topical corticosteroid treatment.

Rate of pregnancy exposure to corticosteroid oral medication was 1.55% among 20,830 malformed cases and 1.41% among 35,727 healthy control births (P = 0.2). Pregnancy exposure to corticosteroid ointment was 0.35% among malformed and 0.33% among control births (P=0.7). The authors reported that the adjusted odds ratio and the analysis of case control pairs did not show any association between the rate of different congenital abnormalities and the corticosteroid treatment during the second and third months of gestation. Based on the results, the authors concluded that treatment with corticosteroids during pregnancy did not appear to increase the risk of congenital abnormalities.

Reviewer Comment:
The authors did not comment on the increased risk of orofacial clefts seen with topical corticosteroids in this study. Based on the information provided in the study, it is not clear

why topical corticosteroids were associated with an increased risk of orofacial clefts. Corticosteroid potency and body surface area of use are not known.

4. **Rodriguez-Pinilla E, Martinez-Frias ML. Corticosteroids during pregnancy and oral clefts: a case-control study. Teratology. 1998;58:2-5.**

Rodriguez-Pinilla and Martinez-Frias conducted a hospital based case control study to determine the relationship between corticosteroid use during pregnancy and oral clefts in the newborn. Data were obtained from the Spanish Collaborative Study of Congenital Malformations (ECEMC). From April 1976 and December 1995, the ECEMC surveyed 1,287,345 live born infants. Of those, 24,088 (1.9%) were malformed and 28,517 were selected as controls. Of the malformed infants, 540 cases were excluded due to a lack of data about drug intake during the first trimester of pregnancy, and 882 were excluded from the control group. Cases and controls with known syndromes were also excluded. A total of 1,184 cases with nonsyndromic oral clefts were analyzed for exposure to any systemic corticosteroid during the first trimester of pregnancy. The following three control groups included:

- The specific control of each case (paired controls)
- Controls born at the same hospital as each case during a period of $\pm$ 45 days from the case's date of birth
- Remaining malformed infants without oral clefts

A logistic regression analysis was conducted and illustrated a relationship between exposure to corticosteroids during the first trimester of pregnancy and an increased risk of cleft lip (with or without cleft palate) in the newborn infants (OR = 6.55; CI = 1.44 – 29.76; P = 0.015). This analysis controlled for potential confounder factors such as maternal smoking, maternal hyperthermia, first-degree malformed relatives with cleft lip with or without cleft palate, and maternal treatment with antiepileptics, benzodiazepines, metronidazole, or sex hormones during the first trimester of pregnancy.

Of the 1,184 cases, there were five infants exposed to corticosteroids (0.42%). Table 2 below shows the risk of oral clefts in exposed cases versus the different control groups.

All but one of the exposed cases had cleft lip with or without cleft palate; therefore the authors analyzed these cases separately from those with cleft palate. The results of that analysis are shown in Table 3 below.

The authors provided a detailed description of corticosteroid exposure during the first trimester of pregnancy in cases with oral clefts. These details include the congenital defect seen, dosage, and period of exposure (see Appendix A). Of the cases, there was one case of cleft soft palate from exposure to prednisone 40 mg (two doses) during the 3rd month of pregnancy, three cases of cleft lip with cleft palate from exposure to prednisone 15-30 mg/day during first month of pregnancy, and 4 cases of cleft lip with cleft palate, diaphragmatic hernia, and hypoplasia of the left kidney from exposure to prednisone 30 mg/day during the first trimester and 6th month to the end of pregnancy. Based on these results, the authors concluded that the use of corticosteroids during the first trimester of pregnancy is associated with a risk of cleft lip with or without cleft palate and use should

be restricted to life-threatening situations, diseases without any other safe therapeutic alternative, or cases with replacement therapy.

5. **Carmichael SL, Shaw GM: Maternal corticosteroid use and risk of selected congenital anomalies. Amer J Med Genet. 1999;86:242-244.**

In a case-control study, the California Birth Defects Monitoring Program examined the association between selected congenital anomalies and corticosteroid use one month before to three months after conception (periconceptional period). Case infants and fetal deaths diagnosed with orofacial clefts, conotruncal defects, neural tube defects, and limb anomalies were identified from a total of 552,601 births in 1987 through the end of 1989. Controls without birth defects were randomly selected from the same population. Cases with known genetic syndromes were excluded from the study. The mothers of case and control infants were interviewed by telephone to determine their exposure to medication during the periconceptional period. These interviews took place, on average, 3.7 (cases) or 3.8 (controls) years after birth. Mothers of children with the following anomalies were interviewed:

- Orofacial clefts (n=662, 85% of eligible)
- Conotruncal heart defects (n=207, 87% of eligible)
- Neural tube defects (n=265, 84 of eligible)
- Limb reduction defects (n=165, 82 of eligible)
- Controls (n=734, 78% of eligible)

Orofacial clefts were classified into the following phenotypic groups for further analysis:

- Isolated cleft lip with or without cleft palate (ICLP, n=348)
- Isolated cleft palate (ICP, n= 74)
- Multiple cleft lip with or without cleft palate (MCLP, n=99)
- Multiple cleft palate (MCP, n=74)

Thirteen women in the study reported using corticosteroids for various indications during the four month periconceptional period, see Table 4 below.

Six case mothers of infants with ICLP and three mothers of infants with ICP used corticosteroids. Two of the case mothers of infants with ICLP used prednisone. Therefore, corticosteroid use was associated with an increased risk for ICLP (odds ratio 5.3, 95% confidence interval 1.1-26.5). No increased risks were observed for the other anomalies studied.

The authors concluded that periconceptional corticosteroid use is associated with an increased risk of isolated orofacial clefts in exposed infants. Recall bias was considered unlikely to be responsible for the findings since increased risks were not observed for other anomalies and it was unlikely that mothers were aware of a possible association between corticosteroid use and clefts.

6. **Park-Wyllie L, Mazzotta P, Pastuszak A, Moretti ME, Beique L, Hunnisett L, Friesen MH, Jacobson S, Kasapinovic S, Chang D, et al. Birth defects after maternal exposure to corticosteroids: prospective cohort study and meta-analysis of epidemiological studies. Teratology. 2000;62:385-392.**

Park-Wyllie, et al. conducted a prospective observational cohort study to determine the fetal safety of maternal prednisone therapy. In addition, a meta-analysis was conducted to determine the risk of major fetal malformation (including oral clefts) from steroid use. Women who voluntarily called the Motherisk Program in Canada for information about fetal risk/safety from use of prednisone during pregnancy were included in the exposed group for the prospective study. The unexposed group consisted of pregnant women who voluntarily contacted the Motherisk Program for safety/risk information about either topical retinoic acid for uncomplicated acne, or oral astemizole for seasonal allergies, neither of which has been associated with an increased risk of major malformations. One year after the expected date of delivery, as calculated by the date of the last menstrual period, all patients were telephoned by Motherisk to collect details about the outcome of

pregnancy, birth weight, and presence or absence of birth defects, and perinatal and neonatal complications. All follow-up details were confirmed by written documentation from the child's physician.

During the period of 1985-1995, a total of 184 women in the exposed group and 188 women in the unexposed group were included in the study and postnatal follow-up. The rate of live born infants were similar in both groups (157/187 vs. 171/188, p=0.06). In the exposed group, 184 women delivered 157 infants (3 sets of twins); the controls included 188 women who delivered 171 live-born infants. The number of elective terminations was higher in the exposed group (16/187 vs. 2/188, p=0.002). A reason for the terminations was not obtained. Babies born to exposed mothers were smaller (mean 3,112g vs. 3,428g, p=0.0001), born earlier (mean 38 weeks vs. 39.5 weeks, p=0.0001), and more likely to be premature (27/158 vs. 9/172, p=0.0001). There was no statistical difference observed in the rate of major anomalies between the two groups (exposed: 4/111, controls: 3/172; p=0.3). Table 5 below illustrates the characteristics of the pregnancy outcomes in the exposed and unexposed women.

The rates of anomalies between the exposed and unexposed group were 3.6% and 2%, respectively. These rates were both considered within the expected baseline range for the population and not significantly different from each other.

The authors performed a meta-analysis of previously published studies to determine the risk of major fetal malformation (including oral clefts) from corticosteroid use during pregnancy. Their search included the following literature databases: Medline (1966–December 1999), EMBASE (1988–October 1999), and Current Contents (January – December 1999). From this search, 455 articles were identified and 10 were accepted for the analysis. Studies were excluded from analysis for the following reasons: case reports, reviews, case series, absence of a control arm, inadequate reporting of fetal outcome, and inability to verify first-trimester exposure.

Of the 10 accepted studies, six were cohort studies and four were case-control studies conducted from 1962–1999. The specific corticosteroid and dosage used by mothers

were not reported in three of the 10 studies (a listing of all the studies included in the meta-analysis is provided in Appendix B). Among the six cohort studies, statistical significance was not achieved for major malformations (cumulative OR = 1.45 [95% CI 0.81–2.60]). The largest study by Heinonen et al. did not distinguish between major and minor abnormalities in the exposed group. When the investigators repeated the analysis without the study by Heinonen et al. the authors detected a greater than three-fold increased risk of oral clefts with fetal exposure to corticosteroids especially during the first trimester of pregnancy (OR = 3.03 [95% CI 1.08, 8.54]). All four case control studies examining the risk of orofacial clefts had a significantly increased odds ratio with an overall odds ratio of 3.35 (95% CI 1.97, 5.69). The phenotype of clefts seen were isolated cleft palate (4), isolated cleft lip (6), cleft lip and palate (5), and cleft lip without palate (10).

When the cohort and case-control studies were combined, a significant correlation between the quality of the studies and their odds ratio was not seen (odds ratio = -0.32).

A pooled sample of malformations in fetuses exposed to corticosteroids revealed that cleft palate was the most commonly reported anomaly with three cases being identified among 390 corticosteroid exposures compared with no cases among 708 controls. A list of all malformations reported in the meta-analysis studies is presented in Appendix C.

The authors concluded that although prednisone does not represent a major teratogenic risk in humans at therapeutic doses, it does increase by an order of 3.4 fold the risk of oral cleft, which is consistent with the existing animal studies.

Reviewer comment:
Based on review of the publication by Heinonen et al., the authors were justified in repeating the analysis of risk for orofacial clefts without the Heinonen data. The study report did not adequately describe study methods and did not distinguish between major and minor malformations. The authors did not specifically comment on the number of cases of cleft lip and/or palate in either study or control groups. It is not clear how the inclusion of minor malformations or how protocol design may have influenced this study's ability to detect a true difference in the risk of major malformations among infants exposed and not exposed to corticosteroids.

7. **Pradat P, Robert-Gnasia E, Di Tanna GL, Rosano A, Lisi A, Mastroiacovo P, Contributors to the MADRE database. First trimester exposure to corticosteroids and oral clefts. Birth Defects Res A Clin Mol Teratol. 2003;67:968-970.**

In 2003, Pradat et al. conducted a case-controlled analysis of the MADRE (Malformation Drug Exposure) database to determine if an association exists between maternal exposure to corticosteroids during pregnancy and cleft palate in the newborn. The MADRE Project is a database that collects data on malformed infants with maternal first trimester drug exposure in different parts of the world. Nine registries participated in the data collection for this study. The investigators defined cases as infants who presented with a malformation belonging to one of the following groups:

- Group I: cleft unspecified (palate or lip)
- Group II: cleft palate
- Group III: cleft lip with or without cleft palate

Infants presenting with any other birth defect not listed in the groups above were controls. All cases included in the study had exposure to corticosteroids alone or in combination during the first trimester of pregnancy. The crude odds ratio for each registry was calculated to determine the association between corticosteroid use and the presence of malformation. To evaluate whether the risk differed across registries, the homogeneity of the odds ratios were tested using the Breslow Day Test. The results of the analysis conducted to test the possible association between corticosteroid use and oral clefts are presented in Table 6 below.

The authors found no association between in-utero corticosteroid exposure and the incidence of orofacial clefts when all corticosteroids were combined together. However, infants born to mothers who used systemic corticosteroids in combination[5] had an odds ratio of 2.1 (95% CI = 1.03-4.26) for orofacial clefts. The authors stated that if all 24 cases exposed to corticosteroids for systemic use (H02A or H02B) are combined, a decreasing trend ($p< 0.001$) in the number of cases per year is observed (11 cases in 1990–1992, eight cases in 1993–1995, four cases in 1996–1998, and one case in 1999–

[5] The authors do not explain what "corticosteroids for systemic use, plain" and "corticosteroids for systemic use, combinations" mean. For the combinations, it is not clear if more than one corticosteroid agent was used sequentially or concomitantly or whether use of topicals was combined with use of systemic agents.

2002). The authors made the assumption that the decreasing trend may be due to efforts over the past years to reduce exposure to environmental dioxins. In addition, the authors assumed that human fetuses may become sensitive to the teratogenic effect of corticosteroids when exposed in utero to environmental pesticides.

Reviewer comment:

1. *This study included a small number of cases. The study did not provide information regarding the underlying maternal condition which required the use of a corticosteroid or the specific corticosteroids used by the mothers. In addition, the control group used in the study may not be the most appropriate group for comparison. Historical matched controls of normals should have been included as a control group.*

2. *The information regarding the possible association between decreasing incidence of orofacial clefts over time and decreasing environmental dioxin levels is unclear. The authors did not comment on whether the incidence of orofacial clefts decreased or remained the same in the general population and did not include a normal historical control (as stated above). They also did not comment on whether there was any trend in corticosteroid doses prescribed to pregnant women. If women were generally receiving lower doses of corticosteroids over time, this may have also contributed to the perceived decreasing number of orofacial cleft cases.*

Data regarding prednisolone and breastfeeding:

Prednisone and prednisolone are secreted into human milk. The American Academy of Pediatrics considers prednisolone and prednisone as maternal medication compatible with breastfeeding. This classification is based on published reports in the literature (#1-3 below). These studies suggest that prednisolone is minimally secreted in human milk. A summary of the major findings of these and other studies are provided below.

1. **Katz FH, Duncan BR. Letter: Entry of prednisolone into human milk. N Eng J Med. 1975; 293 (22):1154.** In a letter to the editor, Katz and Duncan described a case of one woman in 1974 who received prednisone for recurrent iridocyclitis. Milk was obtained by breast pump 120 minutes after a 10 mg dose of prednisone. The levels found in milk were 1.6 mcg/L (prednisolone) and 2.67 mcg/L (prednisone). The authors concluded that an infant taking 1 liter of milk would obtain 28.3 mcg of prednisone/prednisolone, *an amount to not likely to have an adverse effect on the infant.* No additional information was provided in the report.

2. **McKenzie SA, Selley JA, Agnew JE. Secretion of prednisolone into breast milk. Arch Dis Child. 1975; 50(11):894-896.** Seven lactating women were enrolled in the study. Three of the women had been lactating for several months and were about to wean their infants. The remaining four women had recently delivered and elected to bottle feed their infants, however they volunteered for participation in the study. Each woman received radioactive labeled prednisolone 5 mg. The concentration of radioactive drug was measured over a period of 48 hours. The concentration of radioactive drug was highest in the first sample obtained and continued to fall rapidly upon further

measurements. The total recovery per liter of milk during the 48 hours after the dose was 0.14% (range 0.07 to 0.23) of the maternal dose.

3. **Greenberger P, Yaseen O, Frederiksen M, Atkinson A. Pharmacokinetics of prednisolone transfer to breast milk. Clinical Pharmacology and Therapeutics. 1993;53:324-328.** Prednisolone transfer into breast milk was studied in thee nursing women who were weaning breastfeeding and required oral steroid therapy for asthma. Each patient received a 50 mg intravenous dose of prednisolone phosphate. For six hours after the injection, blood and breast milk samples were obtained over timed intervals.

   The authors' results showed that the concentrations of prednisolone in milk declined more rapidly than in serum. This decline was described by the authors as suggesting that exchange between unbound prednisolone in serum and breast milk is relatively rapid and bidirectional.

   An average of 0.025% (range, 0.010% to 0.049%) of the prednisolone dose was recovered in milk. However, milk production ranged from 29 to 136 ml during the six hour interval. Therefore, the authors concluded that prednisolone transfer into breast milk does not appear to pose any significant risk to nursing infants.

4. **Berlin CM, Kaiser DG, Demmers L. Excretion of prednisone and prednisolone in human milk. Pharmacologist. 1979; 21-264.** The excretion of prednisone and prednisolone was assessed in a single patient who received prednisone 120 mg/day for idiopathic thrombocytopenic purpura. Following the single dose of prednisolone, milk was collected at various time intervals to assess the levels of prednisone and prednisolone in milk. The following levels were reported:

Table 7: Breast milk levels of prednisone and prednisolone following a 120 mg oral dose or prednisolone

Hours after dose	Prednisone (ng/ml)	Prednisolone (ng/ml)	Total Steroid (ng/ml)
½	54.1	0	54.1
1	112.9	126.3	239.2
2	153.9	473.1	627.0
4	116.1	131.4	247.5
6	33.9	0	33.9

The combined levels of prednisone and prednisolone peaked after two hours. The peak level of combined prednisone and prednisolone was 627 mcg/L. The authors stated that assuming the infant received 120 ml of milk every four hours; the total possible ingestion would only be 47 mcg, an amount not considered harmful to the infant.

Reviewer comment:
The authors assumed an infant would receive 120 ml of milk every four hours. This is probably a reasonable average estimate but may underestimate actual intake for some exclusively breastfed babies.

5. **Ost L, Wettrell G, Bjorkhem I, Rane A. Prednisolone excretion in human milk. Journal of Pediatrics. 1985; 106 (6): 1008-1011.** The authors studied six lactating women with various diseases receiving long-term treatment with prednisolone at doses of 10 to 80 mg/day. Serum and milk samples were collected over six hours after the morning dose and assayed for prednisolone and endogenous cortisol. The results of the pharmacokinetic data observed are shown in Table 7 below:

Peak milk prednisolone levels occurred about one hour after the oral dose of prednisolone. The milk/serum concentration ratio increased with increasing serum concentration. Milk levels were reported to be 5-25 % of the maternal serum levels. At a dose of prednisolone 80 mg/day, the authors estimated that the infant would ingest less than 0.1% of that dose. This corresponds to less than 10% of the infant's endogenous cortisol production (infants endogenous corticosteroid excretion was estimated to be >2000mcg).

Based on these results, the authors concluded that the concentration of prednisolone in breast milk is independent of the nursing interval and equilibrium between milk and blood is established quickly. Therefore, exposure of the infant to prednisolone may be further minimized if nursing is performed > 4 hours after the dose, i.e. when the peak concentration in the milk has passed. Breastfeeding at maternal prednisolone doses of 20 mg once or twice daily can be permitted. Even doses higher than 20 mg twice daily can possibly be permitted if nursing is performed $\geq$ 4 hours after the dose.

Additional Data: In addition to the studies described above, the Motherisk Program conducted a prospective, follow-up study from January 1988 to June 1991 to assess the short-term effects of various maternal medications on breast-fed infants. Based on calls received by the Motherisk

Program[6], 2018 women inquired about the safety of breast-feeding during treatment with various medications. Follow-up interviews were conducted and out of 838 breast-fed infants, six mothers reported nursing while taking prednisolone (dosage not specified) and no adverse effects in their infants were reported.

At this time, there are limited data regarding adverse effects in infants exposed to prednisolone or prednisone via breast milk, but the total infant dose appears to be small based on breast milk corticosteroid concentrations and the percent maternal dose in breast milk.

DISCUSSION AND CONCLUSIONS

Human and animal studies suggest that use of corticosteroids during the first trimester of pregnancy is associated with an increased risk of orofacial clefts, intrauterine growth restriction and decreased birth weight. Multiple cohort and case controlled studies in humans suggest a three to five-fold increased risk of cleft lip with or without cleft palate when corticosteroids are used during the first trimester of pregnancy. Two prospective case control studies also showed a decrease in birth weight. The risk for decreased fetal growth appears to be dose-related and may be minimized by administering lower corticosteroid dosages. It is likely that underlying maternal conditions contribute to intrauterine growth restriction and decreased birth weight, but it is unclear to what extent these maternal conditions contribute to the increased risk of orofacial clefts.

While the data described above is not ideal, case-control and cohort studies provide the best information for the population being studied. When treating most conditions that require corticosteroid therapy, randomized, placebo-controlled, double-blinded studies would not be ethical. In addition, the majority of studies summarized in this review detect an increased risk of orofacial clefts in humans that is consistent with the positive findings in animal reproductive toxicology studies. Therefore, the risk of infant exposure to prednisolone during pregnancy should be described in labeling and a category change should be made. The risk of infant exposure to prednisolone should be weighed against the benefits of maternal treatment for both the mother and fetus. If prednisolone must be prescribed, the mother should be informed of this risk so that she can actively participate in decision-making involving the use of corticosteroids during her pregnancy. In addition, infants born to mothers who have received corticosteroids during pregnancy should be carefully observed for signs of hypoadrenalism.

Additional information on the fetal effects of corticosteroid use will hopefully become available through additional studies. Currently, the Organization of Teratology Information Specialists (OTIS) is conducting a prospective, observational pregnancy registry entitled, The OTIS

[6] The Motherisk Program at The Hospital for Sick Children in Toronto, Canada is a clinical, research and teaching program dedicated to antenatal drug, chemical, and disease risk counseling. It is affiliated with the University of Toronto. Created in 1985, Motherisk provides evidence-based information and guidance about the safety or risk to the developing fetus or infant, of maternal exposure to drugs, chemicals, diseases, radiation and environmental agents.

Autoimmune Diseases in Pregnancy Project.[7] The goal of this study is to gather information regarding autoimmune diseases, their treatment during pregnancy and the potential effects of the treatment on the developing embryo or fetus. As additional information becomes available, it should be incorporated into corticosteroid product labeling to optimally inform healthcare practitioners and their patients who are pregnant or planning a pregnancy.

Prednisolone crosses into breast milk and breast milk concentrations range from 5 to 25% of maternal serum levels.[8] In a study using radio-labeled prednisone, 0.14% of a 5 mg maternal dose was recovered from breast milk over 48 hours. In a study of one nursing woman using 120mg/day prednisone, peak milk concentrations of drug occurred two hours after maternal dosing, and the calculated total infant daily dose of drug from breast milk was 47 µg. While the published data on infant corticosteroid exposure via breast milk are limited, the expert clinical community considers maternal doses of prednisolone of 20 mg/day safe for use during breastfeeding.[9] Reprotox comments that *even at 80 mg/day the amount of prednisolone secreted in breast milk would be equivalent to less than 10% of a nursing infant's endogenous cortisol production and it is unlikely that such a dose would produce clinically significant effects.*[3] There have been no adverse events reported in infants from exposure to prednisolone via breast milk in the literature. While there are no data to support this assumption, high doses of steroids (> 40 mg/day), particularly for long periods, could potentially produce problems in infant growth and development.[9]

If doses larger than 20 mg/day are needed, some experts recommend breastfeeding mothers wait at least four hours before nursing their baby when the peak concentration in milk has diminished.[8,9] However, there are no data demonstrating that this is necessary. Exclusively breastfed infants usually nurse more often than every four hours during parts of the day. Supplementing with formula may decrease a woman's milk supply. Breastfeeding women using corticosteroids should be encouraged to take their dose immediately after breastfeeding at the time of day when the baby usually has the longest interval between feeds. For women using larger doses of corticosteroid, it may be reasonable to suggest pumping during the four hour interval after dosing and discarding that milk, but there are no good data to support this suggestion.

The risk of infant exposure to prednisolone in breast milk should be weighed against the known benefits of breastfeeding for both the mother and baby. If prednisolone must be used in a breastfeeding mother, the lowest dose should be prescribed to achieve the desired clinical effect.

---

[7] The Organization of Teratology Information Specialists (OTIS) Autoimmune Diseases in Pregnancy Project. http://otispregnancy.org/otis_study_autoimmune.asp

[8] Ost L, Wettrell G, Bjorkhem I, Rane A. Prednisolone excretion in human milk. Journal of Pediatrics. 1985; 106 (6): 1008-1011.

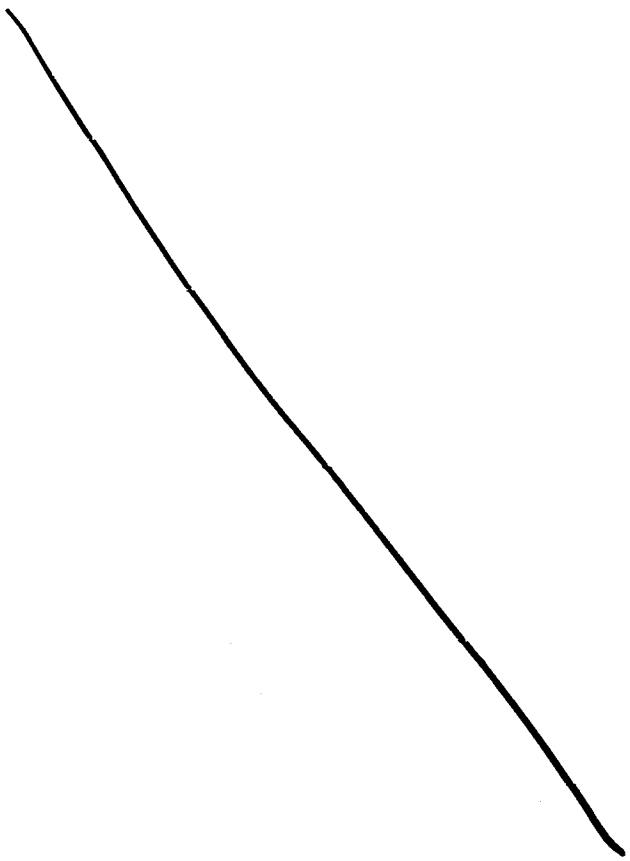
[9] Hale TW. Medications and Mother's Milk 2006. 12th Edition. Hale Publishing, LP. Amarillo, TX.

RECOMMENDATIONS

1. The Office of Surveillance and Epidemiology should be consulted and asked to conduct an AERS database search for reports of teratogenic effects in infants exposed to prednisone or prednisolone during pregnancy. This information may be useful in providing further guidance to prescribing practitioners caring for pregnant women.

2. The Office of Surveillance and Epidemiology should be consulted and asked to conduct an AERS database search for reports of adverse events in infants associated with exposure to prednisone or prednisolone via breast milk. This information may be useful in providing further guidance to prescribing practitioners caring for breastfeeding women.

3. The MHT recommends a pregnancy category D for Flo-Pred (prednisolone) Oral Solution. This recommendation is based on both available human data suggesting an increased risk of orofacial clefts and the benefits of treatment for pregnant women (and their fetuses) with underlying conditions requiring corticosteroid treatment. In addition, recommended revisions to the sponsors proposed labeling are provided below. These labeling recommendations should be considered for all oral corticosteroid labeling.



b(4)

b(4)

24 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Administrative- 8

Appendix C

Richardae Araojo, Pharm.D.
Regulatory Reviewer, Maternal Health Team

Karen Feibus, MD
Team Leader, Maternal Health Team

Lisa Mathis, MD
Associate Director, Pediatric and Maternal Health Staff

Sandra Kweder, MD
Deputy Director, Office of New Drugs

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Chardae Araojo
6/12/2007 10:09:59 AM
CSO

Karen Feibus
6/12/2007 10:25:35 AM
MEDICAL OFFICER

Lisa Mathis
6/21/2007 12:19:58 PM
MEDICAL OFFICER

Sandra L. Kweder
6/27/2007 01:46:08 PM
MEDICAL OFFICER
Agree with recommendations. Expect that an AERS search for birth defects following in utero exposure to prednisolone and related products will be very difficult to interpret due to underlying maternal conditions.

MEMORANDUM

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

DATE: April 25, 2007

TO: Bob Rappaport, MD
Director
Division of Anesthesia, Analgesia, and
Rheumatology Products (HFD-170)

FROM: Nilufer M. Tampal, Ph.D.
Division of Scientific Investigations (HFD-48)

THROUGH: C.T. Viswanathan, Ph.D.
Associate Director - Bioequivalence
Division of Scientific Investigations (HFD-48)

SUBJECT: Review of EIR Covering NDA 22-067, Prednisolone Oral Suspension 15mg/5mL, Syrup 15mg/5mL, and Tablets 3x5mg, Sponsored by Taro Pharmaceuticals U.S.A., Inc.

At the request of HFD-170, the Division of Scientific Investigations conducted an audit of the clinical and analytical portions of the following bioequivalence study:

Study PEN-P5-319: "Single Dose Crossover Comparative Bioavailability Study of Prednisolone 15mg/5mL Suspension versus 15mg/5mL Syrup and versus 3x5mg Tablets in Healthy Male and Female Volunteers/ Fasting State".

The clinical and analytical portions of the study were conducted at two separate sites of [redacted] b(4)
[redacted] No Form FDA 483 was issued following the inspection of the clinical portion of the study (4/10-11/07). Following the inspection of the analytical portion (4/9-12/07) Form FDA 483 was issued (attachment 1). Our evaluation of the significant findings is as follows:

1. Failure to demonstrate a lack of matrix effect in the Method validation in that the matrix effect experiment evaluated only one lot of blank matrix at each quality control (QC) level.

Specifically, the low QC was prepared in lot A, mid QC in lot B, and high QC in lot C. Because each QC was prepared in single and not multiple lots of blank plasma, the experimental design was inadequate to evaluate lot to lot variability at each QC concentration.

For future, the firm needs to revise the experimental design and evaluate the matrix effect using multiple lots of plasma at each QC concentration.

2. **Accuracy of the validation report was not assured. Specifically, the dilution integrity data included in the validation report originated from an earlier project that used a linear regression while the validated method for Study PEN-P5-319 used a quadratic equation to fit the calibration curve.**

While it is objectionable that the firm did not ensure the integrity of all data included in the validation report, recalculation of the dilution integrity data using the quadratic equation found that it met the acceptance criteria.

3. **Lack of documentation for the dilution of quality control samples used to assure the accuracy of Prednisolone concentrations from subject samples that were assayed following dilution in Run 28.**

The firm lacked documentation to confirm the dilution of QCs and for retrieval of blank plasma from the freezer to dilute the QCs and subject samples.

While the firm needs to improve the documentation procedures, this observation is unlikely to impact the study outcome.

Conclusion:

Following our evaluation of the inspectional findings, DSI concludes that the above findings do not significantly impact the study outcome.

After you have reviewed this transmittal memo, please append it to the original NDA submission.

Nilufer M. Tampal, Ph.D.

Final Classification:

b(4)

cc:
HFD-45/RF
HFD-48/Tampal (2)/Himaya/CF
HFD-170/Jani (NDA 22-067)
HFR-SW1580/Stone
Draft: NMT 4/24/07
Edit: JAO 4/25/07
DSI 5737 O:\BE\eircover\22067tar.pred.doc
FACTS 788747

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Amalia Himaya
4/26/2007 04:02:17 PM
CSO

Dr. Viswanathan signed paper copy on 4/26/07 and available upon request.