

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-165

OTHER REVIEW(S)

EXECUTIVE SUMMARY

On October 27, 2008, the Division of Neurology Products (DNP) issued a complete response action for NDA 22-165, a 505(b)(2) application for diclofenac potassium indicated for acute treatment of migraine attacks with or without aura in adults. On December 12, 2008, Kowa Pharmaceuticals America, Inc. submitted a response to the action letter. DNP requested the Maternal Health Team's (MHT) review of the Pregnancy and Nursing Mothers subsections of the resubmitted label.

Diclofenac is a nonsteroidal anti-inflammatory drug (NSAID) that exhibits analgesic and antipyretic properties. In the third trimester, NSAIDs can cause closure or constriction of fetal ductus arteriosus with resultant pulmonary hypertension. Therefore, starting at 30 weeks gestation, NSAIDs should be avoided by pregnant women.

In December 2007, the Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP) consulted the MHT to revise the Pregnancy and Nursing Mothers subsections of NSAID class labeling (see Appendix A for MHT review dated February 2008). Therefore, this review provides labeling recommendations on the sponsors proposed diclofenac potassium label based on NSAID class labeling and available data on diclofenac use during pregnancy and lactation.

Based on a PubMed search of the literature, no new relevant information was identified for inclusion in the Pregnancy subsection of labeling. However, limited human data on the use of diclofenac during lactation was found and suggests that diclofenac may be present in milk at minimal levels (data summarized on pages 3-4 of this review).

Recommendations:

1. The diclofenac Pregnancy and Nursing Mothers subsections of labeling should be updated to include published human data. The MHT's recommended revisions to the sponsors proposed labeling are provided on pages 6-7 of this review.

INTRODUCTION

On October 27, 2008, the Division of Neurology Products (DNP) issued a complete response action for NDA 22-165, a 505(b)(2) application for diclofenac potassium indicated for acute treatment of migraine attacks with or without aura in adults. On December 12, 2008, Kowa Pharmaceuticals America, Inc. submitted a response to the action letter. DNP requested the Maternal Health Team's (MHT) review of the Pregnancy and Nursing Mothers subsections of the resubmitted label.

BACKGROUND

Diclofenac is a nonsteroidal anti-inflammatory drug (NSAID) that exhibits analgesic and antipyretic properties. NSAIDs act primarily through the inhibition of prostaglandin synthesis by altering activity of cyclooxygenase (COX) enzymes. Cyclooxygenase inhibitors can reduce or inhibit arachidonic acid release and block synthesis of prostaglandins and thromboxane, which are involved in maintaining fetal ductus arteriosus patency and regulation of the pulmonary

vasculature¹. In the third trimester, prostaglandin synthetase inhibitors can cause closure or constriction of the fetal ductus arteriosus with resultant pulmonary hypertension. Therefore, starting at 30 weeks gestation, NSAIDs should be avoided by pregnant women.

In December 2007, the Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP) consulted the MHT to revise the Pregnancy and Nursing Mothers subsections of NSAID class labeling (see Appendix A for MHT review dated February 2008). Therefore, this review provides labeling recommendations on the sponsors proposed diclofenac potassium label based on NSAID class labeling and available data on diclofenac use during pregnancy and lactation.

REVIEW OF DATA

This review provides a summary of published data on diclofenac use during pregnancy and lactation. Relevant pregnancy and lactation data from these studies will be recommended for inclusion in the diclofenac Pregnancy and Nursing Mothers subsections of labeling.

Pubmed search terms were:

- Diclofenac and pregnancy
- Diclofenac and fetus
- Diclofenac and neonate
- Diclofenac and lactation
- Diclofenac and breastfeeding

- 1. Review of published data regarding diclofenac exposure during pregnancy:** No new relevant data identified during search.
- 2. Review of published data regarding diclofenac exposure during lactation:** There are limited human data on the use of diclofenac during lactation. Three review articles published in the late 1970s and 1980s describe data on the use of diclofenac in lactating women as summarized below:

Sioufi, et.al and Fowler describe a study of six lactating women (who were not breastfeeding their infants) that received a single 50 mg intramuscular injection of diclofenac sodium shortly after delivery.^{2,3} Milk samples were obtained over a six-hour period and no diclofenac sodium was detected in milk (detection limit 100 ng/mL).²

Reviewer comment:

During the first three days postpartum mothers produce small volumes of colostrum rather than mature milk. Drug levels in colostrum are different than in

¹ Philips JB, Lyrene RK: Prostaglandins, related compounds and perinatal pulmonary circulation changes. Perinatology 1984;11: 565-579.

² Sioufi A, Stierlin H, Schweizer A, et al. Recent findings concerning clinically relevant pharmacokinetics of diclofenac sodium. In Kass (Ed.) Voltaren - new findings, pp. 19-30, Hans Huber Publishers, Bern, 1982.

³ Fowler PD. Voltarol: diclofenac sodium. Clin Rheum Dis. 1979;5:427-64.

mature milk but tend to be higher as tight junctions have not formed between the lactotrophs. Despite limitations in generalizing this data to all lactating mother/infant pairs, these results are reassuring and informative for prescribers and breastfeeding mothers in the immediate postpartum period.

In another study of six mothers who received diclofenac 100 mg daily for one week, diclofenac was not detectable in any of the 59 milk samples obtained (detection limit 10 ng/mL).^{2,4} However, a woman treated with diclofenac 150 mg daily had a milk diclofenac level of 100 µ/L, equivalent to an infant dose of about 0.03 mg/kg/d.⁴

In addition to the information summarized above, a study published by Stolker, et.al was reviewed because the sponsor included results from this study in the Nursing Mothers subsection of the proposed diclofenac label. This study describes the validation of ultra-performance liquid chromatography combined with time-of-flight mass spectrometry (UPLC–ToF-MS) as a method to screen and quantify 101 veterinary drugs, including NSAIDs, in raw (not pasteurized) milk. The study found that among other classes of drugs including NSAIDs, diclofenac was not detected at the recommended concentration of 5 µ/L in raw milk.⁵

Reviewer comments:

- *The authors did not specify the animal that produced the milk samples. The authors only state that milk samples were collected from farmhouses by the Dutch Food and Consumer Product Safety Authority in the Netherlands.*
- *The study conducted by Stolker, et.al does not provide information that can be used to determine the presence and amount of diclofenac in human milk. The physiologic processes by which drugs are excreted into human milk are not comparable to raw milk using a UPLC–ToF-MS method. Therefore, this study should not be included in the proposed label for diclofenac.*

LABELING

Sponsors Proposed Labeling

(b) (4)

A large rectangular area of the document is redacted with a solid grey fill. The redaction covers the majority of the text in the 'Sponsors Proposed Labeling' section.

⁴ Todd PA, Sorkin EM. Diclofenac sodium. A reappraisal of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy. *Drugs*. 1988;35:244-85.

⁵ Stolker AAM, Rutgers P, Oosterink E. Comprehensive screening and quantification of veterinary drugs in milk using UPLC–ToF-MS. *Anal Bioanal Chem* (2008) 391:2309–2322.

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DISCUSSION AND CONCLUSIONS

Pregnant and breastfeeding women are commonly exposed to NSAIDs. As described in NSAID class labeling, starting at 30 weeks gestation, diclofenac, and other NSAIDs, should be avoided by pregnant women as premature closure of the ductus arteriosus in the fetus may occur. Based on the published data summarized in this review, no new relevant information was identified for inclusion in the Pregnancy subsection of labeling. However, limited human data on the use of diclofenac during lactation was found and suggests that diclofenac may be present in milk at minimal levels.

The MHT recommendations for the Pregnancy and Nursing Mothers subsections of labeling are provided below.

Recommendations:

1. The MHT recommends the following revisions to the diclofenac Pregnancy and Nursing Mothers subsections of labeling based on review of published reports provided on pages 3-4 of this review.

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TRACK CHANGES VERSION OF LABEL – provided below

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M E M O R A N D U M

Date: 2-22-2008

Date Consulted: 12-05-2007

From: Leyla Sahin, M.D.
Medical Officer, Maternal Health Team

Through: Karen B. Feibus, M.D.
Medical Team Leader, Maternal Health Team

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

To: Division of Anesthesia, Analgesia, and Rheumatology Products

Drug: Nonsteroidal anti-inflammatory drug (NSAID) class

Subject: NSAID class data review for Pregnancy and Nursing Mothers subsections of labeling

Materials Reviewed: Pubmed, Reprotox, Lactmed, Shepard's catalog of teratogenic agents, ACOG website

(Search terms used: NSAID, aspirin, ibuprofen, naproxen, indomethacin, ketorolac, miscarriage, pregnancy, preterm labor)

Consult Question: The Maternal Health team was asked to review and update the Pregnancy and Nursing Mothers subsections of the NSAID class label. We were asked if late pregnancy should be listed as a contraindication, and whether the reports of NSAID associated miscarriages should be added to the label.

EXECUTIVE SUMMARY

Our review of the literature shows that the NSAID class label regarding teratogenic risk and adverse pregnancy outcome is consistent with published data. Based on the known third

trimester risk of closure of the fetal ductus arteriosus with NSAID use, the Maternal Health Team recommends that the pregnancy category for the NSAID class be maintained Category C for gestational ages less than 30 weeks and changed to category D starting at 30 weeks gestation. Use of two pregnancy categories when human adverse effects are known to occur only during a particular period of gestation has been interpreted to comply with CFR 201.57, and this approach was used for labeling ACE inhibitors. The regulations require that the warnings section contain a pregnancy subsection that describes the human fetal effects and includes the standard regulatory language required for category D drugs. We do not recommend replacing the warning section by a contraindication, as there may be certain obstetrical indications such as preterm labor, degenerating fibroids in pregnancy, etc. where a physician feels that there are contraindications to using other drugs, or other treatments may have failed, and the potential benefit of using NSAIDS outweighs the potential risk. Suggested organization and language are included in Appendix B.

The published studies evaluating a possible association between NSAID use and an increased risk of miscarriage are conflicting and results are confounded by various sources of bias and limited information. Therefore, we do not recommend adding information about miscarriage risk to the class labeling at this time.

Data is available on drug levels in breast milk for various NSAIDs. Therefore, this section should be updated for each NSAID product based on available information.

INTRODUCTION

The NSAID class label was revised in June 2005. This review summarizes the Maternal Health Team's recommended changes to the pregnancy and lactation sections of the NSAID class labeling. Since 2003, there has been ongoing controversy regarding a possible association of NSAID use and increased risk of miscarriage. This review summarizes the findings from these studies and makes recommendations about whether this data should impact labeling at this time.

BACKGROUND

NSAIDS have analgesic, anti-inflammatory, and antipyretic properties. Pregnant and breastfeeding women are commonly exposed to these agents, either inadvertently or advertently¹⁵. NSAIDS act primarily through the inhibition of prostaglandin synthesis by altering the activity of cyclooxygenase (COX) enzymes. Aspirin is classified as a non-selective, irreversible inhibitor of cyclooxygenases. Cyclooxygenase inhibitors can reduce or inhibit arachidonic acid release and block the synthesis of prostaglandins and thromboxane, which are involved in maintaining fetal ductus arteriosus patency and regulation of the pulmonary vasculature¹⁰. In the third trimester, prostaglandin synthetase inhibitors cause closure or constriction of the fetal ductus arteriosus with resultant pulmonary hypertension^{1,4,7,11,14,16} in humans and in animals^{3,8,13}.

Historically, NSAIDS were category B drugs based on negative teratogenic data in animals, and a lack of adequate and well controlled studies in pregnant women. Subsequently, NSAIDS were assigned to the C category due to the known effect of the third trimester risk of closure of the

fetal ductus arteriosus. The current pregnancy and nursing mothers sections of the NSAID class label is in Appendix A.

REVIEW OF DATA

A Pubmed search was performed to identify available information about NSAID use during pregnancy and the risk of miscarriage. The studies identified through this search are summarized below.

1. Nielsen GL, Sorensen HT, Larsen H, Pedersen L: Risk of adverse birth outcome and miscarriage in pregnant users of non-steroidal anti-inflammatory drugs; population based observational study and case-control study. BMJ 2001; 322:266-70.

In 2001, Nielsen et al published a population-based observational (cohort) study and case-control study. The objective of these two studies was to estimate the risk of adverse birth outcome in women who take non-steroidal anti-inflammatory drugs during pregnancy. The authors linked data from a number of national Danish registries including: a prescription drug registry, the Danish birth registry, and one county's hospital discharge registry between 1991 and 1998. The population based cohort study examined the risk of adverse birth outcome (congenital abnormality, low birth weight, and preterm birth), and the case-control study investigated the risk of miscarriage.

In the case-control study, 4268 primigravid women who had miscarriages were compared to 29,750 primigravid controls who had live births. Cases were defined as first recorded miscarriages in women who had filled a prescription for a non-steroidal anti-inflammatory drug in the 12 weeks before the date of discharge from hospital after the miscarriage. The control group was primiparous women who had live births. The first trimester was the exposure period in the control group. The authors calculated risk estimates for time intervals of 1, 2-3, 4-6, 7-9, and 10-12 weeks before the day of discharge after miscarriage. All non-steroidal anti-inflammatory drug prescriptions were categorized according to these periods.

Results

Sixty three of the 4268 women who had miscarriages filled a prescription for an NSAID. The only confounding factor that was adjusted for was age. The authors used logistic regression analyses to estimate the risk of miscarriage associated with NSAIDs. Odds ratios for miscarriage ranged from 6.99 (2.75 to 17.74) when prescriptions were filled during the last week before the miscarriage to 2.69 (1.81 to 4.00) when filled between seven and nine weeks before.

In the cohort study, 1462 pregnant women who filled prescriptions for non-steroidal anti-inflammatory drugs in the period from 30 days before conception to birth were compared to 17,259 pregnant women who were not prescribed any drugs during pregnancy. Odds ratios for congenital abnormality, low birth weight, and preterm birth among women who filled prescriptions for non-steroidal anti-inflammatory drugs were 1.27 (95% confidence interval 0.93 to 1.75), 0.79 (0.45 to 1.38), and 1.05 (0.80 to 1.39) respectively, thus showing that NSAID use during pregnancy did not seem to increase the risk of adverse birth outcomes.

Reviewer's comment

- *Actual use of NSAIDS, dose, and duration of use could not be documented in this study since the study only identified filled prescriptions from a prescription registry. Confounding factors such as indication for usage, concomitant use of other medications in the miscarriage group, and smoking were not adjusted for^{2,6}. While miscarriages were documented by hospital discharge records, this does not account for women who miscarried but were not hospitalized for diagnosis or treatment.*
- *Usually cohort studies calculate a risk ratio, rather than an odds ratio, which is used in case control studies to estimate the relative risk. It is not clear whether the wrong statistical method was applied or whether the correct term was lost in translation.*

2. Nielsen GL, Skriver MV, Pedersen L, Sorensen HT: Danish group reanalyses miscarriage in NSAID users. BMJ 2004; 328(7431):109.

The authors of the previous article updated their data, using the same methodology, to include pregnant women from 1998-2002, including gestational age of the exposed fetus, which was previously not available. The 1599 women with a first recorded miscarriage were compared to primigravid women who delivered after 28 weeks gestation, with 10 controls for every case. Forty five women in the miscarriage group filled a prescription for an NSAID. Odds ratios for miscarriage ranged from 3.35 (0.88-12.79) when NSAID prescriptions were filled during the last week before the miscarriage to 1.59 (0.93-2.70) when filled between 7 and 9 weeks before.

Reviewer's comment

- *These results substantially reduce the strength of their previously reported association between use of NSAIDS and risk of miscarriage.*
- *This dataset included gestational age at NSAID exposure, which the first dataset did not. Gestational age at the time of drug exposure is a factor that could influence any association between NSAID use and the risk of miscarriage.*

3. Li D-K, Liu L, Odouli R: Exposure to non-steroidal anti-inflammatory drugs during pregnancy and risk of miscarriage: population based cohort study. BMJ 2003; 327:368-70.

Kaiser Permanente conducted a population based cohort study to determine whether there is an association between NSAID use and increased risk of miscarriage. The study used a dataset that evaluated prenatal exposure to magnetic fields from 1996 through 1998 (5). Researchers recruited and interviewed 1055 pregnant women in the San Francisco area after pregnancy was confirmed by a positive pregnancy test. Median gestational age at entry to the study was 40 days. At the interview, women were asked about medication use since their last menstrual period and the indication for usage. The study collected information on pregnancy outcomes up to 20 weeks gestation.

Results

Seven women who reported cramping as the reason for taking an NSAID, aspirin or acetaminophen were excluded. Using the Cox proportional hazard regression model, the authors examined the association between NSAID use and risk of miscarriage. After adjusting for maternal age, smoking, education, race, gravity, history of previous miscarriage, use of a hot tub, and multivitamin use, NSAID use was associated with an 80% increased risk of miscarriage [adjusted hazard ratio 1.8 (95% confidence interval 1.0 to 3.2)]. The risk of miscarriage was much higher when NSAIDs were taken around conception [adjusted hazard ratio 5.6 (95% CI 2.3 to 13.7)] or were used for longer than a week [adjusted hazard ratio 8.1 (95% CI 2.8 to 23.4)]. The association of prenatal aspirin risk was numerically similar to that observed for prenatal use of other NSAIDs; however, the association was not statistically significant and was based on a small number of aspirin users (5 in the miscarriage group, and 17 in the non-miscarriage group).

Reviewer's comment

- *The authors' data suggest that use of NSAIDs around the time of conception or use of NSAIDs for longer than one week during pregnancy are associated with an increased risk of miscarriage. An association between NSAID use overall and miscarriage approached but did not reach statistical significance.*
- *The study design and resulting data were limited by a number of factors:*
 - *The study included only a small number of pregnancies identified in which NSAIDs or aspirin were used (n=18 around conception, n=54 after conception)¹².*
 - *The study is limited by potential recall bias, as 61% of cases had already miscarried at the time of the interview (Li personal communication, see Appendix C).*
 - *The association of NSAID use with miscarriage was not the main aim of the study.*
 - *Women were interviewed only once, early in the pregnancy, thus their usage at the time of interview may not have reflected their usage during the remainder of the pregnancy.*
 - *There are confounders in this study with regards to dosing, and indication for use. They did not exclude women who took NSAIDs for fever, auto-immune and connective tissue disorders, which are associated with increased risk of miscarriage.*
 - *There is a lack of accuracy in gestational dating, especially in terms of defining when conception occurred.*

4. Keim SA, Klebanoff MA: Aspirin use and miscarriage risk. *Epidemiology* 2006; 17(4):435-439.

The NIH conducted a case control study to assess the association of aspirin use and miscarriage, using data from the Collaborative Perinatal Project, a prospective cohort study that recruited approximately 54,000 pregnant women at 12 sites in the United States from 1959 to 1965⁹.

Participants were interviewed at each prenatal visit. Data on aspirin use were collected prospectively by in-person interviews and medical record review. At each clinic visit, women were asked about illness and use of medications since the last visit. The same information was also obtained about the month prior to the last menstrual period. Miscarriage was defined as pregnancy loss at less than 140 days from the last menstrual period. Women who miscarried (n = 542) were matched by clinic location and gestational age at enrollment to 2587 women who had live births.

Results

The authors excluded 145 of the initial 784 cases of miscarriage because they had already miscarried at the time of the first interview. Another 97 cases were excluded because of missing information on aspirin use. Aspirin use during the lunar month of pregnancy when miscarriage occurred was not included in the analysis in order to avoid bias due to women possibly having taken it in response to symptoms of miscarriage. Time intervals of interest included the lunar month before the LMP and the first through fourth lunar months of pregnancy. They assessed association with miscarriage by lunar month of pregnancy and groups of lunar months.

The authors derived stratum-adjusted odds ratios from a conditional logistic regression model containing only a term for aspirin use as well as adjusted odds ratios from a conditional logistic regression model containing terms for maternal age, smoking, education, and race. They adjusted for these factors based on previous literature.

Twenty-nine percent of cases (159 cases) and 34% of controls (876 controls) used aspirin during pregnancy. Aspirin use was not associated with an increased risk of miscarriage. Adjusted odds ratios ranged from 0.64 to 0.92 (95% confidence intervals = 0.48–1.38) for individual lunar months of pregnancy and for combinations of lunar months.

Reviewer's comment

- *The NIH study is more powerful because of the large sample size; however, data is limited to evaluating aspirin use.*
- *The exclusion of women who used aspirin in the month that preceded the miscarriage, may have unintentionally eliminated a significant number of women who did not use the aspirin to treat cramps associated with miscarriage.*
- *Study participants reported aspirin use to healthcare practitioners at each prenatal visit. Generally, women during early pregnancy are seen no less often than every four weeks.*

DISCUSSION

Due to methodological flaws, confounding factors, small patient populations, and conflicting findings, it is difficult to interpret the existing data, and draw conclusions regarding the association between NSAID exposure during pregnancy and miscarriage risk. The study by Li (2003) contains the most compelling data but 61% of women were interviewed after they miscarried. This potential for recall bias and the small exposed population combined with other confounding factors calls the reliability of the author's findings into question. Until more robust data become available from large, well designed prospective observational studies, information about any potential association between first trimester NSAID use and increased risk of miscarriage should not be incorporated into NSAID class labeling.

CONCLUSIONS

Based on a review of the literature, the NSAID class label regarding teratogenic risk and adverse pregnancy outcome is consistent with published data. Both animal data and human data show an association between third trimester NSAID use and closure of the fetal ductus arteriosus, resulting in pulmonary hypertension. Therefore, the category should be maintained as Category C for gestational ages less than 30 weeks and changed to D starting at 30 weeks gestation. We prefer to describe these gestational ages in terms of weeks rather than trimesters based on current accuracy of pregnancy dating. Use of two pregnancy categories when human adverse effects are known to occur only during a particular period of gestation is thought to comply with CFR 201.57, and this approach was used previously for labeling ACE inhibitors. The studies on NSAID associated risk of miscarriage are limited and conflicting and not compelling enough to include in labeling at this time.

The section on Nursing Mothers should be updated on an individual basis, based on current available data.

RECOMMENDATIONS

The MHT recommends the following revisions to NSAID class labeling: See Appendix B for the recommended revised label.

1. Maintain pregnancy category C for gestational ages less than 30 weeks.
2. Pregnancy category D after 30 weeks gestation based on human data demonstrating impaired fetal physiology (functional toxicity) with narrowing or closure of the ductus arteriosus with maternal NSAID use after 30 weeks gestation.
3. 21 CFR 201.57 describes required standard regulatory language for category D drugs and requires that human fetal effects be summarized in the Warnings section of the label.
4. We do not recommend replacing the warning section by a contraindication, as there may be certain obstetrical indications such as preterm labor, degenerating fibroids in pregnancy, etc. where a physician feels that there are contraindications to using other drugs, or other treatments may have failed, and the potential benefit of using NSAIDS outweighs the potential risk.

5. Based on a current initiative by the Maternal Health Team to improve the organization and clinical utility of the pregnancy section of labeling, the recommended pregnancy section language includes a risk summary paragraph followed by human data and then by animal data. Specific language is provided in Appendix B.
6. There are published lactation data available for some NSAIDs. In the nursing mothers section of labeling, available data on drug levels in breast milk and any adverse infant effects should be included for each individual drug. Based on available data on the drug, appropriate regulatory language should also be included.
7. Language in the Medication Guide and Information for Patients should be modified to reflect the changes described above.

REFERENCES

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11. Rudolph AM: The effects of nonsteroidal antiinflammatory compounds on fetal circulation and pulmonary function. *Obstet Gynecol* 58 [Suppl]:63s-7s, 1981.
12. Schiavetti B, Clavenna A, Campi R, Bonati M: NSAIDs during pregnancy and risk of miscarriage: true risks or only suspicions? *BMJ* 2004; 328:108.
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APPENDIX A- Current pregnancy section of NSAID label

2 pages withheld after this page as B4 (draft labeling)



APPENDIX C-email communication with the author, 2-28-2008

We had about 61% women with miscarriage were interviewed after their miscarriage largely because we recruited them at very early gestational age when miscarriage happens quickly.

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**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
4/8/2009 10:18:00 AM
CSO

Karen Feibus
4/8/2009 11:16:20 AM
MEDICAL OFFICER
I agree with the content and recommendations contained in
this review.

Lisa Mathis
4/10/2009 02:59:55 PM
MEDICAL OFFICER

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: October 22, 2008

TO: James Reese, Regulatory Health Project Manager
Eric Farkas, M. D., Medical Officer
Division of Neurology Drug Products

THROUGH: Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations

FROM: Antoine El-Hage, Ph.D.
Regulatory Pharmacologist
Good Clinical Practice Branch I
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 22-165

APPLICANT: ProEthic Pharmaceuticals, Inc.

DRUG: Diclofenac Potassium powder for oral solution

NME: No

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATION: Treatment of acute migraine attacks with or without aura in adults

CONSULTATION REQUEST DATE: September 26, 2008

DIVISION ACTION GOAL DATE: October 27, 2008

PDUFA DATE: October 27, 2008

I. BACKGROUND:

Pro-513 (50 diclofenac-K powder for oral solution) is a new formulation of diclofenac containing the potassium salt in a readily soluble, flavored formulation. The powder for oral solution was developed to provide an oral treatment with a rapid onset of action. ProEthic Pharmaceuticals, Inc. has submitted a new drug application for marketing approval of 50 mg diclofenac potassium powder for oral solution compared to placebo in adult subjects with migraine attacks.

The review division requested inspection of protocol PRO-513301: “A multi-center, prospective, randomized, double-blind, parallel group, single dose, placebo controlled study of the efficacy and safety of Pro-513 (50mg Diclofenac Potassium Powder for oral solution) compared to placebo in adult subjects with migraine attacks. The sponsor submitted results from protocol PRO-513301 in support of NDA 22-165.

The primary objective of study protocol PRO- 513301 was to demonstrate the efficacy and safety of a PRO-513 (50mg) diclofenac-K powder for oral solution) as compared to placebo when used to treat a migraine attack with or without aura in adults. The inspection targeted two domestic clinical investigators who enrolled a relatively large number of subjects.

II. RESULTS (by protocol/site):

Name of CI, site #and location	Protocol and # of subjects	Inspection Dates	Final Classification
Joel Saper, M.D Michigan Head Pain Neurological Institute 3120 Professional Drive Department of Pediatrics Ann Arbor, MI 48104 Site #11	Protocol PRO-513301 73 subjects	10/14-20/08	Pending (Preliminary classification NAI)
Jerry Tomasovic, M.D. Road Runner Research Ltd 525 Oak Centre Drive, Suite 400 San Antonio, TX 78258 Site #19	Protocol PRO-513301 54 subjects	10/14-17/08	Pending (Preliminary classification NAI)

Key to Classifications

NAI = No deviations

VAI = Deviation(s) from regulations

OAI = Significant deviations for regulations. Data unreliable.

Pending = Preliminary classification based on e-mail communication from the field; EIR has not been received from the field and complete review of EIR is pending.

Protocol PRO-513301

1. Joel Saper, M.D.
Ann Arbor, MI 48104

Observations noted below are based on an e-mail summary statement from the field investigator; the EIR for this inspection is currently pending. An inspection summary addendum will be generated if conclusions change significantly upon receipt and review of the EIR.

At this site, a total of 70 subjects were screened; 70 subjects were randomized and 66 subjects completed the study. Four subjects were reported as screen failures for not having migraine within the time frame required by the protocol. Informed consent for all subjects was verified. The medical records for 66 subjects' files were reviewed for adverse events. There were no subjects enrolled prior to IRB approval of the protocol and informed consent.

The medical records/source data for 45 subjects were reviewed in depth, and the source data were compared to case report forms and data listings for primary (35 subjects) and secondary (10 subjects) efficacy endpoints. In general the records reviewed were accurate in terms of data entries and reporting of adverse events. There were no limitations to this inspection.

The data appear acceptable in support of the pending application.

2. Jerry Tomasovic, M.D.
San Antonio, TX 78258

Observations noted below are based on an e-mail summary statement from the FDA field investigator; the EIR for this inspection is currently pending. An inspection summary addendum will be generated if conclusions change significantly upon receipt and review of the EIR

At this site a total of 54 subjects were screened and enrolled. 3 subjects were discontinued and 51 subjects completed the study. Informed consent for all subjects was verified.

The medical records/source data for 36 subjects were reviewed in depth including drug accountability records, and source documents were compared to data listings for primary efficacy endpoints and adverse events. In general, the records reviewed were accurate in terms of data entries and reporting of adverse events.

Our investigation found no significant problem that would impact the results. There were no known limitations to this inspection.

The data appear acceptable in support of the pending application.

OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

The inspection of Drs. Saper and Tomasovic revealed no significant problems that would adversely impact data acceptability. Observations noted are based on e-mail summary statements from the field investigators; the EIRs for these inspections are currently pending. An inspection summary addendum will be generated if conclusions change significantly upon receipt and review of the EIRs. The data submitted from the inspected sites are acceptable in support of the pending application.

{See appended electronic signature page}

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/s/

Constance Lewin
10/23/2008 09:42:54 AM
MEDICAL OFFICER
Entered into DFS on behalf of Dr. Antoine El-Hage.