

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-165

PHARMACOLOGY REVIEW(S)

MEMORANDUM

**DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration**

**Division of Neurology Products (HFD-120)
Center for Drug Evaluation and Research**

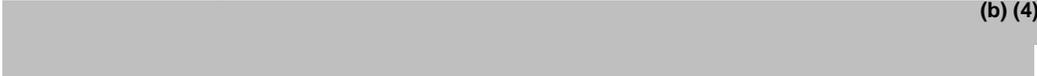
Date: June 16, 2009

From: Lois M. Freed, Ph.D.
Supervisory Pharmacologist

Subject: NDA 22-165 (diclofenac potassium), Amendment 0008/AZ dated December 12, 2008 (received December 16, 2008).

NDA 22-165 is a 505(b)(2) application for diclofenac potassium (50 mg powder sachet) for acute treatment of migraine with or without aura in adults (≥ 18 years of age). The sponsor (Kowa Pharmaceuticals America [formerly, ProEthic Pharmaceuticals]) is relying on the Agency's findings of safety and effectiveness for previously approved diclofenac products (Cataflam® [NDA 20-142, diclofenac potassium] and Voltaren® [NDA 19-201, 20-254], diclofenac sodium) to support marketing approval. The sponsor conducted no nonclinical studies of diclofenac.

The nonclinical information provided by the sponsor was reviewed by D. Charles Thompson, Ph.D. (Pharmacology/Toxicology Review and Evaluation, NDA 22-165, 25 October 2008; see also Memo to File, NDA 22-165, Lois M. Freed, Ph.D., October 27, 2008). Based on this review and on the Agency's clinical opinion that the sponsor's intended use would not raise new safety concerns, Dr. Thompson has concluded that "...there are no obvious impediments to approval from a nonclinical perspective, with one exception." The exception is the lack of "...evidence that [the sponsor has] adequately surveyed the published scientific literature to identify reports of data potentially relevant to the nonclinical safety evaluation of diclofenac." The deficiencies noted by Dr. Thompson are as follows:

- The sponsor's search of published literature was too limited (2004-2007), and appeared incomplete; at least one relevant study published in 2007 was not included in the sponsor's reference list.
-  (b) (4)

These and clinical deficiencies were conveyed to the sponsor in the Agency's Complete Response (CR) letter dated 10/27/2008. Submission 008/AZ is the sponsor response to the Agency's CR letter.

Dr. Thompson has reviewed the literature submitted by the sponsor and has concluded that none of the published studies "...either individually or collectively....constitute data and information of sufficient quality and quantity....as to warrant modification of the pre-existing and approved labeling for the RLD (Cataflam)..."

Of the >100 published studies submitted, Dr. Thompson identified only 12 that, in his opinion, were sufficiently relevant to warrant consideration for inclusion in labeling. The following discussion will primarily focus on the published studies listed below, which include 10 of the 12 identified by Dr. Thompson as well as a few additional published articles not identified by the sponsor. (Two of the 12 studies [Espey LL. *Prostaglandins* 26(1):71-78, 1983; Espey LL et al. *Prostaglandins* 36(6):875-879, 1988] were not examined further since they only evaluated effects of diclofenac and other NSAIDs on stimulated ovulation and/or ovarian hormones in rat or rabbit.)

The selected published studies can be grouped into three general areas of investigation:

- (1) In vitro studies of diclofenac effects on cultured whole embryos (Chan LY et al. *Hum Reprod* 16(11):2390-2393, 2001; Chan LY et al. *Repro Toxicol* 16:841-844, 2002) or neural stem cells (Kudo C et al. *Biochem Pharmacol* 66:289-295, 2003).
- (2) In vivo studies in pregnant animals:
 - Neurohistopathological evaluation of brain or peripheral nerve sections from pregnant animals treated with diclofenac (Canan S *Int J Dev Neuroscience* 26(7):733-738, 2008; Gokcimen A et al. *Brain Res* 1127:185-192, 2007; Korkmaz A et al. *Turk J Med Sci* 24:27-31, 1995; Korkmaz A et al. *Turk J Med Sci* 26:75-79, 1996; Ragbetli MC et al. *Brain Res* 1174:130-135, 2007).
 - Evaluation of effects of diclofenac on other systems when administered to pregnant animals (Cappon GD et al. *Birth Defects Res (Pt B)* 68:47-56, 2003; Davenport SJ et al. *Teratology* 65(6):331, 2002; Gokcimen A et al. *Fetal Diagnosis Therapy* 16:417-422, 2001); Montenegro M, Palomino H. *J Craniofac Genet Dev Biol* 10(1):83-94, 1990).
- (3) Studies in humans (Ericson AE, Kallen BAJ. *Repro Toxicol* 15:371-375, 2001; Kallen BAJ, Olausson PO. *Repro Toxicol* 17:255-261, 2003; Ofori B et al. *Birth Defects Res (Pt B)* 77:268-279, 2006; Ostensen M et al. *Arthritis Res Therapy* 8(3):209, 2006; Siu SSN et al. *Human Reproduction* 15(11):2423-2425, 2000).

In addition, information provided in a fairly recent review of published literature on developmental toxicity of NSAIDs in rats and rabbits (Cook JC et al. *Birth Defects Res (Pt B)* 68:5-26, 2003) was considered. However, for diclofenac the only data cited in this publication were from Montenegro and Palomino (1990).

Comments

Based on examination of the listed published studies, it does not appear that results from any of the studies warrant inclusion in labeling. Although a number of the nonclinical studies report adverse effects of diclofenac on various aspects of development, it is my opinion that none was conducted in a sufficiently rigorous manner to support a change in labeling. A brief discussion of study designs and results follow:

In vitro studies

Chan et al. (2001, 2002) assessed the teratogenic potential of diclofenac (Voltaren) using an in vitro whole rat embryo culture model. Chan et al. (2001) cultured GD 9.5 whole rat embryos with diclofenac for 48 hrs at concentrations of 1.5 to 15 µg/mL. There was no effect of diclofenac on general growth parameters; however, the authors reported a decrease in total morphological score (and in certain individual morphological features examined post hoc) at the two highest concentrations tested (7.5 and 15 µg/mL; highest no-effect concentration of 5 µg/mL). Chan et al. (2002) used the same paradigm to confirm the results of Chan et al. (2001) and to investigate the possible role of oxidative stress. In this study, GD 9.5 whole rat embryos were cultured with diclofenac for 48 hrs at concentrations of 1.5, 7.5, and 15 µg/mL. As in the first study, diclofenac had no effect on general growth parameters, but induced a decrease in total morphological score (and in hind limb, hindbrain, midbrain, and forebrain scores) at the two highest concentrations. In addition, diclofenac was associated with an increase in 8-isoprostaglandin F2α (a marker of oxidative stress) levels at 7.5 and 15 µg/mL.

Kudo et al. (2003) assessed the effects of various NSAIDs, including diclofenac (from Sigma), on proliferation and differentiation of mouse neural stem cells (NSC) into neurons. NSCs were incubated with diclofenac (10-60 µM) for 6 hrs. Diclofenac induced cell death at concentrations of 30 and 60 µM, and increased caspase-3 activity (a marker of apoptosis) at 10-60 µM. The authors suggest that diclofenac's effects may be mediated by COX-3 inhibition.

While these results are interesting, it does not appear that at the present time either of these in vitro models has been sufficiently validated to be useful for regulatory purposes.

In vivo animal studies

- The in vivo studies that assessed neurotoxic effects of diclofenac administered to pregnant animals were conducted by the same laboratory. All cited studies were conducted using the marketed product, Voltaren (diclofenac sodium), and all were conducted in albino rats (strain(s) used was not specified).

In the Korkmaz et al. (1995, 1996) studies, diclofenac was administered at a dose of 1 mg/kg/day i.m. from GD 5 to 19; dams were allowed to deliver and offspring were maintained for 28 days postpartum. In the 1995 study, gestation length was not specified; in the 1996 study, it was noted that there was no effect of diclofenac on gestation length.

Korkmaz et al. (1995) demonstrated a small (8-10%), but statistically significant decrease in the density of cerebellar Purkinje cells in pups of diclofenac-treated dams. However, the study was conducted in only 4 diclofenac-treated dams (and 4 saline-treated dams). Thirty-eight pups (equal number of males and females; total of 20 drug-treated and 18 controls) were examined. Korkmaz et al. (1996) reported a significant decrease in the neuronal density in three subnuclei (dorsal accessory olive, medial accessory olive, principal olive) of the inferior olive nucleus in pups of diclofenac-treated dams. However, the study was conducted in only 6 diclofenac-treated dams and the number of control animals was not specified; 20 pups per group were examined.

In the more recent studies (Canan et al. 2008; Gokcimen et al. 2007; Ragbetli et al. 2007), diclofenac was administered at a dose of 1 mg/kg/day i.p. from GD 5 to 15. Ragbetli et al. (2007) reported a decrease in the number of cerebellar Purkinje cells in pups of diclofenac-treated dams examined at either 4 or 20 weeks post-partum. In this study, there were 10 diclofenac-treated and 10 saline-treated animals. At delivery, 20 male offspring were selected; therefore, only 10/group were examined at each sampling time. [Interestingly, the Korkmaz et al. (1995) study was not cited by Ragbetli et al. (2007).]

Gokcimen et al. (2007) investigated the effects of diclofenac on the number of neurons in the cornu ammonis and dentate gyrus of the hippocampus in pups examined at 4 (10/group) or 20 (10/group) weeks post-partum. The authors reported a significant decrease in the number of pyramidal cells in pups of diclofenac-treated dams ($n = 5$) at 20, but not 4, weeks post-partum relative to controls ($n = 5$ dams); however, this effect was due to an increase in the number of neurons between the two sampling times in controls. The author also reported a significant decrease in granule cells at 4 weeks, but a significant increase at 20 weeks post-partum; in control pups, the number of neurons decreased between 4 and 20 weeks. Overall, differences between diclofenac-treated and control groups were due to “age-related” changes in controls. These changes, which the authors attributed to saline administration, make the apparent diclofenac effects very difficult to interpret.

Canan et al. (2008) evaluated the effects of diclofenac, saline, or no treatment during pregnancy on sciatic nerve in offspring. The number of dams was not specified; postnatal evaluations were conducted at 4 weeks post-partum in 5, 6, and 5 pups from untreated, saline-treated, and diclofenac-treated dams, respectively. Adverse effects on sciatic nerve morphology were detected (e.g., number of axons, myelin thickness); however, the effects were similar in offspring of diclofenac- and saline-treated dams, as compared to untreated controls. As in the study by Gokcimen et al. (2007), saline alone had effects; in this study, they appear adverse.

Although these studies, except for Canan et al. (2008), report adverse effects of diclofenac on CNS/PNS development, none of these studies was adequate by design to support a change in labeling. For example, none of the studies was conducted using an adequate number of dams or offspring. In addition, in none of the studies was the basis for selection of pups to be examined or the total number of pups stated; therefore, it is

impossible to determine how many pups from each dam were evaluated or if at least one offspring from each dam was selected for evaluation.

- In vivo studies to assess the potential adverse effects of diclofenac on embryo-fetal development of other systems include those of Cappon et al. (2003), Gokcimen et al. (2001), and Montenegro & Palomino (1990). Cappon et al. (2003) assessed the effects of diclofenac (manufacturer: Sigma) administered during sensitive periods for heart development and midline closure in Sprague-Dawley rat (treated on GD 9-10, sacrificed on GD 21) and New Zealand White (NZW) rabbit (treated on GD 9-11, sacrificed on GD 29). Pregnant animals (14-19/group) received one of several NSAIDs (including diclofenac at 25 mg/kg by oral gavage) or vehicle at specified times during gestation; all viable fetuses were examined. No effect of diclofenac on the incidence of cardiovascular (e.g., ventricular septal) or midline defects was observed in either species. However, diclofenac was associated with increased post-implantation loss in rats and decreased fetal body weight in both rats and rabbits.

Gokcimen et al. (2001) focused on the liver, kidney, and testes. Wistar rat dams (25/group) were treated on GD 5-20 with either saline i.m. or diclofenac (source not specified; 1 mg/kg i.m.). Gestation was prolonged in diclofenac-treated dams (24-29 vs 21-23 days in controls); this is in contrast to the Korkmaz et al. (1996) study, conducted in the same lab, in which gestation length was not affected at the same dose administered by the same route. Dams were allowed to deliver spontaneously; pups (10/sex/group) were maintained for 4 weeks post-partum. [The basis for selection of pups was not provided, nor was there any way to determine if at least one pup was examined from each dam.] No adverse effects of diclofenac were observed for kidney or testis. Although no changes in the gross morphology of the liver were detected, microscopic changes in offspring of diclofenac-treated pups consisted of: (1) an increase in the number of bile ducts (27%), (2) an increase in the diameter of the portal area (20%), (3) an increase in the width of the sinusoidal area, and (4) an increase in hepatocytes degeneration (“small” in ≈70% of fetuses; “moderate” in ≈30% of fetuses; none in any control fetus).

Montenegro & Palomino (1990) investigated the effect of a single i.m. injection of one of a number of NSAIDs (including diclofenac; source not specified) or vehicle (ethanol), administered on GD 13.5 to AKR mice (15 received diclofenac, 4 mg/kg; 12 received vehicle), on the incidence of cleft palate. Fetuses were delivered on GD 17. All NSAIDs were associated with an increased incidence of cleft palate. Of a total of 114 fetuses exposed to diclofenac, 82% were normal and 12% (14/114) had cleft palate; no control fetus was affected. [Litter data were not provided.] Although data were not provided, the authors stated that “A dose-response experiment...demonstrated a linear increase in cleft palate from 2 mg/kg to 10 mg/kg with all drugs tested except indomethacin...” In a follow-up in vitro assay, mouse palatal processes were collected from fetuses at GD 13.5 or 14.5, and were incubated with an NSAIDs (including diclofenac, 50 µg) for 72 hrs after collection. For diclofenac, the results differed depending on the age of the fetus. In GD 13.5 explants, 47/53 were unfused, whereas in the GD 14.5 explants, only 6/53 were unfused.

The Cappon et al. (2003) study was well-designed and demonstrated no increase in cardiovascular or midline defects associated with diclofenac, but was limited in its assessment. [The post-implantation loss and reduced fetal body weight observed with diclofenac in this study are consistent with findings described in the Cataflam[®] label.] The Gokcimen et al. (2001) study was inadequate by design; it is also unclear what the hepatic findings represent since neither dams nor pups were treated during the 4-week post-partum period. The Montenegro & Palomino (1990) study suggests the potential for diclofenac to induce cleft palate; however, according to the Cataflam[®] label, oral doses of up to 20 mg/kg/day to mice (or up to 10 mg/kg in rat and rabbit) produced no evidence of teratogenicity. Whether or not the differences in route could explain the discrepancy in results is unknown. Based on this discrepancy, and with no ability to adequately evaluate the Montenegro & Palomino (1990) data, it does seem warranted to add the cleft palate findings to labeling, particularly since the study conducted by the innovator was available for detailed review and was conducted using the clinical route.

Clinical studies

The clinical published literature was not examined in detail, since rigorous examination of clinical data is beyond the scope of this memo. In the area of reproductive and developmental toxicology, epidemiological data in humans are relatively insensitive; however, they are arguably the most relevant. None of the four publications identified reported clear evidence of an adverse effect of diclofenac on infants of mothers taking or reported to have taken diclofenac during pregnancy; however, all of these focused almost exclusively on cardiac/cardiovascular defects.

Ericson & Kallen (2001) examined records for infants born in Sweden and reported to the Medical Birth Registry during the period from July 1, 1995 through December 31, 1998, focusing primarily on reports of cardiac defects. The authors noted that “There seems to be no specificity for the type of NSAID drug” and concluded that “The average effect of NSAID use is less than a doubling of the risk of having an infant with a cardiac defect; for an exposed woman this would amount to perhaps a 1.5% risk”; however, the authors did caution that risk may be greater in subset(s) of women. For diclofenac in particular, of 574 exposures, there were 8 reported cardiac defects (1.4%).

Kallen & Olausson (2003) examined records of infants born in Sweden, using the Swedish Medical Birth Registry, during the period from July 1, 1995 through December 31, 2001, focusing primarily on reports of cardiovascular defects (excluding patent ductus arteriosus). The authors reported that the odds ratio of 1.2 for diclofenac (15 cardiac defects in a total of 1362 infants) was “not significant”. In comparison, naproxen use was associated with a significantly increased odds ratio of 1.7 (15 cases of cardiac defect in a total of 1679 exposed infants).

Ofori et al. (2006) examined “three administrative databases of the Province of Quebec” for the period from January 1, 1997 through June 30, 2003 for cases of infant with congenital anomalies, related to in utero exposure to NSAIDs. The primary focus was on “cardiac septal closure and related anomalies”, although other organ systems were

investigated (including respiratory, CNS, musculoskeletal systems). The authors state that the “strongest and most consistent findings were seen with the anomalies related to cardiac septal closure”. However, they concluded that diclofenac was not associated with an increase in anomalies related to cardiac septal closure or the respiratory system. Of 93 women giving birth to an infant with congenital anomalies, only 6 were reported to have filled a prescription for diclofenac. [It should be noted, however, that of 1056 prescriptions filled for an NSAID, only 9% were for diclofenac.]

Ostensen et al. (2006) reported the conclusions of “A panel of 29 international experts” who examined all available published literature in animals and humans on use of (or exposure to) anti-inflammatory (including NSAIDs) and immunosuppressive drugs and pregnancy outcome. No conclusions were made specific to diclofenac.

Labeling recommendations

These recommendations are based on or take into consideration (1) the nonclinical sections of the Cataflam[®] Package Insert approved in 1998 instead of the most recent version of labeling [Nonclinical information included in the 1998 version (based on nonclinical studies conducted by the innovator) was inadvertently removed in 2001.], (2) recommendations by the Maternal Health Team on NDA 22-165 labeling (review dated 4/7/2009), (3) NSAIDs class labeling recommendations by the Maternal Health Team (Memorandum dated 2/22/2008), at the request of DAARP (consult date 12/5/2007), (4) published literature submitted by the sponsor relevant to the “Nursing Mothers” section.

The recommended dose of diclofenac for migraine is 50 mg/day, and safety margins are based on this dose. However, it is of note that in humans, peak levels of the sponsor’s diclofenac sachet (PRO-513) were 109% higher than peak levels following a 50 mg tablet of Cataflam[®], consistent with a shorter time to C_{max} with the sachet (0.25 vs 0.5 hrs.) (cf. Office of Clinical Pharmacology Review, Carol Noory, 9/24/08; pg 9.) (The extent of exposure (i.e., AUC) was similar between the two clinical formulations.) Therefore, to the extent that adverse effects observed in animals reflect C_{max} , the margins may be overestimates.

(b) (4)

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/s/

Lois Freed
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PHARMACOLOGIST

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application Number: 22-165

Submission Number/code: 008/AZ

CDER Stamp Date: 17 December 2008

PDUFA Date: 17 June 2009

Product: PRO-513 (diclofenac potassium) 50 mg powder sachet

Indication: Acute migraine with or without aura in adults

Applicant: Kowa Pharmaceuticals America, Inc.

Review Division: Neurology Products

Reviewer: D. Charles Thompson, R.Ph., Ph.D., D.A.B.T.

Supervisor/Team Leader: Lois Freed, Ph.D.

Division Director: Russell G. Katz, M.D.

Project Manager: Lana Chen

Disclaimer:

NME: N/A

505(b)(2): Yes, CR resubmission (substantially equivalent, standard review)

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1. Executive Summary

1.1. Recommendations

- 1.1.1. From a nonclinical perspective, it is recommended that the application be approved as submitted.
- 1.1.2. It is recommended that nonclinical aspects of approved labeling for the RLD be adopted with modifications based on reintroduction of previously approved and inadvertently removed nonclinical label information.

1.2. Regulatory background:

NDA 22-165 was received by the Agency on 27 September 2007; amendments were subsequently received on 30 October 2007, 18 March 2008 (2), 6 May 2008, and 21 July 2008. On 27 October 2008, a Complete Response (CR) letter was communicated to the sponsor. In that CR letter, the sponsor was advised that they would, among other things, "...need to conduct a comprehensive search of the published scientific literature to identify studies that provide data that may impact the nonclinical sections of labeling. In order to facilitate the review process, copies of all relevant articles should be provided." The sponsor characterizes those portions of the current submission intended as a specific response to the above-noted request in the following manner:

Kowa performed a comprehensive non-clinical toxicology literature search covering the time period from January 1980 to November 2008, and if indicated, has searched for selected supportive clinical literature that may have a bearing on the non-clinical toxicology components of our application....The selection criteria for articles reviewed were any appearance that the article might have the potential to suggest modifications to the Package Insert....Kowa believes that, while there may be new non-clinical toxicology information referenced, the information is insufficient to support our making any changes to the current non-clinical section of the Reference Label Drug – Cataflam® (diclofenac potassium – Novartis) labeling.

1.3. Overall integrated summary and safety evaluation:

The sponsor's submission included slightly more than 100 literature references. A screening level evaluation of said references by this reviewer identified only 12¹ that,

¹ Ragbetli MC, Ozyurt B, Aslan H, Odaci E, Gokcimen A, Sahin B, Kaplan S. Effect of prenatal exposure to diclofenac sodium on Purkinje cell numbers in rat cerebellum: a stereological study. *Brain Res.* 2007 Oct 12;1174:130-5.; Gokcimen A, Ragbetli MC, Baş O, Tunc AT, Aslan H, Yazici AC, Kaplan S. Effect of prenatal exposure to an anti-inflammatory drug on neuron number in cornu ammonis and dentate gyrus of the rat hippocampus: a stereological study. *Brain Res.* 2007 Jan 5;1127(1):185-92.; Canan S, Aktaş A, Ulkay MB, Colakoglu S, Ragbetli MC, Ayyildiz M, Geuna S, Kaplan S. Prenatal exposure to a non-steroidal anti-inflammatory drug or saline solution impairs sciatic nerve morphology: a stereological and histological study. *Int J Dev Neurosci.* 2008 Nov;26(7):733-8.; Korkmaz A., Kaplan S., Ciftci N., Bilgic S. and Ragbetli M.C. A morphometric study of the inferior olivary nucleus in rats treated prenatally with diclofenac sodium. *Turkish Journal of Medical Sciences* 1996 26:1 (75-79).; Korkmaz A., Ciftci N., Ragbetli M.C. and Kaplan S. Cerebellar Purkinje cell loss in rats exposed prenatally to diclofenac sodium. *Turkish Journal of Medical Sciences* 1995 24:1 (27-31).; Gokcimen A., Aydin G., Karaoz E., Ali Malas M. and Oncu M. Effect of diclofenac sodium administration during pregnancy in the postnatal period. *Fetal Diagnosis and Therapy* 2001 16:6 (417-422).; Espey LL, Kohda H, Mori T, and Okamura H. Rat ovarian prostaglandin levels and ovulation as indicators of the strength of non-steroidal anti-inflammatory drugs. *Prostaglandins.* 1988, Dec; 36(6):875-9.; Espey LL. Comparison of the effect of nonsteroidal and steroidal anti-inflammatory agents on prostaglandin production during ovulation in the rabbit. *Prostaglandins.* 1983 Jul;26(1):71-8.; Chan LY, Chiu PY, Siu SS, Lau TK. A study of diclofenac-induced teratogenicity during organogenesis using a whole rat embryo culture model. *Hum Reprod.* 2001 Nov;16(11):2390-3.; Cappon GD, Cook JC, Hurtt ME. Relationship between

on face, hinted at their potentially containing data and information that could impact nonclinical aspects of labeling. Upon further review and evaluation, it is this reviewer's opinion that these references, either individually or collectively, do not constitute data and information of sufficient quality and quantity, nor do they report findings of sufficient weight and significance, as to warrant modification of the pre-existing and approved labeling for the RLD (Cataflam) in developing adequate labeling for the proposed drug product.

Thus, it is recommended that, from a nonclinical perspective, the application be approved as submitted, with the qualification that approved labeling from the RLD be modified via incorporation of nonclinical sections of draft labeling proposed to the sponsor in the previous CR letter, which reflect reintroduction of previously approved and inadvertently removed nonclinical label information from the innovator's approved labeling.

cyclooxygenase 1 and 2 selective inhibitors and fetal development when administered to rats and rabbits during the sensitive periods for heart development and midline closure. *Birth Defects Res B Dev Reprod Toxicol.* 2003 Feb;68(1):47-56.; Davenport SJ, Zauner LR, Cook JC, Hurtt ME, and Cappon GD. Developmental effects of COX inhibitors when administered during the sensitive period of heart development. *Teratology* 2002 Jun;65(6):331.; Montenegro MA and Palomino H. Induction of cleft palate in mice by inhibitors of prostaglandin synthesis. *J Craniofac Genet Dev Biol.* 1990; 10(1):83-94.

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/s/

Donald C Thompson
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PHARMACOLOGIST

Lois Freed
5/30/2009 09:33:40 AM
PHARMACOLOGIST

MEMORANDUM

**DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration**

**Division of Neurology Products (HFD-120)
Center for Drug Evaluation and Research**

Date: October 27, 2008

From: Lois M. Freed, Ph.D.
Supervisory Pharmacologist

Subject: NDA 22-165 (Diclofenac Potassium, September 28, 2007)

NDA 22-165 is a 505(b)(2) application for diclofenac potassium (50 mg powder sachet) for acute treatment of migraine with or without aura in adults (≥ 18 years of age). The sponsor (Kowa Pharmaceuticals America [formerly, ProEthic Pharmaceuticals]) is relying on the Agency's findings of safety and efficacy for previously approved diclofenac products (Cataflam® [NDA 20-142, diclofenac potassium] and Voltaren® [NDA 19-201, 20-254], diclofenac sodium) to support marketing approval. The sponsor conducted no nonclinical studies of diclofenac.

[Redacted] (b) (4)

The sponsor provided the following additional information:

- A nonclinical overview and nonclinical summary documents, which include discussion of the results of a literature search for the period from January 2004 through February 2007 conducted by the sponsor.
- Copies of selected literature references.

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[Redacted]

All nonclinical information provided by the sponsor (except as noted above) was reviewed by D. Charles Thompson, Ph.D. (Pharmacology/Toxicology Review and Evaluation, NDA 22-165, 25 October 2008). Based on this review and on the Agency's

clinical opinion that the sponsor's intended use would not raise new safety concerns, Dr. Thompson has concluded that "...there are no obvious impediments to approval from a nonclinical perspective, with one exception." The exception is the lack of "...evidence that [the sponsor has] adequately surveyed the published scientific literature to identify reports of data potentially relevant to the nonclinical safety evaluation of diclofenac." The deficiencies noted by Dr. Thompson are as follows:

- The sponsor's search of published literature was too limited (2004-2007), and appeared incomplete; at least one relevant study published in 2007 was not included in the sponsor's reference list.

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It is Dr. Thompson's conclusion that, without the results of such a search, adequate product labeling cannot be written for diclofenac; however, Dr. Thompson does not specifically state that the application should not be approved until the sponsor addresses this issue.

Comments

As noted by Dr. Thompson, the clinical team has determined that the sponsor's proposed indication and use will not result in new safety concerns that would require nonclinical studies. Therefore, no additional nonclinical studies of diclofenac are needed (and none was conducted by the sponsor) to support approval of the 505(b)(2) application; labeling will be based on the approved product labeling for the Reference Listed Drugs, Cataflam® and Voltaren®.

The nonclinical portions of labeling for Cataflam® (NDA 20-142; labeling approved 1/24/06) and Voltaren (NDAs 19-201, labeling approved 7/9/07; NDA 20-254, labeling approved 1/24/06) are appended. It is of note that neither provides language for Section 13.1 of labeling. According to the review division (DAARP) that holds the innovator products, much of the nonclinical wording was inadvertently removed from the labeling for Cataflam® and Voltaren®; effort is ongoing to add that wording back into labeling.

The sponsor provided a summary of published literature (2004-2007) on diclofenac, as well as copies of the references cited. The majority of citations were studies of the pharmacology and PK/ADME of diclofenac. The Toxicology Written Summary provided no summary of or references to relevant data. Of the references provided, only one had potential relevance for diclofenac product labeling: Kushima K et al. *Toxicology* 257-267, 2007. In a brief literature search, Dr. Thompson identified a number of published studies of the potential for diclofenac to induce reproductive or developmental toxicity, none of which was provided by the sponsor. For example, a recent study published by Ragbetli et al. (Ragbetli MC et al. *Brain Res* 1174:130-135, 2007) demonstrated a significant reduction in the total number of cerebellar Purkinje cells in the offspring of dams treated with diclofenac (1 mg/kg/i.p.) from Day 5 post-mating through Day 14-15 of gestation.

Current labeling for Cataflam® and Voltaren® states only the potential for diclofenac (and other NSAIDS) to cause a specific adverse effect in late pregnancy (i.e., premature closure of the ductus arteriosus); the nonclinical reproductive toxicology studies are stated to be negative. Therefore, I agree with Dr. Thompson that examination of the available published literature, particularly related to the potential for developmental toxicity, may identify additional adverse effects that need to be described in labeling. I would recommend that the sponsor be asked to address this issue prior to approval.

Preliminary labeling recommendations

These recommendations incorporate the nonclinical sections of the Cataflam® Package Insert, approved in 1998; they may need to be revised, based on the results of the sponsor's literature search.

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/s/

Lois Freed
10/27/2008 06:28:23 PM
PHARMACOLOGIST



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

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	22-165
SERIAL NUMBER:	005
DATE RECEIVED BY CENTER:	28 September 2007
PRODUCT:	Diclofenac Potassium Powder for Oral Solution
INTENDED CLINICAL POPULATION:	Migraine Patients
SPONSOR:	ProEthic Pharmaceuticals
DOCUMENTS REVIEWED:	Vol. 1
REVIEW DIVISION:	Division of Neurology Products (HFD-120)
PHARM/TOX REVIEWER:	D. Charles Thompson
PHARM/TOX SUPERVISOR:	Lois M. Freed
DIVISION DIRECTOR:	Russell G. Katz
PROJECT MANAGER:	Lana Y. Chen

Date of review submission to Division File System (DFS): 25 October 2008

OVERALL EVALUATION AND RECOMMENDATIONS

This 505(b)(2) application for diclofenac potassium powder for oral solution relies on previous Agency findings of nonclinical safety (as reported in labeling) for three approved diclofenac formulations (NDA 20-142: Cataflam[®], diclofenac potassium; NDA 19-201: Voltaren[®], diclofenac sodium; and NDA 20-254: Voltaren-XR[®], extended-release diclofenac sodium) and on literature reports for nonclinical pharmacology, ADME, and toxicology information. For the nonclinical and safety sections of the label, the sponsor proposes to use the current Cataflam labeling. The clinical review team has concluded that the proposed use (dose, dosing regimen, and indication) falls within the domain of the approved RLD dosing regimen(s) and does not represent an increase in exposure to drug or target a different patient population.

The sponsor has provided a brief summary of published literature relevant to the nonclinical pharmacology/toxicology of diclofenac, but the sponsor's search of the literature was confined to publication years 2004 through 2007. In addition, (b) (4)



Since the proposed use does not represent an increase in exposure to drug or target a different patient population and there are no unusual excipients in the new formulation, there are no obvious impediments to approval from a nonclinical perspective, with one exception. It is not clear that the submission provides sufficient information to allow the Division to write adequate product labeling for diclofenac at this time. A cursory survey of the published literature by this reviewer has identified additional published reports of information that may reveal a potential for diclofenac to induce developmental toxicity (e.g., Carp H, et al. *Eur J Obstet Gynecol Reprod Biol* 28(3):273-277, 1988; Foerster M, et al. *Teratology* 50(5):34A, 1994; Ragbetli MC, et al. *Brain Res* 1174:130-135, 2007; Korkmaz A, et al. *Turkish J Med Sci* 24(1):27-31, 1995). This last example reference, published in 2007, indicates that there is at least one potentially relevant study report that the sponsor has not included in its review of the literature.

Thus, the sponsor has not submitted evidence that they have adequately surveyed the published scientific literature to identify reports of data potentially relevant to the nonclinical safety evaluation of diclofenac. Therefore, this reviewer reserves the right to provide recommendations on nonclinical sections of diclofenac labeling until such time as the sponsor has conducted such a comprehensive search of the published scientific literature and submitted copies of all relevant articles to the Division for evaluation.

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/s/

Donald C Thompson
10/25/2008 01:56:17 PM
PHARMACOLOGIST

Lois Freed
10/26/2008 09:12:59 AM
PHARMACOLOGIST
Please see memo for comments.