

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

***APPLICATION NUMBER:***

**20-947**

**OTHER REVIEW(S)**

**MEMORANDUM**

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Drug Marketing, Advertising, and Communications

**\*\*PRE-DECISIONAL AGENCY MEMO\*\***

**Date:** July 15, 2009

**To:** Jessica Benjamin – Regulatory Project Manager  
Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP)

**From:** Mathilda Fienkeng – Regulatory Review Officer  
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Twyla Thompson – Regulatory Review Officer  
Division of Drug Marketing, Advertising, and Communications (DDMAC)

**Subject:** **DDMAC draft labeling comments**  
NDA 20-947 PENNSAID® Topical Solution (diclofenac sodium topical solution)  
1.5% for topical use only

DDMAC has reviewed the proposed product labeling (PI), Medication Guide, carton and container labels for PENNSAID® Topical Solution (diclofenac sodium topical solution) 1.5% for topical use only (Pennsaid) submitted for consult on March 10, 2009.

The following comments are provided using the updated proposed PI and Medication Guide sent via email on July 9, 2009 by Jessica Benjamin. If you have any questions about DDMAC's comments, please do not hesitate to contact us.

**Container and Carton Labels**

The dosing instructions found on the carton and container labels, inadequately describe the proper procedure for correctly administering Pennsaid. We recommend removing these dosing instructions and replacing them with a directive to "Please carefully read the dosing instructions contained inside, before using PENNSAID®."

25 Page(s) Withheld

       § 552(b)(4) Trade Secret / Confidential

  √   § 552(b)(4) Draft Labeling

       § 552(b)(5) Deliberative Process

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

/s/

-----  
Mathilda Fienkeng  
7/15/2009 08:25:01 PM  
DDMAC PROFESSIONAL REVIEWER

**FOOD AND DRUG ADMINISTRATION  
Center for Drug Evaluation and Research  
Division of Drug Marketing, Advertising, and Communications**

## Memorandum

**Date:** November 2, 2006

**To:** Paul Balcer, Regulatory Project Manager  
Division of Anesthesia, Analgesia, and Rheumatology Products

**From:** Michelle Safarik, PA-C, Regulatory Review Officer  
Division of Drug Marketing, Advertising, and Communications

**Subject:** NDA 20-947  
DDMAC labeling comments for PENNSAID Topical Solution  
(diclofenac sodium topical solution) 1.5% w/w

---

Per your consult request dated October 31, 2006, DDMAC has reviewed the revised proposed product labeling (PI) and revised proposed carton and container labeling for PENNSAID Topical Solution (diclofenac sodium topical solution) 1.5% w/w (PENNSAID), and we offer the following comments.

### PI

Please refer to our comments dated October 26, 2006. In addition, we offer the following comments:

#### **Pharmacokinetics**

##### *Absorption*

1. The FDA and the Institute of Safe Medication Practices (ISMP) have launched a nationwide health professional education campaign aimed at reducing the number of common but preventable sources of medication mix-ups and mistakes caused by the use of unclear medical abbreviations. For details about this campaign, including a link to a list of error prone abbreviations, please see the FDA press release available online at: <http://www.fda.gov/bbs/topics/NEWS/2006/NEW01390.html>. In light of this initiative, DDMAC encourages the elimination of these potentially confusing abbreviations. Please consider revising the proposed PI to reflect this nationwide goal. For example, we note that the abbreviation \_\_\_\_\_ is used within the proposed PI. We suggest you instead use the phrase "four times daily."

b(4)

**Carton and Container Labeling**

Please refer to our comments dated October 26, 2006.

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

/s/

-----  
Michelle Safarik  
11/2/2006 12:22:12 PM  
DDMAC REVIEWER

**FOOD AND DRUG ADMINISTRATION  
Center for Drug Evaluation and Research  
Division of Drug Marketing, Advertising, and Communications**

## Memorandum

**Date:** October 26, 2006

**To:** Paul Balcer, Regulatory Project Manager  
Division of Anesthesia, Analgesia, and Rheumatology Products

**From:** Michelle Safarik, PA-C, Regulatory Review Officer  
Constantine Markos, PharmD, Regulatory Review Officer  
Division of Drug Marketing, Advertising, and Communications

**Subject:** NDA 20-947  
DDMAC labeling comments for PENNSAID Topical Solution (1.5% w/w diclofenac sodium)

---

Per your consult request dated August 18, 2006, DDMAC has reviewed the proposed product labeling (PI) and proposed carton and container labeling for PENNSAID Topical Solution (PENNSAID), and we offer the following comments.

### PI

#### **Pharmacokinetics**

##### *Special Populations*

##### Hepatic Insufficiency

1. For consistency with the Voltaren PI, and since hepatic metabolism accounts for almost 100% of diclofenac elimination, would it be possible to add the phrase, "...so patients with hepatic disease may require reduced doses of PENNSAID<sup>®</sup> compared with patients with normal hepatic function."

#### **Clinical Studies**

1. "...PENNSAID<sup>®</sup> treatment resulted in statistically significant clinical improvement compared to \_\_\_\_\_"

**b(4)**

Is it accurate to state that PENNSAID demonstrated both statistically significant improvement as well as clinical improvement? In advertising and promotion, sponsors often translate statistically significant results into

clinical benefits. If this is not appropriate for PENNSAID, we recommend deletion of the word "clinical" as this is promotional in tone.

2. Is WOMAC considered a validated instrument to assess pain, physical function, and patient global assessment in this patient population (and thus considered substantial evidence to include in labeling)?

3. \_\_\_\_\_  
\_\_\_\_\_

b(4)

\_\_\_\_\_ is promotional in tone; we recommend revising the above to a statement that discusses a statistically significant change in score.

4. \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

b(4)

The Clinical Studies section of labeling should discuss efficacy, and not safety, results. Therefore, we recommend moving these statements to the Adverse Reactions section of the proposed PI.

### Indications and Usage

1. For consistency with the Voltaren PI, we recommend deletion of the phrase, \_\_\_\_\_ as it is promotional in tone and minimizes the risks of PENNSAID therapy.

b(4)

### Warnings

1. \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

b(4)

This statement is promotional in tone and minimizes the risks of PENNSAID therapy; we recommend deletion.

### Renal Effects

1. For consistency with the Voltaren PI, is it appropriate to include the following statement: \_\_\_\_\_ when initiating treatment with PENNSAID® in patients with considerable dehydration"? Or, is this statement only applicable to oral formulations of diclofenac?

b(4)

**Precautions**

1. \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

**b(4)**

This statement is promotional in tone and minimizes the risks of PENNSAID therapy; we recommend deletion.

**Skin Reactions**

1. \_\_\_\_\_  
\_\_\_\_\_

**b(4)**

This statement is promotional in tone and minimizes the application site reactions seen with PENNSAID therapy; we recommend deletion.

**Hematological Effects**

1. \_\_\_\_\_  
\_\_\_\_\_

**b(4)**

According to the Clinical Pharmacology – Platelets section of the proposed PI, the ten healthy subjects applied 40 drops to each knee four times a day for 7 days. For clarity, we recommend revising the above statement to specify that the subjects applied 40 drops to each knee for a total of 80 drops.

**Information for Patients**

1. "PENNSAID® Topical Solution \_\_\_\_\_ like other NSAIDs, may cause GI discomfort and, rarely, serious GI side effects...."

**b(4)**

As proposed, this statement minimizes GI side effects. For consistency with the Voltaren PI, we recommend revising this statement to read as follows: "PENNSAID® Topical Solution (1.5% w/w diclofenac sodium), like other NSAIDs, can cause GI discomfort and, rarely, more serious GI side effects..." (emphasis added).

**Laboratory Tests**

1. \_\_\_\_\_  
\_\_\_\_\_

**b(4)**

For consistency with the Precautions-Hepatic Effects section of the proposed PI and the Voltaren PI, we recommend revising the above statement to read as follows: "Patients on long-term treatment with NSAIDs should have their CBC and chemistry profile (including transaminase levels) checked periodically" (emphasis added).

#### *Drug Interactions*

1. For consistency with the Voltaren PI, is it appropriate to include a discussion on drug interactions with cyclosporine? Or, are drug interactions with cyclosporine only applicable for oral formulations of diclofenac?
2. We recommend revising "*Furosemide*" to "*Diuretics*" since this section discusses both furosemide and thiazides.

#### *Pregnancy*

##### Teratogenic Effects

1. For consistency with the Voltaren PI, we recommend adding the following statement: "PENNSAID® should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus."

#### **Adverse Reactions**

##### *Postmarketing Experience*

1. "Nervous:... \_\_\_\_\_

Would it be possible to delete \_\_\_\_\_ since this is not a nervous system side effect?

b(4)

#### **Medication Guide**

##### *What are Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)?*

1. We recommend revising \_\_\_\_\_ to "used."

b(4)

##### *NSAID medicines that need a prescription*

1. We recommend revising "flurbiprofen" to "flurbiprofen."

**Carton and Container Labeling**

**15 mL Physician Sample Carton and Container Label**

\_\_\_\_\_ **Trade Carton and Container Label**

**60 mL Trade Carton and Container Label**

**b(4)**

1. \_\_\_\_\_

For consistency with the proposed PI, we recommend revising this statement to read, **"Not for Ophthalmic or Oral Use."**

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

/s/

-----  
Michelle Safarik  
10/26/2006 02:48:01 PM  
DDMAC 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:** July 15, 2009

**To:** Bob Rappaport, M.D., Director  
Division of Analgesia, Anesthesia, and Rheumatology Products

**Through:** Kellie Taylor, Pharm.D., M.P.H., Team Leader  
Denise Toyer, Pharm.D., Deputy Director  
Carol Holquist, RPh, Director  
Division of Medication Error Prevention and Analysis

**From:** Tara Turner, Pharm.D., Safety Evaluator  
Division of Medication Error Prevention and Analysis

**Subject:** Label and Labeling Review

**Drug Name:** Pennsaid  
(Diclofenac Sodium) Topical Solution 1.5% w/w

**Application Type/Number:** NDA # 20-947

**Applicant:** Nuvo Research Inc.

**OSE RCM #:** 2009-427

## CONTENTS

1	Executive Summary.....	3
2	METHODS AND MATERIALS .....	3
3	RECOMMENDATIONS .....	3
3.1	Comments to the Division.....	4
3.2	Comments to the Applicant.....	4

## **1 EXECUTIVE SUMMARY**

Pennsaid (Diclofenac Sodium) is a topical solution proposed for the treatment of the signs and symptoms of osteoarthritis of the knee. Diclofenac Sodium is currently marketed in oral tablet, topical gel, and ophthalmic solution formulations. Given that Pennsaid will represent a new dosage form of this active ingredient, the Division of Medication Error Prevention and Analysis (DMEPA) considered the vulnerability of the topical solution to cause error.

The labels and labeling have been previously reviewed on 3 occasions by DMEPA (see RCM # 02-0010-2, dated October 12, 2006; 02-0010-1, dated July 8, 2002; and 02-0010, dated March 8, 2002). The majority of issues identified in those reviews have been addressed. However, we continue to be concerned with the lack of prominence of the established name, the location and content of the route of administration statement, and the location of the NDC#.

Our current Label and Labeling Risk Assessment indicates that further improvements can be made to the presentation of the proprietary name and product strength, as well as directions for proper use of the product. We believe the risks we have identified can be addressed and mitigated prior to drug approval, and we provide recommendations in Section 3.

## **2 METHODS AND MATERIALS**

The Division of Medication Error Prevention and Analysis (DMEPA) used the principles of Human Factors and Failure Mode and Effects Analysis (FMEA) in our evaluation of the container labels, carton and insert labeling submitted February 4, 2009 (see Appendices A through F).

## **3 RECOMMENDATIONS**

Our evaluation noted areas where the presentation of information on the container labels, carton and insert labeling can be improved to minimize the potential for medication errors. We provide recommendations on the insert labeling in *Section 3.1 Comments to the Division* for discussion during the review team's label and labeling meetings. *Section 3.2 Comments to the Applicant* contains our recommendations for the container labels and carton labeling. We request the recommendations in Section 3.2 be communicated to the Applicant prior to approval.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications on this review, please contact Chris Wheeler, Project Manager, at 301-796-0151.

### 3.1 COMMENTS TO THE DIVISION

#### A. Insert Labeling

1. We note that the dosing regimen is prone to error. We are concerned that patients may become confused and lose count in the midst of dispensing the recommended dose of 40 drops per knee. The instructions to dispense 10 drops at a time appear to be aimed at mitigating the risk of under- or over-dosing the product, but we are unsure if this strategy would effectively mitigate this risk. For additional patient assistance, it would be helpful to provide dosing aids and instructions regarding how to proceed with the dose if they lose count of the drops. Optimally, we would recommend re-packaging the product so that the dose could be accurately measured and applied in some way other than drops. We would be willing to discuss options with the Applicant post-approval if desired.
2. In the Patient Instructions for Use there is a statement that the dose of 40 drops is equivalent to 1.2 mL. Relocate this information to Section 2: DOSAGE AND ADMINISTRATION. Patients do not need this information because the dose is not measured in terms of volume, and referencing the volume in mL may lead to dosing errors.

### 3.2 COMMENTS TO THE APPLICANT

#### A. Carton Labeling and Container Labels (Trade and Sample)

1. Increase the prominence of the proprietary and established names and the product strength by increasing the font size and weight.
2. Ensure that the entire proprietary name is presented in the same font type (i.e. color, size, and weight).
3. Remove the \_\_\_\_\_ from the proprietary name. **b(4)**
4. Ensure that the established name is at least ½ the size of the proprietary name, to comply with 21 CFR 201.10 (g)(2).
5. Relocate the route of administration statement from the side panel to the principal display panel. Delete the caution against ophthalmic use \_\_\_\_\_ as the \_\_\_\_\_ portion may be overlooked and inadvertently lead to ophthalmic administration. **b(4)**
6. To make room for the route of administration statement, consider relocating the secondary expression of strength \_\_\_\_\_ from the principal display panel to the side panel. **b(4)**
7. We note there is a space marked "Logo" at the bottom of the principal display panel. If any logo is included please ensure that it is not larger than 1/3 of the labeling, and resubmit the labels for review.
8. To comply with 21 CFR 207.35 (b)(3)(i), ensure that the NDC number appears prominently in the top third of the principal display panel or that it appears as part of and contiguous to the bar-code symbol.

9. To comply with 21 CFR 208.24 (d), add a statement regarding the required distribution of a Medication Guide to the principal display panel of the container labels and carton labeling of all 3 package sizes (15 mL, 60 mL, 150 mL). For example, we recommend:

**“Dispense Enclosed Medication Guide To Each Patient”**

6 Page(s) Withheld

√ § 552(b)(4) Trade Secret / Confidential

       § 552(b)(4) Draft Labeling

       § 552(b)(5) Deliberative Process

---

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

---

/s/

-----  
Tara Turner  
7/15/2009 11:19:45 AM  
DRUG SAFETY OFFICE REVIEWER

Kellie Taylor  
7/15/2009 01:19:24 PM  
DRUG SAFETY OFFICE REVIEWER

Carol Holquist  
7/15/2009 05:31:34 PM  
DRUG SAFETY OFFICE REVIEWER

**MEMORANDUM**

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

**DATE:** September 27, 2006

**TO:** Bob Rappaport, M.D., Director  
Division of Anesthesia, Analgesia, and Rheumatology Products

**VIA:** Paul Balcer, Regulatory Health Project Manager  
Division of Anesthesia, Analgesia, and Rheumatology Products

**FROM:** Jeanine Best, M.S.N., R.N., P.N.P.  
Patient Product Information Specialist  
Division of Surveillance, Research, and Communication Support

**THROUGH:** Solomon Iyasu, M.D., M.P.H., Director  
Division of Surveillance, Research, and Communication Support

**SUBJECT:** ODS/DSRCS Review of Medication Guide for Pennsaid Topical Solution — w/w diclofenac sodium), NDA 20-947 **b(4)**

**Background and Summary**

The sponsor submitted a Complete Response for NDA for Pennsaid Topical Solution — w/w diclofenac sodium), NDA 20-947, on June 28, 2006, in response to an August 7, 2002, Non-Approval Letter. **b(4)**

The sponsor submitted the required NSAID Class Labeling including the NSAID Class Medication Guide for this product.

**Comments and Recommendations**

1. Encourage the sponsor to package the Medication Guide with the product in its unit-of use package to ensure patient distribution.
2. Refer the sponsor to 21 CFR 201.24(d). The container or packaging label must state that a Medication Guide is available for this product and the manner in which it (the MG) is to be dispensed (i.e., "Read the enclosed Medication Guide before use.").
3. We recommend the sponsor develop and also package with the product, Patient Instructions for Use, listing step-by-step instructions for product application.

Please call us if you have any questions.

---

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

---

/s/

-----  
Jeanine Best  
9/27/2006 01:23:13 PM  
DRUG SAFETY OFFICE REVIEWER

Toni Piazza Hepp  
9/27/2006 01:31:43 PM  
DRUG SAFETY OFFICE REVIEWER

MEMORANDUM

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

---

CLINICAL INSPECTION SUMMARY

DATE: 12/14/06

TO: Paul Balcer, Regulatory Project Manager  
Larissa Lapteva, M.D., Medical Officer  
Division of Anesthesia, Analgesia and Rheumatology Products, HFD-170

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

FROM: Carolanne Currier, CSO

SUBJECT: Evaluation of Clinical Inspections

NDA: 20-947

APPLICANT: Nuvo Research, Inc.

DRUG: PENNSAID® (diclofenac sodium)

THERAPEUTIC CLASSIFICATION: Standard review

INDICATION: \_\_\_\_\_

CONSULTATION REQUEST DATE: 9/5/06

DIVISION ACTION GOAL DATE: 12/24/06

PDUFA DATE: 12/28/06

I. BACKGROUND:

Diclofenac sodium is a non-selective non-steroidal anti-inflammatory (NSAID) which inhibits both COX-1 and COX-2 enzymes. It is currently marketed in the US in an oral tablet form. PENNSAID® is diclofenac sodium in a solution of DMSO and other ingredients. Nuvo Research, Inc., hypothesized that the topical formulation of PENNSAID® would provide a local analgesic effect while minimizing systemic side effects found with other NSAIDS in oral dosage forms. The topical formulation is approved in Canada and has been submitted as NDA 20-927 to the Division of Anesthetics, Analgesics and Rheumatology Products (DAARP) for US approval.

Protocol PEN-03-112 was identified as the important safety and efficacy protocol in the NDA submission. Protocol PEN-03-112 was designed to evaluate the safety and efficacy of PENNSAID® solution alone and combined with oral diclofenac sodium in subjects with osteoarthritis of the knee. Treatment consisted of a

b(4)

topical solution (either PENNSAID®, a vehicle-controlled solution, or placebo) applied 4 times daily, plus 1 oral tablet (either 100 mg sustained release diclofenac or placebo) once daily, administered in 5 different treatment arms:

1. PENNSAID® + oral diclofenac tablets
2. PENNSAID® + oral placebo tablets
3. Vehicle-controlled solution + oral placebo tablets
4. Placebo solution + oral placebo tablets
5. Placebo solution + oral diclofenac tablets

Efficacy assessments were conducted at baseline and at 4, 8, and 12 weeks. There were 3 primary efficacy variables: the change from baseline to final assessment in the (1) Western Ontario MacMaster (WOMAC) Index LK3.1 pain dimension score, (2) WOMAC Index LK3.1 physical function dimension score, and (3) patient overall health assessment score. Safety assessments, including skin irritation scores, adverse event reports, routine clinical laboratory tests, and ocular visual examinations, were to be performed throughout the trial.

DAARP identified four clinical sites conducting studies with protocol PEN-03-112 that were considered important to their review of the NDA. The Division of Scientific Investigations (DSI) issued assignments on the four sites; two of which were in Canada and two in the US. All inspections have been completed but to date, only one establishment inspection report (EIR) has been received by DSI.

## II. RESULTS (by protocol/site):

Name of CI	City, State	Country	Protocol	Insp. Status	EIR Receipt Date	Classification
David L. Fried, M.D.	Warwick, RI	US	PEN-03-112	Completed	11/15/06	NAI
Sam Miller, M.D.	San Antonio, TX	US	PEN-03-112	Completed	Pending	Pending (VAI)
James Lai, M.D.	Vancouver, BC	Canada	PEN-03-112	Completed	Pending	Pending (VAI)
Stewart Silagy, M.D.	Winnipeg, ON	Canada	PEN-03-112	Completed	Pending	Pending (VAI)

**Key to Classifications** - Classifications in parentheses indicate a preliminary classification.

NAI = No deviation from regulations. Data acceptable.

VAI-No Response Requested= Deviations(s) from regulations. Data acceptable.

VAI-Response Requested = Deviation(s) from regulations. See specific comments below for data acceptability

OAI = Significant deviations for regulations. Data unreliable.

### Protocol # PEN-03-112

#### 1. David L. Fried, M.D., Warwick, Rhode Island:

a. What was inspected: Dr. Fried screened 94 subjects and enrolled 64 subjects in Protocol PEN-03-112. Forty-three subjects completed the study. Study records, including source documents, case report forms, data listings of efficacy endpoints, drug accountability records, and correspondence with the IRB and sponsor, were reviewed for 30 subjects during the inspection. Informed consent forms were reviewed for all subjects

b. Limitations of inspection : None

c. General observations/commentary: During the inspection, no problems were noted with the conduct of the study. Source data matched with that which was on case report forms (CRFs), and the data in source records for efficacy endpoints matched the endpoint data in the line listings provided by the sponsor. All inclusion criteria were met for the subject records reviewed, and there appeared to be no inappropriate concomitant medication use. There was no evidence of underreporting of adverse events.

d. Data acceptability/reliability: From the records reviewed, it appears the data from the Fried study are acceptable for consideration in the NDA review decision.

2. Sam Miller, M.D., San Antonio, Texas:

a. What was inspected: Dr. Miller enrolled 39 subjects into protocol PEN-03-112. Study records, including source documents, case report forms, data listings of efficacy endpoints, drug accountability records, and correspondence with the IRB and sponsor, were reviewed for 20 subjects during the inspection. Informed consent documents were checked for all screened subjects.

b. Limitations of the inspection: None.

c. General observations/commentary: The inspection of Dr. Miller has been completed but the EIR has not been received by DSI. The following inspection findings are from communication with the FDA field investigator and from the Form FDA 483 (Inspectional Observations) that was issued to Dr. Miller at the conclusion of the inspection:

1) Subject 71037 was randomized into the study and received study medication prior to having the protocol-required pregnancy test performed.

2) Subjects 71011 and 71032 were randomized to one knee and subsequently treated on the other knee. All safety and efficacy assessments were made on the treated knee.

3) The study solution was not weighed at baseline per protocol for subjects 71001, 71002, 71006, 71007, and 71010.

d. Data acceptability: From the preliminary findings, it appears that the above protocol deviations would not have affected the validity of the study data, and the data from this site are acceptable for consideration in the NDA review decision. After receipt and final review of the EIR, DAARP will receive a copy of the final letter issued to Dr. Miller, and an inspection summary addendum will be generated if conclusions about the acceptability of the data change.

3. James Lai, M.D., Vancouver, British Columbia, Canada:

a. What was inspected: Study records, including source documents, case report forms, data listings of efficacy endpoints, drug accountability records, and correspondence with the IRB and sponsor, were reviewed for 20 subjects during the inspection. Informed consent forms for all subjects were reviewed.

b. Limitations of the inspection: None

c. General observations/commentary: The inspection of Dr. Lai has been completed but the EIR has not been received by DSI. The following inspection findings are from communication with the FDA field investigator and from the Form FDA 483 that was issued to Dr. Lai at the conclusion of the inspection:

1) Two adverse events (AEs) noted in source documents were not recorded on CRFs: subject 32006 reported laryngitis on 5/4/04, and subject 32006 reported back pain on 6/17/04 and 6/28/04.

2) The protocol prohibited the use of the rescue medication acetaminophen during the 3 calendar days before efficacy assessments at visits 4C, 8C, and 12C. Subjects 32008, 32016, 32023, and 32039 used acetaminophen during the 3 days before the assessment:

Subject	Visit number	Date of assessment visit	Date of last dose of acetaminophen	Number of days before day of assessment
32008	8C	6/28/04	6/26/04	1
32016	8C	7/7/04	7/4/04	2
32023	8C	7/26/04	7/23/04	2
32029	8C	8/13/04	8/10/04	2

3) Baseline progress notes indicate subject 32018's "study knee" was the left knee, however subsequent progress notes indicate the subject's right knee was treated. Reported assessments were for the treated (right) knee.

d. Data acceptability: Four of 20 subject records reported the use of the rescue medication acetaminophen during the 3 days before efficacy assessments. DAARP may want to evaluate the significance of this finding, plus the unreported AEs, on the safety and efficacy profiles of the study.

#### 4. Stewart Silagy, M.D., Winnipeg, Ontario, Canada

a. What was inspected: Dr. Silagy screened 120 subjects and enrolled 50. Thirty-nine subjects completed the study. Study records, including source documents, case report forms, data listings of efficacy endpoints, drug accountability records, and correspondence with the IRB and sponsor, were reviewed in depth for 8 subjects during the inspection. All 50 subjects' records were examined for eligibility and adequate informed consent.

b. Limitations of the inspection: None

c. General observations/commentary: The inspection of Dr. Silagy has been completed but the EIR has not been received by DSI. The following inspection findings are from communication with the FDA field investigator and from the Form FDA 483 that was issued to Dr. Lai at the conclusion of the inspection.

1) Dr. Silagy stated he misunderstood the 3 day calculation for the restriction on the use of acetaminophen before visits 4C, 8C, and 12C. The following subjects took acetaminophen during the 3 days before the assessment visit:

Subject	Visit number	Date of assessment visit	Date of dose(s) of acetaminophen	Number of days elapsed before the day of the assessment
44002	8C	10/20/04	10/17/04	2
	12C	11/16/04	11/13/04	2
44009	12C	11/16/04	11/13/04	2
44012	12C	11/16/04	11/13/04	2
44017	8C	10/19/04	10/16/04	2
44019	4C	9/24/04	9/21/04, 9/22/04, 9/23/04	2, 1, 0
	8C	10/20/04	10/17/04	2
	12C	11/16/04	11/13/04	2
44025	8C	10/20/04	10/17/04	2
44042	4C	9/29/04	9/26/04	2
44046	4C	9/29/04	9/26/04	2
44049	12C	11/25/04	11/22/04	2
44051	12C	12/6/04	12/4/04	1
44053	4C	10/7/04	10/4/04	2

	8C	11/4/04	11/1/04, 11/3/04	2, 0
44063	8C	11/4/04	11/1/04	2
	12C	12/6/04	12/4/04	1
44075	12C	12/17/04	12/14/04	2
44087	8C	12/17/04	12/14/04	2
44092	4C	11/22/04	11/19/04	2
	8C	12/16/04	12/13/04	2
	12C	1/20/05	1/17/05, 1/18/05	2, 1
44099	8C	12/16/04	12/13/04	2
	12C	1/20/05	1/17/05, 1/18/05, 1/19/05	2, 1, 0
44110	4C	3/17/05	3/14/05	2
44119	4C	3/1/05	3/29/05	2

2) The protocol required a washout period of NSAIDS not less than 3 days and not more than 14 calendar days. Subject 44075 stopped taking Vioxx 35 days before the baseline visit, and subject 44054 discontinued the use of oral diclofenac sodium 18 days before the baseline visit.

3) Changes to the radiologist's reports for 16 subjects were made so that the originally recorded data was obscured. White-out was used to change the reports for subjects 44024, 44027, 440375, 44039, 44049, 44071, 44075, 44080, 44083, 44120; data was scribbled-over on reports for subjects 44086, 44092, 44091, 44100, and 44102, and data was over-written on the report for subject #44116.

d. Data acceptability: Two subjects stopped their NSAID medication greater than 14 days before study enrollment. Technically they were not eligible for the study. Eighteen of 50 subject records examined reported the use of acetaminophen during the 3 days before an efficacy assessment, in violation of the protocol. DAARP may want to evaluate the significance of these findings on the efficacy profile of the study.

### III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

The review of the data from Dr. Fried's study with PENNSAID® revealed no problems with the study data or the conduct of the study. The inspections of Drs. Miller, Lai and Silagy have been completed but the EIRs have not been received by DSI. A preliminary review of information from the inspection of Dr. Miller reveals minor deviations from the protocol and record keeping errors, but nothing that would have affected the study results. A preliminary review of the inspections of Drs. Lai and Silagy found 2 unreported AEs and 2 ineligible subjects. In addition, the use of acetaminophen during the 3 days prior to an efficacy assessment data was found for several subjects at each site.

The data from the Fried and Miller sites appear acceptable to be used to support an approval decision for the PENNSAID® NDA. DAARP may want to evaluate the significance of the protocol deviations and unreported AEs noted at the Lai and Silagy sites to determine if the safety or efficacy profiles of those studies would be affected. Upon receipt and review of the outstanding EIRs, DAARP will receive a copy of the letter issued to each investigator outlining the inspection findings. An addendum to this Clinical Inspection Summary will be generated if any finding would appear to significantly impact on the acceptability of data from any site.

{See appended electronic signature page}

Carolanne Currier, CSO

CONCURRENCE:

{ See appended electronic signature page }

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

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

/s/

-----  
Carolanne Currier  
12/14/2006 01:00:56 PM  
CSO

Constance Lewin  
12/14/2006 01:37:47 PM  
MEDICAL OFFICER

MEMORANDUM

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

---

DATE: July 8, 2002

FROM: Robert B. Shibuya, M.D.  
Good Clinical Practice Branch II, HFD-47  
Division of Scientific Investigations

THROUGH: Antoine El-Hage, Ph.D.  
Associate Director  
Good Clinical Practice Branch I & II, HFD 46/47  
Division of Scientific Investigations

SUBJECT: Clinical Inspections Summary – NDA 20-947

TO: Nancy Halonen, Regulatory Project Manager  
James Witter, M.D., Medical Team Leader  
Division of Anti-Inflammatory, Analgesic, and Ophthalmologic  
Drug Products, HFD-550

APPLICANT: Dimethaid Research, Inc.

DRUG: Diclofenac topical lotion (Pennsaid)

CHEMICAL CLASSIFICATION: 3

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATION(S): Relief of pain in the osteoarthritic knee

PDUFA GOAL DATE: August 1, 2002

**1. BACKGROUND**

Osteoarthritis is a very common degenerative condition treated symptomatically with analgesics and anti-inflammatory drugs.

Protocol RA-CP-109 (US) was a multicenter, double-blind, placebo-controlled study with the primary endpoint of pain relief as assessed by the WOMAC Osteoarthritis Index and a Patient Global Assessment. These four clinical sites were selected on the basis of relatively high enrollment rates.

**2. RESULTS (by site):**

Name	City	State	IN	Assigned	Action Date	Reviewer	Class
Fried	Warwick	RI	DA	4/18/02	6/25/02	RBS	VAI
Cohen	Trumbell	CT	DA	4/18/02	6/14/02	RBS	VAI
Stephensen	Winnipeg	CAN	DA	4/19/02	pending	RBS	VAI*
Spirou	Windsor	CAN	DA	4/19/02	pending	RBS	VAI**

\*Per communication with field personnel, a Form FDA 483 was issued for deficiencies with record keeping. The inspection report has not been reviewed by DSI. Should the review change the classification, this will be communicated to the review division.

\*\*Per communication with field personnel, a Form FDA 483 was issued for deficiencies with study drug accountability. The inspection report has not been reviewed by DSI. Should the review change the classification, this will be communicated to the review division.

**Selwyn A. Cohen, M.D. – Protocol RA-CP-109-US**

This site randomized 57 subjects with 21 completing the study. While no Form FDA 483 was issued, we note that 1. The investigator failed to provide progress reports to the IRB and 2. There were record keeping deficiencies in that some of the knee radiographs had not been retained. However, these data appear acceptable.

**David L. Fried, M.D. – Protocol RA-CP-109-US**

This site screened 41 subjects and randomized 27. Records for 15 of the 27 randomized subjects were reviewed in detail. While no Form FDA 483 was issued, we note that the investigator failed to provide progress reports to the IRB. However, these data appear acceptable.

**Michael Stephenson, M.D. – Protocol RA-CP-109**

This site screened 38 subjects, randomized 20 and completed 14. Records for all 38 subjects were reviewed. As noted in the summary table, DSI has not reviewed the inspection report. Communication with the field personnel indicates that a Form FDA 483 was issued for deficiencies with record keeping. At this time, it appears that the data from this site is acceptable for review. DSI will notify the review division should this situation change after formal review.

**Christos Spirou, M.D. – Protocol RA-CP-109**

This site screened 46 subjects, randomized 28, and completed 20. Records for all 46 subjects were reviewed. As noted in the summary table, DSI has not reviewed the inspection report. Communication with the field personnel indicates that a Form FDA 483 was issued for deficiencies with study drug accountability. At this time, it appears that the data from this site is acceptable for review. DSI will notify the review division should this situation change after formal review.

### 3. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

Pending the formal review of the inspection report from \_\_\_\_\_ sites, no major deficiencies were noted in the four sites inspected that could compromise the integrity of the data. Thus, the data reviewed is acceptable. No subsequent actions or follow up inspections should be undertaken.

**b(4)**

#### Key to Classification:

NAI = No deviation from regulations. Data acceptable.

VAI = Minor deviation(s) from regulations. Data acceptable.

VAI-r = Deviations(s) from regulations, response requested. Data acceptable.

OAI = Significant deviations from regulations. Data unreliable.

Antoine El-Hage, Ph.D.  
Associate Director  
Good Clinical Practice Branch I & II, HFD-46/7  
Division of Scientific Investigations

#### DISTRIBUTION

HFD-45/Reading File

HFD-47/El-Hage/Shibuya/Storms

HFD-47/rf/cf

O:\RS\NDA20-947\ClinInspectSumm20-947

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

/s/

-----  
Michele Lackner

7/12/02 12:47:42 PM

TECHNICAL

Original was signed by Drs. ElHage and Shibuya.

MEMORANDUM

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

---

DATE: July 8, 2002

FROM: Robert B. Shibuya, M.D. *RBS*  
Good Clinical Practice Branch II, HFD-47  
Division of Scientific Investigations

THROUGH: Antoine El-Hage, Ph.D.  
Associate Director  
Good Clinical Practice Branch I & II, HFD 46/47  
Division of Scientific Investigations

SUBJECT: Clinical Inspections Summary – NDA 20-947

TO: Nancy Halonen, Regulatory Project Manager  
James Witter, M.D., Medical Team Leader  
Division of Anti-Inflammatory, Analgesic, and Ophthalmologic  
Drug Products, HFD-550

APPLICANT: Dimethaid Research, Inc.

DRUG: Diclofenac topical lotion (Pennsaid)

CHEMICAL CLASSIFICATION: 3

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATION(S): Relief of pain in the osteoarthritic knee

PDUFA GOAL DATE: August 1, 2002

**1. BACKGROUND**

Osteoarthritis is a very common degenerative condition treated symptomatically with analgesics and anti-inflammatory drugs.

Protocol RA-CP-109 (US) was a multicenter, double-blind, placebo-controlled study with the primary endpoint of pain relief as assessed by the WOMAC Osteoarthritis Index and a Patient Global Assessment. These four clinical sites were selected on the basis of relatively high enrollment rates.

### 3. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

Pending the formal review of the inspection report from \_\_\_\_\_ sites, no major deficiencies were noted in the four sites inspected that could compromise the integrity of the data. Thus, the data reviewed is acceptable. No subsequent actions or follow up inspections should be undertaken.

b(4)

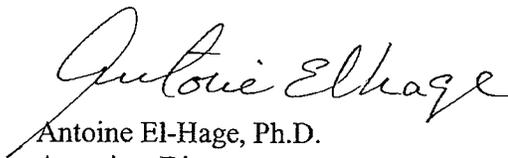
#### Key to Classification:

NAI = No deviation from regulations. Data acceptable.

VAI = Minor deviation(s) from regulations. Data acceptable.

VAI-r = Deviations(s) from regulations, response requested. Data acceptable.

OAI = Significant deviations from regulations. Data unreliable.



Antoine El-Hage, Ph.D.

Associate Director

Good Clinical Practice Branch I & II, HFD-46/7

Division of Scientific Investigations

#### DISTRIBUTION

HFD-45/Reading File

HFD-47/El-Hage/Shibuya/Storms

HFD-47/rf/cf

O:\RS\NDA20-947\ClinInspectSumm20-947

19 Page(s) Withheld

√ § 552(b)(4) Trade Secret / Confidential

       § 552(b)(4) Draft Labeling

       § 552(b)(5) Deliberative Process

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

**DATE:** July 19, 2002

**FROM:** Claudia B. Karwoski, Pharm.D.,  
Safety Evaluator Team Leader  
Division of Drug Risk Evaluation, HFD-430

**THROUGH:** Julie Beitz, M.D., Director  
Division of Drug Risk Evaluation, HFD-430

**TO:** Lee Simon, M.D., Director  
Division of Antiinflammatory, Analgesic and Ophthalmic Drug Products  
(DAAODP), HFD-550

**SUBJECT:** Postmarketing Safety Review—PID D020305  
Drug: Topical Diclofenac (Pennsaid®, NDA 20947)  
Reaction: Review of AERS cases

**INTRODUCTION/EXECUTIVE SUMMARY**

In response to a request by Dr. Tatiana Oussova, MD of the DAAODP, we reviewed adverse event cases in AERS reported in association with topical diclofenac. Specially, they were interested in any signals indicating a likely association of topical diclofenac with serious adverse reactions such as gastrointestinal (GI) bleed, serious skin reactions, and hematological, renal or cardiac events. DAAODP is currently reviewing an application for this product. The product has been available in Europe but the sponsor did not submit postmarketing data from overseas.

We reviewed 31 cases of adverse events reported in association with the use of topical diclofenac. Many of the reactions were serious in nature including seven deaths. The types of events included local reactions as well as systemic reactions including serious skin reactions, hematological, GI events, and several miscellaneous adverse events. In general, these cases were poorly documented or were confounded by the condition that they were treating, other medication, concurrent non-medication therapies, or possibly by underlying disease.

**SELECTION OF CASES**

We searched AERS on June 27, 2002 for all diclofenac reports to date with the following routes of administration – *cutaneous, occlusive dressing technique, topical, transdermal,* and *other*. One hundred thirty-two cases were retrieved, of which 6 were duplicates for a total of 126 cases. We excluded 95 for the following reasons:

- Reports involving other diclofenac formulations - 95
  - Cases involving diclofenac ophthalmic preparations - 71
  - Reports involving oral diclofenac with concomitant topical products – 14
  - Reports involving diclofenac tablets/ampoules/suppositories/unknown formulations – 10

## SUMMARY OF CASES

We reviewed 31 cases of adverse events reported in association with topical diclofenac. In general the cases were not well documented and because they were all foreign, pertinent information might have been lost during translation. The countries of origin included France-16, Germany-10, Hong Kong-1, Japan-1, Israel-1, Spain-1, and the United Kingdom-1. The first case occurred and was reported to the Agency in 1988. Distribution of cases by event year and the year the FDA received the cases are provided below:

Event year:	1988-1, 1990-1, 1992-1, 1993-1, 1994-3, 1995-2, 1996-4, 1997-3, 1998-3, 1999-4, 2000-4, 2001-2, unk-2
FDA received year:	1988-1, 1993-2, 1995-2, 1996-1, 1997-6, 1998-5, 1999-4, 2000-7, 2001-2, 2002-1

### Local reactions (12)

The local reactions included the following:

Skin necrosis (5)  
 Burns (2)  
 Application site reaction (2)  
 Infection of the forefinger (1)  
 Bleeding wound, localized inflammation (1)  
 Sensory disturbance (1)

There were five cases of skin necrosis that appeared to occur at the site of diclofenac application. Three patients were hospitalized, two of which required skin grafting. Two specified that the scarring occurred as a result of the necrosis and one patient reportedly lost the use of her legs. In 2 of the 5 cases, there were additional factors that might have contributed. In one case the patient was undergoing phonophoretic treatment using Voltaren Emulgel as the contact gel. The company for the instrument actually reported the case. The second reported the concurrent treatment of oral Fucidine (fusidic acid) and diclofenac gel for a swollen and warm wound following varicose vein stripping. Eight days after treatment with both products, the patient developed fever and skin necrosis of 15cm diameter. The case that appeared to be the most serious is summarized below.

AERS 3607694-9, MFR # PHRM2000FR01562, France, 2000

An 88-year-old female developed necrotic purpura of both legs sometime during Voltaren Emulgel treatment for gonarthrosis. She was hospitalized for three months,

during which time she underwent grafting of the necrotic areas. She reportedly lost the use of her legs and was hospitalized long term.

There were two cases involving skin burns and two cases that reported application site reactions. The burns were described as second or third degree burns. The two application site reactions were described as erythema, burning sensation, and edema in one case and redness, swelling, and pain in the second case. In 3 of the 4 cases, concurrent physical electrotherapy, iontophoresis, or kinesitherapy appeared to play a role. In both burn cases, allergy testing showed no sensitivity to Voltaren Emulgel.

There was one case involving an elderly female that was treated with both topical diclofenac and oral piroxicam for six days for a finger nodule and developed a local infection and leg edema. Both medications were discontinued and she was treated with antibiotics, tetanus vaccine, and diuretics but reportedly required phalanx amputation.

An elderly female patient reported a bleeding wound and localized inflammation of her right calf. She had reportedly taken topical diclofenac without a prescription for calf pain. The diclofenac did not relieve the calf pain and subsequently she developed an open wound. She was hospitalized and diagnosed with occlusive artery disease.

A 61-year-old male with myalgia developed considerable sensory disturbances and hematoma in the lumbar region of the back and at the right hip after application of Voltaren Emulgel. The patient was receiving several concomitant medications including aspirin. Hospitalization was not required but symptoms at the time of the report were still persisting.

### **Serious Skin Reactions (7)**

The systemic skin reactions included Stevens Johnson syndrome (SJS) or Lyell Syndrome (3), necrotizing fasciitis (1), pemphigus (1), toxic allergic reaction (1), and maculopapular rash (1). Three patients died and three were hospitalized for their events. In two of the cases of SJS, the role of topical diclofenac was impossible to assess because multiple suspect drug products were listed (10 and 33 suspect drugs).

A case of Lyell syndrome and necrotizing fasciitis both resulting in death are described below.

FDA 980880, MFR # 930201-001, France, 1992

A 77 year-old male developed Lyell syndrome. This was apparently discovered as part of an E.L.Y.S survey, the details of which were not provided. According to the report, he was applying Voltaren Emulgel twice per day for an unknown period of time for arthrosis pain. The exact dates of administration in relation to the onset of the event were not provided. One month before hospitalization, he developed pruritus of the face, which was treated with corticoides [sic] (presumably corticosteroids) and antihistamines. He was admitted with erythematous lesion on his face, thorax, and back. He also had buccal erosions but no genital or ocular lesions. He apparently died five days after admission.

FDA 1594520, MFR # 951030-001, Germany, 1994

An 81-year-old female experienced a fall and four days later presented with right arm pain. She was prescribed Voltaren Emulgel. One day later, she presented again with severe continuous pain in the right arm. The arm was swollen and she was hospitalized. A few hours later skin necrosis developed and she underwent fasciotomy. She developed circulatory instability and developed massive metabolic acidosis. The necrosis spread all over her body and she died a few days later from septic shock.

Although it was possible that topical diclofenac played a role in these two cases, the first case was not well documented with respect to the dates of administration and the event date. For the second case, it seems feasible that this event could have occurred as a result of the trauma itself. This case did not mention whether the patient developed compartment syndrome or an equally serious injury and it is not clear whether use of topical diclofenac might have exacerbated this event.

In 2 of the 3 remaining cases, hospitalization was required and the patients were improving on discontinuation of topical diclofenac and other suspected medications. The first involves an elderly woman who developed dysphagia and painful oral and pharyngeal ulcers of three months duration. She had been taking both topical diclofenac and diclofenac suppositories for a number of years. An oral mucosal biopsy was positive for pemphigus vulgaris. A migration inhibition factor test performed with the patient's lymphocytes yielded a positive response to diclofenac. A second case involved a man who developed a toxic allergic reaction after two days of topical diclofenac. No concomitant medications were reported. The reaction was described by the patient as "red skin with fever and chills" and by the physician as "resembling a second-degree burn". There was a case of maculo-papular and vesicular rash reported in association with topical diclofenac and hydroxyzine. The patient was also on other concomitant medications. All medications were discontinued and patient recovered.

### **Gastrointestinal Reactions (2)**

The GI reactions included gastric perforation (1) and GI bleed (1). One patient died and the other required hospitalization. In both cases, the GI events may have been caused by concomitant use of oral NSAIDs. The death case is described below.

FDA 821654, MFR # S8814061, Germany, 1988

A 78-year-old male was hospitalized and died following gastric perforation. He was receiving Voltaren Emulgel for lumbosacral spondylosis. He was also on concomitant oral and parenteral Effekton Retard (diclofenac), which was felt by the reporter to be more likely responsible for the event.

In addition to the case of gastric perforation described above, there is one case of GI bleeding (reported melena, hematemesis, and a decrease in hematocrit) in a 69-year-old male who was receiving topical diclofenac for approximately one week for arthralgias.

The patient was also receiving aspirin 500mg per day for an unknown period of time for headache.

### **Drug Interaction (2)**

There were two cases that reported a possible drug interaction between an anticoagulant (acenocoumarol and warfarin) and topical diclofenac. In one case an 86-year-old female who had been on acenocoumarol for years for a cardiac valve disorder, was placed on topical diclofenac for two days. She developed a left shoulder hematoma that extended to her left arm and breast. Her INR was elevated to 4.5. Topical diclofenac was discontinued, her anticoagulant dose was decreased, and her INR subsequently returned to normal. In the second case a 68-year-old male receiving warfarin for a heart valve replacement was placed on diclofenac gel for joint pain. On day 5 of diclofenac treatment, his INR was 4.0. No further information was provided.

### **Hematological Reactions (2)**

The hematological reactions included hemolytic anemia/thrombocytopenia (1) and agranulocytopenia/thrombopenia (1). One patient died and the other required hospitalization. The death case is described below

FDA 1361653, MFR # 930676-001, Great Britain, 1993

A 75-year-old female with chronic myelomonocytic leukemia was treated with transdermal Voltarol for 89 days and developed autoimmune hemolytic anemia and thrombocytopenia. Laboratory data however was not provided. Her concomitant medication included Co-proxamol (dextropropoxyphene/acetaminophen), isosorbide mononitrate, and aspirin. She was treated with prednisolone 40mg per day and the reaction abated with discontinuation of diclofenac. She later died due to a pulmonary embolus. The time that elapsed between the onset of the event and her death was not evident.

In the second case, four suspect drugs were listed with the most likely agent being colchicine.

### **Miscellaneous Reactions (6)**

The miscellaneous reactions included hypersensitivity/disseminated intravascular coagulation (1), status epilepticus/cardiac arrest (1), renal failure (1), rhabdomyolysis (1), spontaneous abortion (1), and hyponatremia (1). Two patients died and the other four required hospitalization. In the first four cases listed above, the role of topical diclofenac was impossible to assess because multiple suspect drug products were listed (6 to 18 suspect drugs).

There was one case of a 40-year-old female who had a spontaneous abortion at 12 weeks gestation. She was treated sometime during her pregnancy with topical diclofenac for an unknown reason but the treatment dates and duration were unknown. She was taking no other medication and had one previous child who died from chondrodysplasia fetalis.

There was one case of hyponatremia (Na 113 mmol/L) reported in a 71-year-old female with a history hypothyroidism. There was a question of compliance with her thyroid replacement therapy. Fluoxetine, which is labeled for hyponatremia, was also suspected and was temporally related to the event. She was hospitalized and all medications except levothyroxine were discontinued.

## **CONCLUSION**

We reviewed 31 cases of adverse events reported in association with the use of topical diclofenac. Many of the reactions were serious in nature including seven deaths. The types of events included local reactions as well as systemic reactions including serious skin reactions, hematological, GI events, and several miscellaneous adverse events. In general, these cases were poorly documented or were confounded by the condition that they were treating, other medication, concurrent non-medication therapies, or possibly by underlying disease.

---

Claudia B. Karwoski, Pharm.D

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

/s/

-----  
Claudia Karwoski  
7/24/02 08:16:11 AM  
PHARMACIST

Julie Beitz  
7/24/02 01:45:57 PM  
DIRECTOR