CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-947

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

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

Date:	November 2, 2009
To:	Bob Rappaport, M.D. Director **Division of Anesthesia, Analgesia and Rheumatology Products (DAARP)**
Through:	Claudia Karwoski, Pharm.D., Director **Division of Risk Management (DRISK)** LaShawn Griffiths, MSHS-PH, BSN, RN Patient Labeling Reviewer, Acting Team Leader **Division of Risk Management**
From:	Jessica M. Diaz, BSN, RN Patient Product Information Reviewer **Division of Risk Management** Robin Duer, MBA, BSN, RN Patient Product Information Reviewer **Division of Risk Management**
Subject:	DRISK Review of Patient Labeling (Medication Guide and Instructions for Use) and Proposed Risk Evaluation and Mitigation Strategy (REMS)
Drug Name(s):	PENNSAID (diclofenac sodium) Topical Solution
Application Type/Number:	NDA 20-947
Applicant/sponsor:	Nuvo Research, Inc.
OSE RCM #:	2009-2057

1 INTRODUCTION

This review is written in response to a request by the Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP) for the Division of Risk Management (DRISK) to review the proposed Medication Guide (MG), Patient Instructions for Use (IFU), and Risk Evaluation and Mitigation Strategy (REMS) for PENNSAID (diclofenac sodium). Please let us know if you would like a meeting to discuss these comments before sending to the Applicant. The DRISK review of the methodology and survey instruments once submitted by the Applicant to evaluate the REMS will be provided under separate cover.

2 MATERIAL REVIEWED

- Draft PENNSAID (diclofenac sodium) Topical Solution Prescribing Information (PI) submitted on June 28, 2006 and revised by the Review Division throughout the current review cycle
- Draft PENNSAID (diclofenac sodium) Topical Solution Medication Guide (MG) and Instructions for Use (IFU) submitted on October 26, 2009
- PENNSAID (diclofenac sodium) Risk Evaluation and Mitigation Strategy (REMS) Email Request dated October 23, 2009
- Proposed PENNSAID (diclofenac sodium) Risk Evaluation and Mitigation Strategy (REMS), submitted on October 26, 2009

3 RESULTS OF REVIEW

In our review of the MG and IFU we have:

- simplified wording and clarified concepts where possible
- ensured that the MG and IFU are consistent with the PI
- removed unnecessary or redundant information
- ensured that the MG and IFU meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG and IFU meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

In our review of the proposed REMS, we have ensured it meets the statutory requirements under the Food and Drug Administration Act of 2007.

4 CONCLUSIONS AND RECOMMENDATIONS

DRISK concurs with the MG, IFU and the elements of the REMS with revisions provided in this review.

Please note, the timetable for submission of the assessments is required to be approved as part of the REMS, but not the Applicant's proposed information about the details of the REMS evaluation (methodology/instruments) used for the assessments. The methodology and instruments **do not** need to be reviewed or approved prior to approval of the REMS.

We have the following comments and recommendations for DAARP and the Applicant with regard to the proposed REMS.

Comments to DAARP:

Our annotated MG and IFU are appended to this memo (Appendices A and B). Any additional revisions to the PI should be reflected in the MG and IFU.

Comments for Applicant:

See the appended PENNSAID (diclofenac) REMS proposal (Appendix C of this memo) for track changes corresponding to comments in this review.

a. GOAL

Revise your goal as follows:

The goal of this REMS is to inform patients about the serious risks associated with the use of PENNSAID Topical Solution.

b. We have some editorial comments for the Medication Guide distribution plan in this proposed REMS.

c. We acknowledge that you will include the required statement on the label of each container instructing the dispenser to provide the Medication Guide to each patient in accordance with 21 CFR 208.24(d). We recommend the following language.

If unit of use: "Dispense the enclosed Medication Guide to each patient."

If not unit of use: "Dispense the accompanying Medication Guide to each patient."

d. Your proposed timetable for submission of assessments (18 months, 3 years, and 7 years) is acceptable.

We have some editorial comments in this section of the proposed REMS.

e. Appendix D (REMS Supporting Document) was not included with this REMS submission. However, you did include information about assessments in the Proposed REMS. DRISK and DAARP agree to create an Appendix D for you as the REMS Supporting Document is more appropriate for information (See Appendix D of this memo) about the assessments. Please also keep in mind, your detailed plan (i.e. assessment protocol) should be submitted at least 90 days before you plan to conduct the evaluation. The submission should be coded "REMS Correspondence."

Please let us know if you have any questions.

Appendix A: Medication Guide

Medication Guide

For

Non-steroidal Anti-Inflammatory Drugs (NSAIDS)

(See the end of this Medication Guide for a list of prescription NSAID medicines.)

What is the most important information I should know about medicines called Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)?

NSAID medicines may increase the chance of a heart attack or stroke that can lead to death. This chance increases:

- with longer use of NSAID medicines
- in people who have heart disease

NSAID medicines should never be used right before or after a heart surgery called a "coronary artery bypass graft (CABG)."

NSAID medicines can cause ulcers and bleeding in the stomach and intestines at any time during treatment. Ulcers and bleeding:

- can happen without warning symptoms
- may cause death

The chance of a person getting an ulcer or bleeding increases with:

- taking medicines called "corticosteroids" and "anticoagulants"
- longer use
- smoking
- drinking alcohol
- older age
- having poor health

NSAID medicines should only be used:

- exactly as prescribed
- at the lowest dose possible for your treatment
- for the shortest time needed

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

NSAID medicines are used to treat pain and redness, swelling, and heat (inflammation) from medical conditions such as:

- different types of arthritis
- menstrual cramps and other types of short-term pain

Who should not take a Non-Steroidal Anti-Inflammatory Drug (NSAID)?

Do not take an NSAID medicine:

- if you had an asthma attack, hives, or other allergic reaction with aspirin or any other NSAID medicine
- for pain right before or after heart bypass surgery

Tell your healthcare provider:

- about all of your medical conditions.
- about all of the medicines you take. NSAIDs and some other medicines can interact with each other and cause serious side effects. **Keep a list of your medicines to show to your healthcare provider and pharmacist.**
- if you are pregnant. **NSAID medicines should not be used by pregnant women late in their pregnancy.**
- if you are breastfeeding. **Talk to your doctor.**

What are the possible side effects of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)?

Serious side effects include:	**Other side effects include:**
• heart attack • stroke • high blood pressure • heart failure from body swelling (fluid retention) • kidney problems including kidney failure • bleeding and ulcers in the stomach and intestine • low red blood cells (anemia) • life-threatening skin reactions	• stomach pain • constipation • diarrhea • gas • heartburn • nausea • vomiting • dizziness

• life-threatening allergic reactions • liver problems including liver failure • asthma attacks in people who have asthma	

Get emergency help right away if you have any of the following symptoms:

- shortness of breath or trouble breathing
- chest pain
- slurred speech
- weakness in one part or side of your body
- swelling of the face or throat

Stop your NSAID medicine and call your healthcare provider right away if you have any of the following symptoms:

- nausea
- more tired or weaker than usual
- itching
- your skin or eyes look yellow
- stomach pain
- flu-like symptoms
- vomit blood

- there is blood in your bowel movement or it is black and sticky like tar
- unusual weight gain
- skin rash or blisters with fever
- swelling of the arms and legs, hands and feet

These are not all the side effects with NSAID medicines. Talk to your healthcare provider or pharmacist for more information about NSAID medicines.

Other information about Non-Steroidal Anti-Inflammatory Drugs (NSAIDs):

- Aspirin is an NSAID medicine but it does not increase the chance of a heart attack. Aspirin can cause bleeding in the brain, stomach, and intestines. Aspirin can also cause ulcers in the stomach and intestines.
- Some of these NSAID medicines are sold in lower doses without a prescription (over-the-counter). Talk to your healthcare provider before using over-the-counter NSAIDs for more than 10 days.

NSAID medicines that need a prescription

Generic Name	Tradename
Celecoxib	Celebrex®
Diclofenac	Flector, Cataflam®, Voltaren®, Arthrotec™ (combined with misoprostol), Pennsaid® Topical Solution
Diflunisal	Dolobid®
Etodolac	Lodine®, Lodine®XL
Fenoprofen	Nalfon®, Nalfon®200
Flurbirofen	Ansaid®
Ibuprofen	Motrin®, Tab-Profen®, Vicoprofen®* (combined with hydrococ Combunox™ (combined with oxycodone)
Indomethacin	Indocin®, Indocin®SR, Indo-Lemmon™, Indomethagan™
Ketoprofen	Oruvail®
Ketorolac	Toradol®
Mefenamic Acid	Ponstel®
Meloxicam	Mobic®
Nabumetone	Relafen®
Naproxen	Naprosyn®, Anaprox®, Anaprox®DS, EC-Naproxyn®, Naprelar Naprapac® (copackaged with lansoprazole)
Oxaprozin	Daypro®
Piroxicam	Feldene®
Sulindac	Clinoril®
Tolmetin	Tolectin®, Tolectin DS®, Tolectin®600

*Vicoprofen contains the same dose of ibuprofen as over-the-counter (OTC) NSAID, and is usually used for less than 10 days to treat pain. The OTC NSAID

label warns that long term continuous use may increase the risk of heart attack or stroke.

This Medication Guide has been approved by the U.S. Food and Drug Administration. ***DRISK Comment: Do not use italics in patient labeling. Use bolding to highlight important information.]***

DRISK Comment: The name and address of the manufacturer, distributor or packer should be added along with the date the MG was issued.]

Month/Year

Appendix B: Patient Instructions for Use

Patient Instructions for Use

PENNSAID *[DRISK Comment: Applicant should insert phonetic spelling here.]*

(diclofenac sodium)

Topical Solution

Your doctor has prescribed PENNSAID Topical Solution to treat your pain from osteoarthritis in your knee(s) and help you manage your daily activities better.

[DRISK Comment: To avoid redundancy, we deleted identical information from this section that also appears later in the instructions below. Additionally, for clarity we organized the information presented in these IFU into "before, during and after" use and deleted extraneous information.]

Before you use PENNSAID Topical Solution:

- Apply PENNSAID Topical Solution exactly as your doctor tells you. Do not apply PENNSAID® Topical Solution anywhere on your body other than where your doctor tells you.

- Apply PENNSAID Topical Solution on clean, dry skin that does not have any cuts, infections or rashes.

- Use PENNSAID Topical Solution 4 times each day on your knee(s). ***[DRISK Comment: The statement*** ——————————— ——— ***was deleted as it does not appear in the PI. This information must be added in the PI before it can added to the IFU.]*** b(4)

- Do not get PENNSAID Topical Solution in your eyes, nose or mouth. Only use PENNSAID Topical Solution on your skin (topical use). If you get PENNSAID Topical Solution in your eyes, rinse your eyes right away with water or saline. Call your doctor if your eyes are irritated for more than one hour.

DRISK Comment: The ——————————— ***section was deleted as that information is not included in the PI. We agree that this is important information for the patient to know, but this information must be added in the PI before it can added to the IFU.]*** b(4)

Steps for using PENNSAID Topical Solution:

Step 1. Wash your hands with soap and water before and after applying PENNSAID Topical Solution.

Step 2. **Your total dose for each knee is 40 drops of PENNSAID Topical Solution. You will use 10 drops at a time. Put 10 drops of PENNSAID Topical Solution either on your hand or directly on your knee.** *[DRISK Comment: A labeled figure showing this should be added.]*

Step 3. **Spread PENNSAID® Topical Solution evenly on the front, back and sides of your knee. Repeat this step 4 times so that your knee is completely covered with a total of 40 drops of PENNSAID Topical Solution.** *[DRISK Comment: A labeled figure showing this should be added.]*

Step 4. Repeat — 3 for the other knee if needed.

b(4)

After you use PENNSAID Topical Solution:

Do not

- cover your knee with clothing until your knee is completely dry
- put sunscreen, insect repellant, lotion, moisturizer, cosmetics, or other topical medicines on your knee until it is completely dry
- take a shower or a bath for at least 30 minutes after you put PENNSAID® Topical Solution on your knee(s).
- use heating pads or apply bandages to the skin where you have applied PENNSAID® Topical Solution.
- expose your skin to sunlight or artificial light (tanning booths) where you have put PENNSAID® Topical Solution.

How should I store PENNSAID Topical Solution?:

- Store PENNSAID Topical Solution between 59°F to 86°F (15°C to 30°C).

Keep PENNSAID Topical Solution and all medicines out of the reach of children.

Appendix B: Patient Instructions for Use

Patient Instructions for Use

PENNSAID ***[DRISK Comment: Applicant should insert phonetic spelling here.]***

(diclofenac sodium)

Topical Solution

Your doctor has prescribed PENNSAID Topical Solution to treat your pain from osteoarthritis in your knee(s) and help you manage your daily activities better.

[DRISK Comment: To avoid redundancy, we deleted identical information from this section that also appears later in the instructions below. Additionally, for clarity we organized the information presented in these IFU into "before, during and after" use and deleted extraneous information.]

Before you use PENNSAID Topical Solution:

- Apply PENNSAID Topical Solution exactly as your doctor tells you. Do not apply PENNSAID® Topical Solution anywhere on your body other than where your doctor tells you.

- Apply PENNSAID Topical Solution on clean, dry skin that does not have any cuts, infections or rashes.

- Use PENNSAID Topical Solution 4 times each day on your knee(s). ***[DRISK Comment: The statement ———————— was deleted as it does not appear in the PI. This information must be added in the PI before it can added to the IFU.]*** b(4)

- Do not get PENNSAID Topical Solution in your eyes, nose or mouth. Only use PENNSAID Topical Solution on your skin (topical use). If you get PENNSAID Topical Solution in your eyes, rinse your eyes right away with water or saline. Call your doctor if your eyes are irritated for more than one hour.

DRISK Comment: The ———————— section was deleted as that information is not included in the PI. We agree that this is important information for the patient to know, but this information must be added in the PI before it can added to the IFU.] b(4)

Steps for using PENNSAID Topical Solution:

Step 1. Wash your hands with soap and water before and after applying PENNSAID Topical Solution.

Step 2. **Your total dose for each knee is 40 drops of PENNSAID Topical Solution. You will use 10 drops at a time. Put 10 drops of PENNSAID Topical Solution either on your hand or directly on your knee.** *[DRISK Comment: A labeled figure showing this should be added.]*

Step 3. **Spread PENNSAID® Topical Solution evenly on the front, back and sides of your knee. Repeat this step 4 times so that your knee is completely covered with a total of 40 drops of PENNSAID Topical Solution.** *[DRISK Comment: A labeled figure showing this should be added.]*

Step 4. Repeat —— 3 for the other knee if needed.

b(4)

After you use PENNSAID Topical Solution:

Do not

- cover your knee with clothing until your knee is completely dry
- put sunscreen, insect repellant, lotion, moisturizer, cosmetics, or other topical medicines on your knee until it is completely dry
- take a shower or a bath for at least 30 minutes after you put PENNSAID® Topical Solution on your knee(s).
- use heating pads or apply bandages to the skin where you have applied PENNSAID® Topical Solution.
- expose your skin to sunlight or artificial light (tanning booths) where you have put PENNSAID® Topical Solution.

How should I store PENNSAID Topical Solution?:

- Store PENNSAID Topical Solution between 59°F to 86°F (15°C to 30°C).

Keep PENNSAID Topical Solution and all medicines out of the reach of children.

Appendix C: Proposed REMS

NDA 20-947

PENNSAID® (diclofenac sodium)

Topical Solution

Non-Steroidal Anti-Inflammatory Drug (NSAID)

Nuvo Research Inc.

10-7560 Airport Road

Mississauga, ON CANADA

Contact Information:

Herbert Neuman, MD

Chief Medical Officer, Vice President Medical Affairs

Covidien Pharmaceuticals

(314-654-3940)

RISK EVALUATION AND MITIGATION STRATEGY

REMS

I. GOAL:

The goal of this REMS is to inform patients about the serious risks associated with the use of PENNSAID® Topical Solution.

II. REMS ELEMENTS:

A. Medication Guide

Nuvo Research Inc. will ensure a Medication Guide will be dispensed with each PENNSAID® (diclofenac sodium) prescription in accordance with 21 CFR 208.24.

PENNSAID is packaged as a single unit package and the Medication Guide is included as part of the secondary package. It is not intended to be divided prior to dispensing. The Medication Guide is included as part of the secondary package.

Pursuant to 21 CRF 208.24(d), Nuvo Research, Inc. will include the appropriate statement on the outer cartons of the medication to remind the dispenser to provide the patient with the Medication Guide.

B. Timetable for Submission of Assessments

Nuvo Research, Inc. will submit REMS Assessments to the FDA 18 months, 3 years, and 7 years from the date of the approval of the REMS. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. Nuvo Research, Inc. will submit each assessment so it will be received by the FDA on or before the due date.

Appendix D: REMS Supporting Document

NDA 20-947

PENNSAID® (diclofenac sodium)

Topical Solution

REMS Supporting Document

1. Background

PENNSAID (diclofenac sodium) Topical solution is a nonsteroidal anti-inflammatory drug (NSAID) indicated for the treatment of signs and symptoms of osteoarthritis of the knee(s), including pain and impaired ability to perform daily activities.

2. Goals

The goal of this REMS is to inform patients about the serious risks associated with the use of PENNSAID® Topical Solution.

3. Supporting Information on Proposed REMS Elements

a. Medication Guide

A proposed Medication Guide for PENNSAID is attached. The proposed Medication Guide is scientifically accurate and has been created based on the information described in the proposed FPI for PENNSAID. The proposed Medication Guide has been written in non-technical language intended to be understood by patients.

The Medication Guide appears in Section 17.1 of the FPI for PENNSAID. PENNSAID is packaged for sale to distributors, retail pharmacies and other dispensers. The FPI containing the Medication Guide will be included in each PENNSAID product container. In accordance with 21 CFR 208.24(d), each container label will alert authorized dispensers to dispense a Medication Guide with each prescription of PENNSAID.

In accordance with 21 CFR 208.24 (b), Nuvo Research, Inc will make the Medication Guide available for distribution to patients by providing the means to permit authorized dispensers to product the Medication Guides in sufficient numbers to meet the dispenser obligations under 21 CFR 208.24 (e).

b. Timetable for Submission of Assessment of the REMS

Nuvo Research, Inc. will submit REMS Assessments to the FDA 18 months, 3 years, and 7 years from the date of the approval of the REMS.

Nuvo Research, Inc. will ensure the timetable is consistent with the requirements outlined in Title IX, Subtitle A, Section 901 of FDAAA 2007. The timetable may be increased or reduced in frequency, as necessary, by the FDA in accordance with the provisions described in Title IX, Subtitle A, Section 901 FDAAA.

c. Information Needed for Assessments

The Assessment Protocol submission will include methodology and instruments to be used to evaluate the patients' understanding about the safe use of PENNSAID® Topical Solution. This will include, but not be limited to:

- Sample size and confidence associated with that sample size
- How the sample will be determined (selection criteria)
- The expected number of patients to be surveyed
- How the participants will be recruited
- How and how often the surveys will be administered
- Explain controls used to minimize bias
- Explain controls used to compensate for the limitations associated with the methodology
- The survey instruments (questionnaires and/or moderator's guide).
- Any background information on testing survey questions and correlation to the messages in the Medication Guide.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20947	ORIG-1	NUVO RESEARCH INC	PENNSAID(DICLOFENAC SODIUM)1.5% TOP LOTI

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

/s/

ROBIN E DUER
11/02/2009

CLAUDIA B KARWOSKI
11/03/2009
concur

MEMORANDUM

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

DATE: October 23, 2006

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

FROM: Claudia B. Karwoski, Pharm.D., Scientific Coordinator,
Office of Surveillance and Epidemiology, (OSE)

DRUG: PENNSAID (1.5 % w/w diclofenac sodium) Topical Solution

NDA #: 20-947

APPLICANT: Dimethaid International (c/o Nuvo Research)

SUBJECT: Review of Risk Assessment and Risk Management submitted June 28, 2006 with Complete Response to August 7, 2002 NA letter

PID #: D060649

This consult follows a request by the Division of Anesthesia, Analgesia, and Rheumatology Products for the Office of Surveillance and Epidemiology (OSE) to review and comment on the Sponsor's proposed Risk Assessment and Risk Management Plan (RMP) for Pennsaid.

Pennsaid is a topical solution containing diclofenac, a new formulation of an approved product already on the U.S. market. The Sponsor's submission does not identify any unique safety issues with this topical formulation nor would we anticipate that a topical formulation would have additional safety concerns for which a Risk Minimization Action Plan (RiskMAP) or RMP to minimize risk would be normally associated. We also note that oral diclofenac does not have any risk management tools beyond standard product labeling and the NSAID Class Medication Guide.

The sponsor submitted the required NSAID Class Labeling including the NSAID Class Medication Guide for this product and that consult was performed by the OSE Division of Surveillance, Research and Communication Support (DSRCS). Should the review division wish OSE to review any proposed Phase IV protocols or epidemiological post-marketing studies, please provide a consult request.

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/s/

Mary Dempsey
10/23/2006 02:37:58 PM
DRUG SAFETY OFFICE REVIEWER

Claudia Karwoski
10/23/2006 02:48:27 PM
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