

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**20-947**

**CROSS DISCIPLINE TEAM LEADER REVIEW**

## Addendum to Cross-Discipline Team Leader Review

<b>Date</b>	29 October 2009
<b>From</b>	Robert B. Shibuya, M.D.
<b>Subject</b>	Addendum to Cross-Discipline Team Leader Review
<b>NDA/BLA # Supplement#</b>	20-947 (000, 3 <sup>rd</sup> cycle)
<b>Applicant</b>	Dimethaid International, Inc./Nuvo
<b>Date of initial Submission</b>	4 February 2009
<b>Date of major amendment</b>	3 August 2009
<b>PDUFA date</b>	3 November 2009

This addendum will address two issues. The first is the finding of lymphomas in a toxicology study that resulted in my original recommendation not to approve this product. The second is to briefly document why we have concluded that the dimethyl sulfoxide (DMSO) component of the product is not an active ingredient.

### Lymphomas:

In my July 9, 2009 CDTL review, I recommended against approval because of the lymphomas observed in a 26-week rat toxicology study which our Pharmacology/Toxicology (P/T) team could not rule out as treatment-related without a formal carcinogenicity study.

In response to being formally advised that the P/T team was recommending against approval, the Applicant conducted additional testing on the tissues from the rat study and convened a panel of expert veterinary pathologists to review pertinent slides. This was submitted as a major amendment on 3 August 2009. The PDUFA clock was extended three months to permit the review of the submission.

Key findings from the Applicant's extensive review process follow:

1. One low-dose female developed a T-cell lymphoma and one mid-dose female developed a lymphoma that could not be identified with regard to T- or B-cell lineage.
2. Two low -dose males developed epithelial thymomas (one benign, one malignant). This is a new finding following re-review of the slides.
3. No pre-neoplastic or proliferative activity was noted in the test or control groups.

These additional data have been reviewed by Drs. Leshin and Wasserman. Dr. Leshin does not believe that the additional data submitted support the Applicant's conclusion that the lymphoma cases do not constitute a "signal" for carcinogenicity. Dr. Wasserman, with the concurrence of Dr. Paul Brown, believes that the submission supports the conclusion that the cases do not represent a "signal." Drs. Wasserman and Brown conclude this based primarily on the lack of dose response, the blinded reading and opinion by expert pathologists, and the absence of proliferative or pre-neoplastic lesions in treated and control tissues.

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Dr. Wasserman notes the importance of the Applicant completing a two-year carcinogenicity study as soon as possible to confirm this conclusion. He is also recommending reproductive toxicology studies (Segments I and III) for DMSO to be conducted as Post Marketing Requirements.

**DMSO is not an active ingredient:**

Study PEN-03-112 was a randomized, double-blind, active-, placebo-, and vehicle-controlled study of a factorial design. The vehicle contained DMSO at a concentration of 45.5% with the additional excipients found in Pennsaid. In this adequate and well-controlled study, the vehicle showed no analgesic activity. Thus, the data support the conclusion that DMSO, at the concentration in the Pennsaid formulation, does not have analgesic activity.

**Recommendation:**

Approval with postmarketing requirements for carcinogenicity and reproductive toxicity for DMSO.

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

NDA-20947

ORIG-1

DIMETHAID  
RESEARCH INC

PENNSAID(DICLOFENAC  
SODIUM)1.5% TOP LOTI

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ROBERT B SHIBUYA  
10/29/2009

## Cross-Discipline Team Leader Review

<b>Date</b>	9 July 2009
<b>From</b>	Robert B. Shibuya, M.D.
<b>Subject</b>	Cross-Discipline Team Leader Review
<b>NDA/BLA #</b>	20-947 (000, 3 <sup>rd</sup> cycle)
<b>Supplement#</b>	
<b>Applicant</b>	Nuvo Research, Inc.
<b>Date of Submission</b>	4 February 2009
<b>PDUFA Goal Date</b>	4 August 2009
<b>Proprietary Name / Established (USAN) names</b>	Pennsaid topical solution/1.5% w/w diclofenac sodium
<b>Dosage forms / Strength</b>	Topical solution/1.5%
<b>Proposed Indication(s)</b>	"...treatment of signs and symptoms of osteoarthritis of the knee(s)..."
<b>Recommended:</b>	<i>Complete Response</i>

<b>Material Reviewed/Consulted</b>	
OND Action Package, including:	
Primary Medical Officer Review	Nick Olmos-Lau, M.D.
Pharmacology Toxicology Review	L. Steven Leshin, D.V.M, Ph.D. Adam Wasserman, Ph.D.
CMC Review	Olen Stephens, Ph.D. Ali Al-Hakim, Ph.D.
Clinical Pharmacology Review	David Lee, Ph.D. Suresh Doddapaneni, Ph.D.
OSE/DMEPA	Pending
Statistics	Steve Thompon Stella Machado, Ph.D.

### 1. Introduction

This is the third review cycle for this topical formulation of diclofenac [1.5% in 45.5% dimethyl sulfoxide (DMSO)]. The Applicant seeks an indication of the "treatment of signs and symptoms of osteoarthritis of the knee(s), \_\_\_\_\_"

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Pennsaid has a long regulatory history dating back to its initial NDA submission in 1997 which will be covered in greater detail in Section 2 of this review. For the purposes of this introduction, suffice it to say that the deficiencies conveyed in the most recent Approvable Letter, to which the Applicant has currently responded, all pertain to the

chemistry/manufacturing/controls (CMC) and pharmacology/toxicology (P/T) disciplines. However, because the P/T team has raised an issue with malignancies observed in a toxicology study, to completely discuss the risk-to-benefit ratio, the previous clinical data will be briefly described. The recommendation and risk benefit analysis are also influenced by the fact that Voltaren Gel, a topical nonsteroidal anti-inflammatory drug (NSAID) product, indicated for osteoarthritis, has been approved since the last review cycle for this product.

## 2. Background

As noted earlier, Pennsaid has a long, complex regulatory history. This is technically the third review cycle for this product. Previous review cycles and outcomes are summarized following:

### Cycle #0 (not officially a review cycle because the Applicant withdrew the NDA)

Submission date: 15 December 1997

Action date: Not applicable, Applicant withdrew

Action: Not applicable. However, a Non-approvable letter was issued on 16 December 1998

Key Deficiencies:

1. Applicant has not demonstrated substantial evidence of efficacy
2. Fourteen CMC deficiencies

### Cycle #1

Submission date: 7 August 2001

Action date: 7 August 2002

Action: Non-approvable

Key Deficiencies:

1. Demonstrate efficacy at the site of application.
2. Key clinical studies (RA-CP-109 and RA-CP-109US) had inconsistent results based upon the imputation methods.
3. Demonstrate that DMSO is not analgesic and to adequately define the adverse event profile of 45.5% DMSO
4. Inadequate adverse event reporting in long-term studies and a lack of long-term safety data.

### Cycle #2

Submission date: 28 June 2006

Action date: 28 December 2006

Action: Approvable

Deficiencies:

1. Demonstrate that the DMSO component of the product does not, through its solubilizing properties, result in excessive exposure to likely environmental toxins and microbiological agents (e.g., DEET, sunscreen active components), and/or provide data to define a time period after product application during which patients must avoid these exposures and that can be appropriately addressed in the product labeling.
2. Assess the toxicological potential of PENNSAID® in repeat-dose dermal toxicology studies because of the potentially high level of absorption of the product components

due to the DMSO and because DMSO is considered a novel topical excipient due to its high concentration.

3. Limit the \_\_\_\_\_ impurity, which contains a structural alert, to NMT \_\_\_\_\_ micrograms total daily intake. Tighten the acceptance criterion for this \_\_\_\_\_ impurity to NMT \_\_\_\_\_ in the drug product or characterize its genotoxic potential in a minimal genetic toxicology screen. b(4)
4. Limit the extractables from the HDPE bottles according to Agency guidelines or provide appropriate toxicological qualification of these impurities.
5. Switch all packaging from \_\_\_\_\_ to HDPE bottles, after addressing the toxicological potential of the extractables from the HDPE bottles as noted above. b(4)
6. Characterize the carcinogenic potential of PENNSAID via dermal carcinogenicity studies, or provide an adequate scientific rationale for why such information is not necessary for the safe use of the product.
7. Conduct appropriate photostability studies to assess the potential for photodegradation impurities, and characterize the toxicity of any impurities found in these studies if above the qualification threshold described by ICH Q3b guidelines.

As clear in the discussion above, at this time, the only current, outstanding deficiencies pertain to the CMC and P/T disciplines.

Other key points to consider in the current assessment of Pennsaid include the approved therapies for osteoarthritis (OA). Therapies for OA include those delivered by the topical, oral, and injectable routes.

Topical: Capsaicin (Zostrix), salicylates (Aspercreme), and diclofenac (Voltaren gel)

Oral: Various prescription and over-the-counter nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen and acetaminophen combination drugs, and opioid analgesics. All of the oral products have substantial safety issues. The serious gastrointestinal, cardiovascular, and renal toxicities associated with the use of NSAIDs are well recognized as are issues with abuse, misuse, and diversion for narcotics. Even acetaminophen, which has been perceived as relatively safe, is associated with approximately 50,000 Emergency Department visits and approximately 20,000 hospitalizations due to overdose per year in the United States. Because of the toxicities associated with the use of systemic NSAIDs, there has been interest in the development of topical NSAIDs with the goal of decreasing systemic exposure.

Injectable: Intra-articular steroids (Kenalog) and viscosupplementation (Synvisc, Hyalgan)

### 3. CMC/Device

The CMC review was conducted by Olen Stephens, Ph.D. with secondary concurrence by Ali Al-Hakim, Ph.D..

The most recent Action Letter contained three deficiencies related to the CMC discipline and the Applicant provided updated stability data. The deficiencies from the current Action Letter and current review team's assessment included:

- Deficiency 2: The toxicological consequences of a 45.5% DMSO solution  
The toxicological issue for DMSO will be discussed in Section 4.
- Deficiency 3: The specification limit for a potentially genotoxic ——— impurity  
The issues regarding the ——— impurity was addressed to the satisfaction of the CMC and P/T teams.
- Deficiency 4: The effect of 45.5% DMSO on leachables/extractables from the container closure system.

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Seven extractables (potential leachables) were identified and a toxicological assessment was provided through literature research. None of the extractable impurities were noted to accumulate through 12 months. The leachables comprised three of these extractables, but were at sufficiently low levels to not provide a toxicological concern. Thus, Drs. Stephens and Al-Hakim (with agreement by Drs Leshin and Wasserman) concluded that this deficiency has been addressed for potential impurities from inside the container closure system.

Drs. Stephens and Al-Hakim have raised concerns regarding the potential from leachables from the product label arising from contact outside the bottle which is further discussed in Section 4.

The review of the facilities for manufacturing, testing, and packaging from the Office of Compliance is pending.

Drs. Stephens and Al-Hakim have recommended approval from the CMC perspective, pending satisfactory inspections and appropriate labeling to address the label leachables.

#### **4. Nonclinical Pharmacology/Toxicology**

The Pharmacology/Toxicology review was conducted by L. Steven Leshin, Ph.D., D.V.M. with a secondary review by Adam Wasserman, Ph.D.. The pharmacology and toxicology review has not been finalized at this time.

The most recent Action Letter contained three deficiencies related to the P/T discipline and the Applicant provided updated stability data. The deficiencies from the current Action Letter and current review team's assessment included:

- Deficiency 1: Demonstrate that DMSO does not result in excessive exposure to likely environmental toxins and microbiological agents and/or provide data to define a time period where patients must avoid such exposures:
  - Pennsaid is unlikely to markedly enhance exposure to environmental agents.

- **Deficiency 2:** Assess the toxicological potential of DMSO
  - Discussed in detail below.
  
- **Deficiencies 4 & 5:** Leachables
  - The leachables from the HDPE bottles meet acceptable limits.
  - However, in conjunction with CMC, P/T has raised concern about the potential for leachables from the product label. Specifically, Dr. Leshin, noting that DMSO is an excellent solvent, notes that a patient would not reasonably be expected to wash and dry his or her hands after dosing one knee. Thus, the patient could handle the bottle/label with DMSO on the hands and be exposed to constituents of the label. The Applicant conducted an extractability study of a representative label. Dr. Leshin sent the extractables for Computational Toxicology analysis and 3 of 4 of the compounds identified were predicted to be carcinogenic in rodents. However, Dr. Leshin lacks information for leachable compounds and amounts to enable an appropriate toxicological assessment. It is assumed, based on bottle leachables, that the label leachables would also be sufficiently low to mitigate toxicological concern.
  
- **Deficiency 6:** Characterize the carcinogenic potential of Pennsaid via dermal carcinogenicity
  - See Deficiency 2, Toxicology of DMSO.
  
- **Deficiency 7:** Conduct photostability studies, assess the potential for photodegradation impurities and characterize the toxicity of any impurities
  - The photostability studies showed photodegradants similar to Solaraze, a topical diclofenac product indicated for the treatment of actinic ketatosis. While some of the degradants have the potential for genotoxicity and carcinogenicity, Agency policy has been to label to avoid UV exposure in similar circumstances. The P/T team has recommended labeling to address this issue.

The P/T review team has also identified a lack of reliable reproductive toxicology data to inform labeling. Despite the fact that this deficiency was not previously articulated to the Applicant, the proposed patient population for Pennsaid does not exclude women of childbearing potential and reprotox studies should be conducted.

#### **Toxicology of DMSO (Deficiencies 2 & 6)**

Chronic dermal toxicology studies were conducted in minipigs for 52 weeks and rats for 26 weeks. The following test articles were dosed to the skin TID:

- Pennsaid vehicle at 0% DMSO (vehicle)
- Pennsaid vehicle at 9% DMSO (Low-dose=LD)
- Pennsaid vehicle at 45.5% DMSO (Mid-dose=MD)
- Pennsaid vehicle at 90% DMSO (Low-dose=HD)

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The 52-week minipig study showed reversible local toxicity (erythema, slight edema) although one HD female was sacrificed in extremis. The necropsy showed pulmonary inflammation and edema.

The 26-week rat study found more toxicity which might be explained by higher DMSO exposures. Again, reversible local toxicity was noted. There was dose-dependent mortality with 0/50, 1/50, 2/50, and 4/50 animals dying in the vehicle, 9%, 45.5%, and 90% groups, respectively. Dr. Wasserman notes that the pattern of causation for the deaths is not clearly dose-dependent. Information regarding the rat deaths is summarized in Table 1, excerpted from Dr. Wasserman's review.

**Table 1: Mortality summary from 26-week rat DMSO toxicology study**

	Vehicle	LD (9%)	MD (45.5%)	HD (90%)
<b>Male/Female Data</b>				
<i>Mortality – main study</i>				
# deaths <sup>@</sup>	0/50	1/50	2/50	4/50
Explanation	None	Malignant lymphoma (F)	Malignant lymphoma (F)	Urogenital tract obstruction use (F)
			Focal necrosis of brainstem (F)	Unknown (F)
				Unknown (F)
				Unknown (M)

Source: Dr. Wasserman's review

The finding of greatest concern is lymphoma (described as multicentric) found in a single LD and MD female animal. It is important to note that the lymphoma sign is not dose-related nor did it occur in males. Drs. Leshin and Wasserman have evaluated these malignancies in detail, including obtaining a statistical consult to better understand the import of the finding. As concluded by Dr. Wasserman and supported by the statistical team, the possibility that these lymphomas are treatment-related cannot be excluded.

The only way to ensure that the DMSO was not responsible for the lymphomas is to perform a formal carcinogenicity study in the rat. This study was not submitted in this complete response, although the need for an evaluation of carcinogenicity had been previously conveyed to the Applicant. Dr. Wasserman notes a June 2007 communication where the Applicant was specifically advised to begin their two-year carcinogenicity studies as soon as possible. The Executive Carcinogenicity Assessment Committee conveyed their recommendations in response to the Applicant's protocol for the dermal carcinogenicity study of DMSO in January 2009.

The P/T team is recommending against approval.

## 5. Clinical Pharmacology/Biopharmaceutics

The Clinical Pharmacology review was conducted by David Lee, Ph.D. with a secondary review by Suresh Doddapaneni, Ph.D.

Dr. Lee reviewed Study PEN-07-116, a relative bioavailability study comparing Pennsaid to Solaraze Gel (NDA 21-005). This was an open-label, multiple-dose, 8-week, maximum usage pharmacokinetic study. Briefly, the study showed that Pennsaid has approximately 1/3 the bioavailability for diclofenac as Solaraze for both C<sub>max</sub> and AUC. The study also assayed for DMSO and the levels varied between below the level of quantitation to \_\_\_\_\_ ng/mL.

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The Clinical Pharmacology team is recommending approval from the Clinical Pharmacology perspective.

## 6. Clinical Microbiology

Per Dr. Larissa Lapteva's 2006 review, the microbiology was reviewed in 2002 and no issues were identified.

## 7. Clinical/Statistical- Efficacy

No new efficacy data were submitted. The Applicant submitted two Phase 1 studies, one to examine the drying time of the solution on the knee and one to assess transepidermal water loss. The Applicant did not propose to include any references to these two studies in labeling. The Division of Dermatology and Dental Products was informally consulted and felt that these studies were not useful for labeling or understanding the risk-benefit for this product, particularly given the safety database size. Briefly, the studies submitted showed: 1. The drying time (0.15 mL Pennsaid to 100 cm<sup>2</sup> of the knee) is approximately 15 minutes and 2. Pennsaid does not cause an increase in transepidermal water loss.

While no new efficacy data were submitted, a brief review of the key efficacy data is contained in the risk-benefit assessment (Section 12).

## 8. Safety

No new safety data from clinical trials were submitted.

Pennsaid is marketed in Canada, the United Kingdom, Italy, and Greece. The submission contains a section regarding the foreign marketing data. Key points include: approximately \_\_\_\_\_ have been sold worldwide and approximately \_\_\_\_\_ samples have been distributed worldwide. Pennsaid has not been removed from these foreign markets for reasons of safety or efficacy. The foreign safety reporting (since 2003) includes the following adverse events:

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- *Body as a whole:* abdominal pain, accidental injury, allergic reaction, asthenia, back pain, body odor, chest pain, edema, face edema, halitosis, headache, lack of drug effect, neck rigidity, pain

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- *Cardiovascular*: palpitation, cardiovascular disorder
- *Digestive*: diarrhea, dry mouth, dyspepsia, gastroenteritis, decreased appetite, mouth ulceration, nausea, rectal hemorrhage, ulcerative stomatitis
- *Metabolic and Nutritional*: creatinine increased
- *Musculoskeletal*: leg cramps, myalgia
- *Nervous*: depression, dizziness, drowsiness, lethargy, paresthesia, paresthesia at application site
- *Respiratory*: asthma, dyspnea, laryngismus, laryngitis, pharyngitis
- *Skin and Appendages: At the Application Site*: contact dermatitis, contact dermatitis with vesicles, dry skin, pruritus, rash;
- *Other Skin and Appendages Adverse Reactions*: eczema, rash, pruritus, skin discoloration, urticaria
- *Special senses*: abnormal vision, blurred vision, cataract, ear pain, eye disorder, eye pain, taste perversion
- *Urogenital*: breast enlargement

The postmarketing data submitted do not substantially change the overall impression of the safety profile of this drug.

In light of the P/T findings, a brief review of the key safety data is contained in the risk benefit assessment (Section 12).

## 9. Advisory Committee Meeting

No Advisory Committee meeting has held for this product.

## 10. Pediatrics

Osteoarthritis is on the list of indications where studies required under the Pediatric Research Equity Act are waived because it occurs so infrequently in the pediatric population. The Applicant's request for waiver was accepted by both the Division and the Pediatric Research Committee.

## 11. Other Relevant Regulatory Issues

There are no other regulatory issues to discuss.

## 12. Labeling

Input from the Division of Medication Errors and Prevention Analysis/Office of Surveillance and Epidemiology is pending at this time.

Key comments regarding the draft label follow:

- The indication is unacceptable. It reads, "...treatment of signs and symptoms of osteoarthritis of the knee(s), \_\_\_\_\_  
\_\_\_\_\_ The last part of this indication has not been supported in clinical trials.
- The adverse events section makes a number of comparisons to oral diclofenac. Since studies were not designed as safety superiority studies, these claims are unacceptable.
- The clinical trials section includes all five treatment groups studied in Study 112. This would lead the reader to think that Pennsaid alone is likely to be equally effective as oral diclofenac, a conclusion that the study was not designed to assess.
- The necessity of washing and drying hands before and after application should be emphasized.

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### 13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

Complete Response

- Risk Benefit Assessment

#### DMSO Toxicology:

The finding of concern in the current submission is that of multicentric lymphoma observed in two female rats in a 26-week toxicology study, a finding that the statistical consultants cannot rule out as possibly treatment-related. The Pharm/Tox team is recommending against approval until a formal carcinogenicity study is completed and reviewed.

Despite Dr. Rappaport's advice to commence the carcinogenicity study in June 2007, the Applicant has not started the carcinogenicity study that would better define this risk.

#### Clinical Efficacy:

In light of the rat toxicology findings, it is appropriate to review the clinical trial data to make an overall risk-benefit assessment. The finding of efficacy for Pennsaid was predominantly supported by Study PEN-03-112 (Study 112) which was reviewed by Dr. Lapteva. Briefly, Study 112 was a randomized, double-blind, placebo-controlled, factorial study in patients with osteoarthritis of the knee. Eligible patients were randomized to one of five treatment groups: were randomized into the five groups (arms) as follows:

- i. PENNSAID + oral diclofenac ("combination" arm)
- ii. PENNSAID + oral placebo ("PENNSAID" arm)
- iii. Vehicle-control solution (45.5% DMSO) + oral placebo ("vehicle control" arm)

- iv. Placebo solution (2.3%DMSO) + oral placebo (“placebo” arm)
- v. Placebo solution + oral diclofenac (“oral diclofenac” arm)

Patients were treated for 12-weeks and the primary efficacy variables were the WOMAC pain and function subscales and a patient overall health assessment scale. Table 2 shows the summary data for the primary efficacy endpoints.

**Table 2: Summary data (mean), primary endpoints, Study 112**

Endpoint	Group i	Group ii	Group iii	Group iv	Group v
N	151	154	161	155	151
Mean Δ WOMAC pain	-6.95	-6.02	-4.70	-4.74	-6.43
Mean Δ WOMAC function	-18.69	-15.75	-12.13	-12.34	-17.48
Mean Δ Patient Global	-0.95	-0.95	-0.65	-0.37	-0.88

Source: Summarization from Table 11 of Dr. Lapteva’s review

Study 112 showed that the high-concentration DMSO alone did not have an analgesic effect. It also showed that Pennsaid-alone separated from both a true placebo and the high-concentration DMSO. It was surprising to note that, for point estimates, the Pennsaid-only arm reasonably approximated the oral diclofenac arm (-6.02, -15.75, and -0.95 versus -6.43, -17.48, and -0.88). There was considerable variability in this study; the standard deviations approximated the means. This study was not designed to compare the arms with active drug.

While Study 112 met the criteria for statistical significance, the observed treatment effect size can be assessed in the context of the theoretical maximal treatment effect size. A 0-4 point rating scale was used to assess 5 items for the pain subscale and 17 items for the function subscale. Therefore, the maximum potential improvement is 20 and 68 on the pain and function subscales, respectively. The patient global was also based on a 0-4 point scale; therefore, 4 points was the maximum potential improvement. The actual differences in means in patients treated with Pennsaid (Group ii) and true placebo (Group iv) were 1.28, 3.41, and 0.58 for WOMAC pain, WOMAC function, and the patient overall health assessment, respectively. These differences are small in magnitude, particularly in the context of the theoretical maximums.

I concur with Drs. Lapteva and Siegel that Pennsaid is associated with a small treatment benefit.

Clinical Safety:

Table 3 is summarized from Dr. Lapteva’s review. It shows that the most common adverse events related to Pennsaid are related to the skin. However, there is evidence of systemic diclofenac exposure, notably the rate of dyspepsia, abdominal pain, nausea, and edema, all associated with the use of NSAIDs, which were all observed at a minimum of twice the rate of the vehicle arm and the placebo arm. Oral diclofenac did have substantially higher rates of these systemic adverse events

compared to Pennsaid. Pennsaid use is not completely benign from the perspective of systemic toxicity.

**Table 3: Most common adverse events (n and %), Pennsaid development program**

Preferred Term	Pennsaid*	Placebo*	Vehicle*	Oral Diclofenac*	Pennsaid + oral diclofenac*
Dry skin (application site)	292 (32)	17 (5)	123 (20)	8 (2)	30 (20)
Contact dermatitis	83 (9)	6 (2)	25 (4)	6 (1)	12 (8)
Dyspepsia	72 (8)	13 (4)	23 (4)	87 (19)	5 (3)
Abdominal pain	54 (6)	10 (3)	10 (2)	78 (17)	3 (2)
Pruritis (application site)	34 (4)	7 (2)	20 (3)	2 (<1)	1 (<1)
Nausea	33 (4)	3 (1)	10 (2)	44 (10)	5 (3)
Edema	26 (3)	0	4 (<1)	27 (6)	4 (3)

\*N = 911 for Pennsaid; 332 for Placebo, 603 for Vehicle Control; 462 for Oral Diclofenac, and 152 for Pennsaid + Oral Diclofenac

Source: Summarization from Table 34 of Dr. Lapteva's review

The last item to consider in the risk benefit assessment is the fact that Voltaren Gel is now approved for the indication of OA. Since Pennsaid contains the same moiety delivered via the identical route of administration, it seems unlikely that Pennsaid represents an advance in the clinical armamentarium for osteoarthritis although, since no head-to-head comparison was made, it is not possible to compare Pennsaid to Voltaren gel.

If the malignancies observed in the rat toxicology study are relevant to the clinical safety of this product, the potential consequence to the public health could be substantial, given the high morbidity and mortality associated with lymphoma.

Therefore, until the malignancies observed in the nonclinical program can be adequately shown not to be of significance for clinical use through a negative carcinogenicity study, I do not believe that the benefits of Pennsaid compensate for the risks.

1. The treatment effect, while statistically significant, is very modest.
  2. Pennsaid is associated with substantial local toxicity. NSAID-related systemic toxicity including GI symptoms and peripheral edema has been reported at rates greater than or equal to twice that of placebo.
  3. The product does not address an unmet medical need in that Voltaren Gel is now legally marketed.
- Recommendation for Postmarketing Risk Evaluation and Management Strategies

This product will require a NSAID Medication Guide and, therefore, a Medication Guide-only REMS.

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- **Recommendation for other Postmarketing Requirements and Commitments**

As noted by Drs. Leshin and Wasserman, if this product is approved at this time, a reproductive toxicity program should be completed as a postmarketing commitment.

- **Recommended Comments to Applicant**

1. The 26-week rat DMSO toxicology study showed a potential signal for malignancy in that two rats developed multicentric lymphoma, a rare malignancy. The possibility that the lymphomas were treatment-related cannot be ruled out. A formal carcinogenicity study must be conducted to further assess this risk.
2. Given the modest efficacy noted in clinical trials, without a better understanding of the finding of lymphomas in rats, the risks of the drug outweigh the benefits.
3. Conduct a reproductive toxicity program to properly inform labeling.

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/s/

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Robert Shibuya  
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