

PRODUCT MONOGRAPH

Pr PENNSAID®

(1.5% w/w diclofenac sodium solution)

Topical Anti-inflammatory – Analgesic

Paladin Labs Inc.
6111 Royalmount Avenue, Suite 102
Montreal, Quebec
H4P 2T4

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Control No. 128974

PENNSAID® is a registered trademark of NUVO RESEARCH INC.

PrPENNSAID®

(1.5% w/w diclofenac sodium solution)

PHARMACOLOGIC/THERAPEUTIC CLASSIFICATION

Topical Anti-inflammatory – Analgesic

ACTIONS AND CLINICAL PHARMACOLOGY

Diclofenac sodium is a non-steroidal anti-inflammatory drug (NSAID) of the arylacanoic acid group, with analgesic and anti-inflammatory properties. The mode of action of diclofenac sodium is not fully known, but it is considered to be primarily through its inhibitory effects on prostaglandin synthesis by interfering with the action of prostaglandin synthetase/cyclo-oxygenase, isoforms 1 and 2 (COX-1 and COX-2). It does not act through the pituitary-adrenal axis. Diclofenac sodium does not alter the course of the underlying disease in patients with osteoarthritis; it has been found to relieve pain, reduce swelling and tenderness, and increase mobility.

CLINICAL TRIALS

Study 1

In an 84-day (12-week), double-blind, vehicle-controlled clinical trial in patients with osteoarthritis of the knee, the efficacy of PENNSAID® was demonstrated by three primary variables—pain and physical function, as measured with the WOMAC LK3.1 Osteoarthritis Index—plus Patient Global Assessment. Efficacy was confirmed by the secondary variable, stiffness, as measured by WOMAC LK3.1 Osteoarthritis Index. For all treated patients (ALL), descriptive statistical analysis revealed that the PENNSAID® group showed greater improvement in scores than the vehicle-control group for all variables. Based on ANCOVA, using baseline score as a covariate, PENNSAID® was

found to be statistically significantly ($p < 0.05$) more effective than vehicle-control for all variables (see Table 1).

Table 1: Study 2 Efficacy Data for 84-day Vehicle-Controlled Study

Improvement in Score of:	ALL			
	N	Mean Baseline score (S.D.)	Mean Change in score ¹ (S.D.)	p value ² PENNSAID® > C
Pain				
PENNSAID®	164	13.0 (3.3)	-5.9 (4.7)	p = 0.0017
Vehicle-control (C)	162	13.0 (3.4)	-4.4 (4.4)	
Physical Function				
PENNSAID®	164	42.0 (11.7)	-15.3 (15.2)	p = 0.0024
Vehicle-control (C)	162	41.3 (11.6)	-10.3 (13.9)	
Patient Global Assessment				
PENNSAID®	164	3.1 (0.7)	-1.3 (1.2)	p = 0.0052
Vehicle-control (C)	162	3.1 (0.7)	-1.0 (1.1)	
Stiffness				
PENNSAID®	164	5.2 (1.5)	-1.8 (2.1)	p = 0.0086
Vehicle-control (C)	162	5.2 (1.5)	-1.3 (2.0)	

¹ Final - Baseline; WOMAC LK3.1

² ANCOVA (baseline score as a covariate)

Study 2

In a 42-day (6-week), double-blind, vehicle-controlled clinical trial in patients with osteoarthritis of the knee, the efficacy of PENNSAID® was demonstrated by three primary variables—pain and physical function, as measured with the WOMAC LK3.1 Osteoarthritis Index—plus Patient Global Assessment. Efficacy was confirmed by the secondary variable, stiffness, as measured by WOMAC LK3.1 Osteoarthritis Index. For all treated patients (ALL), descriptive statistical analysis revealed that the PENNSAID® group showed greater improvement in scores than the vehicle-control group for all variables. Based on ANCOVA, using baseline score as a covariate, PENNSAID® was found to be statistically significantly ($p < 0.05$) more effective than the vehicle-control for all variables (see Table 2).

Table 2. Study 2: Efficacy Data for 42-day Vehicle-Controlled Study

Improvement in Score of:	ALL			
	N	Mean Baseline score (S.D.)	Mean Change in score ¹ (S.D.)	p value ² PENNSAID® > C
Pain				
PENNSAID®	107	13.0 (3.2)	-5.3 (5.0)	p = 0.0040
Vehicle-control (C)	109	12.8 (3.1)	-3.4 (4.3)	
Physical Function				
PENNSAID®	107	40.7 (12.0)	-13.0 (16.2)	p = 0.0041
Vehicle-control (C)	109	40.4 (11.2)	-7.3 (13.4)	
Patient Global Assessment				
PENNSAID®	107	3.1 (0.8)	-1.2 (1.3)	p = 0.0004
Vehicle-control (C)	109	3.2 (0.8)	-0.7 (1.2)	
Stiffness				
PENNSAID®	107	5.2 (1.5)	-1.7 (2.1)	p = 0.0023
Vehicle-control (C)	109	5.2 (1.5)	-1.0 (1.9)	

¹ Final - Baseline; WOMAC LK3.1

² ANCOVA (baseline score as a covariate)

Study 3

In a 28-day (4-week), double-blind, vehicle- and placebo-controlled clinical trial in patients with osteoarthritis of the knee, the efficacy of PENNSAID® was demonstrated by the primary variable—pain, as measured with the WOMAC LK3.0 Osteoarthritis Index. Efficacy was confirmed by three secondary variables—physical function and stiffness, as measured by the WOMAC LK3.0 Osteoarthritis Index—plus Patient Global Assessment. For all treated patients (ALL) descriptive statistical analysis revealed that the PENNSAID® group showed greater improvement in scores than the vehicle-control and placebo groups for all WOMAC variables and for the Patient Global Assessment. Based on ANOVA (contrast analysis between least squares means) PENNSAID® was found to be statistically significantly ($p < 0.05$) more effective than vehicle-control and placebo for all variables (see Table 3).

Table 3. Study 3: Efficacy Data for 28-day Vehicle- and Placebo-Controlled Study

Improvement in Score of:	ALL			
	N	Mean Baseline score (S.D.)	Mean Change in score ² (S.D.)	p value ¹
Pain				
PENNSAID®	84	9.2 (0.4)	-3.9 (4.4)	PENNSAID® > C; p = 0.008 PENNSAID® > P; p = 0.034
Vehicle-control (C)	80	9.2 (0.4)	-2.3 (3.4)	
Placebo (P)	84	9.6 (0.4)	-2.7 (4.0)	
Physical Function				
PENNSAID®	84	29.5 (13.7)	-11.5 (14.5)	PENNSAID® > C; p = 0.002 PENNSAID® > P; p = 0.017
Vehicle-control (C)	80	30.5 (11.8)	-5.6 (11.1)	
Placebo (P)	84	30.9 (13.1)	-7.2 (12.3)	
Patient Global Assessment³				
PENNSAID®	82	NA ⁴	6.6 (3.1)	PENNSAID® > C; p = 0.040 PENNSAID® > P; p = 0.024
Vehicle-control (C)	76	NA ⁴	7.7 (3.5)	
Placebo (P)	83	NA ⁴	7.8 (3.0)	
Stiffness				
PENNSAID®	84	3.7 (1.7)	-1.5 (1.8)	PENNSAID® > C; p = 0.011 PENNSAID® > P; p = 0.006
Vehicle-control (C)	80	3.5 (1.7)	-0.7 (2.0)	
Placebo (P)	84	3.7 (1.8)	-0.7 (1.9)	

¹ ANOVA (contrast analysis between least squares means)

² Final - Baseline; WOMAC LK3.0

³ Sum of weekly scores; some patients had no Patient Global Assessment data

⁴ NA = Not applicable

Vehicle-control (C) and Placebo (P) were not statistically significantly different for any of the efficacy variables—pain (p = 0.557); physical function (p = 0.412); Patient Global Assessment (p = 0.882); stiffness (p = 0.873).

Study 4

The efficacy of Pennsaid® (50 drops, 3 times a day) versus oral diclofenac (50 mg, 3 times a day) in relieving symptoms of primary osteoarthritis (OA) of the knee was assessed in an 84-day, randomized, double blind, double-dummy clinical study. The three primary efficacy variables were change from baseline to final assessment in (1)

WOMAC Index VA3.1 pain subscale score, (2) WOMAC Index VA3.1 physical function subscale score and (3) Patient Global Assessment score. The primary efficacy results on the Per Protocol (PP) dataset are summarized in Table 4. Efficacy was also supported by secondary efficacy variable, stiffness, as measured by WOMAC Index VA3.1.

Table 4. Study 4: Efficacy data for 84-day study comparing Pennsaid (50 drops tid) and oral diclofenac (50 mg tid) (data normalized to 100 mm) VAS)

		WOMAC Pain	WOMAC Physical Function	Patient Global Assessment	Stiffness
PENNSAID®:	N	237	237	234	237
	Mean Change (SD)	-25.4 (24.0)	-22.4 (23.3)	-29.5 (30.9)	-24.1 (29.5)
Oral Diclofenac:	N	255	255	251	255
	Mean Change (SD)	-28.0 (25.3)	-26.6 (25.3)	-33.8 (30.7)	(-27.3 (30.5)
Absolute Difference of Means (95% CI)		2.7 (-1.7 to 7.0)	4.2(-0.1 to 8.5)	4.3 (-1.2 to 9.8)	3.2 (-2.2 to 8.5)

INDICATIONS AND CLINICAL USE

PENNSAID® is indicated for treatment of the symptoms associated with osteoarthritis of the knee(s) only for a treatment regimen of not more than three months duration, whether continuous or intermittent.

CONTRAINDICATIONS

Active peptic ulcer, a history of recurrent ulceration or active inflammatory disease of the gastrointestinal system.

Known or suspected hypersensitivity to diclofenac sodium or other non-steroidal anti-inflammatory drugs. The potential for cross-reactivity between different NSAIDs must be kept in mind.

PENNSAID[®] should not be used in patients with the complete or partial syndrome of ASA intolerance (rhinosinusitis, urticaria/angioedema, nasal polyps and asthma), in whom asthma, anaphylaxis, urticaria, rhinitis or other allergic manifestations are precipitated by ASA or other non-steroidal anti-inflammatory agents. Fatal anaphylactoid reactions have occurred in such individuals. As well, individuals with the above medical problems are at risk of a severe reaction even if they have taken NSAIDs in the past without any adverse effects.

Significant hepatic impairment or active liver disease.

Severely impaired or deteriorating renal function (creatinine clearance <30 mL/min). Individuals with lesser degrees of renal impairment are at risk of deterioration of their renal function when prescribed NSAIDs and must be monitored.

PENNSAID[®] is not recommended for use with other NSAIDs because of the absence of any evidence demonstrating synergistic benefits and the potential for additive side effects.

PENNSAID[®] contains 45% dimethyl sulfoxide (DMSO), propylene glycol, glycerine and alcohol and should not be used by patients with allergy to any of these substances. Because the long-term safety of PENNSAID[®] is unknown, PENNSAID[®] should not be used for a treatment regimen of longer duration than 3 months.

PENNSAID[®] should not be used in children and pregnant and lactating women as its safety in these groups has not been established.

WARNINGS

Gastrointestinal System (GI):

In clinical studies, PENNSAID® has not been associated with serious GI toxicity, such as peptic ulceration, perforation and GI bleeding commonly associated with NSAIDs.

Serious GI toxicity, such as peptic ulceration, perforation and gastrointestinal bleeding, sometimes severe and occasionally fatal, can occur at any time, with or without symptoms, in patients treated with NSAIDs, including diclofenac sodium.

Gastrointestinal symptoms, such as dyspepsia, are common, usually developing early in therapy. Physicians should remain alert for the signs and symptoms of ulceration and bleeding in patients treated with NSAIDs, even in the absence of previous GI tract symptoms.

In patients observed in clinical trials of NSAIDs given orally, symptomatic upper GI ulcers, gross bleeding, or perforation appear to occur in approximately 1% of patients treated for 3 – 6 months and in about 2 – 4% of patients treated for one year. The incidence of these complications is related to dose, past history of known ulcer disease, and advanced age.

PENNSAID® should be given under close medical supervision to patients with a history of ulcer of the gastrointestinal tract, or inflammatory disease of the gastrointestinal tract, such as ulcerative colitis or Crohn's disease. In these cases the physician must weigh the benefits of treatment against the possible hazards.

Physicians should inform patients about the signs and/or symptoms of serious GI toxicity and instruct them to contact a physician immediately if they experience persistent dyspepsia or other symptoms or signs suggestive of gastrointestinal ulceration or bleeding.

Because serious GI tract ulceration and bleeding can occur without warning symptoms, physicians should follow patients and watch for the signs and symptoms of ulceration and bleeding and should inform the patients of the importance of this follow-up.

If ulceration is suspected or confirmed, or if GI bleeding occurs, PENNSAID® should be discontinued immediately, appropriate treatment instituted and the patient monitored closely.

No studies, to date, have identified any group of patients not at risk of developing ulceration and bleeding. The major risk factors are a prior history of serious GI events and increasing age. Possible risk factors include *Helicobacter pylori* infection, excess alcohol intake, smoking, concomitant oral steroids, anticoagulants, anti-platelet agents (including ASA) and selective serotonin reuptake inhibitors (SSRIs).

Use in the Elderly:

Patients older than 65 years and frail or debilitated patients are most susceptible to a variety of adverse reactions from non-steroidal anti-inflammatory drugs (NSAIDs); the incidence of these adverse reactions increases with dose and duration of treatment. In addition, these patients are less tolerant to ulceration and bleeding. Most reports of fatal GI events are in this population. Older patients are also at risk of lower esophageal ulceration and bleeding.

For such patients, consideration should be given to a starting dose lower than the one usually recommended, with individual adjustment when necessary and under close supervision. See "Precautions" for further advice.

Cross-sensitivity:

Patients sensitive to any one of the NSAIDs may be sensitive to any of the other NSAIDs also.

Aseptic Meningitis:

In rare cases, with some NSAIDs, the symptoms of aseptic meningitis (stiff neck, severe headaches, nausea and vomiting, fever or clouding of consciousness) have been observed. Patients with autoimmune disorders (systemic lupus erythematosus, mixed connective tissue diseases, *etc.*) seem to be pre-disposed. Therefore, in such patients, the physician must be vigilant to the development of this complication.

Use in pregnancy, labour and lactation:

See "Contraindications".

Use in children:

See "Contraindications".

Dermatological:

PENNSAID[®] should not be used under occlusive dressings. Do not apply PENNSAID[®] to open, abraded or infected skin. Avoid contact with the eyes or mucous membranes.

Hypersensitivity:

Dimethyl sulfoxide may initiate the liberation of histamine and occasional hypersensitivity reactions have occurred with topical administration. If anaphylactoid symptoms develop, appropriate therapy should be instituted and further use of PENNSAID[®] immediately discontinued.

PRECAUTIONS

Gastrointestinal System:

There is no definitive evidence that the concomitant administration of histamine H₂-receptor antagonists and/or antacids will either prevent the occurrence of gastrointestinal side effects or allow the continuation of PENNSAID[®] therapy when, and if, these adverse reactions appear.

Renal Function:

In clinical studies with PENNSAID[®], increase in urea or creatinine, or any other renal toxicity has not been observed.

Long-term administration of NSAIDs to animals has resulted in renal papillary necrosis and other abnormal renal pathology. In humans, there have been reports of acute interstitial nephritis with hematuria, proteinuria, and occasionally nephrotic syndrome.

A second form of renal toxicity has been seen in patients with prerenal conditions leading to reduction in renal blood flow or blood volume, where the renal prostaglandins have a supportive role in the maintenance of renal perfusion. In these patients, administration of an NSAID may cause a dose-dependent reduction in prostaglandin formation and may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state.

Diclofenac sodium and its metabolites are eliminated primarily (60%) by the kidneys; therefore, PENNSAID[®] should be used with great caution in patients with impaired renal function. In these cases, utilization of lower doses of PENNSAID[®] should be considered and patients carefully monitored.

Genitourinary Tract:

Some NSAIDs are known to cause persistent urinary symptoms (bladder pain, dysuria, urinary frequency), hematuria or cystitis. The onset of these symptoms may occur at any time after the initiation of therapy with an NSAID. Some cases have become severe on continued treatment. Should urinary symptoms occur, treatment with PENNSAID[®] must be stopped immediately to obtain recovery. This should be done before any urological investigation or treatment is carried out.

Hepatic Function:

As with other NSAIDs, borderline elevations of liver function tests may occur in up to 15% of patients. These abnormalities may progress, may remain essentially unchanged, or may be transient with continued therapy. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of more severe hepatic reaction, while on therapy with PENNSAID[®]. Severe hepatic reactions including jaundice and cases of fatal hepatitis have been reported with NSAIDs.

Although such reactions are rare, if abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (*e.g.* eosinophilia, rash, *etc.*), this drug should be discontinued.

Toxicity studies in animals with high doses of DMSO have shown occasional, transient elevation of liver function tests.

In two clinical trials with PENNSAID[®], a mild elevation of AST was seen in 4 of 117 (3.4%) patients using PENNSAID[®], 2 of 109 (1.8%) using vehicle-control (both of these solutions contained DMSO 45.5%) and 1 of 110 (0.9%) using Placebo. A mild elevation of ALT was seen in 4 of 117 (3.4%) patients using PENNSAID[®], 6 of 111 (5.4%) using vehicle-control and 2 of 108 (1.9%) using placebo. In most cases the increase was minimal and in two patients (one treated with PENNSAID[®], one treated with vehicle-control) the increase was 2.5 times normal. If there is a need to prescribe this drug in the presence of impaired liver function, it must be done under strict observation.

Caution is called for when using diclofenac sodium in patients with hepatic porphyria, since diclofenac sodium may trigger an attack.

Fluid and Electrolyte Balance:

In clinical studies with PENNSAID[®], fluid or electrolyte abnormalities have not been observed.

Fluid retention and edema have been observed in patients treated with diclofenac sodium. Therefore, as with many other NSAIDs, the possibility of precipitating congestive heart failure in elderly patients or those with compromised cardiac function should be borne in mind. PENNSAID[®] should be used with caution in patients with heart failure, hypertension or other conditions predisposing to fluid retention.

With NSAID treatment, there is a potential risk of hyperkalemia, particularly in patients with conditions such as diabetes mellitus or renal failure; elderly patients; or in patients receiving concomitant therapy with β -adrenergic blockers, angiotensin-converting enzyme inhibitors, angiotensin-II receptor antagonists or some diuretics. Patients at risk should be monitored periodically.

Hematology:

In clinical studies with PENNSAID[®], abnormal hemoglobin, WBC or platelet counts have not been observed. Platelet function during treatment with PENNSAID[®] has not been studied.

The effect of PENNSAID[®] on platelet function was studied in 10 healthy patients randomly selected to participate in a sub-study of multiple-dose pharmacokinetic study where 40 drops of PENNSAID[®] were applied to each knee four times a day for 7 days. Following 7-day treatment with PENNSAID[®], the mean change in % aggregation for ADP-collagen-, epinephrine- and arachidonic acid-induced aggregation was 1.31%, -0.19%, 9.85% and -0.95%, respectively. These results indicate that there was no marked effect on platelet aggregation after application of the maximum clinical dose for 7 days.

Drugs inhibiting prostaglandin biosynthesis do interfere with platelet function to varying degrees; therefore, patients who may be adversely affected by such an action should be carefully observed when PENNSAID[®] is administered.

Blood dyscrasias (such as neutropenia, leukopenia, thrombocytopenia, aplastic anemia and agranulocytosis) associated with the use of NSAIDs are rare, but could occur with severe consequences. Patients on long-term diclofenac sodium treatment should have their hemopoietic system evaluated periodically.

Infection:

In common with other NSAIDs, diclofenac sodium may mask the usual signs of infection (*i.e.* fever).

Ophthalmology:

Blurred and/or diminished vision has been reported with the use of NSAIDs. Changes in the refractive index and lens opacities have been seen in non-primate animals with chronic administration of dimethyl sulfoxide, in doses far in excess of those used in humans. If ophthalmological symptoms develop, PENNSAID[®] should be discontinued and an ophthalmologic examination performed.

Central Nervous System:

Some patients may experience drowsiness, dizziness, vertigo, insomnia or depression with the use of PENNSAID[®]. If patients experience these side effects, they should exercise caution in carrying out activities that require alertness.

Hypersensitivity Reactions:

Dimethyl sulfoxide may initiate the liberation of histamine and occasional hypersensitivity reactions have occurred with topical administration. If anaphylactoid symptoms develop, appropriate therapy should be instituted and further use of PENNSAID[®] immediately discontinued.

As with other NSAIDs, allergic reactions, including anaphylactic/anaphylactoid reactions, can occur without prior exposure to drug. Careful questioning for patient history of asthma, nasal polyps, urticaria, and hypotension associated with NSAIDs is important before starting therapy. Because hypersensitivity reactions may occur even at

a low systemic level, the possibility of such adverse effects with PENNSAID[®] cannot be completely excluded.

In rare cases, serious skin reactions such as Stevens-Johnson syndrome, toxic epidermal necrolysis, exfoliative dermatitis and erythema multiforme have been associated with the use of some NSAIDs. Because the rate of these reactions is low, they have usually been noted during post-marketing surveillance in patients taking other medications also associated with the potential development of these serious skin reactions. Thus causality is not clear. These reactions are potentially life-threatening, but may be reversible if the causative agent is discontinued and appropriate treatment instituted. Patients should be advised that if they experience a generalized skin rash they should discontinue PENNSAID[®] and contact their physician for assessment and advice, including which additional therapies to discontinue.

Information Physicians Should Provide to Patients:

PENNSAID[®] should not be used under occlusive dressings.

Do not apply PENNSAID[®] to open, abraded or infected skin.

Do not apply any other medication to treated area.

Avoid contact with the eyes or mucous membranes.

Avoid contact of synthetic fibres with skin wetted with DMSO.

See INFORMATION FOR THE PATIENT

Drug Interactions:

Acetylsalicylic Acid (ASA) or other NSAIDs: The use of PENNSAID® in addition to any other NSAID, including those over-the-counter ones (such as ASA and ibuprofen) is not recommended due to the possibility of additive side effects. Low dose ASA (<325 mg/day) for cardiovascular prophylaxis, is permitted.

Digoxin: Diclofenac sodium may increase the plasma concentration of digoxin. Dosage adjustment of digoxin may be required.

Anticoagulants, Heparin, Thrombolytic Agents and Other Platelet Aggregation Inhibitors: Numerous studies have shown that the concomitant use of NSAIDs and anticoagulants increases the risk of GI adverse events such as ulceration and bleeding.

Because prostaglandins play an important role in hemostasis, and NSAIDs affect platelet function, concurrent therapy of PENNSAID® with warfarin requires close monitoring to be certain that no change in anticoagulant dosage is necessary.

Oral Hypoglycemics: Pharmacodynamic studies have shown no potentiation of effect with concurrent administration with diclofenac sodium; however, there are isolated reports of both hypoglycemic and hyperglycemic effects in the presence of diclofenac sodium, which necessitated changes in the dosage of hypoglycemic agents.

Diuretics: NSAIDs have been reported to decrease the activity of diuretics. Concomitant treatment with potassium-sparing diuretics may be associated with increased serum potassium, thus making it necessary to monitor levels.

Antihypertensives: Like other NSAIDs, diclofenac sodium can reduce the antihypertensive effects of propranolol and other beta-blockers, as well as other antihypertensive agents.

Glucocorticoids: Numerous studies have shown that concomitant use of NSAIDs and oral glucocorticoids increases the risk of GI side effects such as ulceration and bleeding. This is especially the case in older (>65 years of age) individuals.

Methotrexate: Caution should be exercised when NSAIDs are administered less than 24 hours before or after treatment with methotrexate. Elevated blood concentrations of methotrexate may occur, increasing its toxicity.

Acetaminophen: There may be an increased risk of adverse renal effects when administered concomitantly with NSAIDs.

Alcohol: There may be an increased risk of GI side effects, including ulceration or hemorrhage, when taken concomitantly with NSAIDs.

Cyclosporine: The nephrotoxicity of cyclosporine may be increased because of the effects of NSAIDs on renal prostaglandins.

Lithium: Lithium plasma concentrations will increase when administered concomitantly with diclofenac sodium (which affects lithium renal clearance). Dosage adjustment of lithium may be required.

Probenecid: May decrease the excretion and increase serum concentration of NSAIDs, possibly enhancing effectiveness and/or increasing the potential for toxicity. Concurrent therapy of NSAIDs with probenecid requires close monitoring of dosage.

Quinolone Antibacterials: There have been isolated reports of convulsions, which may have been due to concomitant use of quinolones and NSAIDs.

Clinical Laboratory Tests:

Diclofenac sodium increases platelet aggregation time but does not affect bleeding time, plasma thrombin clotting time, plasma fibrinogen, or factors V and VII to XII.

Statistically significant changes in prothrombin and partial thromboplastin times have been reported in normal volunteers. The mean changes were observed to be less than 1 second in both instances, and are unlikely to be clinically important.

Persistently abnormal or worsening renal, hepatic or hematological test values should be followed up carefully since they may be related to therapy.

ADVERSE REACTIONS

Adverse reaction reporting is based on double-blind, controlled clinical studies in which 446 patients were exposed to PENNSAID[®]. Mean drop-out rates were: PENNSAID[®], 22.0%; vehicle-control (C), 28.3%; diclofenac control, 19.2%; placebo, 20.6%.

Application-site, dermatological reactions are the most commonly seen adverse events with PENNSAID[®] (see Table 5).

The most common adverse reactions encountered with oral NSAIDs are gastrointestinal, of which peptic ulcer, with or without bleeding, is the most severe. Fatalities have occurred, particularly in the elderly. The most severe, albeit rare, dermatological reactions observed were erythema multiforme (Stevens-Johnson syndrome and Lyell's syndrome).

The following table lists all adverse events, regardless of causality, occurring in >2% of patients receiving PENNSAID[®] from five controlled studies conducted in patients with osteoarthritis that included a vehicle-control, active-control and/or placebo-control group.

Table 5: Adverse Events Occurring in >2% of PENNSAID® Patients in Five Vehicle-Controlled Studies

Adverse Event	PENNSAID® (n=446) (%)	Control-DMSO ¹ (n=442) (%)	Control-diclofenac ² (n=52) (%)	Placebo ³ (n=175) (%)
Gastrointestinal				
Dyspepsia	4.48	3.85	9.62	4
Nausea	2.02	2.26	3.85	1.71
Central and Peripheral Nervous System				
Paresthesia	2.02	1.58	0	1.14
Paresthesia (Application Site)	7.85	9.05	7.69	10.29
Skin and Appendages				
Application-Site Reaction	2.47	1.13	5.77	1.71
Dry Skin (Application Site)	41.93	23.3	23.08	6.86
Pruritus (Application Site)	2.91	4.52	3.85	4
Rash	2.02	1.81	3.85	2.86
Rash (Application Site)	9.64	4.98	7.69	2.86
Special Senses				
Taste Perversion	3.81	3.62	0	4.57
Respiratory				
Pharyngitis	5.38	2.71	5.77	6.86
Musculoskeletal				
Arthralgia	16.82	16.52	40.38	37.14
Arthrosis	4.04	3.85	3.85	12
Joint Disorder	4.71	5.43	7.69	15.43
Body As A Whole				
Abdominal Pain	3.14	1.58	0	5.14
Back Pain	6.5	5.66	15.38	7.43
Flu Syndrome	4.04	4.07	0	4.57
Headache	12.11	13.12	32.69	26.86
Infection	3.14	2.71	11.54	4.57
Pain	6.05	6.33	17.31	10.86

¹ Contains the full carrier with DMSO, no diclofenac sodium

² Contains negligible DMSO with the full dose of diclofenac sodium

³ Contains negligible DMSO with no diclofenac sodium

The following spontaneous adverse events occurred in 0.2 to 1.8% of patients treated with PENNSAID® regardless of causality:

Gastrointestinal: colitis, constipation, diarrhea, dry mouth, flatulence, gastritis, gastroenteritis, gingivitis, periodontal abscess, rectal disorder, thirst, tooth caries, vomiting;

Central and Peripheral Nervous System: aphasia, confusion, dizziness, depression, dysthymia, hypertonia, insomnia, nervousness, neuritis, sleep disorder, speech disorder, thinking abnormal, vertigo;

Skin and Appendages: acne, acne (application site), contact dermatitis, dry skin, furunculosis, hair disorder, maculopapular rash, nail disorder, pruritus, pustular rash, skin nodule, urticaria, vesiculobullous rash;

Cardiovascular: arrhythmia, arteriosclerosis, bradycardia, cardiovascular disorder, hypertension, myocardial infarction, migraine, palpitation, vasodilation, vasodilation (application site);

Special Senses: amblyopia, cataract, ear pain, eye pain, lacrimation disorder;

Hemic and Lymphatic: ecchymosis;

Urogenital: dysmenorrhea, prostatic specific antigen increase, testis disorder, vaginal hemorrhage;

Metabolic and Nutritional: edema, gout, hypercholesterolemia, peripheral edema;

Respiratory: asthma, bronchitis, congestion, cough increased, dyspnea, epistaxis, rhinitis, sinusitis;

Musculoskeletal: abnormal gait, arthritis, bone pain, leg cramps, myasthenia;

Body as a Whole: accidental injury, allergic reaction, asthenia, body odour, carcinoma, chest pain, chills, face edema, fever, halitosis, hernia, malaise, neck pain, neck rigidity.

In a controlled clinical trial conducted to assess the alternative dose regimen of 50 drops t.i.d, a total of 311 patients received at least one dose of PENNSAID® for mean treatment duration of 66 days. The safety profile observed in this study was consistent with that reported in previous studies, the primary adverse events experienced by PENNSAID® patients being application-site reactions.

In a long-term, uncontrolled clinical trial (approximately 800 patients were treated with PENNSAID® for one year or longer), the adverse event profile was similar to that observed in the controlled clinical trials.

Post-Market Adverse Drug Reactions

In post-marketing surveillance for PENNSAID®, the following adverse reactions have been reported:

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;

Cardiovascular: Cardiovascular disorder, Palpitation;

Digestive: Diarrhea, Dry mouth, Dyspepsia, Mouth ulceration, Nausea, Rectal hemorrhage, Ulcerative stomatitis;

Metabolic and nutritional: Creatinine increased;

Musculoskeletal: Leg cramps, Myalgia;

Nervous: Depression, Dizziness, Drowsiness, Paresthesia, Paresthesia, app. 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 adverse reaction: Rash, Skin discoloration, Urticaria;

Special senses: Abnormal vision, Blurred vision, Cataract, Ear pain, Eye disorder, Eye pain, Taste perversion.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

In the event of ingestion of PENNSAID[®] (1.5% w/w diclofenac sodium in 45% dimethyl sulfoxide), there is no specific antidote. An entire 60 mL bottle of PENNSAID[®] contains approximately 960 mg of diclofenac sodium. Systemic absorption should be prevented as soon as possible by the induction of vomiting, gastric lavage or treatment with activated charcoal. Supportive and symptomatic treatment should be given for complications such as hypotension, renal failure, convulsions, gastrointestinal irritation and respiratory depression. Measures to accelerate elimination (forced diuresis, hemoperfusion, dialysis) may be considered, but may be of limited use because of the high protein binding and extensive metabolism of diclofenac.

A 60 mL bottle of PENNSAID[®] contains approximately 29 g of DMSO, well below any toxic level. (The oral LD₅₀ for monkeys is >4 g/kg. The dermal LD₅₀ of DMSO for monkeys is >11 g/kg). Acute toxicity through inhalation of high vapour concentrations of DMSO, through the use or abuse of PENNSAID[®], is remote. In the event that exposure should occur, it may lead to irritation of the mucous membranes of the upper respiratory tract, wheezing, nausea or vomiting. Treatment includes administration of oxygen or other symptomatic measures as necessary.

In the event of topical application of an excessive dose, wash the area with soap and water as soon as possible. Local irritation may occur. Treatment includes symptomatic measures as necessary.

DOSAGE AND ADMINISTRATION

Table 6 summarizes the recommended dosage and administration of PENNSAID®.

Table 6: Dosage and Administration of PENNSAID® (1.5% w/w diclofenac sodium solution)

Medical Condition	Population (Age Group)	Dose	Route of Administration	Maximum Duration of Treatment (days)
Osteoarthritis of the knee(s)	Adults (≥18 years old)	50 drops per knee, 3 times a day, <u>or</u> 40 drops per knee, 4 times a day	Topical	3 months

The following treatment regimen is recommended for patients:

- PENNSAID® is intended for external use only;
- apply PENNSAID® to clean, dry skin; do not use under bandages or dressings.
- dispense 10 drops of PENNSAID® into the hand, or directly onto the knee;
- spread PENNSAID® evenly around front, back and sides of the knee;
- repeat this procedure until 40 drops or 50 drops (depending on the recommended dose) have been applied and the knee is completely covered;

- to treat the other knee, repeat the procedure;

- allow several minutes for PENNSAID® to dry;

- avoid contact with the eyes or mucous membranes;

- after application of PENNSAID®, wash the hands;

- follow the same procedure 3 times (for 50 drops) or 4 times (for 40 drops), spaced evenly throughout the day. PENNSAID® treatment has no relationship to food intake;

- there is no need to adjust the dosage of PENNSAID® for elderly or debilitated patients;

- PENNSAID® is not indicated for pediatric patients;

- PENNSAID® is indicated for a treatment regimen of not more than three months duration, whether continuous or intermittent;

- PENNSAID® therapy should be discontinued if the application site displays signs of significant skin reaction, including swelling, urticaria or vesiculobullous rash.

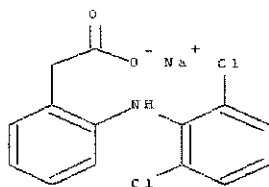
PHARMACEUTICAL INFORMATION

Drug Substance:

Proper Name: Diclofenac sodium, U.S.P.

Chemical Names: 2-[(2,6-dichlorophenyl)amino]benzeneacetic acid monosodium salt

Structural Formula:



Molecular Weight: 318.13

Description: White to off-white powder with a salty, bitter taste. Diclofenac sodium is 2% soluble in water (pH 7.7, 25 °C), practically insoluble in aqueous acidic solutions and sparingly soluble in water at pH 5.2.

Dosage Form: Topical Solution

Composition: diclofenac sodium, dimethyl sulfoxide, ethanol, glycerine and propylene glycol in purified water.

Stability and Storage Recommendations: Store at room temperature (15 – 25 °C).

AVAILABILITY and STORAGE

PENNSAID[®] is a clear, odourless liquid, which contains diclofenac sodium 1.5% w/w in a solution base consisting of dimethyl sulfoxide, glycerine, propylene glycol, ethanol and purified water. It is supplied in low-density polyethylene bottles of 15, 30 and 60 mL and high-density polyethylene bottles of 15, 30, 60 and 120 mL with a plastic dropper cap. Store at room temperature (15 – 25 °C).

INFORMATION FOR THE PATIENT

Diclofenac sodium is one of a large group of non-steroidal anti-inflammatory drugs (also called NSAIDs) and is used to treat the symptoms of certain types of arthritis. It helps to relieve joint pain, swelling, stiffness and fever by reducing the production of certain substances (prostaglandins) and by helping to control inflammation. NSAIDs do not cure arthritis but they support suppression of the inflammation and the tissue-damaging effects of inflammation.

PENNSAID[®] (1.5% w/w diclofenac sodium solution) is a **TOPICAL PRODUCT** which has been prescribed by your doctor. It helps to relieve the symptoms of osteoarthritis in your knee(s): pain, stiffness and reduced function. This medicine will help you only as long as you continue to use it.

You should apply PENNSAID[®] only as directed by your doctor. Do not use more of it, do not use it more often and do not use it for a longer period of time than your doctor ordered. Using too much may increase the chance of unwanted effects, especially if you are an elderly patient.

Be sure to use PENNSAID[®] regularly as prescribed. During treatment, your doctor may decide to adjust the dosage according to your response to the medication.

Stomach upset is one of the common problems with oral NSAIDs. In clinical trials with PENNSAID[®], stomach upset was reported only occasionally. If stomach upset (indigestion, nausea, vomiting, stomach pain or diarrhea) occurs and continues, contact your doctor. PENNSAID[®] can be applied to the knee without regard to food/meal times.

Regular application of any medication to the skin can cause a localized reaction. PENNSAID[®], too, may cause dryness or other irritation of your skin, at the application site.

Do not apply any other topical medication together with PENNSAID®.

Do not take full-strength ASA (acetylsalicylic acid), ASA-containing compounds or other drugs used to relieve symptoms of osteoarthritis while using PENNSAID®, unless directed to do so by your physician. Consult your doctor or pharmacist before taking any other analgesic for fever, headache or other pain.

WHAT DOES PENNSAID® CONTAIN?

- diclofenac sodium;
- dimethyl sulfoxide;
- ethanol;
- glycerine;
- propylene glycol;
- in purified water.

ALWAYS REMEMBER:

THE RISKS OF TAKING THIS MEDICATION MUST BE WEIGHED AGAINST THE BENEFITS IT WILL HAVE.

BEFORE TAKING THIS MEDICATION TELL YOUR DOCTOR AND PHARMACISTS IF YOU:

- or a family member is allergic to or has had a reaction to PENNSAID® (diclofenac sodium) or other anti-inflammatory drugs (such as acetylsalicylic acid (ASA), diclofenac, diflunisal, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, mefenamic acid, piroxicam, tiaprofenic acid, tolmetin, nabumetone,

or tenoxicam) manifesting itself by increased sinusitis, hives, the initiating or worsening of asthma or anaphylaxis (sudden collapse);

-or a family member has had asthma, nasal polyps, chronic sinusitis or chronic urticaria (hives);

-have a history of stomach upset, ulcer, liver, kidney or eye diseases;

-have blood or urine abnormalities;

-have high blood pressure;

-have diabetes;

-are on a special diet such as a low-sodium or low-sugar diet;

-are pregnant or intend to become pregnant while using PENNSAID®;

-are breast feeding or intend to breast feed while using PENNSAID®;

-are taking any other medication (either prescription or non-prescription) such as other NSAIDs, high blood pressure medication, blood thinners, corticosteroids, methotrexate, cyclosporine, lithium, phenytoin, quinolone antibacterials or probenecid;

-have active inflammatory diseases of the gastrointestinal system (*i.e.* Crohn's disease, ulcerative colitis);

-have any other medical problem(s) such as alcohol abuse, bleeding problems, kidney, liver or blood disease;

-have reactions to any other ingredients in this medication; (See “What does Pennsaid Contain”);

WHILE USING THIS MEDICATION:

-tell any other doctor, dentist or pharmacist that you consult or see, that you are using this medication;

-some NSAIDs may cause drowsiness or fatigue in some people taking them. Be cautious about driving or participating in activities that require alertness if you are drowsy, dizzy or lightheaded after using this medication;

-check with your doctor if you are not getting any relief of your arthritis or if any problems develop;

-report any untoward reactions to your doctor. This is very important, as it will aid in the early detection and prevention of potential complications;

-stomach problems may be more likely to occur if you drink alcoholic beverages. Therefore, do not drink alcoholic beverages while using this medication;

-check with your doctor immediately if you experience unexpected weakness while using this medication, or if you vomit any blood or have dark or bloody stools;

-some people may become more sensitive to sunlight than they are normally. Exposure to sunlight or sunlamps, even for brief periods of time, may cause sunburn, blisters on the skin, skin rash, redness, itching or discolouration or vision changes. If you have a reaction from the sun, check with your doctor;

-check with your doctor immediately if chills, fever, muscle aches or pains, or other flu-like symptoms occur, especially if they occur shortly before, or together with, a skin rash. Very rarely, these effects may be the first signs of a serious reaction to this medication;

-YOUR REGULAR MEDICAL CHECKUPS ARE ESSENTIAL.

SIDE EFFECTS OF THIS MEDICATION:

Along with its beneficial effects, PENNSAID[®], like all other NSAIDs, may cause some undesirable reactions, especially when used for a long time or in large doses.

Elderly, frail or debilitated patients often seem to experience more frequent, or more severe, side effects with oral NSAIDs. In clinical studies with PENNSAID[®], this increase has not been observed.

Although not all of these side effects are common, when they do occur, they may require medical attention.

CHECK WITH YOUR DOCTOR IMMEDIATELY IF ANY OF THE FOLLOWING ARE NOTED:

- bloody or black tarry stools;
- shortness of breath, wheezing, any trouble in breathing or tightness in the chest;
- skin rash, hives or swelling, itching;
- vomiting or persistent indigestion, nausea, stomach pain or diarrhea;
- yellow discoloration of skin or eyes;
- any change in the amount of, or colour of, your urine (dark red or brown);

- painful or difficult urination, increased need to urinate;
- swelling of the feet or lower legs;
- malaise, fatigue, loss of appetite;
- blurred vision or any visual disturbance;
- mental confusion, depression, dizziness, lightheadedness, insomnia;
- hearing problems;
- persistent skin reactions at the application site, including dryness, tingling, itchiness or rash;
- bad breath, garlic breath or unusual body odour;
- drowsiness and headache.

Other side effects not listed above may also occur in some patients. If you notice any other effects, check with your doctor.

DOSING:

In order to obtain optimum benefit from PENNSAID[®], you should apply it regularly, exactly as your doctor has prescribed. Incomplete benefit may result if you do not follow instructions carefully.

PENNSAID[®] is intended for external use only. For best results, follow these instructions carefully:

- apply PENNSAID[®] to clean, dry skin;
- do not use under bandages or dressings;

- dispense 10 drops of PENNSAID® into your hand, or directly onto your knee;
- spread PENNSAID® evenly around front, back and sides of your knee;
- repeat this procedure until you have applied 40 or 50 drops (depending on the recommended dose) and your knee is completely covered;
- to treat the other knee, repeat the procedure;
- allow several minutes for PENNSAID® to dry;
- avoid contact of synthetic fibres with skin still wet from application of PENNSAID®;
- do not apply PENNSAID® to open, abraded or infected skin;
- avoid contact with your eyes or mucous membranes;
- after application, wash your hands;
- follow the same procedure 3 times (for 50 drops) or 4 times (for 40 drops), spaced evenly throughout the day;
- do not apply any other medication to the treated area;
- always use PENNSAID® according to your doctor's instructions;

PENNSAID® should not be used longer than 3 months.

If you are not getting adequate relief of your symptoms, speak to your doctor before you stop using PENNSAID®. Although you may notice some improvement within the first few days, it may take a week, or more in some patients, to achieve maximum effect.

WHAT TO DO IF YOU MISS A DOSE:

If you miss a PENNSAID[®] treatment, do not double the next dose. Simply continue with your next scheduled application.

STORAGE:

Store at room temperature (15 – 25 °C).

PENNSAID[®] IS NOT RECOMMENDED FOR USE IN PATIENTS UNDER 18 YEARS OF AGE, SINCE SAFETY AND EFFECTIVENESS HAVE NOT BEEN ESTABLISHED IN THIS AGE GROUP.

DO NOT KEEP OUTDATED MEDICINE OR MEDICINE NO LONGER NEEDED.

KEEP OUT OF THE REACH OF CHILDREN.

THIS MEDICATION HAS BEEN PRESCRIBED FOR YOUR MEDICAL PROBLEM. DO NOT GIVE IT TO ANYONE ELSE.

IF YOU REQUIRE MORE INFORMATION ABOUT THIS DRUG, CONSULT YOUR DOCTOR OR PHARMACIST.

PHARMACOLOGY OF DICLOFENAC SODIUM

Diclofenac sodium is an NSAID with analgesic and antipyretic properties. The mode of action is not fully known but it does not act through the pituitary-adrenal axis. Diclofenac inhibits prostaglandin synthesis by interfering with the action of prostaglandin synthetase/cyclo-oxygenase, isoforms 1 and 2 (COX-1 and COX-2). This inhibitory effect may partially explain its actions. Diclofenac sodium demonstrated excellent analgesic potential when compared to other NSAIDs. The analgesic potential of the most active metabolite of diclofenac sodium was about 50 times less than the potential of the diclofenac sodium itself.

Although diclofenac sodium does not alter the course of the underlying disease, it has been found to relieve pain, reduce fever, swelling and tenderness, and increase mobility in patients with various rheumatic disorders.

CLINICAL PHARMACOLOGY

DICLOFENAC SODIUM

Absorption:

Oral administration: Orally administered diclofenac sodium is rapidly and almost completely absorbed and distributed through the blood to all organs. The plasma concentration shows a linear relationship to the administered dose. After administration on an empty stomach of 50 mg of enteric-coated diclofenac sodium, the mean peak plasma concentration (C_{MAX}) was reported as approximately 1,500 ng/mL after about 2 hours. No accumulation occurs, provided the recommended dosage intervals are observed.

PENNSAID[®]: Following a single application of *PENNSAID*[®] (1.0 mL) to a single knee the knee, the mean peak plasma diclofenac sodium concentration (C_{MAX}) in six volunteers was 9.7 ± 4.7 ng/mL after 24 to 48 hours (T_{MAX}). The mean total urinary recovery of diclofenac sodium was 3.68%.

Following multiple doses of *PENNSAID*[®], 40 drops (one knee) or 80 drops (two knees, four times a day for 84 days, to 20 patients, the mean plasma diclofenac sodium level was 8.95 ± 9.17 ng/mL.

Two additional PK studies had been performed. In an open-label, single-dose pharmacokinetic study, a total of 80 drops of *Pennsaid*[®] were applied on both knees (40 drops per knee). After a single administration of *PENNSAID*[®] a maximum diclofenac concentration in plasma of 8.05 ng/mL was reached in about 10 hours, and diclofenac remained measurable up to 72 hours post-dose in 18 subjects. Mean elimination half-life was 37h (13 subjects).

In an open-label, multiple dose pharmacokinetic study, a total of 80 drops of *Pennsaid*[®] (40 drops per knee), were applied on both knees over 7 days with the final dose on the morning of Day 8. Additionally, pre-dose samples were collected on Day 6, 7 and 8. Diclofenac reached plasma concentration levels at or near steady state on Day 6. After the last dose of *Pennsaid*[®] on Day 8, mean plasma C_{max} value of diclofenac was 19.4 ng/mL and mean T_{max} was 4.0 hrs. The apparent terminal half-life ($t_{1/2}$) was 79.0 hrs.

The effect of *PENNSAID*[®] on platelet function was studied in 10 healthy patients randomly selected in the multi-dose pharmacokinetic study. The results of the average platelet aggregation time following stimulation with ADP, collagen, epinephrine and arachidonic acid indicated that there was no significant effect on platelet aggregation after application of 40 drops of *Pennsaid*[®] to each knee for 7 days.

Distribution:

Diclofenac sodium is extensively bound (99%) to serum albumin. The apparent volume of distribution is 0.12 to 0.17 L/kg.

Biotransformation:

Diclofenac sodium, regardless of the route of application, once systemically absorbed, undergoes single and multiple hydroxylation followed by o-methylation of the hydroxy metabolites, producing 3'-, 4'-, 5-hydroxy, 4'-5-hydroxy and 3'-hydroxy-4'-methoxy derivatives of diclofenac sodium. These phenolic metabolites are largely inactive and, along with the parent compound, are converted mostly to glucuronide conjugates.

Elimination:

Oral administration: Following oral administration, plasma clearance of diclofenac sodium is reported as 263 ± 56 mL/minute. The mean terminal drug half-life in plasma is 1.8 hours. About 60% of the drug and its metabolites are eliminated in the urine and the balance through biliary secretion into the feces. More than 90% of an oral dose is accounted for in elimination products, within 72 hours. About 1% of an oral dose is excreted unchanged in urine.

PENNSAID®:

After topical administration, the mean total urinary recovery of diclofenac sodium after 120 hours was 3.68%. The peak urinary excretion rate was reached by 24 hours and was maintained until 48-72 hours.

DIMETHYL SULFOXIDE (DMSO) PHARAMACOKINETICS IN HUMANS

Following topical application, dimethyl sulfoxide is absorbed and generally distributed throughout the body tissues and fluids. Dimethyl sulfoxide is detectable in serum after 5

minutes. The peak serum concentration occurs in 4 – 6 hours. DMSO is metabolized by oxidation to dimethyl sulfone or by reduction to dimethyl sulfide. Dimethyl sulfoxide and dimethyl sulfone are excreted in the urine and feces. Dimethyl sulfide is a volatile gas that is eliminated through the breath and skin and is responsible for the garlic-like odour sometimes noticed by patients. Trace amounts persist in serum for more than 2 weeks after a single intravesical instillation. No residual accumulation of dimethyl sulfoxide has occurred in patients who have received treatment for protracted periods of time. Following multiple doses of PENNSAID[®], 40 drops (one knee) or 80 drops (two knees) *q.i.d.* for up to 84 days, the mean plasma diclofenac sodium level was 8.95 ± 9.17 ng/mL. The mean whole blood level of dimethyl sulfoxide (DMSO) was 647.8 ± 659.3 ng/mL, in 18 patients, up to 6 hours following the last application

Two additional Pharmacokinetic studies have been performed. In an open-label, single-dose pharmacokinetic study, a total of 80 drops of Pennsaid[®] were applied on both knees (40 drops per knee). After a single administration of PENNSAID, maximum DMSO concentration in plasma of 0.48 µg/mL was reached in about 8 hours, and DMSO remained measurable up to 24 hours post-dose in 18 subjects. Mean elimination half-life was 8.4h (9 subjects).

In an open-label, multiple dose pharmacokinetic study, a total of 80 drops of Pennsaid[®] (40 drops per knee), were applied on both knees over 7 days with the final dose on the morning of Day 8. DMSO reached plasma concentration levels at or near steady state on Day 6. Following the last dose of Pennsaid[®] on Day 8, mean C_{max} value of DMSO was 1.2 µg/mL and mean T_{max} value was 3.8 hrs. The mean apparent terminal half-life ($t_{1/2}$) was 43 hrs. Dimethyl sulfone (DMSO₂) reached plasma concentration levels at or near steady state on Day 6. Following the last dose of Pennsaid[®] on Day 8, C_{max} values of DMSO₂ were 18.0 µg/mL and mean T_{max} value was 9.4 hrs.

TOXICOLOGY STUDIES IN ANIMALS

Acute Toxicity

DICLOFENAC SODIUM:

Species	Route of Administration	LD ₅₀ mg/kg
Mouse	p.o.	389
	i.v.	133
Rat	p.o.	173
	i.v.	106
Guinea-pig	p.o.	1110
	i.v.	127
Rabbit	p.o.	194

Symptoms included bradycardia and convulsions. The most frequent autopsy findings in animals that died were gastric irritation, perforation and their sequelae.

DIMETHYL SULFOXIDE:

The dermal LD₅₀ of DMSO is approximately 40,000 mg/kg in mice and rats. The oral and intravenous LD₅₀ values are >2,500 mg/kg in laboratory animals (mouse, rat, cat, dog and monkey).

There was no evidence of significant change in serum creatinine levels, and no histological change, with DMSO treatment. There was no additional nephrotoxicity in rats with dichromate-induced renal failure that were given DMSO compared to those that were given only the dichromate.

Long-Term Toxicity Studies

DICLOFENAC SODIUM:

Diclofenac sodium given orally to male and female rats, in doses of 0.25, 1.0 and 2.0 mg/kg/day, from 59 weeks (high-dose groups) to 98 weeks (low- and intermediate-dose groups) resulted in high, dose-related mortality caused by severe ulceration of the gastrointestinal tract, with perforated ulcers leading to peritonitis and its sequelae. Hematological patterns showing neutrophilic leucocytosis and anemia were seen in the high- and intermediate-dose groups, particularly females at weeks 52 and 98. Females tended to develop enlarged adrenals and eventually experienced depressed glucose and elevated alkaline phosphatase levels. No increase in tumour incidence was observed in the drug-treated groups as compared to the control group.

Diclofenac sodium, given orally once daily to baboons (*Papio spp.*), at dose levels of 0, 5, 15 (reduced to 10 on day 254) and 50 (reduced to 30 on day 38) mg/kg/day, for up to 52 weeks, caused ulceration of the gastrointestinal tract, constipation and occasional diarrhea. In all groups receiving diclofenac, there was a dose-related fall in serum albumin level. In the recovery groups (controlled, low and intermediate), no intestinal lesions were present.

DIMETHYL SULFOXIDE:

60% or 100% DMSO was applied dermally to the shaved back of dogs and monkeys at doses of 3,300 to 33,000 mg/kg/week for 6 months. Initially, the skin became transiently reddened and warm, particularly with 100% DMSO. With continued application, erythema, desquamation and focal skin lesions occurred at three weeks and lasted for the duration of treatment. No other changes were observed.

DMSO administered in large doses to dogs, rabbits and pigs (particularly by the oral route) caused changes in the refractive index of the lens, with progressive myopia in the

nucleus and an increase in hyperopia in the lens cortex. Chemical analysis indicated a reduction of the usual concentrations of soluble protein, urea, glutathione, uric and amino acid in the lens of affected eyes. The most sensitive animal was the rabbit, where the no observed effect level (NOEL) was 500 mg/kg/day. The lenticular changes seen in pigs after 27 weeks of topical DMSO at 2.7 – 4.5 g/kg doses were reversible. Two months after cessation of treatment, lens alterations regressed. However, following 5 g/day oral DMSO to dogs, lesions persisted after 8 months. No change to the lens of monkeys was detected at oral doses up to 5 g/kg/day for 100 days. The doses required to produce ocular changes in animals are far in excess of those that have been used clinically in humans.

Careful examination of patients who had received treatment with DMSO, 30 gm/day for 3 – 19 months revealed no adverse effects on the eye. In another study, 84 patients treated with DMSO, (average dose of 18.5 mL of 90% DMSO; average duration of 2.5 months) were examined ophthalmoscopically; no toxicity to the eye was observed. These exposures are orders of magnitude higher than the recommended dosage of PENNSAID®.

Daily oral administration to rats of 50% DMSO, 5.0 g/kg for 45 days, caused slight weight loss. Microscopic examination of the liver showed necrosis of the liver cells (degenerative modifications of the hepatocytes) with inflammation and irritation of the portal spaces. However, orally administered doses of 2.0 g/kg affected neither weight gain nor growth of the 5 weeks old young animal. Histopathological examination showed no abnormality. In a study by Smith *et al.* (1967) of rats receiving daily oral DMSO doses of 1.0, 3.0 and 10 g/kg for 59 consecutive days, no grossly adverse effects were observed.

Smith *et al.* (1967) observed the response of three dogs to repeated oral doses of 2.5 – 10 g/kg DMSO, for 14 to 35 days. Halitosis, vomiting and ocular changes were observed. One dog that died had liver degeneration and hemorrhagic gastroenteropathy.

Rhesus monkeys, receiving 2 – 3 g/kg of DMSO intravenously, once daily for nine days, showed no evidence of damage to the liver, kidneys or eyes. Feinman and co-workers administered DMSO orally to monkeys for five consecutive days, at doses up to 4.0 g/kg, and reported no markedly adverse effects.

Carcinogenicity of DMSO in animals has not been determined.

Reproduction Studies

DICLOFENAC SODIUM:

Doses of 2 or 4 mg/kg/day were given orally to male and female rats with no noticeable effect on fertility. Dosing was carried out during pre-mating, mating, gestation and lactation periods. At the higher dose, prolonged gestation and dystocia were observed. Embryo toxicity (low birth weight, failure to survive) was observed at both doses, but it was minimal at 2 mg/kg/day. Post-natal survival and growth of pups from drug-treated females were comparable to those of controls, except for slightly retarded growth at the higher dose.

Teratology studies in mice and rats, at oral doses of 2, 3, 10, and 20 mg/kg/day, showed no teratogenic effects on fetuses. At the higher doses, pronounced gastrointestinal effects were observed in the dams and a marked toxic effect noted in fetuses (reduced birth weights and increased fetal death).

Pregnant rabbits, treated with an oral dose of 5 or 10 mg/animal/day throughout the gestation period, showed a dose-dependent increase in resorption rate, diminished fetus weight, and abnormal skeletal findings. Definite embryo toxicity was observed at the highest dose although there was no evidence to suggest teratogenicity.

DIMETHYL SULFOXIDE:

Studies show that for induction of a teratogenic effect in mammals, very high doses (2,500 -10,000 mg/kg) of DMSO must be administered systemically, not topically.

Mutagenicity Studies

PENNSAID®

PENNSAID® was examined in three mutagenicity studies.

Mutagenicity Study of PENNSAID® in the *Salmonella Typhimurium* Reverse Mutation Assay (*In Vitro*)

No mutagenic effect was observed for PENNSAID® tested up to 5000 µg/plate in any of the test strains in the two experiments with or without metabolic activation.

PENNSAID® **showed no** clastogenic activity in human peripheral lymphocyte cultures at concentrations up to 5000 µg/mL , under either metabolic activation or non-activation conditions.

In the *in vivo* mouse micronucleus assay, PENNSAID®-treated animals at the maximum tolerated dose of 12 mL/kg showed no significant increase in micronucleus frequency compared to negative control, whereas the known clastogenic agent cyclophosphamide induced large and statistically significant increases in micronucleus frequency.

DICLOFENAC SODIUM:

Mutagenicity studies were carried out *in vitro* in bacteria and in mammalian cells, with and without microsomal activation. *In vivo* studies were also performed. Diclofenac sodium was not mutagenic in any of these test systems.

DIMETHYL SULFOXIDE:

DMSO was studied with the Ames *S. typhimurium* test and was found to be non-mutagenic.

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