

## 1 Name of the medicinal product

PENNSAID<sup>®</sup> 16 mg/ml cutaneous solution

## 2 Qualitative and quantitative composition

1 ml cutaneous solution contains: 16.05 mg diclofenac sodium

For excipients, see 6.1

## 3 Pharmaceutical form

Cutaneous solution.

The cutaneous solution is a clear, colourless to pink or orange liquid.

### 4.1 Therapeutic indications

PENNSAID<sup>®</sup> (16 mg/ml diclofenac sodium) is a cutaneous solution that is indicated for the *symptomatic relief of pain associated with osteoarthritis* in superficial joints, including the knee. There is no data on the use of PENNSAID<sup>®</sup> for large, deep joints covered by layers of muscle or other soft tissues, such as the hip or spine.

### 4.2 Posology and method of administration

PENNSAID<sup>®</sup> is applied topically to the painful joint.

After washing the treatment site with soap and water and allowing it to dry, apply a total of about 20 or 40 drops (approximately 0.5 or 1 ml) of PENNSAID<sup>®</sup> (16 mg/ml diclofenac sodium) to a medium (*e.g. wrist*) or large joint (*e.g. knee*), respectively. ***Patients should use up to a maximum of 40 drops four times per day per joint as recommended by the physician.*** To ensure that product does not run off the treatment site, apply the solution in several aliquots of 5 or 10 drops to the medium or large joint. Spread PENNSAID<sup>®</sup> evenly over the treatment area with a hand or fingers. Repeat this procedure until the total amount of PENNSAID<sup>®</sup> has been applied. Follow the same procedure 4 times a day.

***Patients with renal and hepatic impairment:***

***For the use of PENNSAID<sup>®</sup> in patients with hepatic or renal impairment see section 4.4.***

Use in Children: Since no experience has been acquired with PENNSAID<sup>®</sup> in paediatric use, it is not recommended for use in this group of patients.

### 4.3 Contra-indications

PENNSAID<sup>®</sup> (16 mg/ml diclofenac sodium) is contraindicated in pregnant and lactating women and in patients with hypersensitivity to diclofenac or other ingredients of the solution.

Since there exists the potential for cross-sensitivity with other NSAIDs, even from different groups, diclofenac should not be used in patients whom acute asthmatic attacks, urticaria, rhinitis or other allergic manifestations have been precipitated by oral use of acetylsalicylic acid (ASA) or other non-steroidal, anti-inflammatory agents.

Allergy or Skin Sensitivity: PENNSAID<sup>®</sup> also contains dimethyl sulphoxide (DMSO) as a skin penetrant. It should not be used in patients with known history of allergy or skin sensitivity to DMSO.

### 4.4 Special Warnings and Special Precautions for Use

Undesirable effects may be minimised by using the minimum effective dose for the shortest duration necessary to control symptoms.

Elderly: The elderly have an increased frequency of adverse reactions to oral NSAIDs especially gastrointestinal bleeding and perforation, which may be fatal.

Patients with a history of GI toxicity, particularly when elderly, should report any unusual abdominal symptoms (especially GI bleeding) particularly in the initial stages of treatment.

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported very rarely in association with the use of NSAIDs (see 4.8). Patients appear to be at highest risk for these reactions early in the course of therapy: the onset of the reaction occurring in the majority of cases within the first month of treatment. PENNSAID<sup>®</sup> should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Patients should be instructed to wash their hands after the administration procedure to avoid contact with eyes, mucous membranes and skin not intended for treatment.

No other medicinal products should be applied to the affected area simultaneously with PENNSAID<sup>®</sup>.

The likelihood of systemic side effects occurring following the topical application of PENNSAID<sup>®</sup> is very small compared to the frequency of side effects with oral diclofenac, owing to low systemic absorption with PENNSAID<sup>®</sup>. This product should be used with caution in patients with impaired renal function, since isolated cases of systemic reactions resulting in

deterioration of renal function have been reported with topically or orally administered NSAIDs. The lower dose of PENNSAID<sup>®</sup> per joint should be considered.

#### Hepatic System

Mild elevation of liver function tests may occur during treatment with PENNSAID<sup>®</sup>. If abnormal liver function tests persist or worsen, clinical signs or symptoms consistent with liver disease develop, or if other manifestations occur (e.g. eosinophilia, rash), PENNSAID<sup>®</sup> should be discontinued. If there is a need to prescribe this drug in the presence of severe impairment of 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.

#### Gastrointestinal System

Peptic ulceration, perforation and gastrointestinal bleeding, sometimes severe and occasionally (rarely) fatal, in either the presence or absence of previous symptoms have been known to occur during oral and rectal therapy with non-steroidal anti-inflammatory drugs (NSAIDs). However, the maximum serum level of diclofenac, after topical application of PENNSAID<sup>®</sup>, is low (50 times lower than that achieved after 25 mg of orally administered diclofenac). Therefore, PENNSAID<sup>®</sup> (diclofenac sodium) can reasonably be given to patients prone to gastrointestinal tract irritation, including those with a history of previous NSAID-induced peptic ulcer, or other inflammatory disease of the gastrointestinal tract (such as ulcerative colitis or Crohn's disease), under close medical supervision. In these cases the physician must weigh the benefits of treatment against the possible hazards (See CONTRAINDICATIONS and ADVERSE EVENTS). The patient should be instructed to contact a physician immediately if symptoms or signs suggestive of peptic ulceration or gastrointestinal bleeding occur. These reactions may occur at any time during treatment without warning symptoms or signs.

#### Dermatological

PENNSAID<sup>®</sup> should not be used under occlusive dressings. PENNSAID<sup>®</sup> should not be applied to open, abraded or infected skin. Do not use PENNSAID<sup>®</sup> in joint areas where there is a previous skin disease (e.g. psoriasis) unless advised by your physician.] Application of PENNSAID<sup>®</sup> to mucus membranes is not advisable.

#### Hypersensitivity

The dimethyl sulphoxide (DMSO) in PENNSAID<sup>®</sup> may initiate the liberation of histamine and occasional hypersensitivity reactions have been reported with topical administration. If anaphylactoid symptoms develop, appropriate therapy should be instituted and further use of PENNSAID<sup>®</sup> discontinued.

#### Ophthalmology

In animal studies, heavy DMSO dosage, particularly by the oral route, has resulted in abnormal changes to the lens of the eye. In studies of primates and humans,

following both ocular and oral dosage of DMSO, no such changes have been observed.

#### Infection

The anti-inflammatory and analgesic effects of diclofenac sodium may mask the usual signs of infection. Hence, the physician should be alert to the development of localised skin infection in the area that the patient has applied the drug.

The maximum concentration of diclofenac in the blood, after application of the maximum dosage of PENNSAID<sup>®</sup> (1ml), was found to be less than 10 ng/ml. This value is 50 times lower than the maximum concentration of diclofenac in the blood after oral administration of 25 mg of diclofenac.

PENNSAID<sup>®</sup> contains dimethyl sulphoxide (DMSO) which can cause drowsiness and headache and may be irritant to the skin.

### **4.5 Interactions with other medicaments and other forms of interaction**

The listed interactions in this section of the SPC have been observed after systemic administration of diclofenac sodium. The risk associated with the topical use of PENNSAID<sup>®</sup> formulation is not known, but probably low.

#### Acetylsalicylic Acid (ASA):

Serum levels of diclofenac may be reduced when taken with ASA simultaneously. The bioavailability of ASA is reduced by the presence of diclofenac. Although these pharmacokinetic interactions do not appear to be clinically relevant, there is no proven advantage in using these two medications together.

#### Digoxin:

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

#### Lithium:

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

#### Oral hypoglycaemic drugs:

Pharmacodynamic studies have shown no potentiation of effect with concurrent administration with diclofenac; however, there are isolated reports of both hypoglycaemic and hyperglycaemic effects in the dosage of hypoglycaemic agents.

#### Anticoagulants:

NSAIDs may enhance the effects of anti-coagulants, such as warfarin (see section 4.4).

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 it is necessary to monitor blood/plasma levels regularly.

Glucocorticoids:

Concomitant administration may aggravate gastrointestinal side effects.

NSAIDs:

Concurrent oral treatment with two or more NSAIDs may promote the occurrence of side effects (see special warnings and precautions for use).

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, hence toxicity is increased.

Cyclosporine:

Nephrotoxicity of cyclosporine may be increased because of the effect of NSAIDs on renal prostaglandin.

Quinolone Antibacterials:

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

Antihypertensive Agents:

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

Other Drugs

Diclofenac sodium should not be used concomitantly with diclofenac potassium since both exist in plasma as the same active organic ion.

Corticosteroids: increased risk of gastrointestinal ulceration or bleeding (See section 4.4).

Anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs): increased risk of gastrointestinal bleeding (see section 4.4).

#### **4.6 Use during pregnancy and lactation**

PENNSAID<sup>®</sup> is contraindicated during pregnancy and lactation (see sections 4.3 and 5.3).

#### **4.7 Effects on ability to drive and use machines**

Headache, dizziness, light-headedness, and mental confusion have been reported following oral diclofenac therapy. Patients should be aware that these side effects may occur, and be cautioned against operating machinery or motor vehicles should they experience any of these.

#### **4.8 Undesirable Effects**

##### **Topical:**

Undesirable effects are divided into those occurring at the site of application and those occurring as a systemic effect. The following undesirable effects were observed in six double-blind, clinical trials with significantly increased frequency in the PENNSAID<sup>®</sup>-treated group compared with placebo. At the site of application, dry skin (35.80% compared to 6.86% in placebo treated group) and rash (10.44% compared to 2.86% in placebo treated group) were statistically significant. Other Pennsaid undesirable effects statistically significant compared to placebo are constipation (3.83% compared to 0.57%), dyspepsia (8.98% compared to 4%) and flatulence (4.49% compared to 0.57%).

Photoallergic reaction and contact dermatitis have been reported following application of topical diclofenac.

Systemic absorption of diclofenac sodium after topical application of PENNSAID<sup>®</sup> is very low compared with use of diclofenac sodium tablets. However, where PENNSAID<sup>®</sup> is applied to a relatively large area of skin over a prolonged period, the possibility of systemic side-effects similar to systemic effects from oral diclofenac (see below) cannot be completely excluded. Possible systemic side-effects are described below.

##### **Oral:**

Oral administration of diclofenac results in adverse events due to systemic and local gastrointestinal reactions. The most severe gastrointestinal adverse reactions observed were ulceration and bleeding while the most severe albeit rare dermatological reactions observed were erythema multiforme (Stevens-Johnson syndrome and Lyell syndrome). Fatalities have occurred on occasion, particularly in the elderly.

Bullous reactions including Stevens Johnson Syndrome and Toxic Epidermal Necrolysis (very rare)

Oedema, hypertension and cardiac failure have been reported in association with NSAID treatment

Gastrointestinal:

Occasional: epigastric, gastric, or abdominal pain, abdominal cramps, nausea, dyspepsia, anorexia, diarrhoea, vomiting and flatulence.

Rare: gastrointestinal bleeding (bloody diarrhoea, melaena, haematemesis) gastric and intestinal ulcerations with or without bleeding or perforation.

Isolated: lower gut disorders (e.g. non-specific haemorrhagic colitis and exacerbation of ulcerative colitis or Crohn's disease), diaphragm-like intestinal strictures, hyperacidity, stomatitis, glossitis, coated tongue, oesophageal lesions, constipation and pancreatitis.

CNS:

Occasional: dizziness, headache and vertigo.

Rare: drowsiness, malaise, impaired concentration and tiredness.

Isolated: sensory disturbances including paraesthesia, memory disturbance, disorientation, insomnia, irritability, convulsions, depression, anxiety, nightmares, tremor, psychotic reactions and aseptic meningitis.

Special Senses:

Isolated: vision disturbances (blurred vision, diplopia), impaired hearing, tinnitus and taste alteration disorders.

Cardiovascular:

Rare: palpitation, angina and arrhythmias.

Isolated: exacerbation of cardiac failure and hypertension.

Dermatologic:

Occasional: rash and pruritus.

Rare: urticaria.

Isolated: bullous eruption, erythema, eczema, erythema multiforme, Stevens-Johnson syndrome, Lyell syndrome (toxic epidermal necrolysis), erythroderma (exfoliative dermatitis), loss of hair, photosensitivity reactions and purpura including allergic purpura.

Renal System:

Rare: oedema (facial, general, peripheral).

Isolated: acute renal failure, nephrotic syndrome, urinary abnormalities (e.g. haematuria and proteinuria), interstitial nephritis and papillary necrosis.

Haematologic:

Isolated: thrombocytopenia, leukopenia, agranulocytosis, haemolytic anaemia, aplastic anaemia and anaemia secondary to gastrointestinal bleeding.

Hepatic:

Occasional: elevations ( $\geq 3$  times the upper normal limit) of AST, ALT.

Rare: liver function disorders including hepatitis with or without jaundice.

Isolated: fulminant hepatitis.

Hypersensitivity:

Rare: hypersensitivity reaction such as asthma in patients sensitive to ASA e.g., bronchospasm; anaphylactic/anaphylactoid systemic reactions including hypotension.

Isolated: vasculitis and pneumonitis.

#### **4.9 Overdose symptoms, emergency procedures, antidotes**

PENNSAID<sup>®</sup> is intended for external use only. The low systemic absorption of diclofenac from PENNSAID<sup>®</sup> suggests that toxicity from topical overdose is extremely unlikely.

In the event of accidental ingestion, the amount of diclofenac sodium (900 mg) contained in one 60-ml bottle of PENNSAID<sup>®</sup> could cause stomach upset and/or transient renal dysfunction. Absorption should be minimised as soon as possible by administration of activated charcoal. Renal function should be monitored as should gastrointestinal condition for possible irritation or bleeding. Supportive and symptomatic treatment should be given for complications including, for example: hypotension, gastrointestinal haemorrhage and renal failure. Forced diuresis may be of limited use. The amount of DMSO (36 g) would be far below any level dangerous to humans (based on an LD<sub>50</sub> in monkeys of >11 g/kg).

Acute exposure to DMSO through inhalation of high vapour concentrations through the use or abuse of PENNSAID<sup>®</sup> 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.

## 5.1 Pharmacodynamic properties

### Pharmaco-Therapeutic Group

Topical products for Joints and Muscular Pain (M02).

### Mechanism of Action

Diclofenac sodium is a non-steroidal anti-inflammatory drug of the arylacanoic acid group, with analgesic and antipyretic properties. Diclofenac inhibits prostaglandin biosynthesis by irreversibly inactivating prostaglandin synthetase. This decreased formation of prostaglandins results from the competition between diclofenac and arachidonic acid for binding to cyclooxygenase (prostaglandin synthetase). This may partially explain its mechanism of action. Since the anti-inflammatory activity of diclofenac is maintained even in adrenalectomised animals, it does not act through the pituitary-adrenal axis. Diclofenac is considered to be a peripherally acting analgesic.

PENNSAID<sup>®</sup> contains diclofenac sodium in a solution base containing dimethyl sulphoxide (DMSO), which enhances drug penetration through the skin into underlying tissue and joint spaces. There are many mechanisms of action suggested for DMSO, and it is likely that a combination of mechanisms is operational.

## 5.2 Pharmacokinetic properties

### *Absorption*

Diclofenac sodium is rapidly absorbed when administered as an oral solution, rectal suppository, or by intramuscular injection. It is absorbed more slowly when administered as enteric-coated tablets, especially when this dosage form is given with food. Diclofenac is also absorbed percutaneously.

After the topical application of 1.0 ml of PENNSAID<sup>®</sup> (15 mg of diclofenac sodium), the mean peak plasma concentration ( $C_{max}$ ) of diclofenac in plasma is 9.7 ng/ml. This concentration is reached at 24 to 48 hours ( $T_{max}$ ).

### *Distribution and Metabolism*

Although orally administered diclofenac is almost completely absorbed, it undergoes first-pass metabolism so that only 50 – 60% of the drug reaches the systemic circulation in the unchanged form. At therapeutic concentrations it is more than 99% bound to plasma proteins. Diclofenac penetrates synovial fluid and has been detected in breast milk. The terminal plasma half-life is about 1 to 2 hours.

Diclofenac is metabolised to 4'-hydroxydiclofenac, 5-hydroxydiclofenac, 3'-hydroxydiclofenac, 3'-hydroxy-4'-methoxy diclofenac and 4',5-dihydroxydiclofenac.

#### *Elimination*

Diclofenac sodium is excreted in the form of glucuronide and sulphate conjugates, mainly in the urine and the bile. The mean total urinary recovery of diclofenac after 120 hours is 3.68%. The peak urinary excretion rate is reached within 24 hours and is maintained until 48 – 72 hours. Diclofenac sodium and its metabolites are eliminated primarily (60%) by the kidneys.

### **5.3 Preclinical safety data**

Diclofenac sodium has not been shown to be mutagenic in standard *in vitro* and *in vivo* tests. No increase in tumourgenicity has been observed in long-term animal studies with diclofenac sodium.

The excipient DMSO can produce local toxicity, particularly when administered in undiluted form (muscle necrosis, inflammation and oedema, scaling and flaking of skin following intramuscular, subcutaneous, or topical administration, respectively). DMSO has produced teratogenic lesions in a number of mammalian species at doses of approximately 2.5g/kg/day or above, and by different routes of administration.

### **6.1 List of Excipients**

dimethyl sulphoxide  
ethanol  
glycerine  
propylene glycol  
purified water

### **6.2 Major incompatibilities**

Not applicable

### **6.3 Shelf life**

30 ml, 60 ml, 120 ml and 150 ml: 3 years  
15 ml: 18 months  
After first opening: 12 weeks

### **6.4 Special precautions for storage**

Do not store above 25°C. Do not refrigerate.

**6.5 Nature and contents of container**

PENNSAID® is packaged in 20, 40, 75, 140 and 170 ml white, oval high-density polyethylene bottles (which correspond to fill volumes of 15 ml, 30 ml, 60 ml, 120 ml and 150 ml respectively), and are sealed with an 18 mm, white, low-density polyethylene screw cap with a plastic dropper spout. Not all pack sizes may be marketed.

**6.6 Special precautions for disposal**

No special requirements.

**7 Marketing authorisation holder**

DIMETHAID (UK) LIMITED  
Third Floor One London Square  
Cross Lanes  
Guildford, Surrey  
GU1 1UN  
United Kingdom

**8 Marketing authorisation number**

PL 18329/0001

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

21/11/2005

**10 DATE OF REVISION OF THE TEXT**

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