

## **Product Summary**

### **1. Trade Name of the Medicinal Product**

Diclofenac Sodium Injection 75 mg in 3 ml.

### **2. Qualitative and Quantitative Composition**

Each 3 ml solution contains 75 mg diclofenac sodium BP.

### **3. Pharmaceutical Form**

Clear colourless or almost colourless sterile aqueous solution presented in 3 ml glass ampoules.

## **Clinical Particulars**

### **4.1. Therapeutic Indications**

Acute exacerbations of rheumatoid arthritis and osteoarthritis; acute back pain; acute gout; post-operative pain, relief of pain in acute trauma and fractures and renal colic.

### **4.2 Posology and method of administration**

Route of administration: intramuscular injection.

One ampoule once (or in severe cases twice) daily intramuscularly by deep intragluteal injection into the upper outer quadrant. If two injections daily are required it is advised that the alternate buttock be used for the second injection. Diclofenac Sodium Injection should not be given for more than 2 days; if necessary, treatment can be continued with tablets. Diclofenac Sodium Injection should not be administered by the intravenous route.

Renal colic: 1 x 75 mg ampoules intramuscularly. A further ampoule may be administered after 30 minutes if necessary. The total daily dose should not exceed 150 mg.

Elderly: Although the pharmacokinetics of diclofenac are not impaired to any clinically relevant extent in elderly patients, non-steroidal anti-inflammatory drugs should be used with particular caution in such patients as the elderly are at increased risk of the serious consequences of adverse reactions. If an NSAID is considered necessary, the lower dose should be used and the patients should be monitored for GI bleeding during NSAID therapy. (See also 4.4 Special warnings and special precautions for use).

Children: Diclofenac Sodium Injection is not recommended for use in children.

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.4).

### **4.3 Contraindications**

Use in patients with a history of, or active or suspected recurrent peptic ulceration/haemorrhage, or gastrointestinal bleeding (two or more distinct episodes of proven ulceration or bleeding).

Use in patients who are hypersensitive to diclofenac or those in whom attacks of asthma, urticaria, acute rhinitis, angioedema or other signs of hypersensitivity are precipitated by aspirin, ibuprofen or other nonsteroidal anti-inflammatory agents.

Hypersensitivity to Diclofenac or to any of the excipients: sodium metabisulphite, benzyl alcohol, propylene glycol.

Severe heart failure, hepatic failure and renal failure (see section 4.4).

During the last trimester of pregnancy (see section 4.6).

History of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy.

### **4.4. Special Warnings and Precautions for Use**

Caution is required if administered to patients suffering from, or with a history of, bronchial asthma since non-steroidal anti-inflammatory drugs have been reported to cause bronchospasm in such patients.

History of gastrointestinal ulceration, haematemesis or melaena (may occur with or without warning symptoms or a previous history and are generally more serious in the elderly), ulcerative colitis, Crohn's disease, bleeding diathesis or haematological abnormalities.

Patients with a history of peptic ulcer, haematemesis or melaena should be kept under close surveillance. Also patients with renal, cardiac or hepatic impairment and elderly patients should be kept under surveillance, as the use of NSAIDs may result in deterioration of renal function. The lowest effective dose should be employed and renal function should be monitored. Non-steroidal anti-inflammatory drugs should be given with care to patients with a history of heart failure or hypertension since oedema has been reported in association with their use.

Undesirable effects may be minimised by using the minimum effective dose for the shortest possible duration. The elderly are at increased risk of the serious consequences of adverse reactions (see also 4.2 *Posology and method of administration*).

All patients on long-term treatment with non-steroidal anti-inflammatory agents should be kept under regular surveillance, with monitoring of renal and

hepatic function and of haematological parameters. Any evidence of deterioration in function should be regarded as a reason for discontinuing therapy.

Use of diclofenac in patients with hepatic porphyria may provoke an attack.

The importance of prostaglandins in maintaining renal blood flow should be taken into account in patients with impaired cardiac or renal function, those being treated with diuretics or recovering from major surgery. Effects on renal function are usually reversible on withdrawal of diclofenac.

Diclofenac, in common with other NSAIDs, can reversibly inhibit platelet aggregation (see

#### **4.5 Interaction with other medicinal products and other forms of interaction**

Care should be taken in patients treated with any of the following drugs, as interactions have been reported in some cases.

*Anti-Hypertensives:* Concomitant use of NSAIDs and antihypertensive agents may result in a reduced antihypertensive effect.

*Lithium:* Concurrent use with lithium may increase plasma levels and decreased elimination of lithium.

*Cardiac glycosides:* Concurrent use with cardiac glycosides, including digoxin, may exacerbate cardiac failure, reduce GFR and increase plasma glycoside levels.

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

Although clinical investigations indicate that diclofenac does not influence the effect of anticoagulants, there are isolated reports of an increased risk of haemorrhage with combined use of these agents. Therefore, if diclofenac is used concurrently with an anticoagulant, the patient should be monitored closely to ensure that no change is required in the anticoagulant dosage. Like other NSAIDs, diclofenac can reversibly inhibit platelet aggregation.

Clinical studies indicate that diclofenac does not influence the clinical effect of oral hypoglycaemic agents. However, there are isolated reports of hypo- and hyperglycaemic effects which required adjustment of the dosage of the hypoglycaemic agents.

*Cyclosporin:* Nephrotoxicity may be increased by the effect of nonsteroidal anti-inflammatory drugs on renal prostaglandins.

*Mifepristone:* NSAIDs should not be used for 8 to 12 days after mifepristone administration as NSAIDs can reduce the effects of mifepristone.

*Methotrexate:* Decreased elimination of methotrexate.

Caution should be exercised if NSAIDs and methotrexate are administered within 24 hours of each other, since NSAIDs may increase methotrexate plasma levels, resulting in increased toxicity.

*Other analgesics including cyclooxygenase-2 selective inhibitors:*

Concomitant therapy with two or more systemic NSAIDs (including aspirin) should be avoided as it may increase the frequency of side effects (see section 4.4).

*Corticosteroids:* Concomitant therapy with corticosteroids increases the risk of gastrointestinal bleeding or ulceration (see section 4.4).

*Diuretics:* Reduced diuretic effect. Diuretics can increase the risk of nephrotoxicity of NSAIDs.

Various NSAIDs may inhibit the activity of diuretics. As concomitant therapy with potassium-sparing diuretics may be associated with increased serum potassium levels, serum potassium should be monitored.

*Quinolone antibiotics:*

Animal data indicate that NSAIDs can increase the risk of convulsions associated with quinolone antibiotics. Patients taking NSAIDs and quinolones may have an increased risk of developing convulsions.

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

*Tacrolimus:* Possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus.

*Zidovudine:* Increased risk of haematological toxicity when NSAIDs are given with zidovudine. There is evidence of an increased risk of haemarthroses and haematoma in HIV (+) haemophiliacs receiving concurrent treatment with zidovudine and ibuprofen.

#### **4.6 Pregnancy and lactation**

The product should not be used in pregnancy and lactation. There are insufficient reports of use of Diclofenac Sodium Injection during human pregnancy.

Congenital abnormalities have been reported in association with NSAID administration in man, however, these are low in frequency and do not appear to follow any discernable pattern. In view of the known effects of NSAIDs on the foetal cardiovascular system (a closure of the ductus arteriosus), use of NSAIDs in the last trimester of pregnancy is contraindicated. The onset of labour may be delayed and the duration increased with an increased bleeding tendency in both mother and child (see section 4.3). NSAIDs should not be used during the first two trimesters of pregnancy or labour unless the potential benefit to the patient outweighs the potential risk to the foetus.

*Lactation:*

In limited studies so far available, NSAIDs can appear in breast milk in very low concentrations. NSAIDs should, if possible, be avoided when breastfeeding.

See section 4.4 Special warnings and precautions for use, regarding female fertility.

#### 4.7 Effects on Ability to Drive and Use Machines

Undesirable effects such as dizziness, drowsiness, visual disturbances, fatigue or headache, or other central nervous system disturbances are possible after taking NSAIDs. If affected, patients should not drive or operate machinery.

#### 4.8. Undesirable Effects

Side-effects: If serious side effects occur, the product should be withdrawn. The following side effects have been reported in association with diclofenac:-

Gastro-intestinal tract: Occasional: epigastric pain, other gastro-intestinal disorders (e.g. nausea, vomiting, diarrhoea, abdominal cramps, dyspepsia, flatulence, anorexia).

Rare: gastro-intestinal bleeding, peptic ulcer (with or without bleeding or perforation), bloody diarrhoea.

In isolated cases: lower gut disorders (e.g. non-specific haemorrhagic colitis and exacerbations of ulcerative colitis or Crohn's proctocolitis), pancreatitis, aphthous stomatitis, glossitis, oesophageal lesions, constipation.

Central nervous system: Occasional: headache, dizziness, or vertigo. Rare: drowsiness, tiredness, malaise. In isolated cases: disturbances of sensation (paraesthesia), memory disturbance, disorientation, confusion, disturbance of vision (blurred vision, diplopia), impaired hearing, tinnitus, insomnia, irritability, convulsions, depression, anxiety, nightmares, tremor, psychotic reactions. Taste alteration disorders. Optic neuritis has been reported in association with NSAID therapy.

Skin: Occasional: rashes or skin eruptions. Rare: urticaria. In isolated cases: bullous eruptions, eczema, erythema multiforme, Stevens-Johnson syndrome, Lyell's syndrome, (acute toxic epidermolysis), erythroderma (exfoliative dermatitis), loss of hair, photosensitivity reactions, purpura including allergic purpura.

Kidney: In isolated cases: acute renal insufficiency, urinary abnormalities (e.g. haematuria, proteinuria), interstitial nephritis, nephrotic syndrome, papillary necrosis.

Liver: Occasional: elevation of serum aminotransferase enzymes (ALT, AST). Rare: liver function disorders including hepatitis (in isolated cases fulminant) with or without jaundice.

Blood: In isolated cases: thrombocytopenia, leucopenia, agranulocytosis, haemolytic anaemia, aplastic anaemia.

Other organ systems: Rare: oedema, hypersensitivity reactions (e.g. bronchospasm, anaphylactic/anaphylactoid systemic reactions including hypotension). Hypersensitivity reactions to NSAIDs may consist of a) non-specific allergic reactions and anaphylaxis, b) respiratory tract reactivity

comprising asthma, aggravated asthma, bronchospasm or dyspnoea or c) various skin disorders, including rashes (see above) and pruritis. Isolated cases: impotence (association with diclofenac intake is doubtful), palpitation, chest pain, hypertension.

Reactions at the site of injection: Rare: injection site disorders e.g. local pain and induration; in isolated cases: abscesses and local necrosis.

#### **4.9. Overdose**

There is no typical clinical picture associated with acute overdosage. Symptoms of overdosage with NSAIDs may include headache, vomiting, drowsiness, dizziness and fainting. Supportive and symptomatic treatment should be given for complications such as hypotension, renal failure, convulsions, gastro-intestinal irritation, and respiratory depression; specific therapies such as forced diuresis, dialysis or haemoperfusion are probably of no help in eliminating NSAIDs due to their high rate of protein binding and extensive metabolism. Correction of severe electrolyte abnormalities may need to be considered.

### **Pharmacological Properties**

#### **5.1. Pharmacodynamic Properties**

Diclofenac is a non-steroidal agent with analgesic, anti-inflammatory and antipyretic properties. It is an inhibitor of prostaglandin synthetase (cyclo-oxygenase).

Diclofenac sodium in vitro does not suppress proteoglycan biosynthesis in cartilage at concentrations equivalent to the concentrations reached in humans.

#### **5.2. Pharmacokinetic Properties**

Diclofenac sodium is rapidly absorbed from the gut and is subject to firstpass metabolism. Peak plasma concentrations occur within half hour of administration by intramuscular injection. The active substance is 99.7% protein bound and plasma half-life for the terminal elimination phase is 1 - 2 hours. Approximately 60% of the administered dose is excreted via the kidneys in the form of metabolites and less than 1% in unchanged form. The remainder of the dose is excreted via the bile in metabolised form. In patients with impaired renal function, accumulation of diclofenac has not been reported.

#### **5.3. Preclinical Safety Data**

No further information other than that which is included in other sections of the Summary of Product Characteristics.

## **Pharmaceutical Particulars**

### **6.1. List of Excipients**

Sodium metabisulphite BP, propylene glycol BP, benzyl alcohol BP and sodium hydroxide BP (as a 10% w/v solution) and Water for Injections B.P.

### **6.2. Incompatibilities**

Diclofenac Sodium Injection should not be mixed with other injection solutions.

### **6.3. Shelf Life**

3 years (36 months).

### **6.4. Special Precautions for Storage**

Protect from light.  
Store below 25°C.

### **6.5. Nature and Contents of Container**

3 ml clear glass ampoules, glass type 1, Ph. Eur.  
The ampoules are packed in cardboard cartons containing 5 or 10 ampoules.

### **6.6. Instruction for Use/Handling**

If only part of an ampoule is used, discard the remaining solution.

## **Administrative Data**

### **7. Marketing Authorisation Holder**

Antigen International Limited  
Roscrea  
Co. Tipperary  
Ireland.

**8. Marketing Authorization Number**

PL 02848/0181

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

02/03/2009

**10 DATE OF REVISION OF THE TEXT**

02/03/2009