

# New Zealand Datasheet

## Name of Medicine

DICLOFENAC 25 Tablets

Diclofenac potassium tablets 25 mg

## Presentation

Each Diclofenac 25 tablet contains 25 mg of diclofenac potassium. The tablets are white to off-white, round, biconvex film-coated. The diameter is about 6.15 mm with a thickness of about 3.2 mm.

## Uses

### Actions

Pharmacotherapeutic group: Non-steroidal anti-inflammatory drug (NSAID).

Diclofenac 25 contains the potassium salt of diclofenac, a non-steroidal compound with pronounced analgesic, anti-inflammatory, and antipyretic properties.

Diclofenac 25 tablets have a rapid onset of action which makes them particularly suitable for the treatment of acute painful and inflammatory conditions. Inhibition of prostaglandin biosynthesis, which has been demonstrated in experiments, is considered to be fundamental to its mechanism of action. Prostaglandins play a major role in causing inflammation, pain, and fever.

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

### Pharmacodynamic effects

Diclofenac has been found to exert a pronounced analgesic effect in moderate and severe pain. In the presence of inflammation, e.g. due to trauma or following surgical interventions, it rapidly relieves both spontaneous pain and pain on movement and diminishes inflammatory swelling and wound oedema. Clinical studies have also revealed that in primary dysmenorrhoea the active substance is capable of relieving the pain and reducing the extent of bleeding. In migraine attacks Diclofenac has been shown to be effective in relieving the headache and in improving the accompanying symptoms nausea and vomiting.

### Pharmacokinetics

#### Absorption

Diclofenac is rapidly and completely absorbed from diclofenac potassium tablets. The absorption sets in immediately after administration and the same amount is absorbed as from an equivalent dose of diclofenac sodium gastro-resistant tablets. Mean peak plasma concentrations of 3.8 µmol/L are attained after 20 - 60 minutes after ingestion of one tablet of 50 mg. Ingestion together with food has no influence on the amount of diclofenac absorbed although onset and rate of absorption may be slightly delayed.

The amount absorbed is in linear proportion to the size of the dose.

Since about half of diclofenac is metabolized during its first passage through the liver ("first pass" effect), the area under the concentration curve (AUC) is about half as large following oral or rectal administration as it is following a parenteral dose of equal size.

Pharmacokinetic behaviour does not change after repeated administration. No accumulation occurs provided the recommended dosage intervals are observed.

## **Distribution**

99.7 % of diclofenac binds to serum proteins, mainly to albumin (99.4%). The apparent volume of distribution calculated is 0.12-0.17 L/kg.

Diclofenac enters the synovial fluid, where maximum concentrations are measured 2-4 hours after peak plasma values have been reached. The apparent half-life for elimination from the synovial fluid is 3-6 hours. Two hours after reaching peak plasma levels, concentrations of the active substance are already higher in the synovial fluid than in the plasma, and they remain higher for up to 12 hours.

## **Biotransformation**

Biotransformation of diclofenac takes place partly by glucuronidation of the intact molecule, but mainly by single and multiple hydroxylation and methoxylation, resulting in several phenolic metabolites (3'-hydroxy-, 4'-hydroxy-, 5-hydroxy-, 4',5-dihydroxy-, and 3'-hydroxy-4'-methoxy-diclofenac), most of which are converted to glucuronide conjugates. Two of these phenolic metabolites are biologically active, but to a much lesser extent than diclofenac.

## **Elimination**

Total systemic clearance of diclofenac from plasma is  $263 \pm 56$  ml/min (mean value  $\pm$  SD). The terminal half-life in plasma is 1-2 hours. Four of the metabolites, including the two active ones, also have short plasma half-lives of 1-3 hours. One metabolite, 3'-hydroxy-4'-methoxy-diclofenac, has a much longer plasma half-life. However, this metabolite is virtually inactive.

About 60% of the administered dose is excreted in the urine as the glucuronide conjugate of the intact molecule and as metabolites, most of which are also converted to glucuronide conjugates. Less than 1% is excreted as unchanged substance. The rest of the dose is eliminated as metabolites through the bile in the faeces.

## **Characteristics in patients**

No relevant age-dependent differences in the drug's absorption, metabolism, or excretion have been observed.

In patients suffering from renal impairment, no accumulation of the unchanged active substance can be inferred from the single-dose kinetics when applying the usual dosage schedule. At a creatinine clearance of less than 10 mL/min, the calculated steady-state plasma levels of the hydroxy metabolites are about 4 times higher than in normal subjects. However, the metabolites are ultimately cleared through the bile.

In patients with chronic hepatitis or non-decompensated cirrhosis, the kinetics and metabolism of diclofenac are the same as in patients without liver disease.

## **Indications**

Diclofenac 25 tablets are indicated for the short-term treatment of the following acute conditions:

- post-traumatic pain, inflammation and swelling, e.g. due to sprains;
- post-operative pain, inflammation and swelling, e.g. following dental or orthopaedic surgery;
- painful and/or inflammatory conditions in gynaecology, e.g. primary dysmenorrhoea or adnexitis;
- migraine attacks;
- painful syndromes of the vertebral column;
- non-articular rheumatism;
- as an adjuvant in severe painful inflammatory infections of the ear, nose, or throat, e.g. pharyngotonsillitis, otitis. In keeping with general therapeutic principles, the underlying disease should be treated with basic therapy, as appropriate. Fever alone is not an indication.

## **Dosage and Administration**

### **Adults**

After assessing the risk/benefit ratio in each individual patient, the lowest effective dose for the shortest possible duration should be used.

Following an initial loading dose of 50mg, 25-50mg is to be taken every eight hours if necessary. The maximum daily dose is 150mg.

### **MIGRAINE**

An initial loading dose of 50mg, then if necessary a further 25-50mg after 2 hours. The maximum daily dose is 150mg.

The tablets should be swallowed whole with liquid, preferably before meals.

### **Children**

Children over 14 years of age: up to 75mg daily in divided doses.

The dosage strength is such that Diclofenac 25 tablets are not recommended for use in children 14 years of age or below.

## **Contraindications**

Gastric or intestinal ulcer.

Known hypersensitivity to the active substance or the excipients. Like other non-steroidal anti-inflammatory drugs (NSAIDs), Diclofenac 25 is also contraindicated in patients in whom attacks of asthma, urticaria, or acute rhinitis are precipitated by acetylsalicylic acid or other drugs with prostaglandin-synthetase inhibiting activity.

## **Warnings and Precautions**

### **Warnings**

As with other NSAIDs, allergic reactions, including anaphylactic/anaphylactoid reactions, can also occur in rare cases without earlier exposure to the drug.

Like other NSAIDs, Diclofenac 25 may mask the signs and symptoms of infection due to its pharmacodynamic properties.

### **Cardiovascular Thrombotic Events**

Observational studies have indicated that non-selective NSAIDs may be associated with an increased risk of serious cardiovascular events, including myocardial infarction and stroke, which may increase with dose or duration of use. Patients with cardiovascular disease or cardiovascular risk factors may also be at greater risk. To minimise the potential risk of an adverse cardiovascular event in patients taking an NSAID, especially in those with cardiovascular risk factors, the lowest effective dose should be used for the shortest possible duration (see Dosage and Administration).

There is no consistent evidence that the concurrent use of aspirin mitigates the possible increased risk of serious cardiovascular thrombotic events associated with NSAID use.

### **Hypertension**

NSAIDs may lead to the onset of new hypertension or worsening of pre-existing hypertension and patients taking anti-hypertensives with NSAIDs may have an impaired anti-hypertensive response. Caution is advised when prescribing NSAIDs to patients with hypertension. Blood pressure should be monitored closely during initiation of NSAID treatment and at regular intervals thereafter.

### **Heart failure**

Fluid retention and oedema have been observed in some patients taking NSAIDs, therefore caution is advised in patients with fluid retention or heart failure.

## **Gastrointestinal Events**

All NSAIDs can cause gastrointestinal discomfort and rarely serious, potentially fatal gastrointestinal effects such as ulcers, bleeding and perforation which may increase with dose or duration of use, but can occur at any time without warning. Upper GI ulcers, gross bleeding, or perforation caused by NSAIDs occur in approximately 1% of patients treated for 3-6 months and in about 2-4% patients treated for one year. These trends continue with longer duration of use, increasing the likelihood of developing a serious GI event at some time during the course of therapy. However, even short term therapy is not without risk. Gastrointestinal bleeding or ulceration/perforation can occur at any time during treatment, with or without warning symptoms or a previous history.

Caution is advised in patients with risk factors for gastrointestinal events who may be at greater risk of developing serious gastrointestinal events, e.g. the elderly, those with a history of serious gastrointestinal events, smoking and alcoholism. When gastrointestinal bleeding or ulcerations occur in patients receiving NSAIDs, the drug should be withdrawn immediately. Doctors should warn patients about the signs and symptoms of serious gastrointestinal toxicity.

The concurrent use of aspirin and NSAIDs also increases the risk of serious gastrointestinal events.

In the rare cases where gastrointestinal bleeding or ulceration occur in patients receiving Diclofenac 25, the medicine should be withdrawn.

## **Severe Skin Reactions**

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, including Diclofenac 25 (see Adverse Effects). These serious adverse events are idiosyncratic and are independent of dose or duration of use. Patients appear to be at highest risk of 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. Patients should be advised of the signs and symptoms of serious skin reactions and to consult their doctor at the first appearance of skin rash, mucosal lesion or any other sign of hypersensitivity, and Diclofenac 25 should be discontinued.

## **Precautions**

Close medical surveillance is imperative in patients with symptoms indicative of gastrointestinal disorders or a history suggestive of gastric or intestinal ulcer, patients with ulcerative colitis or Crohn's disease, and in patients suffering from impaired hepatic function.

As with other NSAIDs, values of one or more liver enzymes may increase. During prolonged treatment with Diclofenac 25 monitoring of hepatic function is indicated as a precautionary measure. If abnormal liver function tests persist or worsen, if clinical signs or symptoms consistent with liver disease develop, or if other manifestations occur (e.g. eosinophilia, rash, etc.), Diclofenac 25 should be discontinued. Hepatitis may occur without prodromal symptoms.

Caution is called for when using Diclofenac 25 in patients with hepatic porphyria, since Diclofenac 25 may trigger an attack.

Owing to the importance of prostaglandins in maintaining renal blood flow, particular caution is called for in patients with impaired cardiac or renal function, the elderly, patients being treated with diuretics, and patients with substantial extracellular volume depletion of any cause, e.g. before and after major surgery. Monitoring of renal function is recommended as a precautionary measure when using Diclofenac 25 in such cases. Discontinuation of therapy is normally followed by a return to the pretreatment state.

Treatment with Diclofenac 25 in the aforementioned indications usually proves necessary only for a few days. But if, contrary to the recommendations for its use, Diclofenac 25 is administered over a more prolonged period, it is advisable - as with other NSAIDs - to perform blood counts.

Like other NSAIDs, Diclofenac 25 may temporarily inhibit platelet aggregation. Patients with haemostatic disorders should be carefully monitored.

Caution is indicated in the elderly on basic medical grounds. In particular it is recommended that the lowest effective dosage should be used in frail elderly patients or those with a low body-weight.

### **Use in Pregnancy**

During pregnancy Diclofenac 25 should be employed only for compelling reasons and only in the lowest effective doses. As in the case of other prostaglandin-synthetase inhibitors, this applies particularly to the last 3 months of pregnancy (owing to the possibility of uterine inertia and/or premature closure of the ductus arteriosus).

### **Use in Lactation**

Following oral doses of 50 mg administered every 8 hours, the active substance passes into the breast milk, but in quantities so small that no undesirable effects on the infant are to be expected.

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

Patients experiencing dizziness or other central nervous disturbances, including visual disturbances, should not drive or operate machinery.

### **Adverse Effects**

(Including undesirable effects observed with other dosage forms of Diclofenac 25 and diclofenac sodium either in short term or long term use)

The following frequency estimates were used: frequent > 10 %, occasional > 1 - 10 %, rare > 0.001 - 1 %, isolated cases < 0.001 %.

#### **Gastrointestinal tract**

Occasional: epigastric pain, other gastrointestinal disorders such as nausea, vomiting, diarrhoea, abdominal cramps, dyspepsia, flatulence, anorexia.

Rare: gastrointestinal bleeding (haematemesis, melena, bloody diarrhoea), gastric or intestinal ulcer with or without bleeding or perforation.

Isolated cases: aphthous stomatitis, glossitis, oesophageal lesions, diaphragm-like intestinal strictures, lower gut disorders such as non-specific haemorrhagic colitis and exacerbation of ulcerative colitis or Crohn's disease, constipation, pancreatitis.

#### **Central nervous system**

Occasional: headache, dizziness, vertigo.

Rare: drowsiness.

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

#### **Special senses**

Isolated cases: disturbances of vision (blurred vision, diplopia), impaired hearing, tinnitus, taste disturbances.

#### **Skin**

Occasional: rashes or skin eruptions.

Rare: urticaria.

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**

Rare: oedema.

Isolated cases: acute renal failure, urinary abnormalities such as haematuria and proteinuria, interstitial nephritis, nephrotic syndrome, papillary necrosis.

### **Liver**

Occasional: elevation of serum aminotransferase values.

Rare: hepatitis with or without jaundice.

Isolated cases: fulminant hepatitis.

### **Blood**

Isolated cases: thrombocytopenia, leucopenia, haemolytic anaemia, aplastic anaemia, agranulocytosis.

### **Hypersensitivity**

Rare: hypersensitivity reactions such as asthma, systemic anaphylactic/anaphylactoid reactions including hypotension.

Isolated cases: vasculitis, pneumonitis.

### **Cardiovascular system**

Isolated cases: palpitation, chest pain, hypertension, congestive heart failure.

### **Interactions**

(including interactions observed with other dosage forms of Diclofenac 25 and diclofenac sodium)

*Lithium, digoxin:* Diclofenac 25 may raise plasma concentrations of lithium or digoxin.

*Diuretics:* Like other NSAIDs, Diclofenac 25 may inhibit the activity of diuretics. Concomitant treatment with potassium-sparing diuretics may be associated with increased serum potassium levels, which should therefore be monitored.

*NSAIDs:* Concomitant administration of systemic NSAIDs may increase the frequency of side effects.

*Anticoagulants:* Although clinical investigations do not appear to indicate that Diclofenac 25 affects the action of anticoagulants, there are isolated reports of an increased risk of haemorrhage in patients receiving Diclofenac 25 and anticoagulants concomitantly. Close monitoring of such patients is therefore recommended.

*Antidiabetics:* Clinical studies have shown that diclofenac potassium 25 mg tablets can be given together with oral antidiabetic agents without influencing their clinical effect. However, isolated cases have been reported of both hypoglycaemic and hyperglycaemic effects necessitating changes in the dosage of hypoglycaemic agents during treatment with Diclofenac 25.

*Methotrexate:* Caution is called for if NSAIDs are administered less than 24 hours before or after treatment with methotrexate, since blood concentrations of methotrexate may rise and the toxicity of this substance be increased.

*Cyclosporin*: The effects of NSAIDs on renal prostaglandins may increase the nephrotoxicity of cyclosporin.

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

## **Overdosage**

Management of acute poisoning with NSAIDs consists essentially of supportive and symptomatic measures. There is no typical clinical picture associated with overdosage of diclofenac.

The following therapeutic measures should be taken in cases of overdosage:

Supportive and symptomatic treatment are indicated for complications such as hypotension, renal failure, convulsions, gastrointestinal irritation, and respiratory depression.

Specific measures such as forced diuresis, dialysis, or haemoperfusion are unlikely to be helpful in eliminating NSAIDs because of their high protein-binding rate and extensive metabolism.

## **Pharmaceutical Precautions**

Store below 30°C and protect from moisture.

## **Medicine Classification**

Pharmacist Only Medicine

## **Package Quantities**

Blister packs of 30 tablets.

## **Further Information**

## **Instructions for use/handling**

The tablets should be swallowed whole with liquid, preferably before meals.

## **Excipients**

Core: Potassium hydrogen carbonate, Mannitol, Sodium lauryl sulphate, Macrogol 6000, Magnesium stearate.

Coat: Hypromellose, Macrogol 400

## **Incompatibilities**

Not applicable

## **Preclinical safety data**

Diclofenac did not influence fertility of the parent animals (rats) nor the pre-, peri-, and postnatal development of the offspring. No teratogenic effects were detected in mice, rats and rabbits. No mutagenic effects could be demonstrated in various *in vitro* and *in vivo* experiments, and no carcinogenic potential was detected in long-term studies in rats and mice.

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## **Date of Preparation**

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