

# NEW ZEALAND DATA SHEET

## Diclofenac Sandoz

*Diclofenac Sodium Ph Eur, enteric coated tablet, 25 mg and 50 mg*

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### Presentation

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#### 25 mg

Brown-yellow gastro-resistant film coated tablets, round, biconvex faced with a plain rim. Approximate tablet dimensions: diameter 6.1 to 6.3 mm; thickness 2.9 to 3.2 mm. Each tablet contains Diclofenac Sodium Ph Eur 25 mg.

#### 50 mg

Brown-yellow gastro-resistant film coated tablets, round, biconvex faced with a banded rim. Approximate tablet dimensions: diameter 8.0 to 8.3 mm; thickness 3.5 to 3.8 mm. Each tablet contains Diclofenac Sodium Ph Eur 50 mg.

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### Uses

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#### Actions

##### Pharmacotherapeutic group

M01AB05 – Acetic acid derivatives and related substances.

##### Mechanism of action (MoA)

Diclofenac Sandoz contains diclofenac sodium, a non-steroidal compound with pronounced antirheumatic, anti-inflammatory, analgesic, and antipyretic properties. Inhibition of prostaglandin biosynthesis, which has been demonstrated in experiments, is considered fundamental to its mechanism of action. Prostaglandins play a major role in causing inflammation, pain, and fever.

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

##### Pharmacodynamics (PD)

In rheumatic diseases, the anti-inflammatory and analgesic properties of diclofenac elicit a clinical response characterised by marked relief from signs and symptoms such as pain at rest, pain on movement, morning stiffness, and swelling of the joints, as well as by an improvement in function.

In post-traumatic and postoperative inflammatory conditions, diclofenac rapidly relieves both spontaneous pain and pain on movement and reduces inflammatory swelling and wound oedema.

In clinical trials diclofenac has also been found to exert a pronounced analgesic effect in moderate and severe pain of non-rheumatic origin. Clinical studies have also revealed that, in primary dysmenorrhoea, diclofenac is capable of relieving the pain and reducing the extent of bleeding.

##### Pharmacokinetics (PK)

###### Absorption

Diclofenac is completely absorbed from the enteric coated tablet matrix after passing through the stomach. Although absorption is rapid, onset of therapeutic effects may be delayed due to the gastro-resistant coating of the tablet. Mean peak plasma concentrations of 1.5 mcg/ml (5 micromol/l) are attained on average 2 hours after ingestion of one 50 mg tablet. The extent of the amount absorbed is linearly related to the size of the dose. The passage of a tablet through the stomach is slower when ingested with or after a meal than when it is taken before a meal, but the amount of diclofenac

absorbed remains the same. As first pass hepatic metabolism accounts for about half an orally administered dose, the area under the concentration curve (AUC) following oral or rectal administration of diclofenac is about half that following an equivalent parenteral dose.

Pharmacokinetic properties do not change with repeated administration. No accumulation occurs provided the recommended dosage intervals are observed. After administration of diclofenac for 15 days in an oral dose of 25 mg three times daily, there was no evidence of plasma accumulation.

The plasma concentrations attained in children given equivalent doses (mg/kg body weight) are similar to those obtained in adults.

### **Distribution**

Diclofenac binds to serum proteins to the extent of 99.7%, mainly to albumin (99.4%). The apparent volume of distribution calculated is 0.12 to 0.17 l/kg.

A study in patients presenting rheumatoid arthritis and knee joint effusions (n = 16) showed that diclofenac penetrates the synovial fluid, attaining maximum levels 2 to 4 hours after oral administration. The apparent half-life for elimination from the synovial fluid was 3 to 6 hours. Therefore within 4 to 6 hours after oral administration, diclofenac concentrations were already higher in the synovial fluid than they were in the plasma and remained higher for up to 12 hours. These results could possibly explain why the duration of clinical effect is longer than might be inferred from the plasma half-life.

### **Biotransformation**

Diclofenac is partly metabolised by glucuronidation of the intact molecule, but mainly by single and multiple hydroxylation and methoxylation, resulting in several phenolic metabolites, namely 3'-hydroxy-, 4'-hydroxy-, 5-hydroxy-, 4',5-dihydroxy- and 3'-hydroxy-4'-methoxy substituted diclofenac, most of which are converted to glucuronide conjugates. Two of these phenolic metabolites are biologically active, but to a much smaller extent than diclofenac.

### **Elimination**

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

### **Special patient considerations**

No relevant age-dependent differences in the absorption, metabolism, or excretion of diclofenac have been observed.

In patients presenting renal impairment, no accumulation of the unchanged active substance can be inferred from the single-dose kinetics at the usual dosage schedule. At a creatinine clearance of <10 ml/min, the theoretical 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 presenting chronic hepatitis or non-decompensated cirrhosis, the kinetics and metabolism of diclofenac are the same as in patients without liver disease.

### **Indications**

Treatment of: inflammatory and degenerative forms of rheumatism - rheumatoid arthritis, juvenile rheumatoid arthritis, ankylosing spondylitis, osteoarthritis and spondylarthritis, painful syndromes of the vertebral column, non-articular rheumatism; acute attacks of gout; post-traumatic and 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; 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.

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## Dosage and administration

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### **Dosage**

After assessing the risk/benefit ratio in each individual patient, the lowest effective dose for the shortest possible duration should be used. Dosage should be minimised in the elderly and in patients with renal impairment.

### **Adults**

The recommended initial daily dose is 100 to 150 mg. In milder cases, as well as for long-term therapy, 75 to 100 mg daily is usually sufficient. The total daily dose should generally be divided into 2 to 3 doses. To suppress nocturnal pain and morning stiffness, treatment with tablets during the day can be supplemented by the administration of a suppository at bedtime (up to a total maximum daily dose of 150 mg).

In primary dysmenorrhoea, the daily dose should be individually adjusted and is generally 50 to 150 mg. A dose of 50 to 100 mg should be given initially and, if necessary, increased over the course of several menstrual cycles up to a maximum of 200 mg/day. Treatment should be started upon appearance of the first symptoms and, depending on the symptomatology, continued for a few days.

### **Children and adolescents**

Children aged 1 year or over and adolescents should be given 0.5 to 2 mg/kg body weight daily in 2 to 3 divided doses, depending on the severity of the disorder. For treatment of juvenile rheumatoid arthritis, the daily dose can be raised up to a maximum of 3 mg/kg daily, given in divided doses.

The maximum daily dose of 150 mg should not be exceeded. Because of their dosage strength, Diclofenac Sandoz 50 mg enteric coated tablets are not recommended for use in children and adolescents below 14 years of age; Diclofenac Sandoz 25 mg enteric coated tablets could be used in these patients.

### **Geriatrics (Patients aged 65 or over)**

No adjustment of the starting dose is required for elderly patients (see Warnings and Precautions)

### **Renal impairment**

No adjustment of the starting dose is required for renally impaired patients (see Warning and Precautions).

### **Hepatic impairment**

No adjustment of the starting dose is required for hepatically impaired patients (see Warnings and Precautions).

### **Administration**

The tablets should be swallowed whole with liquid, preferably before meals, and must not be divided or chewed.

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## Contraindications

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Contraindicated in patients with gastrointestinal ulceration, haemorrhagic diathesis, asthma. Relatively contraindicated in liver dysfunction.

Active gastric or intestinal ulcer, bleeding or perforation.

Severe hepatic, renal or cardiac failure (refer to [Warnings and precautions](#)).

Known hypersensitivity to the active substance or to any of the excipients. In common with other non-steroidal anti-inflammatory drugs (NSAIDs), diclofenac is also contraindicated in patients in whom attacks of asthma, urticaria, or acute rhinitis are precipitated by acetylsalicylic acid or other NSAIDs.

Last trimester of pregnancy (refer to [Warnings and precautions - pregnancy and lactation](#)).

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## Warnings and precautions

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### **Warnings**

In common with other NSAIDs, diclofenac may, in rare cases, provoke allergic responses, including anaphylactic or anaphylactoid reactions, in patients with no previous exposure to the medicine.

In common with other NSAIDs, diclofenac 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 (refer to [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, including diclofenac; therefore caution is advised in patients with fluid retention or heart failure.

### **Gastrointestinal effects**

Gastrointestinal bleeding, ulceration or perforation, which may increase with dose or duration of use and which can be fatal, have been reported with all NSAIDs, including diclofenac, and may occur at any time during treatment, with or without warning symptoms or a previous history of serious gastrointestinal events. They generally have more serious consequences in the elderly. If gastrointestinal bleeding or ulceration occurs in patients receiving diclofenac, the medicine should be discontinued. Upper gastrointestinal ulcers, gross bleeding, or perforation caused by NSAIDs, including diclofenac, occur in approximately 1% of patients treated for 3 to 6 months and in about 2 to 4% of patients treated for one year. These trends continue with longer duration of use, increasing the likelihood of developing a serious gastrointestinal event at some time during the course of therapy. However, even short term therapy is not without risk.

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.

Caution is recommended in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as systemic corticosteroids, anticoagulants, anti-platelet agents or selective serotonin-reuptake inhibitors (refer to [Interactions](#)). The concurrent use of aspirin and

NSAIDs also increases the risk of serious gastrointestinal adverse effects.

Prescribers should warn patients about the signs and symptoms of serious gastrointestinal toxicity.

### **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 (refer to [Adverse drug reactions](#)). 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 made aware of the signs and symptoms of serious skin reactions and be advised to consult their physician at the first appearance of skin rash, mucosal lesions or any other sign of hypersensitivity. In these circumstances, diclofenac treatment should be discontinued.

## **Precautions**

### **Interactions with other NSAIDs**

The concomitant use of diclofenac with systemic NSAIDs including cyclooxygenase-2 selective inhibitors, should be avoided due to the absence of any evidence demonstrating synergistic benefits and the potential for additive adverse effects.

### **Geriatrics**

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

This medicine contains lactose and therefore is not recommended for patients with rare hereditary problems of galactose intolerance, severe lactase deficiency or glucose-galactose malabsorption.

### **Pre-existing asthma**

In patients with asthma, seasonal allergic rhinitis, swelling of the nasal mucosa (i.e. nasal polyps), chronic obstructive pulmonary diseases or chronic infections of the respiratory tract (especially if linked to allergic rhinitis-like symptoms), reactions to NSAIDs like asthma exacerbations (so-called intolerance to analgesics / analgesics-asthma), Quincke's oedema or urticaria are more frequent than in other patients. Therefore, special precaution is recommended in such patients (readiness for emergency). This is applicable as well for patients who are allergic to other substances, e.g. with skin reactions, pruritus or urticaria.

### **Gastrointestinal effects**

In common with all NSAIDs, including diclofenac, close medical surveillance is imperative and particular caution should be exercised when prescribing diclofenac for patients with symptoms indicative of gastrointestinal disorders or with a history suggestive of gastric or intestinal ulceration, bleeding or perforation (refer to [Adverse effects](#)). The risk of gastrointestinal bleeding is higher with increasing NSAID doses and in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation and in the elderly.

To reduce the risk of gastrointestinal toxicity in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation, and in the elderly, the treatment should be initiated and maintained at the lowest effective dose. Combination therapy with protective agents (e.g. proton pump inhibitors or misoprostol) should be considered for these patients, and also for patients requiring concomitant use of medicinal products containing low-dose acetylsalicylic acid (ASA)/aspirin or other medicinal products likely to increase gastrointestinal risk.

Patients with a history of gastrointestinal toxicity, particularly the elderly, should report any unusual abdominal symptoms (especially gastrointestinal bleeding). Caution is recommended in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as systemic corticosteroids, anticoagulants, anti-platelet agents or selective serotonin-reuptake inhibitors (refer to [Interactions](#)).

Close medical surveillance and caution should also be exercised in patients with ulcerative colitis or Crohn's disease, as well as in patients suffering from pre-existing dyshaemopoiesis or disorders of blood coagulation, as their condition may be exacerbated (refer to Adverse drug reactions).

### **Hepatic effects**

Close medical surveillance is required when prescribing diclofenac to patients presenting impaired hepatic function, as their condition may be exacerbated.

In common with other NSAIDs, including diclofenac, elevations of one or more hepatic enzymes may occur during diclofenac therapy. During prolonged diclofenac treatment, regular 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), diclofenac treatment should be discontinued. Rare cases of severe hepatic reactions including jaundice and fatal fulminant hepatitis, have been reported. Severe hepatotoxicity may develop without prodromal symptoms, so transaminases should be measured periodically in patients receiving long-term therapy with diclofenac. To minimise the possibility of hepatic injury becoming severe between transaminase measurements, physicians should inform patients of the warning signs and symptoms of hepatotoxicity (e.g. nausea, fatigue, lethargy, pruritus, jaundice, abdominal tenderness in the right upper quadrant and flu-like symptoms) and the appropriate actions to take should these signs and symptoms appear.

Diclofenac may provoke an attack in patients presenting hepatic porphyria.

### **Renal effects**

As a class, NSAIDs have been associated with renal papillary necrosis and other pathology during long-term administration in animals.

As fluid retention and oedema have been reported in association with NSAID therapy, including diclofenac, particular caution is necessary for patients presenting impaired cardiac or renal function (refer to Contraindications), history of hypertension, substantial extracellular volume depletion from any cause, e.g. before or after major surgery, the elderly and patients receiving concomitant treatment with diuretics or medicines that can significantly modulate renal function. Monitoring of renal function is recommended as a precautionary measure when using diclofenac in such cases. Discontinuation of therapy is usually followed by recovery to the pre-treatment state.

### **Haematological effects**

As with other NSAIDs, diclofenac may temporarily inhibit platelet aggregation. Patients with haemostatic disorders should be carefully monitored.

During prolonged treatment, a slight reduction in haemoglobin has been noted in some patients. On rare occasions, blood dyscrasias have been reported. Periodic blood counts are therefore recommended.

## ***Pregnancy and lactation***

### **Use in pregnancy**

Assigned Category C by the Australian Drug Evaluation Committee. This category includes medicines which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human foetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.

The use of diclofenac in pregnant women has not been studied and consequently, the safety of diclofenac in pregnancy has not been established. NSAIDs inhibit prostaglandin synthesis and, when given during the latter part of pregnancy, may cause premature closure of the foetal ductus arteriosus, foetal renal impairment, inhibition of platelet aggregation, delayed labour and birth. Therefore diclofenac should not be administered during the first two trimesters of pregnancy or to women who are likely to become pregnant unless the potential benefit to the mother outweighs the risk to the foetus. Diclofenac treatment during the third trimester of pregnancy is contraindicated owing to the possibility of uterine inertia and/or premature closure of the ductus arteriosus (refer to

Contraindications). Animal studies have not shown any directly or indirectly harmful effects on pregnancy, embryonal/foetal development, parturition or postnatal development (refer to Other - preclinical safety data).

## **Women of child-bearing potential, breast-feeding and fertility**

### **Women of child-bearing potential**

There are no data to suggest any recommendations for women of child-bearing potential.

### **Use in lactation**

In common with other NSAIDs, diclofenac passes into the breast milk in small amounts. Therefore, to avoid harmful exposure to the infant, diclofenac should not be taken during breast feeding.

### **Fertility**

In common with other NSAIDs, diclofenac may impair female fertility and is not recommended for women attempting to conceive. For women who have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of diclofenac treatment should be considered.

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

This medicine is likely to produce minor or moderate adverse effects. Patients experiencing visual disturbances, dizziness, vertigo, somnolence or other central nervous system disturbances while taking diclofenac, should refrain from driving or using machines.

### ***Other***

#### **Preclinical safety data**

##### *Carcinogenesis, mutagenesis, impairment of fertility*

Preclinical data from acute and repeated dose toxicity studies, as well as from genotoxicity, mutagenicity, and carcinogenicity studies with diclofenac revealed no specific hazard for humans at the intended therapeutic doses. There was no evidence that diclofenac had a teratogenic potential in mice, rats or rabbits.

Diclofenac did not impair the fertility of parent animals in rats. The prenatal, perinatal and postnatal development of the offspring was not affected.

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## **Adverse effects**

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Adverse drug reactions from clinical trials and/or spontaneous or literature reports are listed by MedDRA system organ class. With each organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): very common (> 1/10); common ( $\geq 1/100$ , < 1/10); uncommon ( $\geq 1/1,000$ , < 1/100); rare ( $\geq 1/10,000$ , < 1/1,000); very rare (1/10,000).

The following adverse effects include those reported with either short-term or long-term use of diclofenac enteric coated gastro-resistant tablets and/or other pharmaceutical forms of diclofenac.

### ***Common (from 1 in 100 to 1 in 10)***

#### **Gastrointestinal disorders**

Nausea, vomiting, diarrhoea, dyspepsia, abdominal pain, flatulence, anorexia, decreased appetite.

**Hepatobiliary disorders**

Transaminases increased.

**Nervous system disorders**

Headache, dizziness.

**Otic and labyrinth disorders**

Vertigo.

**Skin and subcutaneous tissue disorders**

Rash.

***Rare (from 1 in 10,000 to 1 in 1,000)*****Gastrointestinal disorders**

Gastritis, gastrointestinal haemorrhage, haematemesis, haemorrhagic diarrhoea, melaena, gastrointestinal ulcer (with or without bleeding or perforation).

**General disorders and administration site conditions**

Oedema.

**Hepatobiliary disorders**

Hepatitis, jaundice, liver disorder.

**Immune system disorders**

Hypersensitivity, anaphylactic and anaphylactoid reactions (including hypotension and shock).

**Nervous system disorders**

Somnolence.

**Respiratory, thoracic and mediastinal disorders**

Asthma (including dyspnoea).

**Skin and subcutaneous tissue disorders**

Urticaria.

***Very rare (below 1 in 10,000, including isolated reports)*****Blood and lymphatic system disorders**

Thrombocytopenia, leucopenia, anaemia (including haemolytic and aplastic anaemia), agranulocytosis, positive Coombs' test.

**Cardiac disorders**

Palpitations, chest pain, cardiac failure, myocardial infarction.

**Gastrointestinal disorders**

Colitis (including haemorrhagic colitis and exacerbation of ulcerative colitis or Crohn's disease), constipation, stomatitis, glossitis, oesophageal disorder, intestinal diaphragmdisease, intestinal strictures, pancreatitis.

**General disorders and administration site conditions**

Impotence (association with diclofenac intake is doubtful). Toxic shock syndrome has been reported in patients administered NSAIDs post-operatively.



**Hepatobiliary disorders**

Hepatitis fulminant, hepatic necrosis, hepatic failure.

**Immune system disorders**

Angioneurotic oedema (including facial oedema).

**Nervous system disorders**

Paraesthesia, memory impairment, convulsion, anxiety, tremor, aseptic meningitis, taste disturbances, cerebrovascular accident, myoclonic encephalopathy (described in two patients).

**Ophthalmic disorders**

Visual impairment, vision blurred, diplopia.

**Otic and labyrinth disorders**

Tinnitus, hearing impaired.

**Psychiatric disorders**

Disorientation, depression, insomnia, nightmare, irritability, psychotic disorder.

**Renal and urinary disorders**

Acute renal failure, haematuria, proteinuria, nephrotic syndrome, tubulointerstitial nephritis, renal papillary necrosis.

**Respiratory, thoracic and mediastinal disorders**

Pneumonitis.

**Skin and subcutaneous tissue disorders**

Dermatitis bullous, eczema, erythema, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome), exfoliative dermatitis, alopecia, loss of hair, photosensitivity reaction, Henoch-Schonlein purpura, allergic purpura, pruritus.

**Vascular disorders**

Hypertension, vasculitis.

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**Interactions**

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The following interactions include those observed with diclofenac enteric coated tablets and/or other pharmaceutical presentations of diclofenac.

***Medicines and other pharmacologically active substances*****Potent CYP2C9 inhibitors**

Caution is recommended when co-prescribing diclofenac with potent CYP2C9 inhibitors (such as sulfapyrazole and voriconazole), which could result in a significant increase in peak plasma concentrations and exposure to diclofenac due to inhibition of diclofenac metabolism.

**Lithium**

If used concomitantly, diclofenac may raise plasma concentrations of lithium. Monitoring of the serum lithium level is recommended.

**Digoxin**

If used concomitantly, diclofenac may raise plasma concentrations of digoxin. Monitoring of the serum digoxin level is recommended.

**Diuretics and antihypertensive agents**

In common with other NSAIDs, concomitant use of diclofenac with diuretics or antihypertensive agents, e.g. beta-blockers, angiotensin converting enzyme (ACE) inhibitors, may cause a decrease in their antihypertensive effect. Therefore, the combination should be administered with caution and patients, especially the elderly, should have their blood pressure periodically monitored. Patients should be adequately hydrated and consideration should be given to monitoring renal function after initiation of concomitant therapy and periodically thereafter, particularly for diuretics and ACE inhibitors due to the increased risk of nephrotoxicity. Concomitant treatment with potassium-sparing medicines may be associated with increased serum potassium levels which should be monitored frequently (refer to Warnings and precautions).

**Combined use of ACE inhibitors or angiotensin receptor antagonists, anti-inflammatory drugs and thiazide diuretics**

The use of an ACE inhibiting drug (ACE inhibitor or angiotensin receptor antagonist), an anti-inflammatory medicine (NSAID or COX-2 inhibitor) and a thiazide diuretic at the same time increases the risk of renal impairment. This includes use in fixed-combination products containing more than one class of compound. Combined use of these medications should be accompanied by increased monitoring of serum creatinine, particularly at the institution of the combination. The combination of medicines from these three classes should be used with caution particularly in elderly patients or those with pre-existing renal impairment.

**Other NSAIDs and corticosteroids**

The concomitant use of diclofenac with systemic NSAIDs, including cyclooxygenase-2 selective inhibitors, should be avoided due to the absence of any evidence demonstrating synergistic benefits and the potential for additive undesirable effects. Concomitant administration of diclofenac and other systemic NSAIDs or corticosteroids may increase the frequency of gastrointestinal undesirable effects. Concurrent treatment with aspirin lowers the plasma concentration, peak plasma levels and AUC values of diclofenac. The use of both drugs concurrently is not recommended (refer to Warnings and precautions).

**Anticoagulants and anti-platelet agents**

Caution is recommended since concomitant administration could increase the risk of bleeding (refer to Warnings and precautions). The concurrent use of NSAIDs and warfarin has been associated with severe, sometimes fatal, haemorrhage. The exact mechanism of the interaction between NSAIDs and warfarin is unknown, but may involve enhanced bleeding from NSAID-induced gastrointestinal ulceration or an additive effect of anticoagulation by warfarin and inhibition of platelet function by NSAIDs. Accordingly, diclofenac should be used with caution in combination with warfarin and such patients should be closely monitored.

**Selective serotonin reuptake inhibitors (SSRIs)**

Concomitant administration of systemic NSAIDs, including diclofenac, with SSRIs may increase the risk of gastrointestinal bleeding (refer to Warnings and precautions).

**Antidiabetics**

Clinical studies show that diclofenac does not generally mediate the clinical effects of oral antidiabetic medicines. However, there have been isolated reports of both hypoglycaemic and hyperglycaemic effects that necessitated changes in the dosage of the antidiabetic medicine during concomitant treatment with diclofenac. For this reason, monitoring of the blood glucose level is recommended as a precautionary measure during concomitant therapy.

**Methotrexate**

Caution is recommended when NSAIDs, including diclofenac, are administered less than 24 hours before or after methotrexate treatment, since blood concentrations of methotrexate may rise with increased risk of toxicity.

**Cyclosporin**

In common with other NSAIDs, diclofenac may increase the nephrotoxicity of cyclosporin due to the effect on renal prostaglandins. Therefore, it should be given at doses lower than those recommended for patients not receiving cyclosporin.

**Drugs known to cause hyperkalaemia**

Concomitant treatment with potassium-sparing diuretics, cyclosporine, tacrolimus or timethoprin may be associated with increased serum potassium levels, which should therefore be monitored frequently (see Warnings and Precautions).

**Quinolone antibacterials**

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

**Potent CYP2C9 inhibitors**

Caution is recommended when co-prescribing diclofenac with potent CYP2C9 inhibitors (such as sulfapyrazole and voriconazole), which could result in a significant increase in peak plasma concentrations and exposure to diclofenac due to inhibition of diclofenac metabolism.

Concomitant administration of voriconazole with diclofenac may increase plasma diclofenac levels.

**Phenytoin**

When using phenytoin concomitantly with diclofenac, monitoring of phenytoin plasma concentrations is recommended due to an expected increase in exposure to phenytoin.

***Abnormal laboratory test results***

None reported.

***Food and alcohol***

None reported.

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**Overdosage**

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Contact the Poisons Information Centre on 0800 POISON or 0800 764766 for advice on management of overdose.

***Signs and symptoms***

There is no typical clinical picture resulting from diclofenac overdose. Overdose can cause symptoms such as vomiting, gastrointestinal haemorrhage, diarrhoea, dizziness, tinnitus or convulsions. In the event of significant poisoning, acute renal failure and liver damage are possible.

***Management***

Management of acute poisoning with NSAIDs, including diclofenac, essentially consists of supportive measures and symptomatic treatment given for complications such as hypotension, renal failure, convulsions, gastrointestinal disorders, and respiratory depression. Haematological and biochemical parameters, and the presence or absence of blood in the stools, should be monitored.

Special measures such as forced diuresis, dialysis or haemoperfusion are probably of no help in eliminating NSAIDs, including diclofenac, due to the high protein binding and extensive metabolism.

Activated charcoal may be considered after ingestion of a potentially toxic overdose, and gastric decontamination, e.g. vomiting, gastric lavage, after ingestion of a potentially life-threatening overdose.

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## Pharmaceutical precautions

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### ***Instructions for use/handling***

Diclofenac Sandoz enteric coated tablets should be swallowed whole with liquid, preferably before meals, and must not be divided or chewed.

### ***Incompatibilities***

None known.

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

Store at or below 25°C. Store in the original package. Keep out of the reach and sight of children.

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## Medicine classification

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Prescription Medicine.

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## Package quantities

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Packs of 50 tablets in blister strips.

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## Further information

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### ***List of excipients***

Microcrystalline cellulose, calcium hydrogen phosphate, lactose, maize starch, methacrylic acid copolymer, sodium starch glycollate, talc, magnesium stearate, triethyl citrate, colloidal silicon dioxide, iron oxide pigments, titanium dioxide.

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## Name and address

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Novartis New Zealand Limited  
Private Bag 65904 Mairangi Bay  
Auckland 0754

Telephone: 0800 354 335

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## Date of preparation

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25 May 2012