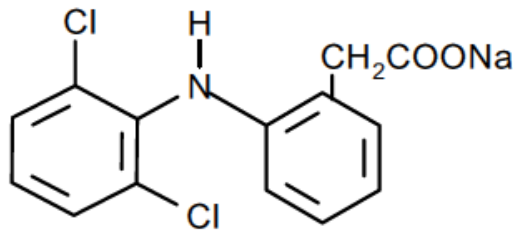


**APO-DICLOFENAC ENTERIC COATED TABLETS****NAME OF THE MEDICINE**

Diclofenac sodium.

Chemical Name: Sodium 2-[(2,6-dichlorophenyl)-amino] phenyl]-acetate

Structural Formula:

Molecular Formula:  $C_{14}H_{10}Cl_2NNaO_2$ 

Molecular Weight: 318.13

CAS Registry Number: 15307-79-6

**DESCRIPTION**

Diclofenac sodium is an odourless, yellowish-white, crystalline powder sparingly soluble in water. It is a phenylacetic acid derivative, structurally similar to both the phenylalkanoic acid and the anthranilic acid series of compounds.

Each tablet contains 25 mg or 50 mg of diclofenac sodium. In addition, each tablet contains the following inactive ingredients: lactose, calcium hydrogen phosphate, microcrystalline cellulose, maize starch, sodium starch glycollate, magnesium stearate, colloidal anhydrous silica, methacrylic acid copolymer, triethyl citrate, talc, titanium dioxide and iron oxide yellow.

**PHARMACOLOGY****Pharmacological Actions**

Diclofenac sodium, a non-steroidal compound, exhibits pronounced antirheumatic, anti-inflammatory, analgesic and antipyretic properties.

As with other NSAIDs, its mode of action is not known; however, its ability to inhibit prostaglandin synthesis may be involved in the anti-inflammatory effect.

In rheumatic diseases, the anti-inflammatory and analgesic properties of diclofenac elicit a clinical response characterised by 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 addition, clinical studies have revealed that in primary dysmenorrhoea, diclofenac is capable of relieving the pain and reducing the extent of bleeding. Low concentrations of diclofenac sodium inhibit the aggregation of platelets induced in vitro by collagen and by adenosine diphosphate. Diclofenac sodium in vitro does not suppress proteoglycan biosynthesis in canine cartilage at concentrations equivalent to the concentrations reached in humans. It is unknown whether or not diclofenac sodium affects the integrity of human osteoarthritic cartilage.

## Pharmacokinetics

### Absorption

Diclofenac is completely absorbed from the enteric-coated tablets after their passage through the stomach. Following ingestion of one tablet with or after a meal, its passage through the stomach is slower than when it is taken before a meal, but the amount of active substance absorbed remains the same. In fasting subjects, the mean peak plasma concentration of 1.5 µg/mL (5 µmol/L) is attained on average 2 hours after ingestion of one tablet of 50 mg. The plasma concentrations, as measured by the area under the time-concentration curve, are in linear relation to the size of the dose.

After administration of diclofenac for 15 days in an oral dose of 25 mg three times daily, there was no evidence of the drugs accumulation in plasma.

### Distribution

In a study in 16 patients with rheumatoid arthritis and knee joint effusions it was found that diclofenac enters the synovial fluid where maximum concentrations were measured 2 to 4 hours after oral administration. The apparent half-life for elimination from the synovial fluid was 3 to 6 hours. Only 4 to 6 hours after administration, therefore, concentrations of the active substance 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 short plasma half-life of diclofenac.

Diclofenac becomes bound to serum proteins to the extent of 99.7%, chiefly to albumin (99.4%).

### Metabolism

Following oral administration, about half the active substance is metabolised during its first passage through the liver ("first-pass" effect).

The total systemic clearance of diclofenac in plasma is  $263 \pm 56$  mL/min (mean value  $\pm$  SD). The terminal half-life in plasma is 1 to 2 hours.

The biotransformation of diclofenac partly involves glucuronidation of the intact molecule, but mainly single and multiple hydroxylation followed by glucuronidation.

### Excretion

About 60% of the administered dose is excreted in the urine in the form of metabolites from one of the two previously mentioned processes. Less than 1% is excreted as unchanged substance. The remainder of the dose is eliminated as metabolites through the bile in the faeces.

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

In patients suffering from renal impairment, no accumulation of the unchanged active substance could be inferred from the single-dose kinetics when applying the usual dosage schedule. At a creatinine clearance of < 10 mL/min, the theoretical steady-state plasma levels of metabolites are four times higher than in normal subjects. However, the metabolites appear to be satisfactorily cleared through the bile.

In the presence of impaired hepatic function (chronic hepatitis, non-decompensated cirrhosis), the kinetics and metabolism of diclofenac were the same as in patients without liver disease.

## INDICATIONS

- Inflammatory and degenerative forms of rheumatism: rheumatoid arthritis and osteoarthritis.
- Relief of acute or chronic pain states in which there is an inflammatory component.
- Symptomatic treatment of primary dysmenorrhoea.

## CONTRAINDICATIONS

- Gastric or duodenal ulcer, gastrointestinal bleeding or perforation.
- Patients who are hypersensitive to the active ingredient, diclofenac, or any of the excipients contained in the tablets.
- Last trimester of pregnancy (see **PRECAUTIONS, Use in Pregnancy**).
- Hepatic failure (see **PRECAUTIONS**)
- Renal failure (see **PRECAUTIONS**)
- Severe cardiac failure (see **PRECAUTIONS**)
- Patients in whom diclofenac, aspirin or other NSAIDs induce asthma, urticaria, or other allergic-type reactions because severe, rarely fatal, anaphylactic type reactions to diclofenac have been reported in such patients.

## PRECAUTIONS

### 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 (see **DOSAGE AND ADMINISTRATION**).

Treatment with diclofenac is generally not recommended in patients with established cardiovascular disease (congestive heart failure, established ischemic heart disease, peripheral arterial disease) or uncontrolled hypertension. If needed, patients with established cardiovascular disease, uncontrolled hypertension, or significant risk factors for cardiovascular disease (e.g. hypertension, hyperlipidemia, diabetes mellitus and smoking) should be treated with diclofenac only after careful consideration and only at doses  $\leq$  100 mg daily when treatment continues for more than 4 weeks.

As the cardiovascular risks of diclofenac may increase with dose and duration of exposure, the lowest effective daily dose should be used for the shortest duration possible. The patient's need for symptomatic relief and response to therapy should be re-evaluated periodically, especially when treatment continues for more than 4 weeks.

Patients should remain alert for the signs and symptoms of serious arteriothrombotic events (e.g. chest pain, shortness of breath, weakness, slurring of speech), which can occur without warnings. Patients should be instructed to see a physician immediately in case of such an event.

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.

### Peri-operative bleeding:

Pre-operative administration of diclofenac may increase the risk of post-operative bleeding. T

Since diclofenac may temporarily inhibit platelet aggregation, children undergoing minor procedures such as tonsillectomy, myringotomy, circumcision, orchidopexy and strabismus surgery should be carefully monitored.

### 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, including diclofenac 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

Close medical surveillance is imperative and particular caution should be exercised when prescribing NSAIDs, including diclofenac in patients with symptoms indicative of gastrointestinal disorders (GI) or with a history suggestive of gastro-intestinal ulceration, bleeding or perforation (see **ADVERSE REACTIONS**).

Upper GI ulcers, gross bleeding or perforation caused by NSAIDs, including diclofenac occur in approximately 1% of patients treated for 3-6 months and in about 2-4% of patients treated in one year. The risk of GI bleeding is higher with increasing NSAID doses, with increasing duration of use and in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation and in the elderly. Gastric or duodenal ulceration, perforation or gastrointestinal bleeding, which can be fatal, have been reported in patients receiving diclofenac. Studies to date have not identified any subset of patients who are not at risk of developing these problems.

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.

The concurrent use of aspirin and NSAIDs, including diclofenac also increases the risk of serious gastrointestinal adverse events.

To reduce the risk of GI 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. Gastrointestinal bleeding, ulceration and perforation in general have more serious consequences in the elderly. They can occur at any time during treatment with or without warning symptoms or a previous history. In instances where gastrointestinal bleeding or ulcerations occur in patients receiving diclofenac, the drug should be withdrawn immediately. Physicians should warn patients about what the signs and symptoms of serious gastrointestinal toxicity and what steps to take if they occur.

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 GI toxicity, particularly the elderly, should report any unusual abdominal symptoms (especially GI 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 (see **PRECAUTIONS, Interactions with Other Medicines**).

Close medical surveillance and caution should also be exercised in patients with ulcerative colitis or with Crohn's disease, as well as in patients suffering from severe pre-existing dyshaemopoiesis or disorders of blood coagulation, as their condition may be exacerbated (see **ADVERSE EFFECTS**).

### Serious Skin Reactions

Serious skin reactions, some of them fatal, including exfoliative dermatitis, toxic epidermal necrolysis (TEN) and Stevens-Johnson Syndrome (SJS), have been reported very rarely in association with the use of NSAIDs, including diclofenac (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 should be discontinued.

**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 such as 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. This is applicable as well for patients who are allergic to other substances, e.g. with skin reactions, pruritus or urticaria.

**Liver**

Close medical surveillance is required when prescribing diclofenac to patients with impaired liver function, as their condition may be exacerbated (see **CONTRAINDICATIONS**).

As with other NSAIDs, including diclofenac elevations of one or more liver enzymes may occur during diclofenac therapy. These laboratory abnormalities may progress, remain unchanged, or revert to normal despite continued therapy. Borderline elevations [i.e. 1.2 to 3 times the upper limit of normal (ULN)], or greater elevations of transaminases occurred in about 15% of diclofenac-treated patients. In clinical trials, meaningful elevations (i.e. more than 3 times the ULN) of AST and/or ALT occurred in about 4% of patients treated for several months, including marked elevations (i.e. more than 8 times the ULN) in about 1% of patients. Transaminase elevations were seen more frequently in patients with osteoarthritis than in those with rheumatoid arthritis (refer to **ADVERSE EFFECTS**).

Transaminase elevations were reversible on cessation of therapy, and even among patients with marked elevations, signs and symptoms of liver disease occurred only in isolated cases. Most patients with borderline elevations did not have therapy interrupted, and transaminase elevations in most of these cases disappeared or did not progress. There were no identifying features to distinguish those patients who developed marked elevations from those who did not.

In addition to the enzyme elevations seen in clinical trials, 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. The optimum times for making the measurements are not known. In most patients who have developed marked transaminase elevations, abnormal tests occurred during the first 2 months of therapy with diclofenac. Based on this experience the first transaminase measurement should be made no later than 8 weeks after the start of diclofenac treatment. As with other NSAIDs, including diclofenac if abnormal liver tests persist or worsen, if clinical signs and/or symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g. eosinophilia, rash, etc), diclofenac should be discontinued.

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 action to take should these signs and symptoms appear.

Caution should be exercised when using diclofenac in patients with hepatic porphyria, since diclofenac may trigger an attack.

**Kidney**

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

Fluid retention and oedema have been reported in association with NSAID therapy, including diclofenac. Owing to the importance of prostaglandins for maintaining renal blood flow, particular caution is called for in patients with impaired cardiac or renal function, history of hypertension, in the elderly, in patients being treated with diuretics or medicinal products that can significantly impact renal function, and in those with extracellular volume depletion from any cause, e.g. in the peri- or post-operative phase of major surgical operations (see **CONTRAINDICATIONS**). Monitoring of renal function as a precautionary measure is therefore recommended when using diclofenac in such cases. Discontinuation of therapy is typically followed by recovery to the pre-treatment state.

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

The use of an ACE inhibiting drug (ACE-inhibitors or angiotensin receptor antagonist), an anti-inflammatory drug (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 drug. Combined use of these medications should be accompanied by increased monitoring of serum creatinine, particularly at the institution of the combination. The combination of drugs from these three classes should be used with caution particularly in elderly patients or those with pre-existing renal impairment.

**Infection**

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

**Haematological Effects**

Like 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.

**Hypersensitivity**

As with other NSAIDs, allergic reactions, including anaphylactic / anaphylactoid reactions, have been reported with diclofenac. These reactions can occur without earlier exposure to the drug.

**Effects on Ability to Drive or Use Machines**

Patients experiencing visual disturbances, dizziness, vertigo, somnolence or other central nervous disturbances while taking diclofenac should refrain from driving a vehicle or operating machines.

**Lactose**

Diclofenac tablets contain lactose and therefore are not recommended for patients with rare hereditary problems of galactose intolerance, severe lactase deficiency or glucose-galactose malabsorption.

**Effects on fertility**

The use of diclofenac may impair female fertility and is not recommended in women attempting to conceive. In women who have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of diclofenac should be considered.

**Use in Pregnancy (Category “C”)**

NSAIDs inhibit prostaglandin synthesis and, when given during the latter part of pregnancy, may cause closure of the foetal ductus arteriosus, foetal renal impairment, inhibition of platelet aggregation and delay labour and birth.

The use of diclofenac in pregnant women has not been studied and safety in pregnancy has not been established. Therefore, diclofenac should not be used in pregnant women during the first two trimesters or in women who are likely to become pregnant unless the potential benefit to the mother outweighs the risk to the foetus. Use of diclofenac during the third trimester of pregnancy is contraindicated owing to the possibility of uterine inertia and/or premature closure of the ductus arteriosus (see **CONTRAINDICATIONS**).

**Use in Lactation**

Following oral doses of 50 mg administered every 8 hours, the active substance, diclofenac, passes into the breast milk. As with other drugs which are excreted in milk, diclofenac is not recommended for use in nursing women.

**Paediatric Use**

Diclofenac is not recommended for use in children as safety and efficacy in this age group have not been established.

**Use in the Elderly**

In elderly patients, who are generally more prone to side effects, particular caution should be exercised. It is recommended that the lowest effective dosage be used in elderly patients or those with a low body weight.

**Carcinogenicity / Genotoxicity**

Dietary administration of diclofenac to mice and rats at doses up to 0.5 mg/kg/day revealed no carcinogenic activity. However, the plasma concentration of diclofenac at this dose level was 20 to 100 times lower than that in humans. Administration of higher doses to rats and mice resulted in increased mortality due to gastrointestinal ulceration. Diclofenac showed no mutagenic or carcinogenic effects in the studies conducted.

**INTERACTIONS WITH OTHER MEDICINES**

The following interactions include those observed with diclofenac and/or other pharmaceutical forms of diclofenac:

**Lithium / Digoxin**

When given together with preparations containing lithium or digoxin, diclofenac may raise their plasma concentrations and these concentrations should be monitored during treatment with diclofenac.

**Diuretics and Anti-Hypertensive Agents**

Like 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. When NSAIDs, including diclofenac are combined with diuretics, ACE inhibitors or angiotensin II receptor antagonists, the risk of worsening of renal function, including possible acute renal failure (which is usually reversible) may be increased in some patients, especially when renal function is compromised (e.g. dehydrated or elderly patients). Patients should be adequately hydrated and monitoring of renal function is recommended after initiation of concomitant therapy and periodically thereafter. Concomitant treatment with potassium-sparing drugs may be associated with increased serum potassium levels, thus making it necessary to monitor the latter (see **PRECAUTIONS, Kidney**).

**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 effect. 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.

**Anticoagulants and anti-platelet agents**

Caution is recommended since concomitant administration could increase the risk of bleeding (see **PRECAUTIONS, Gastrointestinal Effects**). 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. Diclofenac should be used with caution in combination with warfarin and such patients should be closely monitored.

**Selective Serotonin Re-uptake Inhibitors (SSRIs)**

Concomitant administration of systemic NSAIDs, including diclofenac and SSRIs may increase the risk of

gastrointestinal bleeding (see **PRECAUTIONS, Gastrointestinal Effects**).

### **Antidiabetic Agents**

Diclofenac can be given together with oral antidiabetic agents without influencing their clinical effect. However there are isolated reports of both hypoglycaemic and hyperglycaemic effects in the presence of diclofenac, which necessitated changes in the dosage of antidiabetic agents. For this reason, monitoring of blood glucose levels is recommended as a precautionary measure during concomitant therapy.

### **Methotrexate**

Caution should be exercised when NSAIDs, including diclofenac are administered less than 24 hours before or after treatment with methotrexate, since the blood concentration of methotrexate may rise and the toxicity of this substance be increased.

### **Cyclosporin**

Nephrotoxicity of cyclosporin may be enhanced through effects of NSAIDs, including diclofenac, on renal prostaglandins. Therefore, diclofenac should be given at doses lower than those that would be used in patients not receiving cyclosporin.

### **Drugs Known To Cause Hyperkalemia**

Concomitant treatment with potassium-sparing drugs (e.g. diuretics, cyclosporin, tacrolimus or trimethoprim) may be associated with increased serum potassium levels, which should therefore be monitored frequently (see **PRECAUTIONS**)

### **Glucocorticoids**

The addition of glucocorticoids to NSAIDs, though sometimes necessary for therapeutic reasons, may aggravate gastrointestinal side effects.

### **Quinolone Antibacterials**

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

### **Potent CYP2C9 inhibitors**

Caution is recommended when co-prescribing diclofenac with potent CYP2C9 inhibitors (such as sulfinpyrazone 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.

## **ADVERSE EFFECTS**

Adverse reactions are ranked under heading of frequency, the most frequent first, using the following convention: common ( $\geq 1/100$ ,  $< 1/10$ ); uncommon ( $\geq 1/1,000$ ,  $< 1/100$ ); rare ( $\geq 1/10,000$ ,  $< 1/1,000$ ); very rare ( $< 1/10,000$ ), including isolated reports.

The following undesirable effects include those reported with diclofenac tablets and/or other pharmaceutical forms of diclofenac, with either short-term or long-term use:

### **Blood and Lymphatic System Disorders**

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

### **Immune System Disorders**

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



Very rare: Angioneurotic oedema (including face oedema).

### **Psychiatric Disorders**

Very rare: Disorientation, depression, insomnia, nightmare, irritability, psychotic disorder.

### **Nervous System Disorders**

Common: Headache, dizziness.

Rare: Somnolence.

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

### **Eye Disorders**

Very rare: Visual disturbance, vision blurred, diplopia.

### **Ear and Labyrinth Disorders**

Common: Vertigo.

Very rare: Tinnitus, hearing impaired.

### **Cardiac Disorders**

Uncommon\*: Myocardial infarction, cardiac failure, palpitations, chest pain.

\* The frequency reflects data from long-term treatment with a high dose (150 mg/day).

### **Vascular Disorders**

Very rare: Hypertension, vasculitis.

### **Respiratory, Thoracic and Mediastinal Disorders**

Rare: Asthma (including dyspnoea).

Very rare: Pneumonitis.

### **Gastrointestinal Disorders**

Common: Nausea, vomiting, diarrhoea, dyspepsia, abdominal pain, flatulence, anorexia.

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

Very rare: Colitis (including haemorrhagic colitis and exacerbation of ulcerative colitis or Crohn's disease), constipation, stomatitis, glossitis, oesophageal disorder, diaphragm-like intestinal strictures, pancreatitis.

### **Hepatobiliary Disorders**

Common: Transaminases increased.

Rare: Hepatitis, jaundice, liver disorder.

Very rare: Fulminant hepatitis, hepatic necrosis, hepatic failure.

### **Skin and Subcutaneous Tissue Disorders**

Common: Rashes or skin eruptions.

Rare: Urticaria.

Very rare: Bullous eruptions, eczema, erythema, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome), dermatitis exfoliative, loss of hair, photosensitivity reaction, purpura, allergic purpura, pruritus.

### Renal and Urinary Disorders

Very rare: Acute renal failure, haematuria, proteinuria, nephrotic syndrome, interstitial nephritis, renal papillary necrosis.

### General disorders and administration site conditions:

Common: Application site irritation.

Rare: Oedema.

Very rare: Impotence (association with diclofenac intake is doubtful).

### Description of Selected Adverse Drug Reactions

#### Arteriothrombotic events

Meta-analysis and pharmacoepidemiological data point towards an increased risk of arteriothrombotic events (for example myocardial infarction) associated with the use of diclofenac, particularly at a high dose (150 mg daily) and during long-term treatment (see **PRECAUTIONS**). A recent meta-analysis (CNT) estimates that, in comparison with placebo, allocation to diclofenac caused around 3 additional major vascular events per 1000 participants per year. This estimate reflects data from long term treatment with high dose diclofenac (150 mg/day).

### DOSAGE AND ADMINISTRATION

After assessing the risk/benefit ratio in each individual patient, the lowest effective dose for the shortest possible duration should be used. Adverse effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see **PRECAUTIONS**).

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

Initial dosage is 75 to 150 mg daily. For long-term therapy, 75 to 100 mg daily is usually sufficient.

The daily dose should generally be prescribed in two or three divided doses.

In primary dysmenorrhoea the daily dosage, which should be individually adapted, is generally 50 to 150 mg. Initially, a dose of 50 to 100 mg should be given and, if necessary, raised in 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.

### OVERDOSAGE

#### Symptoms

There is no typical clinical picture resulting from an overdosage of diclofenac. Overdosage 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.

#### Treatment

Management of acute poisoning with NSAIDs consists essentially of supportive and symptomatic treatment.

The therapeutic measures to be taken in cases of overdosage are as follows:

Activated charcoal may reduce absorption of the medicine if given within one or two hours after ingestion. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via nasogastric tube, once the airway is protected.

Supportive and symptomatic treatment should be given for complications such as hypotension, renal

failure, convulsions, gastrointestinal disorder, and respiratory depression. Haematological and biochemical parameters, and the presence or absence of blood in the stools, should be monitored.

Specific therapies such as forced diuresis, dialysis, or haemoperfusion are probably of no help in eliminating NSAIDs, because of their high protein-binding rate and extensive metabolism.

**Contact the Poison Information Centre on 13 11 26 (Australia) for advice on the management of overdose.**

## **PRESENTATION AND STORAGE CONDITIONS**

**APO- Diclofenac** enteric coated tablets are intended for oral administration.

Each tablet contains diclofenac sodium 25 or 50mg as the active ingredient.

### **25 mg Tablets**

Brown yellow film-coated tablet, biconvex with an intact surface and uniform colour.

Blister Pack (PP/Al or PVC/PVDC/Al) of 50 tablets (AUST R 160729)

### **50 mg Tablets**

Brown yellow film –coated tablet, biconvex with facet on both sides, intact surface and uniform colour.

Blister Pack (PP/Al or PVC/PVDC/Al) of 50 tablets (AUST R 160730)

Not all strengths, pack types and/or pack sizes may be available

### **Storage**

Store below 25°C.

## **NAME AND ADDRESS OF THE SPONSOR**

Apotex Pty Ltd  
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Macquarie Park NSW 2113

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## **POISON SCHEDULE OF THE MEDICINE**

S4: Prescription Only Medicine.

**Date of first inclusion in the Australian Register of Therapeutic Goods (the ARTG):** 22 June 2001

**Date of most recent amendment:** 17 October 2014