AUSTRALIAN PRODUCT INFORMATION

DICLOFENAC SODIUM VIATRIS

Diclofenac sodium enteric coated tablets

1 NAME OF THE MEDICINE

Diclofenac sodium

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

DICLOFENAC SODIUM VIATRIS tablets are enteric coated and contain either 25 mg or 50 mg of diclofenac sodium.

Excipients with known effect: Contains sugars as lactose and trace amounts of sulfites.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

DICLOFENAC SODIUM VIATRIS 25 mg is available as a round brown coloured enteric-coated tablet.

DICLOFENAC SODIUM VIATRIS 50 mg is available as a round brown coloured enteric-coated tablet.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC 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.

4.2 DOSE AND METHOD OF 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 minimized by using the lowest effective dose for the shortest duration necessary to control symptoms (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). Patients on long term treatment should be reviewed regularly with regards to efficacy, risk factors and ongoing need for treatment.

Dose

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

The daily dosage should generally be prescribed in 2 or 3 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.

Method of administration

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

4.3 CONTRAINDICATIONS

- Gastric or duodenal ulcer and gastro-intestinal bleeding or perforation.

- Patients who are hypersensitive to the active ingredient, diclofenac, or any of the excipients contained in the tablets.
- Third trimester of pregnancy (see Section 4.6 FERTILITY, PREGNANCY AND LACTATION).
- Patients with severe hepatic impairment (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).
- Renal failure (See Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).
- Severe or cardiac failure (See Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).
- Treatment of perioperative pain in setting of coronary artery bypass surgery (CABG).
- Patients in whom diclofenac, aspirin or other NSAIDs induce asthma, angioedema, urticaria or other allergic-type reactions because severe, rarely fatal, anaphylactic type reactions to diclofenac have been reported in such patients.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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, history of atherosclerotic cardiovascular disease or cardiovasular risk factors may also be at greater risk (See Section 4.2 DOSE AND METHOD OF 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 ≤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.

Physicians and 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 informed about signs and/or symptoms of serious cardiovascular toxicity and 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.

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

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 Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

Upper gastrointestinal (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 for 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.

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 pre-existing dyshaemopoiesis or disorders of blood coagulation, as their conditions may be exacerbated (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

NSAIDs, including diclofenac, may be associated with increased risk of gastro-intestinal anastomotic leak. Close medical surveillance and caution are recommended when using DICLOFENAC SODIUM VIATRIS after gastro-intestinal surgery.

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 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 Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS and Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

Severe Skin Reactions

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis, and Drug Reaction with Eosinophilia with Systemic Symptoms (DRESS) (see Drug Reaction with Eosinophilia with Systemic Symptoms (DRESS)) have been reported very rarely in association with the use of NSAIDs, including diclofenac (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE 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 legion or any other sign of hypersensitivity, and DICLOFENAC SOIDUM VIATRIS should be discontinued.

Drug Reaction with Eosinophilia with Systemic Symptoms (DRESS)

DRESS has been reported in patients taking NSAIDs. Some of these events have been fatal or lifethreatening. DRESS typically, although not exclusively, presents with fever, rash, lymphadenopathy, and/or facial swelling. Other clinical manifestations may include hepatitis, nephritis, haematological abnormalities, myocarditis, or myositis. Sometimes symptoms of DRESS may resemble an acute viral infection. Eosinophilia is often present. Because this disorder is variable in its presentation, other organ systems not noted here may be involved. It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, discontinue the NSAID and evaluate the patient immediately.

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.

Infection

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

Hypersensitivity

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

Lactose Intolerance

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

Peri-operative Bleeding:

Pre-operative administration of diclofenac may increase the risk of post-operative bleeding. Since diclofenac may temporarily inhibit platelet aggregation, children undergoing minor procedures such as tonsillectomy, myringotomy, circumcision, orchidopexy and strabismus surgery should be carefully monitored.

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.

Hypersensitivity

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

Use in hepatic impairment

Close medical surveillance is required when prescribing diclofenac to patients with impaired hepatic function, as their condition may be exacerbated (see Section 4.3 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 (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE 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.

Use in renal impairment

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 Section 4.3 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.

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.

Paediatric use

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

Effects on laboratory tests

Haematological effects

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

During prolonged treatment with diclofenac 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.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

The following interactions include those observed with diclofenac tablets 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 antihypertensive 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 (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

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.

Anticoagulants and anti-platelet agents

Caution is recommended since concomitant administration could increase the risk of bleeding (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). 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 reuptake inhibitors (SSRIs)

Concomitant administration of systemic NSAIDs including diclofenac, and SSRIs may increase the risk of gastrointestinal bleeding (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

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. Therefore, monitoring of the blood glucose level is recommended as a precautionary measure during concomitant therapy.

There have also been isolated reports of metabolic acidosis when diclofenac was co-administered with metformin, especially in patients with pre-existing renal impairment.

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.

Ciclosporin and tacrolimus

Nephrotoxicity of ciclosporin 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 ciclosporin or tacrolimus.

Drugs known to cause hyperkalemia

Concomitant treatment with potassium-sparing drugs (e.g. diuretics, ciclosporin, tacrolimus or trimethoprim) may be associated with increased serum potassium levels, which should therefore be monitored frequently (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

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.

CYP2C9 inducers:

Caution is recommended when co-prescribing diclofenac with CYP2C9 inducers (such as rifampicin), which could result in a significant decrease in plasma concentration and exposure to diclofenac.

Phenytoin

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

4.6 FERTILITY, PREGNANCY AND LACTATION

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 – 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, fetal renal impairment with subsequent oligohydramnios and/or premature closure of the ductus arteriosus (see Section 4.3 CONTRAINDICATIONS).

Data from epidemiological studies suggest an increased risk of miscarriage after the use of a prostaglandin synthesis inhibitor in early pregnancy.

Australian Categorisation Definition of Category C: Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.

Use of DICLOFENAC SODIUM VIATRIS during the third trimester of pregnancy is contraindicated owing to the possibility of uterine inertia, premature closure of the ductus arteriosus and oligohydramnios and neonatal renal impairment (see Oligohydramnios and neonatal renal impairment).

Oligohydramnios and Neonatal Renal Impairment:

Use of NSAIDs from about 20 weeks gestation may cause foetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment.

These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation. Oligohydramnios is often, but not always, reversible with treatment discontinuation.

Complications of prolonged oligohydramnios may, for example, include limb contractures and delayed lung maturation. In some post-marketing cases of impaired neonatal renal function, invasive procedures such as exchange transfusion or dialysis were required.

If, after careful consideration of alternative treatment options for pain management, NSAID treatment is necessary from about 20 weeks to the end of the second trimester, limit use to the lowest effective dose and shortest duration possible. Use of DICLOFENAC SODIUM VIATRIS during the third trimester of pregnancy is contraindicated (see Use in pregnancy – Pregnancy Category C). Consider ultrasound monitoring of amniotic fluid if treatment extends beyond 48 hours. Discontinue treatment with NSAIDs if oligohydramnios occurs.

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 that are excreted in milk, diclofenac is not recommended for use in breastfeeding women.

4.7 EFFECTS ON ABILITY TO DRIVE AND 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.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Adverse reactions are ranked under heading of frequency, the most frequent first, using the following convention: common (≥ 1/100, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥ 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, leukopenia, anaemia (including haemolytic 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*:	Palpitations, chest pain, cardiac failure, myocardial infarction.
Frequency unknown:	Kounis syndrome

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) gastrointestinal stenosis, or perforation, which may lead to peritonitis, proctitis (diclofenac suppositories).
Very rare:	Colitis (including haemorrhagic colitis, ischemic colitis and exacerbation of ulcerative colitis or Crohn's disease), constipation, stomatitis, glossitis, oesophageal disorder, diaphragm-like intestinal strictures, pancreatitis, haemorrhoids aggravated (diclofenac suppositories).

Hepatobiliary disorders

Common:	Transaminases increased.

Rare:	Hepatitis, jaundice, liver disorder.
Very rare:	Fulminant hepatitis, hepatic necrosis, hepatic failure.

Pregnancy, puerperium and perinatal conditions

Unknown:	Oligohydramnios, neonatal renal impairment

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.
Unknown:	Drug Reaction with Eosinophilia with Systemic Symptoms (DRESS)

Renal and urinary disorders

Very rare:	Acute kidney injury (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). Worsening of haemorrhoids has been reported with use of diclofenac suppositories. Toxic shock syndrome has been reported in patients administered NSAIDs post-operatively.

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

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 Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). 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).

Visual effects

Visual disturbances such as visual impairment, blurred vision or diplopia appear to be NSAID class effects and are usually reversible on discontinuation. A likely mechanism for the visual disturbances is the inhibition of prostaglandin synthesis and other related compounds that alter the regulation of retinal blood flow resulting in potential changes in vision. If such symptoms occur during diclofenac treatment, an ophthalmological examination may be considered to exclude other causes.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Management of acute poisoning with NSAIDs, including diclofenac, consists essentially of supportive measures and symptomatic treatment. 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.

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, including diclofenac, because of their high protein-binding rate and extensive metabolism.

For information on the management of overdose, contact the Poison Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

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

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

Clinical trials

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.

5.2 PHARMACOKINETIC PROPERTIES

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/litre) 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.

Distribution

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).

Excretion

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

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

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 that the duration of clinical effect is longer than might be inferred from the short plasma half-life of diclofenac.

The biotransformation of diclofenac involves partly glucuronidation of the intact molecule but mainly single and multiple hydroxylation followed by glucuronidation. About 60% of the administered dose is excreted in the urine in the form of metabolites from one of these two 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 drug's 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 <10mL/min, the theoretical steady-state plasma levels of metabolites are about 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.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Diclofenac showed no mutagenic effects in the studies conducted.

Carcinogenicity

Dietary administration of diclofenac to mice and rats at doses up to 0.5mg/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.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

The excipients include: lactose monohydrate, calcium hydrogen phosphate dihydrate, microcrystalline cellulose, maize starch, sodium starch glycollate, magnesium stearate, colloidal anhydrous silica, methacrylic acid copolymer, triethyl citrate, purified talc, titanium dioxide and iron oxide yellow.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

The enteric coated tablets are available in 50's in PP/Al or PVC/PVDC/Al blister packs

Some strengths, pack sizes and/or pack types may not be marketed.

Australian Register of Therapeutic Goods (ARTG)

AUST R 165707 – DICLOFENAC SODIUM VIATRIS diclofenac sodium 25 mg enteric coated tablet blister pack

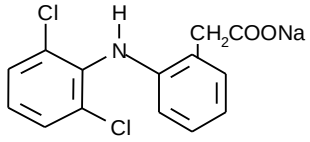
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

Structural formula:



Chemical name: sodium 2-[(2,6-dichlorophenyl)-amino] phenyl]-acetate

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

Molecular weight: 318.1

CAS number

15307-79-6

The active ingredient of DICLOFENAC SODIUM VIATIRS tablets is sodium 2-[(2,6-dichlorophenyl)-amino] phenyl]-acetate (=diclofenac sodium), a phenylacetic acid derivative, structurally similar to both the phenylalkanoic acid and the anthranilic acid series of compounds. Diclofenac sodium is an odourless, yellowish-white, crystalline powder sparingly soluble in water.

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8 SPONSOR

Alphapharm Pty Ltd trading as Viatris

Level 1, 30 The Bond

30-34 Hickson Road

Millers Point NSW 2000

www.viatris.com.au

Phone: 1800 274 276

9 DATE OF FIRST APPROVAL

11/01/2010

10 DATE OF REVISION

29/11/2023

Summary table of changes

Section Changed	Summary of new information
All	Change of trade name from “FENAC” to “DICLOFENAC SODIUM VIATRIS”. Minor editorial changes.
4.4	Addition of warning on increased risk of gastro-intestinal anastomotic leak.
4.6	Revision of wording of section on Oligohydramnios and Neonatal Renal Impairment to emphasise that diclofenac should not be used in the second trimester.
6.5	Update to product description to align with the ARTG.

DICLOFENAC SODIUM VIATRIS_pi\Nov23/00