
1 PRODUCT NAME

DICLOFENAC SANDOZ

25 mg enteric coated tablet

50 mg enteric coated tablet

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Diclofenac Sandoz 25 mg tablet contains Diclofenac Sodium 25 mg

Each Diclofenac Sandoz 50 mg tablet contains Diclofenac Sodium 50 mg

Excipients with known effect: lactose monohydrate

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

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.

4 CLINICAL PARTICULARS

4.1 Therapeutic 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;

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- 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.

4.2 Dose and method of administration

Dosage

Diclofenac Sandoz should only be prescribed when the benefits are considered to outweigh the potential risks. 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 Section 4.4 Special warnings and precautions for use).

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 Section 4.4 Special warnings and precautions for use).

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Established cardiovascular disease or significant cardiovascular risk factors

Treatment with diclofenac is generally not recommended in patients with established cardiovascular disease or uncontrolled hypertension. If needed, patients with established cardiovascular disease, uncontrolled hypertension or significant risk factors for cardiovascular disease should be treated with diclofenac only after careful consideration and only at doses ≤ 100 mg daily if treated for more than 4 weeks (see Section 4.4 Special warnings and precautions for use).

Renal impairment

Contraindicated in patients with renal failure (see Section 4.3 Contraindications).

No specific studies, have been carried out in patients with renal impairment, therefore, no specific dose adjustment recommendations can be made. Caution is advised when administering diclofenac to patients with mild to moderate renal impairment (see Section 4.4 Special warnings and precautions for use).

Hepatic impairment

Contraindicated in patients with hepatic failure (see Section 4.3 Contraindications).

No specific studies, have been carried out in patients with hepatic impairment, therefore, no specific dose adjustment recommendations can be made. Caution is advised when administering diclofenac to patients with mild to moderate hepatic impairment (see Section 4.4 Special warnings and precautions for use).

Administration

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

4.3 Contraindications

- Contraindicated in patients with gastrointestinal ulceration, haemorrhagic diathesis, asthma. Relatively contraindicated in liver dysfunction.
- Active gastric or intestinal ulcer, bleeding or perforation.
- Hepatic failure.
- Renal failure (GFR < 15 mL/min/1.73m²).
- Severe cardiac failure (refer to Section 4.4 Special warnings and precautions for use).
- Known hypersensitivity to the active substance or to any of the excipients (refer to Section 6.1 List of excipients).
- In common with other non-steroidal anti-inflammatory drugs (NSAIDs), diclofenac is also contraindicated in patients in whom attacks of asthma, angioedema, urticaria, or acute rhinitis are precipitated by acetylsalicylic acid or other NSAIDs.
- Last trimester of pregnancy (refer to Section 4.6 Fertility, pregnancy and lactation).

4.4 Special warnings and precautions for use

Warnings

Patients on long-term treatment should be reviewed regularly with regards to efficacy, adverse effects, the development of risk factors and the on-going need for therapy. Consideration should be given to monitoring blood pressure, haemoglobin levels and renal function.

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. Patients with previous myocardial infarction (within the last 6 to 12 months) should not use diclofenac. Treatment with diclofenac is generally not recommended in patients with established cardiovascular disease (e.g. congestive heart failure, established ischaemic heart disease or 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 (see Section 4.2 Dose and method of administration). The patient's need for symptomatic relief and response to therapy should be reevaluated periodically, especially when treatment continues for more than 4 weeks.

Prescribers should inform the individual patient of the possible increased risk when prescribing diclofenac for patients at high risk of cardiovascular events.

Physicians and patients should remain alert for such events, even in the absence of previous cardiovascular symptoms. Patients should be informed about the signs and/or symptoms of cardiovascular toxicity and the steps to take should they occur.

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 warning. 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.

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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 Section 4.5 Interaction with other medicines and other forms of interaction).

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 Section 4.8 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 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.

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Diclofenac should be discontinued at the first appearance of skin rash, mucosal lesions or any other sign of hypersensitivity.

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

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 (see Section 4.5 Interaction with other medicines and other forms of interaction).

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 (see Section 4.2 Dose and method of administration).

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.

Masking signs of infections

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

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 Section 4.8 Undesirable 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

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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 Section 4.5 Interaction with other medicines and other forms of interaction).

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 Section 4.8 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 after gastrointestinal surgery.

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

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renal function (refer to Section 4.3 Contraindications), history of hypertension, substantial extracellular volume depletion from any cause, e.g. before or after major surgery (see section 4.3), 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.

4.5 Interaction with other medicines and other forms of interaction

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 sulfinpyrazone 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 Section 4.4 Special warnings and precautions for use).

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 Section 4.4 Special warnings and precautions for use).

Anticoagulants and anti-platelet agents

Caution is recommended since concomitant administration could increase the risk of bleeding (refer to 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. 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 Section 4.4 Special warnings and precautions for use).

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.

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 is recommended when NSAIDs, including diclofenac, are administered less than 24 hours before or after methotrexate treatment, since blood concentrations of methotrexate may

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rise with increased risk of toxicity.

Ciclosporin and tacrolimus

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

Drugs known to cause hyperkalaemia

Concomitant treatment with potassium-sparing 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).

Quinolone antibacterials

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

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.

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.

Abnormal laboratory test results

None reported.

Food and alcohol

None reported.

4.6 Fertility, pregnancy and lactation

Use in pregnancy

Risk Summary

There are insufficient data on the use of diclofenac in pregnant women. Some epidemiological studies suggest an increased risk of miscarriage after use of a prostaglandin synthesis inhibitor (such as NSAIDs) in early pregnancy, however the overall data are inconclusive.

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Diclofenac has been shown to cross the placental barrier in humans. Use of NSAIDs, including diclofenac, can cause uterine inertia, premature closure of the fetal ductus arteriosus and fetal renal impairment leading to oligohydramnios.

Because of these risks, diclofenac should not be used during the first two trimesters of pregnancy unless the expected benefits to the mother outweigh the risks to the foetus.

Premature Closure of Fetal Ductus Ateriosus

As with other NSAIDs, use of diclofenac during the third trimester of pregnancy is contraindicated owing to the possibility of premature closure of the ductus arteriosus (see Section 4.3 Contraindications).

Human data

Published literature reports that the use of NSAIDs during the third trimester of pregnancy may cause premature closure of the fetal ductus arteriosus.

Breastfeeding

Like 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.

Human data

Diclofenac was detected in a low concentration (100 ng/mL) in breast milk in one nursing mother treated orally with a diclofenac salt of 150 mg/day. The estimated dose ingested by an infant consuming breast milk is equivalent to 0.03 mg/kg/day.

Fertility

Female fertility

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

Male fertility

There is no human data on the effect of diclofenac on male fertility.

Oligohydramnios/Fetal Renal Impairment

Risk of fetal renal impairment with subsequent oligohydramnios has been observed when NSAIDs (including diclofenac) were used from the 20th week of pregnancy onwards.

If an NSAID is necessary from the 20th week gestation to the end of the 2nd trimester, limit the use to the lowest effective dose and shortest duration possible. If diclofenac treatment extends beyond 48 hours, consider monitoring with ultrasound for oligohydramnios. If oligohydramnios occurs, discontinue diclofenac and follow up according to clinical practice.

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Human data

Published studies and post-marketing reports describe maternal NSAID use at about 20 weeks gestation or later in pregnancy associated with fetal renal impairment leading to oligohydramnios. 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. In many cases, but not all, the decrease in amniotic fluid was transient and reversible with cessation of the drug.

Labour or Delivery

There are no studies on the effects of diclofenac during labour or delivery. As with other NSAIDs, use of diclofenac during the third trimester of pregnancy is contraindicated owing to the possibility of uterine inertia (see section 4.3).

4.7 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.

4.8 Undesirable effects

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.

Ear and labyrinth disorders

Vertigo.

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Skin and subcutaneous tissue disorders

Rash.

Uncommon (from 1 in 1,000 to 1 in 100)

Cardiac disorders*

Palpitations, chest pain, cardiac failure, myocardial infarction.

Frequently Unknown: Kounis syndrome

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), gastrointestinal stenosis, or perforation, which may lead to peritonitis.

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.

Gastrointestinal disorders

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

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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, blurred vision, diplopia.

Ear and labyrinth disorders

Tinnitus, impaired hearing.

Psychiatric disorders

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

Renal and urinary disorders

Acute kidney injury (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.

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

Description of selected adverse drug reactions

Arteriothrombotic events

Meta-analysis and pharmacoepidemiological data point towards a small increased risk of arteriothrombotic events (for example myocardial infarction) associated with the use of diclofenac, particularly at high dose (150 mg daily) and during long-term treatment (see Section 4.4 Special warnings and precautions for use).

Visual effects

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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 of suspected adverse reactions

Reporting suspected adverse reaction after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>.

4.9 Overdose

Signs and symptoms

There is no typical clinical picture resulting from diclofenac overdosage. 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.

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.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

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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.

5.2 Pharmacokinetic properties

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

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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.

Diclofenac was detected in a low concentration (100 ng/mL) in breast milk in one nursing mother. The estimated amount ingested by an infant consuming breast milk is equivalent to a 0.03 mg/kg/day dose.

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.

5.3 Preclinical safety data

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.

Oligohydramnios/Fetal Renal Impairment

Reproductive and developmental studies in animals demonstrated that diclofenac administration during organogenesis did not produce teratogenicity despite the induction of maternal toxicity and fetal toxicity in mice at oral doses up to 20 mg/kg/day (0.41 times the maximum recommended human dose [MRHD] of diclofenac, 200 mg/day, based on body surface area (BSA) comparison), and in rats and rabbits at oral doses up to 10 mg/kg/day (0.41 and 0.81 times, respectively, the MRHD based on BSA comparison).

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In a study in which pregnant rats were orally administered 2 or 4 mg/kg diclofenac (0.08 and 0.16 times the MRHD based on BSA) from Gestation Day 15 through Lactation Day 21, significant maternal mortality (caused by gastrointestinal ulceration and peritonitis) was noted. These maternally toxic doses were associated with dystocia, prolonged gestation, intrauterine growth retardation, and decreased fetal survival.

Administration of NSAIDs (including diclofenac) inhibited ovulation in the rabbit and implantation and placentation in the rat, and led to premature closure of the fetal ductus arteriosus.

Labour or Delivery

In animal studies, NSAIDs, including diclofenac, inhibit prostaglandin synthesis, cause delayed parturition, and increase the incidence of stillbirth.

Fertility

Diclofenac administered to male and female rats at 4 mg/kg/day (approximately 0.16 times the MRHD based on BSA comparison) did not affect fertility.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Calcium hydrogen phosphate dihydrate
Colloidal silicon dioxide
Iron oxide yellow
Lactose monohydrate
Magnesium stearate
Maize starch
Methacrylic acid copolymer
Microcrystalline cellulose
Sodium starch glycollate
Purified talc
Titanium dioxide
Triethyl citrate

6.2 Incompatibilities

None known.

6.3 Shelf life

18 months

6.4 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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6.5 Nature and contents of container

Packs of 50 tablets in PVDC/PVC Aluminium blister strips.

6.6 Special precautions for handling, reconstitution and disposal

No special requirements.

7 MEDICINE SCHEDULE

Prescription Medicine.

8 SPONSOR

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9 DATE OF FIRST APPROVAL

24 Sep 2009

10 DATE OF REVISION OF THE TEXT

14 Dec 2022

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.6	Moved text to improve clarity. Changes include: text about crossing of placental barrier, male fertility. Revised section Oligohydramnios and Neonatal Renal Impairment to include statement about limiting the use to the lowest effective dose and shortest duration possible. Also monitoring for oligohydramnios if treatment extends beyond 48 hours.
5.3	Expanded section to include data and subheadings <i>Oligohydramnios/ Fetal Renal Impairment</i> also <i>Labour or Delivery and Fertility</i> .