Between text matter to 2D Code the blank space should be min. 5mm.

Pharma code should be at least 8mm height after folding the Outserts, this is minimum required height to read on line during packing.

Position / Orientation shall be changed depending upon the Printer's Machine suitability.

DICLOFENAC POTASSIUM CAPSULES

DICLOFENAC POTASSIUM CAPSULES

1051502

Do not print pink colour line.

- Space for 15 Digit Sequential 2D Data matrix Barcode shall be printed by the vendor.
- 2D data matrix should be minimum 8mm to 10mm height & width.
- 2D data matrix should be printed in the middle of the blank space in the folded Outsert.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use DICLOFENAC POTASSIUM CAPSULES safely and effectively. See full prescribing information for DICLOFENAC POTASSIUM CAPSULES.

Diclofenac Potassium Capsules, for oral use

Initial U.S. Approval: 1988

WARNING: RISK OF SERIOUS CARDIOVASCULAR AND GASTROINTESTINAL EVENTS

See full prescribing information for complete boxed warning.

- **Nonsteroidal anti-inflammatory drugs (NSAIDs) cause an increased risk of serious cardiovascular thrombotic events, including myocardial infarction and stroke, which can be fatal. This risk may occur early in treatment and may increase with duration of use (5.1)**
- **Diclofenac Potassium Capsules are contraindicated in the setting of coronary artery bypass graft (CABG) surgery (4, 5.1)**
- **NSAIDs cause an increased risk of serious gastrointestinal (GI) adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients and patients with a prior history of peptic ulcer disease and/or GI bleeding are at greater risk for serious GI events (5.2)**

-------------RECENT MAJOR CHANGES-------------

Warnings and Precautions (5.9) 01/2025

------------INDICATIONS AND USAGE---------------

Diclofenac Potassium Capsules are a non-steroidal anti-inflammatory drug indicated for relief of mild to moderate acute pain in adult and pediatric patients 12 years of age and older. (1)

---------DOSAGE AND ADMINISTRATION-----------

- Use the lowest effective dosage for shortest duration consistent with individual patient treatment goals (2.1)
- The dosage is 25 mg four times a day

---------DOSAGE FORMS AND STRENGTHS--------

Diclofenac Potassium Capsules: 25 mg (3)

--------------CONTRAINDICATIONS-----------------

- Known hypersensitivity to diclofenac or any components of the drug product (4)
- History of asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs (4)
- In the setting of CABG surgery (4)
- Diclofenac Potassium Capsules contains gelatin and should not be given to patients with known hypersensitivity to bovine protein. (4)

----------WARNINGS AND PRECAUTIONS----------

- Hepatotoxicity: Inform patients of warning signs and symptoms of hepatotoxicity. Discontinue if abnormal liver tests persist or worsen or if clinical signs and symptoms of liver disease develop (5.3)
- Hypertension: Patients taking some antihypertensive medications may have impaired response to these therapies when taking NSAIDs. Monitor blood pressure (5.4, 7)
- Heart Failure and Edema: Avoid use of Diclofenac Potassium Capsules in patients with severe heart failure unless benefits are expected to outweigh risk of worsening heart failure (5.5)
- Renal Toxicity: Monitor renal function in patients with renal or hepatic impairment, heart failure, dehydration, or hypovolemia. Avoid use of Diclofenac Potassium Capsules in patients with advanced renal disease unless benefits are expected to outweigh risk of worsening renal function (5.6)
- Anaphylactic Reactions: Seek emergency help if an anaphylactic reaction occurs (5.7)
- Exacerbation of Asthma Related to Aspirin Sensitivity: Diclofenac Potassium Capsules are contraindicated in patients with aspirin-sensitive asthma. Monitor patients with preexisting asthma (without aspirin sensitivity) (5.8)
- Serious Skin Reactions: Discontinue Diclofenac Potassium Capsules at first appearance of skin rash or other signs of hypersensitivity (5.9)
- Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS): Discontinue and evaluate clinically (5.10).
- Fetal Toxicity: Limit use of NSAIDs, including Diclofenac Potassium Capsules, between about 20 to 30 weeks in pregnancy due to the risk of oligohydramnios/fetal renal dysfunction. Avoid use of NSAIDs in women at about 30 weeks gestation and later in pregnancy due to the risks of oligohydramnios/fetal renal dysfunction and premature closure of the fetal ductus arteriosus (5.11, 8.1).
- Hematologic Toxicity: Monitor hemoglobin or hematocrit in patients with any signs or symptoms of anemia (5.12, 7)

----------------ADVERSE REACTIONS----------------

Most common adverse reactions (incidence ≥ 1%) are gastrointestinal experiences including abdominal pain, constipation, diarrhea, dyspepsia, nausea, vomiting, dizziness, headache, somnolence, pruritus, and increased sweating (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Strides Pharma Inc. at 1-877-244-9825 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------------DRUG INTERACTIONS----------------

- Drugs that Interfere with Hemostasis (e.g. warfarin, aspirin, SSRIs/SNRIs): Monitor patients for bleeding who are concomitantly taking Diclofenac Potassium Capsules with drugs that interfere with hemostasis. Concomitant use of Diclofenac Potassium Capsules and analgesic doses of aspirin is not generally recommended (7)
- ACE Inhibitors, Angiotensin Receptor Blockers (ARB), or Beta-Blockers: Concomitant use with Diclofenac Potassium Capsules may diminish the antihypertensive effect of these drugs. Monitor blood pressure (7)
- ACE Inhibitors and ARBs: Concomitant use with Diclofenac Potassium Capsules in elderly, volume depleted, or those with renal impairment may result in deterioration of renal function. In such high risk patients, monitor for signs of worsening renal function (7)
- Diuretics: NSAIDs can reduce natriuretic effect of furosemide and thiazide diuretics. Monitor patients to assure diuretic efficacy including antihypertensive effects (7)
- Digoxin: Concomitant use with Diclofenac Potassium Capsules can increase serum concentration and prolong half-life of digoxin. Monitor serum digoxin levels (7)

---------USE IN SPECIFIC POPULATIONS----------

Infertility: NSAIDs are associated with reversible infertility. Consider withdrawal of Diclofenac Potassium Capsules in women who have difficulties conceiving (8.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 01/2025

FULL PRESCRIBING INFORMATION: CONTENTS*

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FULL PRESCRIBING INFORMATION

WARNING: RISK OF SERIOUS CARDIOVASCULAR AND GASTROINTESTINAL EVENTS

Cardiovascular Thrombotic Events

- **Nonsteroidal anti-inflammatory drugs (NSAIDs) cause an increased risk of serious cardiovascular thrombotic events, including myocardial infarction and stroke, which can be fatal. This risk may occur early in treatment and may increase with duration of use [*see Warnings and Precautions (5.1)*].**
- **Diclofenac Potassium Capsules are contraindicated in the setting of coronary artery bypass graft (CABG) surgery [*see Contraindications (4) and Warnings and Precautions (5.1)*].**

Gastrointestinal Bleeding, Ulceration, and Perforation

- **NSAIDs cause an increased risk of serious gastrointestinal (GI) adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients and patients with a prior history of peptic ulcer disease and/or GI bleeding are at greater risk for serious GI events [*see Warnings and Precautions (5.2)*].**

1 INDICATIONS AND USAGE

Diclofenac Potassium Capsules are indicated for relief of mild to moderate acute pain in adult and pediatric patients 12 years of age and older.

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Instructions

Carefully consider the potential benefits and risks of Diclofenac Potassium Capsules and other treatment options before deciding to use Diclofenac Potassium Capsules. Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals [*see Warnings and Precautions (5)*].

For treatment of mild to moderate acute pain in adult and pediatric patients 12 years of age and older, the dosage is 25 mg four times a day.

2.2 Dosage Adjustments in Patients with Hepatic Impairment

Patients with hepatic disease may require reduced doses of Diclofenac Potassium Capsules compared to patients with normal hepatic function [*see Clinical Pharmacology (12)*]. As with other diclofenac products, start treatment at the lowest dose. If efficacy is not achieved with the lowest dose, discontinue use.

2.3 Non-Interchangeability with Other Formulations of Diclofenac

Different dose strengths and formulations of oral diclofenac are not interchangeable. This difference should be taken into consideration when changing strengths or formulations. The only approved dosing regimen for Diclofenac Potassium Capsules are 25 mg four times a day.

3 DOSAGE FORMS AND STRENGTHS

Diclofenac Potassium Capsules: 25 mg

4 CONTRAINDICATIONS

Diclofenac Potassium Capsules are contraindicated in the following patients:

- Known hypersensitivity (e.g., anaphylactic reactions and serious skin reactions) to diclofenac or any components of the drug product [*see Warnings and Precautions (5.7, 5.9)*]
- History of asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs. Severe, sometimes fatal, anaphylactic reactions to NSAIDs have been reported in such patients [*see Warnings and Precautions (5.7, 5.8)*]
- In the setting of coronary artery bypass graft (CABG) surgery [*see Warnings and Precautions (5.1)*]
- Diclofenac Potassium Capsules contains gelatin and is contraindicated in patients with known hypersensitivity to bovine protein.

5 WARNINGS AND PRECAUTIONS

5.1 Cardiovascular Thrombotic Events

Clinical trials of several COX-2 selective and nonselective NSAIDs of up to three years duration have shown an increased risk of serious cardiovascular (CV) thrombotic events, including myocardial infarction (MI) and stroke, which can be fatal. Based on available data, it is unclear that the risk for CV thrombotic events is similar for all NSAIDs. The relative increase in serious CV thrombotic events over baseline conferred by NSAID use appears to be similar in those with and without known CV disease or risk factors for CV disease.

However, patients with known CV disease or risk factors had a higher absolute incidence of excess serious CV thrombotic events, due to their increased baseline rate. Some observational studies found that this increased risk of serious CV thrombotic events began as early as the first weeks of treatment. The increase in CV thrombotic risk has been observed most consistently at higher doses.

To minimize the potential risk for an adverse CV event in NSAID-treated patients, use the lowest effective dose for the shortest duration possible. Physicians and patients should remain alert for the development of such events, throughout the entire treatment course, even in the absence of previous CV symptoms. Patients should be informed about the symptoms of serious CV events and the steps to take if they occur.

There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious CV thrombotic events associated with NSAID use. The concurrent use of aspirin and an NSAID, such as diclofenac, increases the risk of serious gastrointestinal (GI) events [*see Warnings and Precautions (5.2)*].

Status Post Coronary Artery Bypass Graft (CABG) Surgery

Two large, controlled clinical trials of a COX-2 selective NSAID for the treatment of pain in the first 10–14 days following CABG surgery found an increased incidence of myocardial infarction and stroke. NSAIDs are contraindicated in the setting of CABG [*see Contraindications (4)*].

Post-MI Patients

Observational studies conducted in the Danish National Registry have demonstrated that patients treated with NSAIDs in the post-MI period were at increased risk of reinfarction, CV-related death, and all-cause mortality beginning in the first week of treatment. In this same cohort, the incidence of death in the first year post-MI was 20 per 100 person years in NSAID-treated patients compared to 12 per 100 person years in non-NSAID exposed patients. Although the absolute rate of death declined somewhat after the first year post-MI, the increased relative risk of death in NSAID users persisted over at least the next four years of follow-up.

Avoid the use of Diclofenac Potassium Capsules in patients with a recent MI unless the benefits are expected to outweigh the risk of recurrent CV thrombotic events. If Diclofenac Potassium Capsules is used in patients with a recent MI, monitor patients for signs of cardiac ischemia.

5.2 Gastrointestinal Bleeding, Ulceration, and Perforation

NSAIDs, including diclofenac, cause serious gastrointestinal (GI) adverse events including inflammation, bleeding, ulceration, and perforation of the esophagus, stomach, small intestine, or large intestine, which can be fatal. These serious adverse events can occur at any time, with or without warning symptoms, in patients treated with NSAIDs. Only one in five patients who develop a serious upper GI adverse event on NSAID therapy is symptomatic. Upper GI ulcers, gross bleeding, or perforation caused by NSAIDs occurred in approximately 1% of patients treated for 3-6 months, and in about 2%-4% of patients treated for one year. However, even short-term NSAID therapy is not without risk.

Risk Factors for GI Bleeding, Ulceration, and Perforation

Patients with a prior history of peptic ulcer disease and/or GI bleeding who used NSAIDs had a greater than 10-fold increased risk for developing a GI bleed compared to patients without these risk factors. Other factors that increase the risk of GI bleeding in patients treated with NSAIDs include longer duration of NSAID therapy; concomitant use of oral corticosteroids, aspirin, anticoagulants, or selective serotonin reuptake inhibitors (SSRIs); smoking; use of alcohol; older age; and poor general health status. Most postmarketing reports of fatal GI events occurred in elderly or debilitated patients. Additionally, patients with advanced liver disease and/or coagulopathy are at increased risk for GI bleeding.

Strategies to Minimize the GI Risks in NSAID-treated patients:

- Use the lowest effective dosage for the shortest possible duration.
- Avoid administration of more than one NSAID at a time.
- Avoid use in patients at higher risk unless benefits are expected to outweigh the increased risk of bleeding. For such patients, as well as those with active GI bleeding, consider alternate therapies other than NSAIDs.
- Remain alert for signs and symptoms of GI ulceration and bleeding during NSAID therapy.
- If a serious GI adverse event is suspected, promptly initiate evaluation and treatment, and discontinue Diclofenac Potassium Capsules until a serious GI adverse event is ruled out.
- In the setting of concomitant use of low-dose aspirin for cardiac prophylaxis, monitor patients more closely for evidence of GI bleeding [*see Drug Interactions (7)*].

5.3 Hepatotoxicity

In clinical trials of diclofenac-containing products, meaningful elevations (i.e., more than 3 times the ULN) of AST (SGOT) were observed in about 2% of approximately 5,700 patients at some time during diclofenac treatment (ALT was not measured in all studies).

In a large open-label, controlled trial of 3,700 patients treated with oral diclofenac sodium for 2–6 months, patients were monitored first at 8 weeks and 1,200 patients were monitored again at 24 weeks. Meaningful elevations of ALT and/or AST occurred in about 4% of the 3,700 patients and included marked elevations (greater than 8 times the ULN) in about 1% of the 3,700 patients. In that open-label study, a higher incidence of borderline (less than 3 times the ULN), moderate (3–8 times the ULN), and marked (greater than 8 times the ULN) elevations of ALT or AST was observed in patients receiving diclofenac when compared to other NSAIDs. Elevations in transaminases were seen more frequently in patients with osteoarthritis than in those with rheumatoid arthritis.

Almost all meaningful elevations in transaminases were detected before patients became symptomatic. Abnormal tests occurred during the first 2 months of therapy with diclofenac in 42 of the 51 patients in all trials who developed marked transaminase elevations.

In postmarketing reports, cases of drug-induced hepatotoxicity have been reported in the first month, and in some cases, the first 2 months of NSAID therapy, but can occur at any time during treatment with diclofenac. Postmarketing surveillance has reported cases of severe hepatic reactions, including liver necrosis, jaundice, fulminant hepatitis with and without jaundice, and liver failure. Some of these reported cases resulted in fatalities or liver transplantation.

In a European retrospective population-based, case-controlled study, 10 cases of diclofenac associated drug-induced liver injury with current use compared with non-use of diclofenac were associated with a statistically significant 4-fold adjusted odds ratio of liver injury. In this particular study, based on an overall number of 10 cases of liver injury associated with diclofenac, the adjusted odds ratio increased further with female sex, doses of 150 mg or more, and duration of use for more then 90 days.

Physicians should measure transaminases at baseline and periodically in patients receiving long-term therapy with Diclofenac Potassium Capsules, because severe hepatotoxicity may develop without a prodrome of distinguishing symptoms. The optimum times for making the first and subsequent transaminase measurements are not known. Based on clinical trial data and postmarketing experiences, transaminases should be monitored within 4 to 8 weeks after initiating treatment with diclofenac. However, severe hepatic reactions can occur at any time during treatment with 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, abdominal pain, diarrhea, dark urine, etc.), Diclofenac Potassium Capsules should be discontinued immediately.

Inform patients of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, diarrhea, pruritus, jaundice, right upper quadrant tenderness, and "flu-like" symptoms). If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), discontinue Diclofenac Potassium Capsules immediately, and perform a clinical evaluation of the patient.

To minimize the potential risk for an adverse liver-related event in patients treated with Diclofenac Potassium Capsules, use the lowest effective dose for the shortest duration possible. Exercise caution when prescribing Diclofenac Potassium Capsules with concomitant drugs that are known to be potentially hepatotoxic (e.g., acetaminophen, antibiotics, antiepileptics).

5.4 Hypertension

NSAIDs, including Diclofenac Potassium Capsules, can lead to new onset of hypertension or worsening of pre-existing hypertension, either of which may contribute to the increased incidence of CV events. Patients taking angiotensin converting enzyme (ACE) inhibitors, thiazide diuretics, or loop diuretics may have impaired response to these therapies when taking NSAIDs [*see Drug Interactions (7)*].

Monitor blood pressure (BP) during the initiation of NSAID treatment and throughout the course of therapy.

5.5 Heart Failure and Edema

The Coxib and traditional NSAID Trialists' Collaboration meta-analysis of randomized controlled trials demonstrated an approximately two-fold increase in hospitalizations for heart failure in COX-2 selective-treated patients and nonselective NSAID-treated patients compared to placebo-treated patients. In a Danish National Registry study of patients with heart failure, NSAID use increased the risk of MI, hospitalization for heart failure, and death.

Additionally, fluid retention and edema have been observed in some patients treated with NSAIDs. Use of diclofenac may blunt the CV effects of several therapeutic agents used to treat these medical conditions (e.g., diuretics, ACE inhibitors, or angiotensin receptor blockers [ARBs]) [*see Drug Interactions (7)*].

Avoid the use of Diclofenac Potassium Capsules in patients with severe heart failure unless the benefits are expected to outweigh the risk of worsening heart failure. If Diclofenac Potassium Capsules is used in patients with severe heart failure, monitor patients for signs of worsening heart failure.

5.6 Renal Toxicity and Hyperkalemia

Renal Toxicity

Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury.

Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of an NSAID may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, dehydration, hypovolemia, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors or ARBs, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state.

No information is available from controlled clinical studies regarding the use of Diclofenac Potassium Capsules in patients with advanced renal disease. The renal effects of Diclofenac Potassium Capsules may hasten the progression of renal dysfunction in patients with preexisting renal disease.

Correct volume status in dehydrated or hypovolemic patients prior to initiating Diclofenac Potassium Capsules. Monitor renal function in patients with renal or hepatic impairment, heart failure, dehydration, or hypovolemia during use of Diclofenac Potassium Capsules [*see Drug Interactions (7)*]. Avoid the use of Diclofenac Potassium Capsules in patients with advanced renal disease unless the benefits are expected to outweigh the risk of worsening renal function. If Diclofenac Potassium Capsules are used in patients with advanced renal disease, monitor patients for signs of worsening renal function.

Hyperkalemia

Increases in serum potassium concentration, including hyperkalemia, have been reported with use of NSAIDs, even in some patients without renal impairment. In patients with normal renal function, these effects have been attributed to a hyporeninemic-hypoaldosteronism state.

5.7 Anaphylactic Reactions

Diclofenac has been associated with anaphylactic reactions in patients with and without known hypersensitivity to diclofenac and in patients with aspirin-sensitive asthma [see *Contraindications (4) and Warnings and Precautions (5.8)*].

Seek emergency help if an anaphylactic reaction occurs.

5.8 Exacerbation of Asthma Related to Aspirin Sensitivity

A subpopulation of patients with asthma may have aspirin-sensitive asthma which may include chronic rhinosinusitis complicated by nasal polyps; severe, potentially fatal bronchospasm; and/or intolerance to aspirin and other NSAIDs. Because cross-reactivity between aspirin and other NSAIDs has been reported in such aspirin-sensitive patients, Diclofenac Potassium Capsules are contraindicated in patients with this form of aspirin sensitivity [*see Contraindications (4)*]. When Diclofenac Potassium Capsules are used in patients with preexisting asthma (without known aspirin sensitivity), monitor patients for changes in the signs and symptoms of asthma.

5.9 Serious Skin Reactions

NSAIDs, including diclofenac, can cause serious skin adverse reactions such as exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. NSAIDs can also cause fixed drug eruption (FDE). FDE may present as a more severe variant known as generalized bullous fixed drug eruption (GBFDE), which can be life-threatening. These serious events may occur without warning. Inform patients about the signs and symptoms of serious skin reactions, and to discontinue the use of Diclofenac Potassium Capsules at the first appearance of skin rash or any other sign of hypersensitivity. Diclofenac Potassium Capsules are contraindicated in patients with previous serious skin reactions to NSAIDs [*see Contraindications (4)*].

5.10 Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) has been reported in patients taking NSAIDs such as Diclofenac Potassium Capsules. Some of these events have been fatal or life-threatening. DRESS typically, although not exclusively, presents with fever, rash, lymphadenopathy, and/or facial swelling. Other clinical manifestations may include hepatitis, nephritis, hematological 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 Diclofenac Potassium Capsules and evaluate the patient immediately.

5.11 Fetal Toxicity:

Premature Closure of Fetal Ductus Arteriosus

Avoid use of NSAIDs, including Diclofenac Potassium Capsules, in pregnant women at about 30 weeks gestation and later. NSAIDs, including Diclofenac Potassium Capsules, increase the risk of premature closure of the fetal ductus arteriosus at approximately this gestational age.

Oligohydramnios/Neonatal Renal Impairment

Use of NSAIDs, including Diclofenac Potassium Capsules, at about 20 weeks gestation or later in pregnancy may cause fetal 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 postmarketing cases of impaired neonatal renal function, invasive procedures such as exchange transfusion or dialysis were required.

If NSAID treatment is necessary between about 20 weeks and 30 weeks gestation, limit Diclofenac Potassium Capsules use to the lowest effective dose and shortest duration possible. Consider ultrasound monitoring of amniotic fluid if Diclofenac Potassium Capsules treatment extends beyond 48 hours. Discontinue Diclofenac Potassium Capsules if oligohydramnios occurs and follow up according to clinical practice *[see Use in Specific Populations (8.1)]*.

5.12 Hematologic Toxicity

Anemia has occurred in NSAID-treated patients. This may be due to occult or gross blood loss, fluid retention, or an incompletely described effect on erythropoiesis. If a patient treated with Diclofenac Potassium Capsules has any signs or symptoms of anemia, monitor hemoglobin or hematocrit.

NSAIDs, including Diclofenac Potassium Capsules, may increase the risk of bleeding events. Co-morbid conditions such as coagulation disorders or concomitant use of warfarin, other anticoagulants, antiplateletagents (e.g., aspirin), serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) may increase this risk. Monitor these patients for signs of bleeding [*see Drug Interactions (7)*].

5.13 Masking of Inflammation and Fever

The pharmacological activity of Diclofenac Potassium Capsules in reducing inflammation, and possibly fever, may diminish the utility of diagnostic signs in detecting infections.

5.14 Laboratory Monitoring

Because serious GI bleeding, hepatotoxicity, and renal injury can occur without warning symptoms or signs, consider monitoring patients on long-term NSAID treatment with a CBC and a chemistry profile periodically [*see Warnings and Precautions (5.2, 5.3, 5.6)*].

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling:

- Cardiovascular Thrombotic Events [*see Warnings and Precautions (5.1)*]
- GI Bleeding, Ulceration and Perforation [*see Warnings and Precautions (5.2)*]
- Hepatotoxicity [*see Warnings and Precautions (5.3)*]
- Hypertension [*see Warnings and Precautions (5.4)*]
- Heart Failure and Edema [*see Warnings and Precautions (5.5)*]
- Renal Toxicity and Hyperkalemia [*see Warnings and Precautions (5.6)*]
- Anaphylactic Reactions [*see Warnings and Precautions (5.7)*]
- Serious Skin Reactions [*see Warnings and Precautions (5.9)*]
- Hematologic Toxicity [*see Warnings and Precautions (5.12)*]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared with the rates in clinical trials of another drug and may not reflect the rates observed in practice.

The safety of Diclofenac Potassium Capsules was evaluated in 965 adult subjects. In patients treated with Diclofenac Potassium Capsules 25 mg (N=345) or a higher dose, three or four times a day, for 4 to 5 days, the most common adverse reactions (i.e., reported in ≥ 1% of Diclofenac Potassium Capsules treated patients) were as follows: gastrointestinal experiences including abdominal pain, constipation, diarrhea, dyspepsia, nausea, vomiting, dizziness, headache, somnolence, pruritus, and increased sweating. (see Table 1)

The safety of Diclofenac Potassium Capsules was evaluated in 125 pediatric patients, 12 years to 17 years of age. Forty-nine (49) patients with mild to moderate acute pain from a surgical procedure or an acute painful condition were treated with Diclofenac Potassium Capsules 25mg up to four times a day, for 4 days. Seventy-six (76) pediatric patients who underwent insertion of either orthodontic separators or arch wires were treated with a single-dose of either Diclofenac Potassium Capsules 25mg or Diclofenac Potassium Capsules 50mg after completion of the procedure. The most common adverse reactions in the multiple-dose studies were nausea (14.3%), headache (10.2%), constipation (8.2%), abdominal pain (4.1%), vomiting (4.1%), dizziness (4.1%), back pain (4.1%), and musculoskeletal pain (4.1%).

Table 1: Incidence of Treatment Emergent Adverse Reactions with Incidence ≥ 1% of Diclofenac Potassium Capsules Treated Patients in Multiple-Dose Studies

MedDRA System Organ Class and Preferred Term	Diclofenac Potassium Capsules* 25 mg n=345 n (%)	Placebo* n=327 n (%)
Any Adverse Events	144 (41.7)	181 (55.4)
Nausea	57 (16.5)	66 (20.2)
Headache	43 (12.5)	56 (17.1)
Abdominal Pain	24 (7.0)	11 (3.4)
Vomiting	20 (5.8)	17 (5.2)
Dizziness	12 (3.5)	66 (20.2)
Constipation	11 (3.2)	9 (2.8)
Somnolence	9 (2.6)	6 (1.8)
Diarrhea	8 (2.3)	9 (2.8)
Pruritus	5 (1.4)	6 (1.8)
Dyspepsia	4 (1.2)	8 (2.4)
Sweating Increase	4 (1.2)	2 (0.6)

*There was greater use of concomitant opioid rescue medication in placebo treated patients than in Diclofenac Potassium Capsules treated patients.

In patients taking other NSAIDs, the most frequently reported adverse experiences occurring in approximately 1%-10% of patients are:
Gastrointestinal experiences including: abdominal pain, constipation, diarrhea, dyspepsia, flatulence, gross bleeding/perforation, heartburn, nausea, GI ulcers (gastric/duodenal) and vomiting.

Abnormal renal function, anemia, dizziness, edema, elevated liver enzymes, headaches, increased bleeding time, pruritus, rashes, and tinnitus.

Additional adverse experiences reported in patients taking other NSAIDs occasionally include:

Body as a Whole*:* fever, infection, sepsis

Cardiovascular System*:* congestive heart failure, hypertension, tachycardia, syncope

Digestive System*:* dry mouth, esophagitis, gastric/peptic ulcers, gastritis, gastrointestinal bleeding, glossitis, hematemesis, hepatitis, jaundice

Hemic and Lymphatic System*:* ecchymosis, eosinophilia, leukopenia, melena, purpura, rectal bleeding, stomatitis, thrombocytopenia

Metabolic and Nutritional*:* weight changes

Nervous System*:* anxiety, asthenia, confusion, depression, dream abnormalities, drowsiness, insomnia, malaise, nervousness, paresthesia, somnolence, tremors, vertigo

Respiratory System*:* asthma, dyspnea

Skin and Appendages*:* alopecia, photosensitivity, sweating increased

Special Senses*:* blurred vision

Urogenital System*:* cystitis, dysuria, hematuria, interstitial nephritis, oliguria/polyuria, proteinuria, renal failure

Other adverse reactions in patients taking other NSAIDs, which occur rarely are:

Body as a Whole*:* anaphylactic reactions, appetite changes, death

Cardiovascular System*:* arrhythmia, hypotension, myocardial infarction, palpitations, vasculitis

Digestive System*:* colitis, eructation, liver failure, pancreatitis

Hemic and Lymphatic System*:* agranulocytosis, hemolytic anemia, aplastic anemia, lymphadenopathy, pancytopenia

Metabolic and Nutritional*:* hyperglycemia

Nervous System*:* convulsions, coma, hallucinations, meningitis

Respiratory System*:* respiratory depression, pneumonia

Skin and Appendages*:* angioedema, toxic epidermal necrolysis, erythema multiforme, exfoliative dermatitis, Stevens-Johnson Syndrome, urticaria

Special Senses*:* conjunctivitis, hearing impairment

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of diclofenac. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Skin and Appendages: Exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), and fixed drug eruption (FDE).

Medication Guide for Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

What is the most important information I should know about medicines called Nonsteroidal Anti-inflammatory Drugs (NSAIDs)?

NSAIDs can cause serious side effects, including:

- **Increased risk of a heart attack or stroke that can lead to death.** This risk may happen early in treatment and may increase:
  - o with increasing doses of NSAIDs
  - o with longer use of NSAIDs

Do not take NSAIDs right before or after a heart surgery called a "coronary artery bypass graft (CABG)." Avoid taking NSAIDs after a recent heart attack, unless your healthcare provider tells you to. You may have an increased risk of another heart attack if you take NSAIDs after a recent heart attack.

- **Increased risk of bleeding, ulcers, and tears (perforation) of the esophagus (tube leading from the mouth to the stomach), stomach and intestines:**
  - o anytime during use
  - o without warning symptoms
  - o that may cause death

  The risk of getting an ulcer or bleeding increases with:
  - o past history of stomach ulcers, or stomach or intestinal bleeding with use of NSAIDs
  - o taking medicines called "corticosteroids", "anticoagulants", "SSRIs", or "SNRIs"
  - o increasing doses of NSAIDs
  - o longer use of NSAIDS
  - o smoking
  - o drinking alcohol
  - o older age
  - o poor health
  - o advanced liver disease
  - o bleeding problems

  NSAIDs should only be used:
  - o exactly as prescribed
  - o at the lowest dose possible for your treatment
  - o for the shortest time needed

What are NSAIDs?

NSAIDs are used to treat pain and redness, swelling, and heat (inflammation) from medical conditions such as different types of arthritis, menstrual cramps, and other types of short-term pain.

Who should not take NSAIDs?

Do not take NSAIDs:

- if you have had an asthma attack, hives, or other allergic reaction with aspirin or any other NSAIDs.
- right before or after heart bypass surgery.

Before taking NSAIDS, tell your healthcare provider about all of your medical conditions, including if you:

- have liver or kidney problems
- have high blood pressure
- have asthma
- are pregnant or plan to become pregnant. Taking NSAIDs at about 20 weeks of pregnancy or later may harm your unborn baby. If you need to take NSAIDs for more than 2 days when you are between 20 and 30 weeks of pregnancy, your healthcare provider may need to monitor the amount of fluid in your womb around your baby. **You should not take NSAIDs after about 30 weeks of pregnancy.**
- are breastfeeding or plan to breast feed**.**

Tell your healthcare provider about all of the medicines you take, including prescription or over-the-counter medicines, vitamins or herbal supplements. NSAIDs and some other medicines can interact with each other and cause serious side effects. **Do not start taking any new medicine without talking to your healthcare provider first.**

What are the possible side effects of NSAIDs?

NSAIDs can cause serious side effects, including:

See "What is the most important information I should know about medicines called Nonsteroidal Anti-inflammatory Drugs (NSAIDs)?

- new or worse high blood pressure
- heart failure
- liver problems including liver failure
- kidney problems including kidney failure
- low red blood cells (anemia)
- life-threatening skin reactions
- life-threatening allergic reactions
- **Other side effects of NSAIDs include:** stomach pain, constipation, diarrhea, gas, heartburn, nausea, vomiting, and dizziness.

Get emergency help right away if you get any of the following symptoms:

- shortness of breath or trouble breathing

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Dimension	**500 x 500 mm**	Pack	NA
New Item Code	**1051502**	Old Item Code	1051224
Colour Shades	**BLACK**	No. of Colours	1

Change Control No.	PC-ODF/2024/871 - Record Number: 443660	Artwork Version	6.0
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- slurred speech
- chest pain
- swelling of the face or throat
- weakness in one part or side of your body

Stop taking your NSAID and call your healthcare provider right away if you get any of the following symptoms:

- nausea
- vomit blood
- more tired or weaker than usual
- diarrhea
- there is blood in your bowel movement or it is black and sticky like tar
- itching
- unusual weight gain
- your skin or eyes look yellow
- skin rash or blisters with fever
- indigestion or stomach pain
- swelling of the arms, legs, hands and feet
- flu-like symptoms

If you take too much of your NSAID, call your healthcare provider or get medical help right away.

These are not all the possible side effects of NSAIDs. For more information, ask your healthcare provider or pharmacist about NSAIDs.

Call your doctor for medical advice about side effects. You may report side effects to Strides Pharma Inc at 1-877-244-9825 or go to www.strides.com or FDA at 1-800-FDA-1088

Other information about NSAIDs

- Aspirin is an NSAID but it does not increase the chance of a heart attack. Aspirin can cause bleeding in the brain, stomach, and intestines. Aspirin can also cause ulcers in the stomach and intestines.
- Some NSAIDs are sold in lower doses without a prescription (over-the counter). Talk to your healthcare provider before using over-the-counter NSAIDs for more than 10 days.

General information about the safe and effective use of NSAIDs

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use NSAIDs for a condition for which it was not prescribed. Do not give NSAIDs to other people, even if they have the same symptoms that you have. It may harm them.

If you would like more information about NSAIDs, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about NSAIDs that is written for health professionals.

Manufactured by:
Strides Pharma Science Limited
Bengaluru - 562106, India.

Distributed by:
Strides Pharma Inc.
East Brunswick, NJ 08816

Revised: 01/2025

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Medication Guide available at: www.strides.com/diclo-pot-caps/

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7 DRUG INTERACTIONS

See Table 3 for clinically significant drug interactions with diclofenac.

Table 3: Clinically Significant Drug Interactions with diclofenac

Drugs That Interfere with Hemostasis	
Clinical Impact:	• Diclofenac and anticoagulants such as warfarin have a synergistic effect on bleeding. The concomitant use of diclofenac and anticoagulants have an increased risk of serious bleeding compared to the use of either drug alone. • Serotonin release by platelets plays an important role in hemostasis. Case-control and cohort epidemiological studies showed that concomitant use of drugs that interfere with serotonin reuptake and an NSAID may potentiate the risk of bleeding more than an NSAID alone.
Intervention:	Monitor patients with concomitant use of Diclofenac Potassium Capsules with anticoagulants (e.g., warfarin), antiplatelet agents (e.g., aspirin), selective serotonin reuptake inhibitors (SSRIs), and serotonin norepinephrine reuptake inhibitors (SNRIs) for signs of bleeding [*see Warnings and Precautions (5.12)*].
Aspirin	
Clinical Impact:	Controlled clinical studies showed that the concomitant use of NSAIDs and analgesic doses of aspirin does not produce any greater therapeutic effect than the use of NSAIDs alone. In a clinical study, the concomitant use of an NSAID and aspirin was associated with a significantly increased incidence of GI adverse reactions as compared to use of the NSAID alone [*see Warnings and Precautions (5.2)*].
Intervention:	Concomitant use of Diclofenac Potassium Capsules and analgesic doses of aspirin is not generally recommended because of the increased risk of bleeding [*see Warnings and Precautions (5.12)*]. Diclofenac Potassium Capsules is not a substitute for low dose aspirin for cardiovascular protection.
ACE Inhibitors, Angiotensin Receptor Blockers, and Beta-Blockers	
Clinical Impact:	• NSAIDs may diminish the antihypertensive effect of angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), or beta-blockers (including propranolol).
	• In patients who are elderly, volume-depleted (including those on diuretic therapy), or have renal impairment, co-administration of an NSAID with ACE inhibitors or ARBs may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible.
Intervention:	• During concomitant use of Diclofenac Potassium Capsules and ACE-inhibitors, ARBs, or beta-blockers, monitor blood pressure to ensure that the desired blood pressure is obtained. • During concomitant use of Diclofenac Potassium Capsules and ACE-inhibitors or ARBs in patients who are elderly, volume-depleted, or have impaired renal function, monitor for signs of worsening renal function [*see Warnings and Precautions (5.6)*]. • When these drugs are administered concomitantly, patients should be adequately hydrated. Assess renal function at the beginning of the concomitant treatment and periodically thereafter.
Diuretics	
Clinical Impact:	Clinical studies, as well as post-marketing observations, showed that NSAIDs reduced the natriuretic effect of loop diuretics (e.g., furosemide) and thiazide diuretics in some patients. This effect has been attributed to the NSAID inhibition of renal prostaglandin synthesis.
Intervention:	During concomitant use of Diclofenac Potassium Capsules with diuretics, observe patients for signs of worsening renal function, in addition to assuring diuretic efficacy including antihypertensive effects [*see Warnings and Precautions (5.6)*].
Digoxin	
Clinical Impact:	The concomitant use of diclofenac with digoxin has been reported to increase the serum concentration and prolong the half-life of digoxin.
Intervention:	During concomitant use of Diclofenac Potassium Capsules and digoxin, monitor serum digoxin levels.
Lithium	
Clinical Impact:	NSAIDs have produced elevations in plasma lithium levels and reductions in renal lithium clearance. The mean minimum lithium concentration increased 15%, and the renal clearance decreased by approximately 20%. This effect has been attributed to NSAID inhibition of renal prostaglandin synthesis.
Intervention:	During concomitant use of Diclofenac Potassium Capsules and lithium, monitor patients for signs of lithium toxicity.
Methotrexate	
Clinical Impact:	Concomitant use of NSAIDs and methotrexate may increase the risk for methotrexate toxicity (e.g., neutropenia, thrombocytopenia, renal dysfunction).
Intervention:	During concomitant use of Diclofenac Potassium Capsules and methotrexate, monitor patients for methotrexate toxicity.
Cyclosporine	
Clinical Impact:	Concomitant use of Diclofenac Potassium Capsules and cyclosporine may increase cyclosporine's nephrotoxicity.
Intervention:	During concomitant use of Diclofenac Potassium Capsules and cyclosporine, monitor patients for signs of worsening renal function.
NSAIDs and Salicylates	
Clinical Impact:	Concomitant use of diclofenac with other NSAIDs or salicylates (e.g., diflunisal, salsalate) increases the risk of GI toxicity, with little or no increase in efficacy [*see Warnings and Precautions (5.2)*].
Intervention:	The concomitant use of diclofenac with other NSAIDs or salicylates is not recommended.
Pemetrexed	
Clinical Impact:	Concomitant use of Diclofenac Potassium Capsules and pemetrexed may increase the risk of pemetrexed associated myelosuppression, renal, and GI toxicity (see the pemetrexed prescribing information).
Intervention:	During concomitant use of Diclofenac Potassium Capsules and pemetrexed, in patients with renal impairment whose creatinine clearance ranges from 45 to 79 mL/min, monitor for myelosuppression, renal and GI toxicity.
	NSAIDs with short elimination half-lives (e.g., diclofenac, indomethacin) should be avoided for a period of two days before, the day of, and two days following administration of pemetrexed. In the absence of data regarding potential interaction between pemetrexed and NSAIDs with longer half-lives (e.g., meloxicam, nabumetone), patients taking these NSAIDs should interrupt dosing for at least five days before, the day of, and two days following pemetrexed administration.
CYP2C9 Inhibitors or Inducers:	
Clinical Impact	Diclofenac is metabolized by cytochrome P450 enzymes, predominantly by CYP2C9. Co-administration of diclofenac with CYP2C9 inhibitors (e.g. voriconazole) may enhance the exposure and toxicity of diclofenac whereas co-administration with CYP2C9 inducers (e.g. rifampin) may lead to compromised efficacy of diclofenac.
Intervention:	A dosage adjustment may be warranted when diclofenac is administered with CYP2C9 inhibitors or inducers [*see Clinical Pharmacology (12.3)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Use of NSAIDs, including Diclofenac Potassium Capsules, can cause premature closure of the fetal ductus arteriosus and fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. Because of these risks, limit dose and duration of Diclofenac Potassium Capsules use between about 20 and 30 weeks of gestation, and avoid Diclofenac Potassium Capsules use at about 30 weeks of gestation and later in pregnancy *(see Clinical Considerations, Data)*.

Premature Closure of Fetal Ductus Arteriosus

Use of NSAIDs, including Diclofenac Potassium Capsules, at about 30 weeks gestation or later in pregnancy increases the risk of premature closure of the fetal ductus arteriosus.

Oligohydramnios/Neonatal Renal Impairment

Use of NSAIDs at about 20 weeks gestation or later in pregnancy has been associated with cases of fetal renal dysfunction leading to oligohydramnios, and in some cases, neonatal renal impairment.

Data from observational studies regarding other potential embryofetal risks of NSAID use in women in the first or second trimesters of pregnancy are inconclusive.

In animal reproduction studies, no evidence of malformations was observed in mice, rats, and rabbits given diclofenac during the period of organogenesis at doses up to approximately 1, 1, and 2 times, respectively, the maximum recommended human dose (MRHD) of Diclofenac Potassium Capsules, despite the presence of maternal and fetal toxicity at these doses. In published studies, administration of clinically relevant doses of diclofenac to pregnant rats produced adverse effects on brain, kidney, and testicular development *[see Data]*. Based on animal data, prostaglandins have been shown to have an important role in endometrial vascular permeability, blastocyst implantation, and decidualization. In animal studies, administration of prostaglandin synthesis inhibitors such as diclofenac, resulted in increased pre-and post-implantation loss. Prostaglandins also have been shown to have an important role in fetal kidney development. In published animal studies, prostaglandin synthesis inhibitors have been reported to impair kidney development when administered at clinically relevant doses.

The estimated background risk of major birth defects and miscarriage for the indicated population(s) is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Premature Closure of Fetal Ductus Arteriosus:
Avoid use of NSAIDs in women at about 30 weeks gestation and later in pregnancy, because NSAIDs, including Diclofenac Potassium Capsules, can cause premature closure of the fetal ductus arteriosus *(see Data)*.

Oligohydramnios/Neonatal Renal Impairment:
If an NSAID is necessary at about 20 weeks gestation or later in pregnancy, limit the use to the lowest dose and shortest duration possible. If Diclofenac Potassium Capsules treatment extends beyond 48 hours, consider monitoring with ultrasound for oligohydramnios. If oligohydramnios occurs, discontinue Diclofenac Potassium Capsules and follow up according to clinical practice *(see Data)*.

Labor or Delivery

There are no studies on the effects of Diclofenac Potassium Capsules during labor or delivery. In animal studies, NSAIDS, including diclofenac, inhibit prostaglandin synthesis, cause delayed parturition, and increase the incidence of stillbirth.

Data

Human Data

Premature Closure of Fetal Ductus Arteriosus:
Published literature reports that the use of NSAIDs at about 30 weeks of gestation and later in pregnancy may cause premature closure of the fetal ductus arteriosus.

Oligohydramnios/Neonatal Renal Impairment:
Published studies and postmarketing reports describe maternal NSAID use at about 20 weeks gestation or later in pregnancy associated with fetal 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. In many cases, but not all, the decrease in amniotic fluid was transient and reversible with cessation of the drug. There have been a limited number of case reports of maternal NSAID use and neonatal renal dysfunction without oligohydramnios, some of which were irreversible. Some cases of neonatal renal dysfunction required treatment with invasive procedures, such as exchange transfusion or dialysis.

Methodological limitations of these postmarketing studies and reports include lack of a control group; limited information regarding dose, duration, and timing of drug exposure; and concomitant use of other medications. These limitations preclude establishing a reliable estimate of the risk of adverse fetal and neonatal outcomes with maternal NSAID use. Because the published safety data on neonatal outcomes involved mostly preterm infants, the generalizability of certain reported risks to the full-term infant exposed to NSAIDs through maternal use is uncertain.

Diclofenac has been shown to cross the placental barrier in humans.

Animal data

Reproductive and developmental studies in animals demonstrated that diclofenac sodium administration during organogenesis did not produce malformations despite the induction of maternal toxicity and fetal toxicity in mice at oral doses up to 20 mg/kg/day (approximately equivalent to the maximum recommended human dose [MRHD] of Diclofenac Potassium Capsules, 100 mg/day, based on body surface area (BSA) comparison), and in rats and rabbits at oral doses up to 10 mg/kg/day (approximately 1 and 2 times, respectively, the MRHD based on BSA comparison).

In a study in which pregnant rats were orally administered 2 or 4 mg/kg diclofenac (0.2 and 0.4 times the MRHD based on BSA comparison) from Gestation Day 15 through Lactation Day 21, significant maternal toxicity (peritonitis, mortality) was noted. These maternally toxic doses were associated with dystocia, prolonged gestation, reduced fetal weights and growth, and reduced fetal survival. Diclofenac has been shown to cross the placental barrier in mice and rats.

In published studies, diclofenac administration to pregnant rats prolonged gestation and produced liver toxicity and neuronal loss in offspring (1 mg/kg, IP; 0.1 times the MRHD based on BSA comparison), impaired nephrogenesis in the kidney (3.6 mg/kg, IP; 0.3 times the MRHD based on BSA comparison), and caused adverse effects on the developing testes (6.1 mg/kg, PO; 0.6 times the MRHD based on BSA comparison).

8.2 Lactation

Risk Summary

Data from published literature reports with oral preparations of diclofenac indicate the presence of diclofenac in small amounts human milk *(see Data)*. There are no data on the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Diclofenac Potassium Capsules and any potential adverse effects on the breastfed infant from the Diclofenac Potassium Capsules or from the underlying maternal condition.

Data

One woman treated orally with a diclofenac salt, 150 mg/day, had a milk diclofenac level of 100 mcg/L, equivalent to an infant dose of about 0.03 mg/kg/day. Diclofenac was not detectable in breast milk in 12 women using diclofenac (after either 100 mg/day orally for 7 days or a single 50 mg intramuscular dose administered in the immediate postpartum period).

8.3 Females and Males of Reproductive Potential

Infertility

Females

Based on the mechanism of action, the use of prostaglandin-mediated NSAIDs, including Diclofenac Potassium Capsules, may delay or prevent rupture of ovarian follicles, which has been associated with reversible infertility in some women *[see Clinical Pharmacology (12.1)]*. Published animal studies have shown that administration of prostaglandin synthesis inhibitors has the potential to disrupt prostaglandin-mediated follicular rupture required for ovulation. Small studies in women treated with NSAIDs have also shown a reversible delay in ovulation. Consider withdrawal of NSAIDs, including Diclofenac Potassium Capsules, in women who have difficulties conceiving or who are undergoing investigation of infertility.

Males

Published studies in adult male rodents report that diclofenac, at clinically relevant doses, can produce adverse effects on male reproductive tissues. The impact of these findings on male fertility is not clear *[See Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

The safety and effectiveness of Diclofenac Potassium Capsules in pediatric patients 12 years to 17 years of age have been established. Use of Diclofenac Potassium Capsules in this age group is based on extrapolation of efficacy from adequate and well-controlled studies in adults and supported by pharmacokinetic and safety data from two open-label studies in 49 patients 12 years to 17 years of age with mild to moderate acute pain and one active-controlled study in 76 pediatric patients 12 years to 16 years of age with orthodontic discomfort. Based on the available data, the plasma diclofenac concentration in adolescent patients was comparable to that observed in healthy adults. The safety profile of Diclofenac Potassium Capsules in adolescent patients was similar to adults.

The safety and effectiveness of Diclofenac Potassium Capsules in patients less than 12 years of age have not been established.

8.5 Geriatric Use

Elderly patients, compared to younger patients, are at greater risk for NSAID-associated serious cardiovascular, gastrointestinal, and/or renal adverse reactions. If the anticipated benefit for the elderly patient outweighs these potential risks, start dosing at the low end of the dosing range, and monitor patients for adverse effects [*see Warnings and Precautions (5.1, 5.2, 5.3, 5.6, 5.13)*].

Diclofenac is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

10 OVERDOSAGE

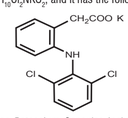
Symptoms following acute NSAID overdosages have been typically limited to lethargy, drowsiness, nausea, vomiting, and epigastric pain, which have been generally reversible with supportive care. Gastrointestinal bleeding has occurred. Hypertension, acute renal failure, respiratory depression, and coma have occurred, but were rare [*see Warnings and Precautions (5.1, 5.2, 5.4, 5.6)*].

Manage patients with symptomatic and supportive care following an NSAID overdosage. There are no specific antidotes. Consider emesis and/or activated charcoal (60 to 100 grams in adults, 1 to 2 grams per kg of body weight in pediatric patients) and/or osmotic cathartic in symptomatic patients seen within four hours of ingestion or in patients with a large overdosage (5 to 10 times the recommended dosage). Forced diuresis, alkalinization of urine, hemodialysis, or hemoperfusion may not be useful due to high protein binding.

For additional information about overdosage treatment contact a poison control center (1-800-222-1222).

11 DESCRIPTION

Diclofenac Potassium Capsules are a nonsteroidal anti-inflammatory drug, available as liquid-filled capsules of 25 mg base, equivalent to 28.3 mg potassium salt for oral administration. Diclofenac potassium is a white to slight yellowish crystalline powder. It is sparingly soluble in water at 25°C. The chemical name is benzeneacetic acid, 2-[(2,6dichlorophenyl) amino]-, monopotassium salt. The molecular weight is 334.24. Its molecular formula is $C_{14}H_{10}Cl_2NKO_2$, and it has the following chemical structure.



The inactive ingredients in Diclofenac Potassium Capsules include: polyethylene glycol 400, glycerin, sorbitol, povidone, polysorbate 80, hydrochloric acid, purified water. The capsule shell contains gelatin, glycerin, lecithin, medium chain triglyceride, purified water, sorbitol and opacode black ink (Shellac*Glaze, Isopropyl Alcohol, Ferrosoferric oxide, n-Butyl Alcohol, Propylene Glycol, Ammonium Hydroxide 28 %).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Diclofenac has analgesic, anti-inflammatory, and antipyretic properties.

The mechanism of action of Diclofenac Potassium Capsules, like that of other NSAIDs, is not completely understood but involves inhibition of cyclooxygenase (COX-1 and COX-2).

Diclofenac is a potent inhibitor of prostaglandin synthesis in vitro. Diclofenac concentrations reached during therapy have produced in vivo effects. Prostaglandins sensitize afferent nerves and potentiate the action of bradykinin in inducing pain in animal models. Prostaglandins are mediators of inflammation. Because diclofenac is an inhibitor of prostaglandin synthesis, its mode of action may be due to a decrease of prostaglandins in peripheral tissues.

12.3 Pharmacokinetics

The pharmacokinetics of Diclofenac Potassium Capsules was assessed in 24 healthy, normal adult volunteers who received 25 mg Diclofenac Potassium Capsules under fasting conditions. The mean pharmacokinetic parameters for Diclofenac Potassium Capsules are shown in Table 4. The pharmacokinetics of Diclofenac Potassium Capsules was also assessed in pediatric patients 12 to 17 years of age [see *Specific Populations: Pediatric*] and was also found to be similar to adults.

Table 4: Mean Pharmacokinetics of Diclofenac Potassium Capsules in Adults

PK Parameter	Number of Subjects	Mean ± Standard Deviation
T_{max} (hr)	24	0.47 ± 0.17
Terminal Half-life (hr)	24	1.07 ± 0.29
C_{max} (ng/mL)	24	1087 ± 419
AUC(0-∞) (ng.h/mL)	24	597 ± 151

Absorption

Diclofenac is 100% absorbed after oral administration compared to IV administration as measured by urine recovery. However, due to first-pass metabolism, only about 50% of the absorbed dose is systemically available. After repeated oral administration, no accumulation of diclofenac in plasma occurred.

The extent of diclofenac absorption is not significantly affected when Diclofenac Potassium Capsules is taken with food. However, the rate of absorption is reduced by food, as indicated by a two-fold increase of T_{max} and a 47% decrease in C_{max}.

Distribution

The apparent volume of distribution (V/F) of diclofenac potassium is 1.3 L/kg.

Diclofenac is more than 99% bound to human serum proteins, primarily to albumin. Serum protein binding is constant over the concentration range (0.15-105 µg/mL) achieved with recommended doses.

Diclofenac has been shown to cross the placental barrier in humans.

Diclofenac diffuses into and out of the synovial fluid. Diffusion into the joint occurs when plasma levels are higher than those in the synovial fluid, after which the process reverses and synovial fluid levels are higher than plasma levels. It is not known whether diffusion into the joint plays a role in the effectiveness of diclofenac.

Elimination

Metabolism

Five diclofenac metabolites have been identified in human plasma and urine. The metabolites include 4'-hydroxy-, 5-hydroxy-, 3'-hydroxy-, 4',5-dihydroxy- and 3'-hydroxy- 4'-methoxy diclofenac. The major diclofenac metabolite, 4'-hydroxy-diclofenac, has very weak pharmacologic activity. The formation of 4'-hydroxy diclofenac is primarily mediated by CPY2C9. Both diclofenac and its oxidative metabolites undergo glucuronidation or sulfation followed by biliary excretion. Acylglucuronidation mediated by UGT2B7 and oxidation mediated by CPY2C8 may also play a role in diclofenac metabolism. CYP3A4 is responsible for the formation of minor metabolites, 5-hydroxy and 3'-hydroxy- diclofenac.

In patients with renal dysfunction, peak concentrations of metabolites 4'-hydroxy-and 5-hydroxy-diclofenac were approximately 50% and 4% of the parent compound after single oral dosing compared to 27% and 1% in normal healthy subjects.

Excretion

Diclofenac is eliminated through metabolism and subsequent urinary and biliary excretion of the glucuronide and the sulfate conjugates of the metabolites. Little or no free unchanged diclofenac is excreted in the urine. Approximately 65% of the dose is excreted in the urine, and approximately 35% in the bile as conjugates of unchanged diclofenac plus metabolites. Because renal elimination is not a significant pathway of elimination for unchanged diclofenac, dosing adjustment in patients with mild to moderate renal dysfunction is not necessary. The terminal half-life of unchanged diclofenac is approximately 1 hour.

Specific Populations

Pediatric: The pharmacokinetics of Diclofenac Potassium Capsules was assessed in 24 pediatric patients 12 years to 17 years of age with mild to moderate acute pain who received 25mg Diclofenac Potassium Capsules every six hours as needed for pain for up to four days. The mean pharmacokinetic parameters of Diclofenac Potassium Capsules on Day 1 in pediatric patients 12 years to 17 years of age are shown in Table 5. Peak plasma levels were noted in one hour, with an elimination half-life of less than 2 hours. The pharmacokinetics of Diclofenac Potassium Capsules in pediatric patients 12 years to 17 years of age was similar to that in adults.

Table 5: Mean Pharmacokinetics of Diclofenac Potassium Capsules (Day1) in Pediatric Patients 12 Years to 17 Years of Age

PK Parameter	Number of Subjects	Mean ± Standard Deviation
T_{max} (hr)	24	0.94 ± 0.42
Terminal Half-life (hr)	24	1.81 ± 0.92
C_{max} (ng/mL)	24	699 ± 464
AUC(0-∞) (ng.h/mL)	24	659 ± 208

Race: Pharmacokinetic differences due to race have not been studied.

Hepatic Impairment: Hepatic metabolism accounts for almost 100% of diclofenac elimination. Therefore, in patients with hepatic impairment, start with the lowest dose and if efficacy is not achieved, consider use of an alternate product [*see Warnings and Precautions (5.3)]*

Renal Impairment: Diclofenac pharmacokinetics has been investigated in subjects with renal insufficiency. In patients with renal impairment (inulin clearance 60-90, 30-60, and <30 mL/min; N=6 in each group), AUC values and elimination rate were comparable to those in healthy subjects [*see Warnings and Precautions (5.6)]*.

Drug Interaction Studies

Aspirin: When NSAIDs were administered with aspirin, the protein binding of NSAIDs were reduced, although the clearance of free NSAID was not altered. The clinical significance of this interaction is not known. See Table 3 for clinically significant drug interactions of NSAIDs with aspirin [*see Drug Interactions (7)*].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Long-term carcinogenicity studies in rats given diclofenac sodium up to 2 mg/kg/day (approximately 0.2 times the maximum recommended human dose (MRHD) of Diclofenac Potassium Capsules, 100 mg/day, based on body surface area (BSA) comparison) have revealed no significant increase in tumor incidence. A 2-year carcinogenicity study conducted in mice employing diclofenac sodium at doses up to 0.3 mg/kg/day (approximately 0.014 times the MRHD based on BSA comparison) in males and 1 mg/kg/day (approximately 0.04 times the MRHD based on BSA comparison) in females did not reveal any oncogenic potential.

Mutagenesis

Diclofenac sodium did not show mutagenic activity in in vitro point mutation assays in mammalian (mouse lymphoma) and microbial (yeast, Ames) test systems and was nonmutagenic in several mammalian in vitro and in vivo tests, including dominant lethal and male germinal epithelial chromosomal aberration studies in Chinese hamsters.

Impairment of Fertility

Diclofenac sodium administered to male and female rats at 4 mg/kg/day (approximately 0.4 times the MRHD based on BSA comparison) did not affect fertility.

However, published studies report that treatment of adult male rats with diclofenac by the oral route at 10 mg/kg (1 times the MRHD based on BSA comparison) for 14 days and at 0.25 mg/kg (0.025 times the MRHD based on BSA comparison) for 30 days produced adverse effects on male reproductive hormones and testes.

14 CLINICAL STUDIES

The efficacy of Diclofenac Potassium Capsules in adults was demonstrated in two multicenter, randomized, double-blind, placebo- controlled, parallel arm, multiple-dose clinical trials comparing Diclofenac Potassium Capsules 25 mg and placebo in patients with pain following bunionectomy with osteotomy. Once patients met the criteria for randomization (pain intensity ≥4 on a 0-10 numerical pain rating scale) they received their initial dose of study medication followed by a remedication dose when requested by the patient, and were then dosed every six hours over four days. Pain intensity was recorded at 3 and 6 hours postdose during the fixed dosing period. In Study 1, mean baseline pain intensity scores were 6.9 in the Diclofenac Potassium Capsules group (range: 4 – 10) and 7.3 in the placebo group (range: 4 – 10). In both studies, patients treated with Diclofenac Potassium Capsules had a lower mean pain intensity score over the 48-hour inpatient period following the first remedication dose (see Figure 1). The median time to onset of pain relief was less than one hour for Diclofenac Potassium Capsules 25 mg across the clinical trials. The results were similar in Study 2.

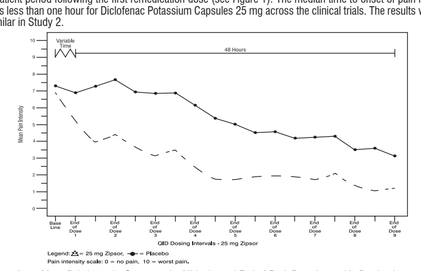


Figure 1 Mean Pain Intensity Scores at the Midpoint and End of Each Dose Interval in Postbunionectomy Pain Study 1

16 HOW SUPPLIED/STORAGE AND HANDLING

Diclofenac Potassium Capsules 25 mg, are translucent, pale yellow, liquid-filled capsules printed with "25" in black ink supplied as:

NDC Number 64380-841-06	Bottles of 100 Capsules
NDC Number 64380-841-11	Bottles of 120 Capsules

Storage

Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

Protect from moisture and light. Dispense in tight, light resistant container as defined in USP.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide) that accompanies each prescription dispensed. Inform patients, families, or their caregivers of the following information before initiating therapy with Diclofenac Potassium Capsules and periodically during the course of ongoing therapy.

Cardiovascular Thrombotic Events

Advise patients to be alert for the symptoms of cardiovascular thrombotic events, including chest pain, shortness of breath, weakness, or slurring of speech, and to report any of these symptoms to their health care provider immediately [*see Warnings and Precautions (5.1)*].

Gastrointestinal Bleeding, Ulceration, and Perforation

Advise patients to report symptoms of ulcerations and bleeding, including epigastric pain, dyspepsia, melena, and hematemesis to their health care provider. In the setting of concomitant use of low-dose aspirin for cardiac prophylaxis, inform patients of the increased risk for and the signs and symptoms of GI bleeding [*see Warnings and Precautions (5.2)*].

Hepatotoxicity

Inform patients of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, pruritus, diarrhea, jaundice, right upper quadrant tenderness, and "flu-like" symptoms). If these occur, instruct patients to stop Diclofenac Potassium Capsules and seek immediate medical therapy [*see Warnings and Precautions (5.3)*].

Heart Failure and Edema

Advise patients to be alert for the symptoms of congestive heart failure including shortness of breath, unexplained weight gain, or edema and to contact their healthcare provider if such symptoms occur [*see Warnings and Precautions (5.5)*].

Anaphylactic Reactions

Inform patients of the signs of an anaphylactic reaction (e.g., difficulty breathing, swelling of the face or throat). Instruct patients to seek immediate emergency help if these occur [*see Contraindications (4) and Warnings and Precautions (5.7)*].

Serious Skin Reactions, including DRESS

Advise patients to stop taking Diclofenac Potassium Capsules immediately if they develop any type of rash or fever and to contact their healthcare provider as soon as possible [*see Warnings and Precautions (5.9, 5.10)*].

Female Fertility

Advise females of reproductive potential who desire pregnancy that NSAIDs, including Diclofenac Potassium Capsules, may be associated with a reversible delay in ovulation [*see Use in Specific Populations (8.3)*].

Fetal Toxicity

Inform pregnant women to avoid use of Diclofenac Potassium Capsules and other NSAIDs starting at 30 weeks gestation because of the risk of the premature closing of the fetal ductus arteriosus. If treatment with Diclofenac Potassium Capsules is needed for a pregnant woman between about 20 to 30 weeks gestation, advise her that she may need to be monitored for oligohydramnios if treatment continues for longer than 48 hours *[see Warnings and Precautions (5.11) and Use in Specific Populations (8.1)]*.

Avoid Concomitant Use of NSAIDs

Inform patients that the concomitant use of Diclofenac Potassium Capsules with other NSAIDs or salicylates (e.g., diflunisal, salsalate) is not recommended due to the increased risk of gastrointestinal toxicity, and little or no increase in efficacy [see *Warnings and Precautions (5.2)* and *Drug Interactions (7)*]. Alert patients that NSAIDs may be present in "over the counter" medications for treatment of colds, fever, or insomnia.

Use of NSAIDs and Low-Dose Aspirin

Inform patients not to use low-dose aspirin concomitantly with Diclofenac Potassium Capsules until they talk to their healthcare provider [see *Drug Interactions (7)*].

US Patents: 6,365,180; 7,662,858; 7,884,095; 7,939,518; 8,110,606; 6,287,594; 8,623,920

Manufactured by:
Strides Pharma Science Limited
Bengaluru - 562106, India.

Distributed by:
Strides Pharma Inc.
East Brunswick, NJ 08816

Revised: 01/2025

Medication Guide available at: www.strides.com/diclo-pot-caps/

1051502

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Colour Shades	**BLACK**	No. of Colours	1

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