CARDIOVASCULAR RISK

- NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk.
- Diclofenac sodium is contraindicated for the treatment of perioperative pain in the setting of coronary artery bypass graft (CABG) surgery.

GASTROINTESTINAL RISK

- NSAIDs cause an increased risk of serious gastrointestinal adverse events including inflammation, 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 are at greater risk for serious gastrointestinal events.

For the use of a Registered Medical Practitioner only

1. GENERIC NAME & BRAND NAME

Tramadol Hydrochloride IR & Diclofenac Sodium SR Tablets
Durapain®

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each bilayered tablet contains:
Tramadol Hydrochloride I.P.....50 mg
(as immediate release layer)
Diclofenac Sodium I.P.....75 mg
(as sustained release layer)
Excipients……....q.s.
Color: Sunset Yellow FCF & Ferric oxide Red USP-NF

3. DOSAGE FORM AND STRENGTH

Refer section 1 & 2

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATION

For the symptomatic treatment of moderate to severe pain in adult patients.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

Recommended dose is 1 tablet twice daily after meals or as directed by the physician.
Duration: for a period not exceeding 5 days

4.3 CONTRAINDICATIONS

Contraindicated in patients with

- Patients who have previously demonstrated hypersensitivity to tramadol, diclofenac or any component of the formulation.
- In cases of acute intoxication with alcohol, hypnotics, centrally acting analgesics, opioids or psychotropic drugs
- In common with other opioid analgesics it should not be administered to patients who are receiving monoamine oxidase (MAO) inhibitors or within two weeks of their withdrawal.
- In epilepsy, not adequately controlled by treatment.
- For use in narcotic withdrawal treatment.
- Patients at risk of developing respiratory depression and addiction
- Patients who have experienced asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs. Severe, rarely fatal, anaphylactic-like reactions to diclofenac have been reported in such patients.
- Perioperative pain in the setting of coronary artery bypasses graft surgery

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Keep out of reach of children.
Not for veterinary use.
Indicated for severe acute pain only for a period not exceeding 5 days.

Tramadol:
Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should consult a physician prior to use.

Acute abdominal conditions
The administration of tramadol may complicate the assessment of patients with acute abdominal conditions.

Respiratory depression
When large doses of tramadol are administered with anaesthetic medications or alcohol, respiratory depression may result. Tramadol should be administered cautiously in patients at risk of respiratory depression.

Increased intracranial pressure, head trauma, shock or reduced levels of consciousness
Tramadol should be used with caution in patients with increased intracranial pressure, shock, head injury or a reduced level of consciousness of uncertain origin.

Renal and hepatic disease
With the prolonged half-life in these conditions, steady state achievement is delayed, so that it may take several days for elevated plasma concentrations to develop.

Serotonin syndrome
Serotonin syndrome, a potentially life-threatening condition, has been reported in patients receiving tramadol in combination with other serotonergic agents or tramadol alone (see sections 4.5, 4.8 and 4.9).
If concomitant treatment with other serotonergic agents is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose escalations.
Symptoms of serotonin syndrome may include mental status changes, autonomic instability, neuromuscular abnormalities and/or gastrointestinal symptoms.
If serotonin syndrome is suspected, a dose reduction or discontinuation of therapy should be considered depending on the severity of the symptoms. Withdrawal of the serotonergic drugs usually brings about a rapid improvement.

Renal disease
In patients with renal insufficiency the tramadol elimination is delayed. In cases of severe renal insufficiency tramadol is not recommended.

Hepatic disease
Metabolism of tramadol and M1 is reduced in patients with advanced liver cirrhosis. In cirrhotic patients, dosage reduction is recommended.

Patients physically dependent on opioids
Tramadol is not recommended as a substitute in opioid-dependent patients. In patients with a tendency for drug abuse or dependence, treatment with tramadol should only be carried out for short periods under strict medical supervision.

Seizure risk
Convulsions are reported in patients receiving tramadol. The risk is increased when doses of tramadol exceed the recommended upper daily dose limit Patients with epilepsy or the ones susceptible to seizures should only be treated with tramadol if there are compelling circumstances.

Anaphylactoid reactions
Serious and rarely fatal anaphylactoid reactions have been reported in patients taking tramadol. These reactions often occur after the first dose. Other reported reactions include pruritus, bronchospasm, hives and angioedema.

Long-term use
When long term tramadol treatment is required, careful and regular monitoring should be carried out to establish whether, and to what extent, ongoing treatment is necessary.

Labour and delivery
The use of tramadol in pregnant women prior to or during labour is not recommended unless the potential benefits outweigh the risks, because safe use in pregnancy has not been established. Chronic use during pregnancy may cause neonatal withdrawal

symptoms. If tramadol were to be used during labour, it may lead to respiratory depression in the new-born.

Sleep-related breathing disorders:
Opioids can cause sleep-related breathing disorders including central sleep apnoea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the total opioid dosage.

Adrenal insufficiency
Opioid analgesics may occasionally cause reversible adrenal insufficiency requiring monitoring and glucocorticoid replacement therapy. Symptoms of acute or chronic adrenal insufficiency may include e.g. severe abdominal pain, nausea and vomiting, low blood pressure, extreme fatigue, decreased appetite, and weight loss.

Diclofenac:
Cardiovascular Effects: NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk. To minimize the potential risk for an adverse cardiovascular event in patients treated with an NSAID, the lowest effective dose should be used for the shortest duration possible.

Hypertension: NSAIDs can lead to onset of new hypertension or worsening of pre-existing hypertension and hence should be used with caution in hypertensive patients. Patients on thiazides or loop diuretics may have impaired response to these therapies when taking NSAIDs.

Fluid retention and edema: Fluid retention and edema have been observed in some patients' takings NSAIDs; hence the drug should be used with caution in patients with fluid retention, hypertension or heart failure.

Risk of gastrointestinal (GI) ulceration, bleeding and perforation with NSAID therapy: Caution should be exercised in patients with previous history of peptic ulcer disease and / or gastrointestinal bleeding. NSAIDs cause an increased risk of serious gastrointestinal adverse events including inflammation, bleeding, ulceration and perforation of the stomach or intestines; these events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk of serious gastrointestinal events.

Several co-therapies and co-morbid conditions such as treatment with oral corticosteroids, anticoagulants, longer duration of NSAID therapy, smoking, alcoholism, older age and poor general health status may increase the risk of GI bleeding.

To minimize the risk of GI events, the lowest effective dose should be used for the shortest possible duration.

Hepatic effects: Borderline elevations of one or more liver tests may occur in some patients on this preparation. In patients on chronic treatment, periodic monitoring of transaminases is recommended. If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), the drug should be discontinued.

Renal effects: Not recommended in patients with advanced renal disease.
Caution advised in patients with considerable dehydration. In dehydrated patients, it is advisable to rehydrate the patient first and then start the therapy.

Long-term administration of diclofenac has been reported to cause papillary necrosis and other renal injury. Patients at high risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics /
ACE inhibitors and the elderly. Discontinuation of therapy is usually followed by recovery to the pretreatment state.

Hematological effects: Patients on NSAIDs should have their hemoglobin or hematocrit checked if they exhibit any signs or symptoms of anemia.
Patients receiving the drug, who may be adversely affected by alterations in platelet function, such as those with coagulation disorders or patients receiving anticoagulants, should be carefully monitored.

Preexisting Asthma: The drug should not be used in patients with aspirin-sensitive asthma and should be used with caution in all patients with preexisting asthma.

Laboratory tests: Patients on long term treatment with NSAIDs, should have their CBC and a chemistry profile (including transaminases) checked periodically. If clinical signs and symptoms consistent with liver or renal disease develop, systemic manifestations occur, or if abnormal liver tests persist or worsen, the drug should be discontinued.

Anaphylactoid reaction: As with other NSAIDs, anaphylactoid reactions may occur in patients without known prior exposure to the drug. Diclofenac should not be given to patients with the aspirin triad.

Skin Reactions: NSAIDs may cause serious skin adverse events such as exfoliative dermatitis, Stevens - Johnson syndrome and toxic epidermal necrolysis, which can be fatal. Patients should be informed about the signs and symptoms of serious skin manifestations and use of the drug should be stopped at the first appearance of skin rash or any other sign of hypersensitivity.

Sleep-related breathing disorders: Opioids can cause sleep-related breathing disorders including central sleep apnoea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the total opioid dosage.

Adrenal insufficiency: Opioid analgesics may occasionally cause reversible adrenal insufficiency requiring monitoring and glucocorticoid replacement therapy. Symptoms of acute or chronic adrenal insufficiency may include e.g. severe abdominal pain, nausea and vomiting, low blood pressure, extreme fatigue, decreased appetite, and weight loss.

General: The pharmacological activity of diclofenac in reducing fever and inflammation may diminish the utility of these diagnostic signs in detecting complications of presumed non-infectious, painful conditions.

4.5 DRUGS INTERACTIONS

Drug	Drug Interaction	Remarks
CNS depressants	The combination of tramadol with mixed opiate agonists/antagonists (eg. buprenorphine, pentazocine) is not advisable because the analgesic effect of a pure agonist may be theoretically reduced in such circumstances.	Tramadol should be used with caution and in reduced dosages when administered to patients receiving CNS depressants such as alcohol, opioids, anaesthetic agents, phenothiazines, tranquillisers or sedative hypnotics.
Serotonergic agents	Concomitant therapeutic use of tramadol and serotonergic medicines such as selective serotonin re-uptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), MAO inhibitors, tricyclics antidepressants and mirtazapine may cause serotonin a potentially life-threatening condition.	
Coumarin derivatives	Concomitant use may increase international normalised ratio (INR) with major bleeding and ecchymoses in some patients.	Caution should be exercised during concomitant treatment with tramadol and coumarin derivatives (eg. warfarin)

Drugs which reduce the seizure threshold	Tramadol can induce convulsions and increase the potential for selective serotonin re-uptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants, antipsychotics and other seizure-threshold-lowering drugs (such as bupropion, mirtazapine, tetrahydrocannabinol) to cause convulsions.	
MAO inhibitors	Tramadol inhibits the uptake of noradrenaline and serotonin.	Tramadol should not be used in patients who are taking MAO inhibitors or who have taken them within the last fourteen days.
Carbamazepine	Concomitant administration of tramadol with carbamazepine causes a significant increase in tramadol metabolism, presumably through metabolic induction by carbamazepine.	Patients receiving chronic carbamazepine doses of up to 800 mg daily may require up to twice the recommended dose of tramadol.
Quinidine, phenothiazines, antipsychotic agents	Drugs that selectively inhibit that isoenzyme may cause increased concentrations of tramadol and decreased concentrations of M1.	
Probenecid	Paracetamol excretion may be affected and plasma concentrations altered when given with probenecid.	
Chloramphenicol	Paracetamol may increase chloramphenicol concentrations.	
Alcohol and anticonvulsant agents	The risk of paracetamol toxicity may be increased in patients receiving other potentially hepatotoxic drugs or drugs that induce liver microsomal enzymes such as alcohol and anticonvulsant agents.	

Gastric emptying drugs	Paracetamol absorption is decreased by substances that decrease gastric emptying,	
Colestyramine	Colestyramine reduces the absorption of paracetamol if given within 1 hour of paracetamol.	
Anticoagulant / Antiplatelet drugs		Dosage may require reduction if used concomitantly with paracetamol for a prolonged period of time.

4.6 USE IN SPECIAL POPULATIONS (SUCH AS PREGNANT WOMEN, LACTATING WOMEN, PAEDIATRIC PATIENTS, GERIATRIC PATIENTS ETC.)

Pregnancy: The use of the drug during pregnancy should be avoided.

Nursing mothers: In nursing mothers, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric use: Safety and effectiveness have not been established.

Elderly: The drug should be used with particular caution in the elderly patients.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The drug may cause drowsiness and this effect may be potentiated by alcohol and other CNS depressants. Adequate care and precaution advised.

4.8 UNDESIRABLE EFFECTS

Cardiac disorders: tachycardia, palpitations, chest pain, cardiac failure, myocardial infarction, flushing, bradycardia

Investigations: increase in blood pressure

Vascular disorders: orthostatic dysregulation, Hypertension, vasculitis

Respiratory, thoracic and mediastinal disorders: Dyspnoea, asthma, pneumonitis, respiratory depression, worsening of asthma, bronchospasm, hiccups

Gastrointestinal disorders: Nausea, vomiting, constipation, dyspepsia, diarrhea, abdominal pain, flatulence, urge to vomit, elevations in serum transaminases, hepatitis, jaundice, fatal fulminant hepatitis, liver failure

Metabolism and nutrition disorders: changes in appetite, weight changes, hyperglycemia

Hepatobiliary disorders: elevated liver enzymes

Nervous system disorders: dizziness, autonomic nervous effects (mainly dry mouth, perspiration), Somnolence, memory impairment, convulsion, anxiety, tremor, aseptic meningitis, taste disturbances, cerebrovascular accident, headache sedation, asthenia, trembling, speech disorders, paraesthesia, coordination disturbance, tremor, seizures, involuntary muscle contractions, syncope, serotonin syndrome

Psychiatric disorders: Hallucinations, confusional state, disorientation, depression, insomnia, nightmare, irritability, psychotic disorder, sleep disturbance, delirium, anxiety, nightmares, changes in mood, changes in activity (usually suppression, occasionally increase), changes in cognitive and sensorial capacity (eg. decision behaviour, perception disorders)

Musculoskeletal and connective tissue disorders: Motor system weakness, Isolated cases of rhabdomyolysis

General disorders and administration site conditions: fatigue

Endocrine: Syndrome of inappropriate antidiuretic hormone secretion characterized by hyponatremia secondary to decreased free-water excretion

Skin and subcutaneous tissue disorders: Rash, pruritus photosensitivity, sweating increased eczema, alopecia, bullous eruptions, allergic purpura, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, tissue necrosis, erythroderma
Severe pustular psoriasis, pruritic maculopapular eruption, nicolau syndrome

Immune system disorders: Shock reactions, Angioneurotic oedema, anaphylaxis, allergic reactions

Renal and urinary disorders: Cystitis, dysuria, nephrotic syndrome, interstitial nephritis, renal papillary necrosis, acute renal failure, urinary frequency, nocturia, proteinuria, and hematuria, anuria

Eye disorders: Miosis, visual disturbance, diplopia, mydriasis, and visual disturbance (blurred vision)

Blood and lymphatic system disorders: Ecchymosis, eosinophilia, purpura, rectal bleeding, stomatitis, anemia, leukopenia, thrombocytopenia, hemolytic anemia, spontaneous bruising associated with increased bleeding times, purpura, agranulocytosis, aplastic anemia, lymphadenopathy, pancytopenia

Ear and labyrinth disorders: Vertigo, Tinnitus, hearing impairment

4.9 OVERDOSAGE

Symptoms of over dosage are typical of other opioid analgesics and include miosis, vomiting, cardiovascular collapse, sedation and coma, seizures and respiratory depression. Serotonin syndrome has also been reported.

In treating an overdose, primary attention should be given to maintaining adequate ventilation along with general supportive treatment. While naloxone will reverse some, but not all, symptoms caused by over dosage with tramadol, the risk of seizures is also increased with naloxone administration; fits can be controlled with diazepam. Tramadol is minimally eliminated from the serum by hemodialysis or hemofiltration.

Diclofenac:

Patients should be managed by symptomatic and supportive care. There are no specific antidotes. Emesis and / or activated charcoal and / or osmotic cathartic may be indicated in patients seen within 4 hours of ingestion with symptoms or following a large overdose (5 to 10 times the usual dose). Forced diuresis, alkalinisation of urine, haemodialysis or hemoperfusion may not be useful due to high protein binding.

5. PHARMACOLOGICAL PROPERTIES

5.1 MECHANISM OF ACTION

Tramadol is a centrally acting opioid analgesic. It is a non-selective pure agonist at μ-, δ- and κ-opioid receptors with a higher affinity for the μ-receptor. Other mechanisms which may contribute to its analgesic effect are inhibition of neuronal reuptake of noradrenaline and enhancement of serotonin release. Diclofenac's mode of action is not known and may be related to prostaglandin synthesis

5.2 PHARMACODYNAMICPROPERTIES

Tramadol is a centrally-acting synthetic analgesic of the amino cyclohexanol group with opioid-like effects. Tramadol is not derived from natural sources, nor is it chemically related to opiates. Low affinity binding of the parent compound to μ-opioid receptors and higher affinity binding of the principal active metabolite is from where the opioid-like activity of tramadol derived from. M1 is up to 6 times more potent than tramadol in producing analgesia and 200 times more potent in μ-opioid binding.

Apart from analgesia, tramadol may produce other symptoms similar to that of opioids including: dizziness, constipation, sweating, somnolence, nausea and pruritus. However, tramadol causes significantly less respiratory depression than morphine. Tramadol has not been shown to cause histamine release as opposed to morphine. At therapeutic doses, tramadol has no clinically significant effect on heart rate, left ventricular function or cardiac index. Orthostatic changes in blood pressure have been observed.

Diclofenac is a nonsteroidal anti-inflammatory drug (NSAID) and exhibits anti-inflammatory, analgesic, and antipyretic activity.

5.3 PHARMACOKINETIC PROPERTIES

Parameters	Tramadol	Diclofenac
Absorption	Rapidly and almost completely absorbed after oral administration, absorption delay of approximately thirty minutes, absorption half-life (t½) is 23 ± 11 minutes Mean peak plasma concentration (Cmax) is approximately 280 ng/mL Mean absolute bioavailability (fabs) is 68-72%	Diclofenac is well absorbed orally
Distribution	Rapidly distributed in the body, with a volume of distribution of 2 – 3 L/kg in young adults, which is reduced by about 25% in those aged over 75 years. Crosses the placental and blood-brain barriers. Very small amounts of tramadol and M1 are found in breast milk	The apparent volume of distribution calculated is 0.12 to 0.17 L/kg. Diclofenac enters the synovial fluid, where maximum concentrations are measured 2 to 4 hours after peak plasma values have been attained
Plasma Protein Binding	20% and is independent of concentration up to 10 µg/mL	99.7 %. Bound mainly to albumin
Metabolism	Extensively metabolised after oral administration. major metabolic pathways appear to be N - and O - demethylation and glucuronidation or sulfation in the liver	Biotransformation of diclofenac takes place partly by glucuronidation of the intact molecule, but mainly by single and multiple hydroxylation and methoxylation, resulting in several phenolic metabolites most of which are converted to glucuronide conjugates

Excretion	Tramadol and its metabolites are excreted mainly by the kidneys, with a cumulative renal excretion (tramadol and metabolites) of approximately 95%. 15 – 19% is excreted in the urine as unmetabolised drug. Total clearance is approximately 430 – 610 mL/min.	Total systemic clearance of diclofenac from plasma is 263.56 mL/min. About 60 % is excreted in the urine as the glucuronide conjugate, less than 1 % is excreted as unchanged substance. The rest is eliminated as metabolites through the bile in the faeces.
Half-life	In young adults, the half-life of tramadol is 5 – 7 h and the half-life of M1 is 6 – 8 h.	Elimination from the synovial fluid is 3 to 6 hours. The terminal half-life in plasma is 1 to 2 hours

6. NONCLINICAL PROPERTIES

6.1 ANIMAL TOXICOLOGY OR PHARMACOLOGY

On repeated oral and parenteral administration of tramadol for 6 - 26 weeks in rats and dogs and oral administration for 12 months in dogs, hematological, clinico-chemical and histological investigations showed no evidence of any substance-related changes. Central nervous manifestations only occurred after high doses considerably above the therapeutic range: restlessness, salivation, convulsions, and reduced weight gain. Rats and dogs tolerated oral doses of 20 mg/kg and 10 mg/kg body weight respectively, and dogs rectal doses of 20 mg/kg body weight without any reactions.

In rats tramadol dosages from 50 mg/kg/day upwards caused toxic effects in dams and raised neonate mortality. In the offspring retardation occurred in the form of ossification disorders and delayed vaginal and eye opening. Male fertility was not affected. After higher doses (from 50 mg/kg/day upwards) females exhibited a reduced pregnancy rate. In rabbits there were toxic effects in dams from 125 mg/kg upwards and skeletal anomalies in the offspring.

In some in-vitro test systems there was evidence of mutagenic effects. In-vivo studies showed no such effects. According to knowledge gained so far, tramadol can be classified as non-mutagenic.

Studies on the tumorigenic potential of tramadol hydrochloride have been carried out in rats and mice. The study in rats showed no evidence of any substance-related increase in the incidence of tumours. In the study in mice there was an increased incidence of liver cell adenomas in male animals (a dose-dependent, nonsignificant increase from 15 mg/kg

upwards) and an increase in pulmonary tumours in females of all dosage groups (significant, but not dose-dependent)

7.0 DESCRIPTION

DURAPAIN is supplied for oral administration, as a bilayered tablet of Tramadol Hydrochloride & Diclofenac Sodium. Each bilayerd tablet of DURAPAIN contains Tramadol Hydrochloride I.P 50 mg (as immediate release layer), Diclofenac Sodium I.P 75 mg (as sustained release layer).

8.0 PHARMACEUTICAL PARTICULARS

8.1 INCOMPATIBILITIES

Not Applicable

8.2 SHELF-LIFE

Refer pack

8.3 PACKAGING INFORMATION

Refer pack

8.4 STORAGE CONDITION AND HANDING INSTRUCTIONS

Refer pack

9. PATIENT COUNSELLING INFORMATION

Tramadol hydrochloride - the active substance in Tramadol - is a painkiller belonging to the class of opioids that acts on the central nervous system. It relieves
pain by acting on specific nerve cells of the spinal cord and brain.

Tramadol is used for the treatment of moderate to severe pain. You must talk to a doctor if you do not feel better.

Diclofenac sodium is one of a group of medicines called non-steroidal anti-inflammatory drugs (NSAIDs). NSAIDs reduce pain and inflammation. They relieve pain, reduce swelling and ease inflammation in conditions affecting the joints, muscles and tendons including: Rheumatoid arthritis, osteoarthritis, acute gout (painful inflammation of the joints especially in the feet and hands). ankylosing spondylitis (form of spinal arthritis).
Backache, sprains and strains, soft tissue sports injuries, frozen shoulder, dislocations and fractures

Conditions affecting the tendons for example, tendonitis, tenosynovitis, bursitis.
They are also used to treat pain and inflammation associated with dental and minor surgery.

Do not take Tramadol - if you are allergic to active substance or any of the other ingredients of this medicine (listed in section 6). - if you are under the influence of alcohol or sedative drugs including sleeping pills, other pain-killers or tranquilizer medicines - if you are taking,

or have taken in the last two weeks, certain medicines called “monoamine oxidase inhibitors” or MAOIs (used to treat e.g. depression, and the antibiotic linezolid). The combination could result in a serious, potentially life-threatening interaction - if you have epilepsy that is not controlled with your current medicine; - as a substitute in drug withdrawal.

Do not take Diclofenac Sodium if:

- you are allergic to diclofenac sodium, aspirin, ibuprofen or to any other NSAID, or any of the other ingredients of DICLOFLEX tablets (these are listed under section 6 "CONTENTS OF THE PACK AND OTHER INFORMATION" of the leaflet). Signs of a hypersensitivity reaction include swelling of the face and mouth (angioedema), breathing problems, chest pain, runny nose, skin rash or any other allergic type reaction.
- you have now, or have ever had, two or more distinct episodes of stomach (gastric) or duodenal (peptic) ulcer, or bleeding in the digestive tract (this can include blood in vomit, bleeding when emptying bowels, fresh blood in faeces or black, tarry faeces)
- you have had stomach or bowel problems after you have taken other NSAIDs
- you have heart, kidney or liver failure
- you have established heart disease and/or cerebrovascular disease, e.g. if you have had a heart attack, stroke, mini-stroke (TIA) or blockages to blood vessels to the heart or brain or an operation to clear or bypass blockages.
- you have or have had problems with your blood circulation (peripheral arterial disease).
- you are more than six months pregnant
- Do not take Tramadol at the same time as medicines called “monoamine oxidase inhibitors” or MAOIs (which are used to treat e.g. depression), or if you have taken MAOIs in the past 2 weeks. The pain-relieving effect of Tramadol may be weakened and/or shortened if you also take medicines containing: - carbamazepine (used to treat epilepsy) - pentazocine, nalbuphine or buprenorphine (pain killers) - ondansetron (used to stop you feeling sick).
- The risk of side effects increases if you take Tramadol at the same time as: - if you are taking medicines which may cause convulsions (fits), such as certain antidepressants or antipsychotics. The risk having a fit may increase if you take
- Tramadol at the same time. Your doctor will tell you whether Tramadol is suitable for you. - if you are taking certain antidepressants. Tramadol may interact with these medicines and you may experience symptoms such as involuntary, rhythmic contractions of muscles, including the muscles that control movement of the eye, agitation, excessive sweating, tremor, exaggeration of reflexes, increased muscle tension, body temperature above 38 °C. - sedative medicines such as tranquillizers, sleeping pills, antidepressants and other pain relievers (morphine, codeine); you may feel excessively drowsy or feel that you might faint - medicines that prevent blood clotting, such as warfarin; the dose of these medicines may need to be reduced, otherwise there could be an increased risk of potentially serious bleeding.

- Concomitant use of Tramadol and sedative medicines such as benzodiazepines or related drugs increases the risk of drowsiness, difficulties in breathing (respiratory depression), coma and may be life-threatening. Because of this, concomitant use should only be considered when other treatment options are not possible. However if your doctor does prescribe Tramadol together with sedative medicines the dose and duration of concomitant treatment should be limited by your doctor.
- You should take the lowest effective dose of Diclofenac Sodium for the shortest possible time particularly if you are underweight or elderly.
- There is a small increased risk of heart attack or stroke when you are taking any medicine like Diclofenac Sodium. The risk is higher if you are taking high doses for a long time. Always follow the doctor's instructions on how much to take and how long to take it for.
- If at any time while taking DICLOFLEX you experience any signs or symptoms of problems with your heart or blood vessels such as chest pain, shortness of breath, weakness or slurring of speech, contact your doctor immediately.
- Whilst you are taking these medicines your doctor may want to give you a check-up from time to time.

- If you have a history of stomach problems when you are taking NSAIDs, particularly if you are elderly, you must tell your doctor straight away if you notice any unusual symptoms.
- Because it is an anti-inflammatory medicine, Diclofenac Sodium tablets may reduce the symptoms of infection, for example, headache, and high temperature. If you feel unwell and need to see a doctor, remember to tell him or her that you are taking Diclofenac Sodium tablets.

10. DETAILS OF MANUFACTURER
Refer Pack for manufacturer details.

Marketed By:
Abbott Healthcare Pvt. Ltd.
Angel Space, Bldg. D-4, Gala No. 1 to 3 &
11 to 13 Ground Floor, 101 to 106 &
111 to 116 First Floor, 201 to 206 & 211 to 216
2nd Floor, Pimplas, Dist. Thane, Bhiwandi - 421 302, India.

11. DETAILS OF PERMISSION OR LICENCE NUMBER
Refer Pack for Permission/License details

12. DATE OF REVISION
Version 7.0; Dated 10/02/2025

For Product Complaints/Adverse events or Queries please write to
webmasterindia@abbott.com