For the use of only a Registered Medical Practitioner or a Hospital or a Laboratory

Not to be sold by retail without the prescription of a Registered Medical Practitioner

Prescribing Information

1. Generic Name

Diclofenac Sodium and Paracetamol Tablets IP
(Brand Name: DICLOTAL®-FORTE Tablets)

Paracetamol: Box Warning About Its Liver Toxicity
Taking more than daily dose may cause serious liver damage or allergic reactions (e.g., swelling of the face, mouth and throat, difficulty in breathing, itching or rash). The risk of liver injury primarily occurs when patient take multiple products containing paracetamol/acetaminophen at one time and exceed the current maximum dose of 4,000 mg within a 24-hour period.

2. Qualitative and Quantitative Composition

Each uncoated tablet contains:
Diclofenac Sodium IP …….. 50 mg.
Paracetamol IP ……. 325 mg.
Excipients ……. q.s.

3. Dosage Form and Strength

Dosage Form: Tablets.
Dosage Strength: Diclofenac sodium 50 mg and paracetamol 325 mg per tablet.

4. Clinical Particulars

4.1 Therapeutic Indication

DICLOTAL-FORTE Tablets are indicated for the relief of pain and inflammation in various conditions:

- Acute musculoskeletal disorders such as sprains and strains.
- Muscular and traumatic pain.
- Musculoskeletal and joint disorders such as rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis.
- Low back pain.
- Peri-articular disorders such as bursitis and tendinitis.
- Acute gout.
- Post-operative pain.

- Renal colic.
- Migraine.

4.2Posology and Method of Administration

For oral administration in adults. Usual recommended dose: 1 tablet of DICLOTAL-FORTE to be administered three times daily.
DICLOTAL-FORTE Tablets to be taken whole with liquid, preferably with or after food.
The recommended maximum daily dose of diclofenac sodium in adults is 150 mg in 2 or 3 divided doses. The maximum recommended dose of paracetamol in adults is 4 gram per day in divided doses.
Or, as prescribed by the physician.

4.3Contraindications

DICLOTAL-FORTE Tablets are contraindicated in following conditions:

- Known hypersensitivity to diclofenac or to paracetamol or to any component of the formulation.
- Active or history of recurrent peptic ulcer/hemorrhage.
- Severe heart failure, hepatic failure, and renal failure.
- History of gastrointestinal (GI) bleeding or perforation, relating to previous non-steroidal anti-inflammatory drug (NSAID) therapy.
- During the last trimester of pregnancy.
- Patients in whom attacks of asthma, urticaria, or acute rhinitis are precipitated by aspirin or other NSAIDs.
- Acute porphyria.

4.4Special Warnings and Precautions for Use

Diclofenac

Cardiovascular Thrombotic Events: Clinical trials of several cyclooxygenase 2 (COX-2) selective and nonselective NSAIDs of up to 3 years duration have shown an increased risk of serious cardiovascular (CV) thrombotic events, myocardial infarction, and stroke, which can be fatal. All NSAIDs, both COX-2 selective and nonselective, may have a similar risk. Patients with known CV disease or risk factors for CV disease may be at greater risk. To minimize the potential risk for an adverse CV event in patients treated with an NSAID, the lowest effective dose should be used for the shortest duration possible. Physicians and patients should remain alert for the development of such events, even in the absence of previous CV symptoms. Patients should be informed about the signs and/or symptoms of serious CV events and the steps to take if they occur.
Hypertension: NSAIDs can lead to onset of new hypertension or worsening of preexisting hypertension, either of which may contribute to the increased incidence of CV events. Patients taking thiazides or loop diuretics may have impaired response to these therapies when taking

NSAIDs. NSAIDs, including diclofenac sodium, should be used with caution in patients with hypertension. Blood pressure (BP) should be monitored closely during the initiation of NSAID treatment and throughout the course of therapy.

Congestive Heart Failure and Edema: Fluid retention and edema have been observed in some patients taking NSAIDs. Diclofenac sodium should be used with caution in patients with fluid retention or heart failure.

Gastrointestinal (GI) Effects - Risk of GI Ulceration, Bleeding, and Perforation: NSAIDs, including diclofenac sodium, can cause serious GI adverse events including inflammation, bleeding, ulceration, and perforation of the 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 irrespective of whether the therapy duration is long-/short-term.

NSAIDs should be prescribed with extreme caution in those with a prior history of ulcer disease or GI bleeding. Patients with a prior history of peptic ulcer disease and/or GI bleeding who use NSAIDs have a greater than 10-fold increased risk for developing a GI bleed compared to patients with neither of these risk factors. Other factors that increase the risk for GI bleeding in patients treated with NSAIDs include concomitant use of oral corticosteroids or anticoagulants, longer duration of NSAID therapy, smoking, alcohol, older age, and poor general health status. Most spontaneous reports of fatal GI events are in elderly or debilitated patients and therefore, special care should be taken in treating this population.

To minimize the potential risk for an adverse GI event in patients treated with an NSAID, the lowest effective dose should be used for the shortest possible duration. Patients and physicians should remain alert for signs and symptoms of GI ulceration and bleeding during NSAID therapy and promptly initiate additional evaluation and treatment if a serious GI adverse event is suspected. This should include discontinuation of the NSAID until a serious GI adverse event is ruled out. For high risk patients, alternate therapies that do not involve NSAIDs should be considered.

Renal Effects: Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injuries. 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, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors, 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 sodium in patients with advanced renal disease. Therefore, treatment with diclofenac sodium is not recommended in these patients with advanced renal disease. If diclofenac sodium therapy must be initiated, close monitoring of the patient's renal function is advisable.

Hepatic Effects: Elevations of one or more liver function tests may occur at any time during therapy with diclofenac sodium. These laboratory abnormalities may progress, may remain unchanged, or may be transient with continued therapy. Post-marketing 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.

Physicians should measure transaminases periodically in patients receiving long-term therapy with diclofenac, 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 post-marketing 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 sodium should be discontinued immediately. To minimize the possibility that hepatic injury will become severe between transaminase measurements, physicians should 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), and the appropriate action patients should take if these signs and symptoms appear. The lowest effective dose should be used for the shortest duration possible. Caution should be exercised in prescribing diclofenac sodium with concomitant drugs that are known to be potentially hepatotoxic (e.g., antibiotics, anti-epileptics).

Anaphylactic Reactions: As with other NSAIDs, anaphylactic reactions may occur both in patients with the aspirin triad and in patients without known sensitivity to NSAIDs or known prior exposure to diclofenac sodium. Diclofenac sodium should not be given to patients with the aspirin triad. This symptom complex typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking aspirin or other NSAIDs. Anaphylaxis-type reactions have been reported with NSAIDs, including diclofenac sodium. Emergency help should be sought in cases where an anaphylactic reaction occurs.

Skin Reactions: NSAIDs, including diclofenac sodium, can cause serious skin adverse events such as exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. These serious events may occur without warning. Patients should be informed about the signs and symptoms of serious skin manifestations and use of the drug should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.

Haematological Effects: Anemia is sometimes seen in patients receiving NSAIDs, including diclofenac sodium. This may be due to fluid retention, occult or gross GI blood loss, or direct effect on erythropoiesis by an unknown mechanism. Patients on long-term treatment with NSAIDs, including diclofenac sodium, should have their hemoglobin or hematocrit checked if they exhibit any signs or symptoms of anemia.

NSAIDs inhibit platelet aggregation and have been shown to prolong bleeding time in some patients. Unlike aspirin, their effect on platelet function is quantitatively less, of shorter duration, and reversible. Patients receiving diclofenac sodium 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: Caution is required if administered to patients suffering from, or with, a previous history of bronchial asthma since NSAIDs have been reported to precipitate bronchospasm in such patients. Patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin-sensitive asthma has been associated with severe bronchospasm which can be fatal. Since cross-reactivity, including bronchospasm, between aspirin and other NSAIDs has been reported in such aspirin-sensitive patients, diclofenac sodium should not be administered to patients with this form of aspirin sensitivity and should be used with caution in patients with preexisting asthma.

Hyperkalemia: Increase in serum potassium concentration (hyperkalemia) has 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.

General: Diclofenac sodium cannot be expected to substitute for corticosteroids or to treat corticosteroid insufficiency.

NOT FOR VETERINARY USE.

Paracetamol

Hepatotoxicity: Significant overdose of paracetamol can lead to hepatotoxicity in some patients. Thus, do not exceed the recommended dose. The hazards of overdose are greater in those with non-cirrhotic alcoholic liver disease.

Other Paracetamol-Containing Products: Do not take with any other paracetamol-containing products, so as to avoid the chances of overdose.

Renal and Hepatic Impairment: Care is advised in the administration of paracetamol to patients with severe renal or severe hepatic impairment.

Alcohol: Chronic heavy alcohol abusers may be at increased risk of liver toxicity from excessive paracetamol use, although rarely.

4.5Drug Interactions

Diclofenac

Drugs That Interfere with Hemostasis: Diclofenac and anticoagulants such as warfarin have a synergistic effect on bleeding. The concomitant use of diclofenac and anticoagulants has 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.

Monitor patients with concomitant use of diclofenac 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.

Aspirin: Controlled clinical studies showed that the concomitant use of NSAIDs and analgesic doses of aspirin does not produce 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. Concomitant use of diclofenac and analgesic doses of aspirin is not generally recommended because of the increased risk of bleeding.

NSAIDs and Salicylates: 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. Thus, concomitant use of diclofenac with other NSAIDs or salicylates is not recommended.

Methotrexate: Concomitant use of NSAIDs and methotrexate may increase the risk for methotrexate toxicity (e.g., neutropenia, thrombocytopenia, renal dysfunction). During concomitant use of diclofenac and methotrexate, monitor patients for methotrexate toxicity.

Cyclosporine: Concomitant use of diclofenac and cyclosporine may increase cyclosporine's nephrotoxicity. During concomitant use of diclofenac and cyclosporine, monitor patients for signs of worsening renal function.

Diuretics: Clinical studies, as well as post-marketing observations, have shown that diclofenac sodium can reduce the natriuretic effect of furosemide and thiazides in some patients. This response has been attributed to inhibition of renal prostaglandin synthesis. During concomitant therapy with NSAIDs, the patient should be observed closely for signs of renal failure, as well as to assure diuretic efficacy.

Lithium: NSAIDs have produced an elevation of plasma lithium levels and a reduction in renal lithium clearance. The mean minimum lithium concentration increased 15% and the renal clearance was decreased by approximately 20%. These effects have been attributed to inhibition of renal prostaglandin synthesis by the NSAID. Thus, when NSAIDs and lithium are administered concurrently, subjects should be observed carefully for signs of lithium toxicity.

Digoxin: The concomitant use of diclofenac with digoxin has been reported to increase the serum concentration and prolong the half-life of digoxin. Monitoring of serum digoxin level is recommended when diclofenac and digoxin are administered concomitantly.

Antihypertensive Drugs (ACE-Inhibitors, Angiotensin Receptor Blockers, and Beta-Blockers): NSAIDs may diminish the antihypertensive effect of angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), or beta-blockers (including propranolol). During concomitant use of diclofenac and ACE-inhibitors, ARBs, or beta-blockers, monitor blood pressure to ensure that the desired blood pressure is obtained. When these drugs are administered concomitantly in patients who are elderly, volume-depleted, or have impaired renal function, monitoring of signs for worsening of renal function is recommended. Also, patients should be adequately hydrated and assess renal function at the beginning of the concomitant treatment and periodically thereafter.

Pemetrexed: Concomitant use of diclofenac and pemetrexed may increase the risk of pemetrexed-associated myelosuppression, renal, and GI toxicity.

Tacrolimus: There is a possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus. This might be mediated through renal antiprostagladin effects of both NSAID and calcineurin inhibitor.

Quinolone Antimicrobials: Convulsions may occur due to an interaction between quinolones and NSAIDs. This may occur in patients with or without a previous history of epilepsy or convulsions. Therefore, caution should be exercised when considering the use of a quinolone in patients who are already receiving an NSAID.

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

Colestipol and Cholestyramine: These drugs can induce a delay or decrease in absorption of diclofenac. Therefore, it is recommended to administer diclofenac at least one hour before or 4 to 6 hours after administration of colestipol/ cholestyramine.

Cardiac Glycosides: Concomitant use of cardiac glycosides and NSAIDs in patients may exacerbate cardiac failure, reduce GFR, and increase plasma glycoside levels.

Potassium-Sparing Diuretics, Cyclosporine, Tacrolimus, or Trimethoprim: Concomitant treatment of diclofenac with either of these drugs may be associated with increased serum potassium levels (hyperkalemia), which should therefore be monitored frequently.

CYP2C9 Inhibitors or Inducers: 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 coadministration with CYP2C9 inducers (e.g., rifampin) may lead to compromised efficacy of diclofenac. A dosage adjustment may be warranted when diclofenac is administered with CYP2C9 inhibitors or inducers.

Paracetamol

Cholestyramine: The speed of absorption of paracetamol is reduced by cholestyramine. Therefore, cholestyramine should not be taken within one hour, if maximal analgesia is required.

Metoclopramide and Domperidone: The absorption of paracetamol is increased by metoclopramide and domperidone. However, concurrent use need not be avoided.

Warfarin: The anti-coagulant effect of warfarin and other coumarins may be enhanced by prolonged regular use of paracetamol with increased risk of bleeding; occasional doses have no significant effect.

Chloramphenicol: Concomitant administration of paracetamol and chloramphenicol results in increased plasma concentration of chloramphenicol.

Alcohol, Anticonvulsants, or Isoniazid: Concomitant administration of alcohol, anticonvulsants, or isoniazid with paracetamol may increase risk of hepatotoxicity.

4.6Use in Special Populations

Pregnant Women

Diclofenac: Pregnancy Category C; Paracetamol: Pregnancy Category B. For this combination product, there are no adequate or well controlled studies available in pregnant women. Epidemiological studies in human pregnancy have shown no ill effects due to paracetamol used in the recommended dosage. Use of NSAIDs, including diclofenac, during the third trimester of pregnancy increases the risk of premature closure of the fetal ductus arteriosus. Data from observational studies regarding potential embryofetal risks of NSAID use in women in the first or second trimesters of pregnancy are inconclusive. However, congenital abnormalities have been reported with use of NSAIDs in humans. DICLOTAL-FORTE Tablets should not be used during the first two trimesters of pregnancy unless the potential benefit to the patient outweighs the potential risk to fetus. DICLOTAL-FORTE Tablets are contraindicated in the third trimester (> 30 weeks of gestation) of pregnancy.

There are no studies on the effects of diclofenac during labor or delivery. In animal studies, NSAIDs, including diclofenac, inhibit prostaglandin synthesis, causes delayed parturition, and increase the incidence of stillbirth. Thus, DICLOTAL-FORTE Tablets are not recommended for use in labor or delivery pain.

Lactating Women

In limited studies so far available, NSAIDs can appear in breast milk in very low concentrations. Paracetamol is excreted in breast milk, but not in a clinically significant amount. Because of the potential for serious adverse reactions in nursing infants with diclofenac, 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.

Paediatric Patients

Safety and effectiveness in paediatric patients have not been established. DICLOTAL-FORTE Tablets are not intended for use in children.

Geriatric Patients

Elderly patients with normal renal and hepatic function may be given the same dose as recommended for adults. 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.

Both, diclofenac and paracetamol are substantially excreted by the kidney, and the risk of toxic reactions to these drugs 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.

Renal Impairment Patients

DICLOTAL-FORTE Tablets are contraindicated in patients with severe renal impairment or in patients with preexisting renal disease. Caution is advised while administering this product in patients with mild to moderate renal impairment.

Hepatic Impairment Patients
DICLOTAL-FORTE Tablets are contraindicated in patients with severe hepatic impairment.

4.7Effect on Ability to Drive and Use Machines

Undesirable effects such as dizziness, drowsiness, fatigue, and visual disturbances are possible after taking NSAIDs, including diclofenac. If affected, patients should not drive or operate machinery.

4.8Undesirable Effects

Diclofenac

The most frequently reported adverse experiences occurring in approximately 1 to 10% of patients are gastrointestinal experiences such as abdominal pain, constipation, diarrhea, dyspepsia, flatulence, gross bleeding/perforation, heartburn, nausea, GI ulcers (gastric/duodenal), and vomiting. Other less frequently reported adverse effects (non-gastrointestinal origin) are abnormal renal function, anemia, dizziness, edema, elevated liver enzymes, headaches, increased bleeding time, pruritus, rashes, and tinnitus.
Additional adverse experiences reported occasionally/rarely include:
Body as a Whole: Fever, infection, sepsis, anaphylactic reactions, appetite changes.
Cardiovascular System: Congestive heart failure, hypertension, tachycardia, syncope, arrhythmia, hypotension, myocardial infarction, palpitations, vasculitis.
Digestive System: Dry mouth, esophagitis, gastric/peptic ulcers, gastritis, gastrointestinal bleeding, glossitis, hematemesis, hepatitis, jaundice, colitis, eructation, fulminant hepatitis with and without jaundice, liver failure, liver necrosis, pancreatitis.
Urogenital System: Cystitis, dysuria, hematuria, interstitial nephritis, oliguria/polyuria, proteinuria, renal failure.
Haematologic and Lymphatic System: Ecchymosis, eosinophilia, leukopenia, melena, purpura, rectal bleeding, stomatitis, thrombocytopenia, agranulocytosis, hemolytic anemia, aplastic anemia, lymphadenopathy, pancytopenia.
Metabolic and Nutritional: Weight changes, hyperglycemia.
Nervous System: Anxiety, asthenia, confusion, depression, dream abnormalities, drowsiness, insomnia, malaise, nervousness, paresthesia, somnolence, tremors, vertigo, convulsions, coma, hallucinations, and meningitis.
Respiratory System: Asthma, dyspnea, respiratory depression, pneumonia.
Skin and Appendages: Alopecia, photosensitivity, increased sweating, angioedema, toxic epidermal necrolysis, erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome, urticaria.

Special Senses: Blurred vision, conjunctivitis, hearing impairment.

Paracetamol

Adverse effects of paracetamol are rare. However, hypersensitivity including skin rash and fixed drug eruption (FDE) may occur. There have been reports of blood dyscrasias including thrombocytopenic purpura, methaemoglobenemia and agranulocytosis, but these were not necessarily related to paracetamol. Overdosage with paracetamol can result in severe hepatotoxicity and sometimes acute renal tubular necrosis. If there is a pre-existing liver insufficiency, paracetamol can be hepatotoxic even in normal dosage. Increased levels of aspartate aminotransferase and hepatic transaminases may occur. Nausea, vomiting, abdominal pain, diarrhea, constipation, dyspepsia, dry mouth, heartburn have also been reported commonly with the use of paracetamol.

4.9Overdose

Diclofenac

Symptoms: Symptoms following acute NSAID overdose are usually limited to lethargy, drowsiness, nausea, vomiting, and epigastric pain, which are generally reversible with supportive care. Gastrointestinal bleeding can occur. Hypertension, acute renal failure, respiratory depression and coma may occur, but are rare. Anaphylactoid reactions have been reported with therapeutic ingestion of NSAIDs, and may occur following an overdose.

Treatment: Following an NSAID overdose, patients should be managed by symptomatic and supportive care. There are no specific antidotes. Emesis and/or activated charcoal (60 to 100 g in adults, 1 to 2 g/kg in children) 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, alkalinization of urine, hemodialysis, or hemoperfusion may not be useful due to high protein binding.

Paracetamol

Symptoms: Ingestion of 5 gram or more of paracetamol may lead to liver damage. Symptoms of paracetamol overdose in the first 24 hours are pallor, nausea, vomiting, anorexia, and abdominal pain. Liver damage may become apparent 12 to 48 hours after ingestion. Abnormalities of glucose metabolism and metabolic acidosis may occur. In severe poisoning, hepatic failure may progress to encephalopathy, hemorrhage, hypoglycemia, cerebral edema, and death. Acute renal failure with acute tubular necrosis, manifesting as loin pain, hematuria and proteinuria, may develop even in the absence of severe liver damage. Cardiac arrhythmias and pancreatitis have been reported.

Management: Immediate treatment is essential in the management of paracetamol overdose. Treatment with activated charcoal should be considered if the overdose has been taken within 1 hour. Plasma paracetamol concentration should be measured at 4 hours or later after ingestion (earlier concentrations are unreliable). Treatment with N-acetylcysteine (FDA approved antidote)

may be used up to 24 hours after ingestion of paracetamol. However, the maximum protective effect is obtained up to 8 hours post-ingestion.

5. Pharmacological Properties

5.1 Mechanism of Action

Diclofenac

Like all other NSAIDs, the mechanism of action of diclofenac is related to inhibition of prostaglandin biosynthesis by inhibition of the cyclooxygenase (COX) enzyme. Diclofenac sodium is a non-selective, reversible, and competitive inhibitor of COX, subsequently blocking the conversion of arachidonic acid into prostaglandin (PG) precursors. This leads to an inhibition of the formation of prostaglandins that are involved in pain, inflammation and fever.

Paracetamol

Analgesic Effect: Paracetamol may act predominantly by inhibiting prostaglandin synthesis in the central nervous system (CNS) and to a lesser extent, through a peripheral action by blocking pain-impulse generation. The peripheral action may also be due to inhibition of prostaglandin synthesis or inhibition of the synthesis or actions of other substances that sensitise pain receptors to mechanical or chemical stimulation.

Antipyretic Effect: Paracetamol produces antipyretic effect by acting centrally on the hypothalamic heat-regulation center to produce peripheral vasodilation resulting in increased blood flow through the skin, sweating and heat loss. The central action involves inhibition of prostaglandin synthesis in the hypothalamus.

5.2Pharmacodynamic Properties

Diclofenac

Diclofenac is a non-steroidal anti-inflammatory drug which exhibits anti-inflammatory, analgesic, and antipyretic effects.

Paracetamol

Paracetamol is a centrally acting analgesic and antipyretic agent.

5.3Pharmacokinetic Properties

Diclofenac

Diclofenac sodium is rapidly absorbed from the gut and is subject to first-pass metabolism. Tablets give peak plasma concentrations after 1 to 4 hours. The active substance is 99.7% protein bound and plasma half-life for the terminal elimination phase is 1 to 2 hours.

Diclofenac sodium enters the synovial fluid, where maximum concentrations are measured 2 to 4 hours after the peak plasma values have been obtained. The apparent half-life for elimination from the synovial fluid is 3 to 6 hours. Two hours after reaching the peak plasma values, concentrations

of the active substance are already higher in the synovial fluid than they are in the plasma, and they remain higher for up to 12 hours.
Approximately 60% of the administered dose is excreted via the kidneys in the form of metabolites and less than 1% in unchanged form. The remainder of the dose is excreted via the bile in metabolized form. In patients with impaired renal function no accumulation of diclofenac sodium has been reported.

Paracetamol

Paracetamol is readily absorbed from the GI tract with peak plasma concentrations occurring about 30 minutes to 2 hours after ingestion. Paracetamol is metabolized in the liver and excreted in the urine mainly as the glucuronide and sulphate conjugates. Less than 5% is excreted as unchanged paracetamol. The elimination half-life varies from about 1 to 4 hours. Plasma-protein binding is negligible at usual therapeutic concentrations, but increases with increasing concentrations.

6. Nonclinical Properties

6.1 Animal Toxicology

Diclofenac

Carcinogenesis: Long-term carcinogenicity studies in rats given diclofenac sodium up to 2 mg/kg/day (approximately 0.1 times the maximum recommended human dose (MRHD) of diclofenac 200 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 0.007 times the MRHD based on BSA comparison) in males and 1 mg/kg/day (approximately 0.02 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 non-mutagenic in several mammalian *in vitro* and *in vivo* tests, including dominant lethal and male germinal epithelial chromosomal studies in mice, and nucleus anomaly and chromosomal aberration studies in Chinese hamsters.
Impairment of Fertility: Diclofenac sodium administered to male and female rats at 4 mg/kg/day (approximately 0.2 times the MRHD based on BSA comparison) did not affect fertility.
Teratogenicity: Reproductive and developmental studies in animals demonstrated that diclofenac sodium administration during organogenesis did not produce teratogenicity despite the induction of maternal toxicity and fetal toxicity in mice at oral doses up to 20 mg/kg/day (approximately 0.5 times the MRHD on BSA comparison), and in rats and rabbits at oral doses up to 10 mg/kg/day (approximately 0.5 and 1 times, respectively, the MRHD based on BSA comparison). In a study in which pregnant rats were orally administered 2 or 4 mg/kg diclofenac (0.1 and 0.2 times the MRHD based on BSA) 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.

Paracetamol

Preclinical data reveal no special hazard for humans with paracetamol based on conventional studies of single and repeated dose toxicity, genotoxicity and carcinogenicity. Studies for the evaluation of toxicity to reproduction and development are not available.

7. Description

DICLOTAL-FORTE Tablets are white, circular, biconvex, uncoated tablets plain on both sides.

Each tablet of DICLOTAL-FORTE contains 50 mg of diclofenac sodium and 325 mg of paracetamol for oral administration in adults.

Diclofenac Sodium

Diclofenac Sodium is the sodium salt form of diclofenac, a benzene acetic acid derivate and non-steroidal anti-inflammatory drug (NSAID) with analgesic, antipyretic and anti-inflammatory activity.

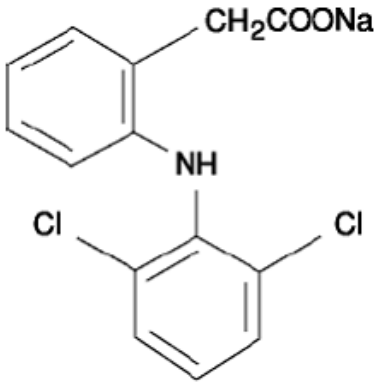
Diclofenac sodium is an odorless, white to off-white crystalline, and slightly hygroscopic powder.

Molecular Weight: 318.14 g/mol.

Chemical Name: 2-[(2,6-dichlorophenyl)amino] benzeneacetic acid, monosodium salt.

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

Structural Formula:



Paracetamol

Paracetamol, also called as acetaminophen, is a slightly bitter, white, odorless, crystalline powder.

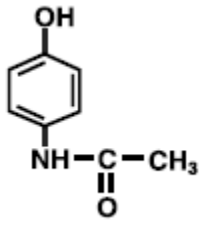
Paracetamol is a non-opiate, non-salicylate analgesic and antipyretic agent.

Molecular Weight: 151.16 g/mol.

Chemical Name: 4'-hydroxyacetanilide.

Molecular Formula: $C_8H_9NO_2$.

Structural Formula:



Inactive ingredients (excipients) of DICLOTAL-FORTE Tablets contain Microcrystalline Cellulose, Colloidal Silicon Dioxide, Polyvinylpyrrolidone, K-30, Starch, Methylparaben, Paraben, Propyl Paraben, Propyl Glycol, Purified water, Magnesium Stearate, Sodium Starch Glycollate.

8. Pharmaceutical Particulars

8.1 Incompatibilities

None known.

8.2 Shelf-life

36 Months.

8.3Packaging Information

Strip of 10 tablets.

8.4Storage and Handling Instructions

Store protected from light and moisture at a temperature below 30°C.
Keep out of reach of children.

9. Patient Counseling Information

- NSAID medicines should be used exactly as prescribed, at the lowest dose possible, and for the shortest time needed.
- NSAID medicines may increase the chance of a heart attack or stroke. This chance increases with longer use of NSAID medicines and in people who have heart disease.
- Do not take NSAID medicines for pain right before or after a heart bypass surgery.
- NSAID medicines can cause ulcers and bleeding in the stomach and intestines at any time during treatment. Ulcers and bleeding can happen without warning symptoms.
- Do not take an NSAID medicine if you had an asthma attack, urticaria/itching, or other allergic reaction with aspirin or any other NSAID medicine.

- Not to use with any other drug containing paracetamol (prescription or over-the- counter - OTC). Users to ask a doctor or pharmacist, if they are not sure about presence of paracetamol in the drug taken for other illnesses.
- Pregnant women should avoid use of NSAID medicines especially in the last 3 months of pregnancy. Breastfeeding mothers are advised to consult their doctor before use of this medicine.

10. Details of Manufacturer

Blue Cross Laboratories Pvt Ltd.
A-12, MIDC Ambad, Nashik - 422 010.

11. Details of Permission or License Number with Date

Mfg. Lic. No.: BD/25.
Date of FDA Product Permission: 28/03/2002.

12. Date of Revision

February 2023.

MADE IN INDIA BY
BLUE CROSS LABORATORIES PVT LTD.
A-12, M.I.D.C., NASHIK-422 010.
Regd. Off.: Peninsula Chambers, G. K. Marg, Mumbai-400 013.