Front

DICLOMAC®

(Diclofenac Sodium)

Tablet

ڈیکلومیک

COMPOSITION:

DICLOMAC TABLET 50 mg:

Each enteric coated tablet contains:

Diclofenac Sodium BP ..... 50 mg.

Product Specs.: BP

Cardiovascular Risk:

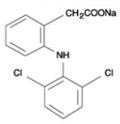
- NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk.
- Diclofenac Sodium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

Gastrointestinal Risk:

- NSAIDs cause an increased risk of serious gastrointestinal 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 are at greater risk for serious gastrointestinal events.

DESCRIPTION:

DICLOMAC (diclofenac sodium enteric-coated tablets), is a benzene-acetic acid derivative. **DICLOMAC** is available as (enteric-coated) tablets of 50 mg for oral administration. The chemical name is 2-[(2,6-dichlorophenyl) amino] benzeneacetic acid, monosodium salt. The molecular weight is 318.14. Its molecular formula is $C_{14}H_{10}Cl_2NNaO_2$, and it has the following structural formula.



CLINICAL PHARMACOLOGY:

Pharmacodynamics:

DICLOMAC (Diclofenac sodium enteric-coated tablets), is a nonsteroidal anti-inflammatory drug (NSAID) that exhibits anti-inflammatory, analgesic, and antipyretic activities in animal models. The mechanism of action of **DICLOMAC**, like that of other NSAIDs, is not completely understood but may be related to prostaglandin synthetase inhibition.

Pharmacokinetics:

Absorption:

Diclofenac is 100% absorbed after oral administration as measured by urine recovery. However, due to first-pass metabolism, only about 50% of the absorbed dose is systemically available. Food has no significant effect on the extent of diclofenac absorption. However, there is usually a delay in the onset of absorption of 1 to 4.5 hours and a reduction in peak plasma levels of <20%.

Distribution: The apparent volume of distribution (V/F) of diclofenac sodium is 1.4 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 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.

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. 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. However, diclofenac metabolites undergo further glucuronidation and sulfation followed by biliary excretion. One diclofenac metabolite 4'-hydroxy- diclofenac has very weak pharmacologic activity.

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 2 hours.

Special Populations:

Pediatric: The pharmacokinetics of **DICLOMAC** has not been investigated in pediatric patients.

Race: Pharmacokinetics differences due to race have not been identified.

Hepatic insufficiency: **DICLOMAC** is contraindicated for patients with hepatic failure. Hepatic metabolism accounts for almost 100% of **DICLOMAC** elimination, so patients with hepatic disease may require reduced doses of **DICLOMAC** compared to patients with normal hepatic function.

Renal insufficiency: Diclofenac is contraindicated in patients with renal failure (GFR less than 15mL/min/1.73m^2).

INDICATIONS AND USAGE:

Carefully consider the potential benefits and risks of **DICLOMAC** and other treatment options before deciding to use Diclofenac Sodium. Adverse effects may be minimized by using lowest effective dose for shortest duration necessary to control symptoms.

DICLOMAC is indicated.

- For relief of signs and symptoms of osteoarthritis
- For relief of signs and symptoms of inflammatory and degenerative form of rheumatism, rheumatoid arthritis, ankylosing spondylitis, painful syndrome of vertebral column, non-articular rheumatism
- Acute attacks of gout
- Post traumatic and post-operative pain, inflammation and swelling eg dental or orthopedic surgery
- Painful or inflammatory conditions in gynecology eg primary dysmenorrhea or adnexitis
- As adjuvant therapy in severe painful inflammatory conditions of the ear, nose and throat e.g. pharyngotonsillitis, otitis in keeping with general therapeutic principles, the underlying disease should be treated with therapy as appropriate. Fever only is not an indication,

CONTRAINDICATIONS:

DICLOMAC (diclofenac sodium enteric-coated tablets), is contraindicated in patients with known hypersensitivity to diclofenac. **DICLOMAC** should not be given to patients who have experienced asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs. Severe, rarely fatal, anaphylactic-like reactions to NSAIDs have been reported in such patients. **DICLOMAC** is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery.

WARNINGS:

CARDIOVASCULAR EFFECTS:

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, 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, including Diclofenac sodium can lead to onset of new hypertension or worsening of pre-existing 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 **DICLOMAC**, 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 renal effects:

Fluid retention and edema have been observed in some patients taking NSAIDs. **DICLOMAC** should be used with caution in patients with fluid retention or heart failure.

Gastrointestinal effects - risk of ulceration, bleeding, and perforation:

NSAIDs, including **DICLOMAC**, can cause serious gastrointestinal (GI) adverse events including inflammation, bleeding, ulceration, and perforation of the stomach, small intestine, or large intestine, which can be fatal. 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 occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year. NSAIDs should be prescribed with extreme caution in those with a prior history of ulcer disease or gastrointestinal bleeding. Patients with a prior history of peptic ulcer disease and/or gastrointestinal 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, use of 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:

Caution should be used when initiating treatment with **DICLOMAC** in patients with considerable dehydration. Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury.

Advanced renal disease:

Treatment with **DICLOMAC** is not recommended in these patients with advanced renal disease. If **DICLOMAC** therapy must be initiated, close monitoring of the patient's renal function is advisable.

Anaphylactoid reactions:

As with other NSAIDs, anaphylactoid reactions may occur in patients without known prior exposure to **DICLOMAC**. **DICLOMAC** 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. Emergency help should be sought in cases where an anaphylactoid reaction occurs.

Skin reactions:

NSAIDs, including **DICLOMAC**, 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.

Pregnancy:

In late pregnancy, as with other NSAIDs, **DICLOMAC** should be avoided because it may cause premature closure of the ductus arteriosus.

PRECAUTIONS:

General:

DICLOMAC (Diclofenac sodium enteric-coated tablets), cannot be expected to substitute for corticosteroids or to treat corticosteroid insufficiency. Abrupt discontinuation of corticosteroids may lead to disease exacerbation. Patients on prolonged corticosteroid therapy should have their therapy tapered slowly if a decision is made to discontinue corticosteroids. The pharmacological activity of **DICLOMAC** in reducing fever and inflammation may diminish the utility of these diagnostic signs in detecting complications of presumed noninfectious, painful conditions.

Hepatic effects:

Borderline elevations of one or more liver tests may occur in up to 15% of patients taking NSAIDs including **DICLOMAC**. These laboratory abnormalities may progress, may remain unchanged, or may be transient with continuing therapy. Based on this experience, in patients on chronic treatment with **DICLOMAC**, periodic monitoring of transaminases is recommended. In addition, rare cases of severe hepatic reactions, including jaundice and fatal fulminant hepatitis, liver necrosis and hepatic failure, some of them with fatal outcomes have been reported.

Hematological effects:

Anemia is sometimes seen in patients receiving NSAIDs, including **DICLOMAC**. This may be due to fluid retention, occult or gross GI loss, or an incompletely described effect upon erythropoiesis. Patients on long-term treatment with NSAIDs, including **DICLOMAC**, 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 **DICLOMAC** 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:

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 nonsteroidal anti-inflammatory drugs has been reported in such aspirin-sensitive patients, **DICLOMAC** should not be administered to patients with this form of aspirin sensitivity and should be used with caution in patients with preexisting asthma.

Laboratory tests:

Because serious GI tract ulcerations and bleeding can occur without warning symptoms, physicians should monitor for signs or symptoms of GI bleeding. In patients on long-term treatment with NSAIDs, including **DICLOMAC**, the CBC and a chemistry profile (including transaminase levels) should be checked periodically. If clinical signs and symptoms consistent with liver or renal disease develop, systemic manifestations occur (e.g., eosinophilia, rash, etc.) or if abnormal liver tests persist or worsen, **DICLOMAC** should be discontinued.

DRUG INTERACTIONS:

Aspirin: When **DICLOMAC** is administered with aspirin, its protein binding is reduced. The clinical significance of this interaction is not known; however, as with other NSAIDs, concomitant administration of Diclofenac and aspirin is not generally recommended because of the potential of increased adverse effects.

Methotrexate: NSAIDs have been reported to competitively inhibit methotrexate accumulation in rabbit kidney slices. This may indicate that they could enhance the toxicity of methotrexate. Caution should be used when NSAIDs are administered concomitantly with methotrexate.

Cyclosporine: **DICLOMAC**, like other NSAIDs, may affect renal prostaglandins and increase the toxicity of certain drugs. Therefore, concomitant therapy with **DICLOMAC** may increase cyclosporine's nephrotoxicity. Caution should be used when **DICLOMAC** is administered concomitantly with cyclosporine.

ACE-inhibitors: Reports suggest that NSAIDs may diminish the antihypertensive effect of ACE inhibitors. This interaction should be given consideration in patients taking NSAIDs concomitantly with ACE inhibitors.

Diuretics: Clinical studies, as well as post-marketing observations, have shown that **DICLOMAC** 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.

Warfarin: The effects of warfarin and NSAIDs on GI bleeding are synergistic, such that users of both drugs together have a risk of serious GI bleeding higher than users of either drug alone.

Pregnancy.

Teratogenic effects:

Pregnancy Category C:

Reproductive studies conducted in rats and rabbits have not demonstrated evidence of developmental abnormalities. However, animal reproduction studies are not always predictive of human response. There are no adequate and well-controlled studies in pregnant women.

Nonteratogenic effects: Because of the known effects of nonsteroidal anti-inflammatory drugs on the fetal cardiovascular system (closure of ductus arteriosus), use during pregnancy (particularly late pregnancy) should be avoided.

Labor and delivery:

In rat studies with NSAIDs, as with other drugs known to inhibit prostaglandin synthesis, an increased incidence of dystocia, delayed parturition, and decreased pup survival occurred. The effects of DICLOMAC on labor and delivery in pregnant women are unknown.

Nursing mothers:

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from DICLOMAC, 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.

Geriatric use:

As with any NSAIDs, caution should be exercised in treating the elderly (65 years and older).

ADVERSE REACTIONS:

In patients taking DICLOMAC (diclofenac sodium enteric-coated tablets), or 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 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, 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

OVERDOSAGE:

Symptoms following acute NSAID overdoses 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. Patients should be managed by symptomatic and supportive care following a NSAID overdose. 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.

DOSAGE AND ADMINISTRATION:

Carefully consider the potential benefits and risks of **DICLOMAC** and other treatment options before deciding to use **DICLOMAC**. Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals.

General target population:

Adults:

The recommended initial daily dose is 100-150 mg in milder cases, as well as, for long term therapy, 75 to 100 mg is usually sufficient. The total daily dose should generally be divided into 2 to 3 separate doses. In primary dysmenorrhea, the daily dose should be individually adjusted and is generally 50 to 150 mg. A dose of 50 to 100 mg should be given initially and if necessary increased over the course of several menstrual cycles upto maximum of 200 mg/day. Treatment should be started on appearance of first symptom and depending on the symptology continued for a few days.

Special Population:

Pediatric patients (below 18 years of age):

Children aged 1 year and over and adolescents should be given 0.5 to 2 mg/kg/body weight 2-3 separate doses depending upon the severity of the disorder.

For the treatment of juvenile Rheumatoid Disorder, the daily dose can be raised upto a maximum of 3 mg/kg daily, separate doses. Maximum daily dose of 150 mg should not be exceeded.

Geriatric patients (aged 65 years or above):

No adjustment of starting dose is generally required for elderly patients, however caution is indicated on basic medical grounds, especially for frail elderly patients or those with low body weight.

Renal impairment:

Diclofenac is contraindicated in patients with renal failure (GFR less than 15mL/min/1.73m^2).

Hepatic impairment:

Caution is advised when administering Diclofenac to patients with mild to moderate hepatic impairment. However, it is contraindicated in patients with hepatic failure.

INSTRUCTIONS:

- Store below 30°C.
- Protect from heat, sunlight and moisture.
- Keep out of the reach of children.
- To be sold on the prescription of a registered medical practitioner only.

PRESENTATION:

DICLOMAC TABLET 50 mg : Pack of 2 x 10 tablets.

ہدایات:

۳۰ درجہ سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔
گرمی، دھوپ اور نمی سے بچائیں۔
بچوں کی پہنچ سے دور رکھیں۔
صرف ڈاکٹر کے نسخہ پر فروخت کریں۔

FOR FURTHER INFORMATION PLEASE CONTACT:

Manufactured by:
CCL Pharmaceuticals (Pvt.) Ltd.
62 Industrial Estate, Kot Lakhpat, Lahore, Pakistan.

3018
25015-0012-001-0000-0000

Back