INSTRUCTION
for medical use
DICLOTOL®

Composition:
*active substance:* aceclofenac;
1 tablet contains 100 mg of aceclofenac;
*excipients:* microcrystalline cellulose, croscarmellose sodium, anhydrous colloidal silicium dioxide, stearic acid, Opadry-YS-1-7027 white (hydroxypropyl methylcellulose, titanium dioxide (E 171), triacetin).

Pharmaceutical form. Film coated tablets.


Clinical characteristics.
Indications. Symptomatic treatment of pain syndrome and inflammation at osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, and other diseases of the musculoskeletal system accompanied by pain (namely, scapulohumeral periarthritis and extra-articular rheumatism).
As analgesic agent in states accompanied by pain (including back pain, toothache, and primary (functional) dysmenorrhea).

Contraindications.
- Hypersensitivity to aceclofenac or any drug excipients.
- Anamnesis information as for ability of acetylsalicylic acid and other non-steroidal anti-inflammatory drugs to cause asthmatic attacks, bronchospasms, acute rhinitis episodes, and allergic rashes; hypersensitivity to such drugs.
- Gastric or duodenal ulcer in acute phase or in anamnesis, or a suspected one, gastrointestinal bleeding, other existing bleedings or impaired coagulation.
- Severe heart failure or severe kidneys and liver functions disorders.

Administration and dosage.
Undesirable effects can be minimized by administering the drug during the shortest possible period necessary for symptoms control.
Diclotol® film coated tablets should be administered orally with at least ½ glass of liquid.
Diclotol® can be taken with food.

Adults
Maximum recommended dose is 200 mg per day split in two intakes of 100 mg (one tablet in the morning and one in the evening).

Elderly patients
Generally, dose adjustment is not required.

Liver failure
Patients with mild or moderate liver failure should have lower doses of aceclofenac. Recommended initial dose is 100 mg per day.

**Renal failure**
There is no information as for necessary adjustment of aceclofenac dose for patients with renal failure, yet, this group of patients should administer the drug carefully.

**Adverse reactions.**
The most common adverse reactions in clinical trials were gastrointestinal tract reactions (dyspepsia 7.5%, stomach pain 6.2%, nausea 1.5%, diarrhea 1.5%), in isolated cases dizziness had place. In addition, there are registered complaints of skin reaction, including itching and rash, along with liver enzymes figures abnormalities. Clinical trials and epidemiologic evidence prove that administration of some NSAIDs (especially, long-term intake of high doses) may result in increased risk of arterial thrombotic events (namely, myocardial infarct and insult).

<table>
<thead>
<tr>
<th>SOCMedDRa</th>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
<th>Very rare / occasionally</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemopoiesis and lymphatic system disorders</td>
<td>&gt;1/100, &lt;1/10</td>
<td>&gt;1/1000, &lt;1/100</td>
<td>Anemia</td>
<td>Granulocytopenia, thrombocytopenia, neutropenia, hemolytic anemia</td>
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<tr>
<td>Immune system disorders</td>
<td></td>
<td></td>
<td></td>
<td>Hyperpotassemia</td>
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<tr>
<td>Metabolic and nutritional disorders</td>
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<tr>
<td>Psychiatric disorders</td>
<td></td>
<td></td>
<td></td>
<td>Depression, unusual dreams, insomnia</td>
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<tr>
<td>Central nervous system disorders</td>
<td>Dizziness</td>
<td></td>
<td></td>
<td>Paresthesia, tremor, somnolence, headache, dysgeusia (taste impairments)</td>
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<tr>
<td>Vision disorders</td>
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<td>Vision impairments</td>
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<td>Ear and labyrinth disorders</td>
<td></td>
<td></td>
<td>Vertigo, tinnitus</td>
<td></td>
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<tr>
<td>Heart disorders</td>
<td></td>
<td></td>
<td>Arterial hypertension, complicated arterial hypertension, heart failure</td>
<td>Palpitation</td>
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<tr>
<td>Vascular disorders</td>
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<td>Hyperemia, flush, vasculitis</td>
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<tr>
<td>Respiratory system and mediastinal disorders</td>
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<td>Wheeze</td>
<td>Bronchospasm, stridor</td>
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<tr>
<td>Gastrointestinal tract disorders</td>
<td>Dyspepsia, stomach pain, nausea, diarrhea</td>
<td>Flatulence, gastritis, constipation, vomiting, oral cavity ulcers</td>
<td>Melena (including hemorrhagic diarrhea), ulcers in part of gastrointestinal tract, gastrointestinal bleedings</td>
<td>Stomatitis, bloody vomiting, gastric ulcer, pancreatitis</td>
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<tr>
<td>Hepatobiliary system disorders</td>
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<td>Hepatitis</td>
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<td>Skin disorders</td>
<td></td>
<td>Itching, exanthema, dermatitis, urticaria</td>
<td>Facial edema</td>
<td>Hemorrhagic rash, eczema, severe skin and mucous membranes reactions</td>
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<tr>
<td>Kidneys and urinary system disorders</td>
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<td>Nephrotic syndrome, renal failure</td>
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<tr>
<td>General disorders and local reactions</td>
<td></td>
<td></td>
<td></td>
<td>Edema, increased fatigability, foot muscles convulsions</td>
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<tr>
<td>Laboratory examinations results</td>
<td>Liver enzymes increasing</td>
<td>Increase of urea and creatinine blood levels</td>
<td>Alkaline phosphatase level increase, body weight increase</td>
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Reactions noticed at NSAIDs administration include (very rare (<1/10000)) kidneys and urinary system disorders – in particular, interstitial nephritis.

**Overdose.**

**Symptoms**
Symptoms include headache, nausea, vomiting, upper abdominal pain, gastrointestinal bleedings and irritation, in rare cases – diarrhea, disorientation, exaltation, coma, somnolence, vertigo, tinnitus, arterial hypotension, respiratory failure, unconsciousness, in isolated cases – convulsions. Severe toxication may cause acute renal failure and liver damage.

**Methods of treatment**
Patients should receive symptomatic treatment if necessary. Activated carbon intake is recommended within one hour after swallowing of potentially toxic drug quantity. Alternatively, adults should undergo gastric lavage within one hour after life-threatening overdose. Such specific therapeutical measures as dialysis or hemoperfusion will most probably be ineffective in NSAIDs elimination due to their high protein-binding ability and extensive metabolism. Sufficient diuresis ensuring is necessary. Meticulous monitoring of kidneys and liver functions is required. Patients should be observed at least for 4 hours after swallowing of potentially toxic drug quantity. In case frequent and continuous convulsions occur, patient should have intravenous diazepam introduction. Other methods are determined by physical condition of the patient. Generally, acute NSAIDs intoxication treatment includes maintenance and symptomatic therapy.
Administration during pregnancy or breastfeeding.

Pregnancy
There is no clinical data concerning aceclofenac administration in pregnant women. Prostaglandin synthesis inhibition may have negative effect on pregnancy and/or embryo / fetus development. Epidemiological studies provide evidence of increasing recurrent pregnancy loss risk, along with heart defects and gastroschisis development at prostaglandin synthesis inhibitors use in early pregnancy. Absolute risk of cardiovascular disorders increases from less than 1% to about 1.5%. Risk grows in proportion to dose increase and therapy duration. Prostaglandin synthesis inhibitors use in animals resulted in increased pre- and post-implantation losses and deaths of embryo. Besides, there was a rise in frequency of congenital disorders, including cardiovascular ones, in animals after prostaglandin synthesis inhibitors use in organogenetic period of pregnancy. Administration of Diclotol® in the I–II pregnancy trimesters is recommended only in case of evident necessity. Pregnancy planning women or pregnant women in the I–II trimesters should administer the lowest doses of Diclotol® and have the shortest possible therapy duration. Administration of any prostaglandin synthesis inhibitors in the III trimester may influence fetus in the following ways:
- cardiopulmonary toxicity (premature ductus arteriosus closure and pulmonary hypertension);
- renal functions worsening that can result in renal failure with oligohydramnios signs).
At the end of the pregnancy, pregnant woman and fetus can be affected in the following ways:
- possible bleeding time increasing, platelet aggregation decreasing, even with the lowest drug doses;
- uterine contractility inhibition leading to prolonged labor.
Diclotol® is contraindicated in the III trimester.

Breastfeeding period
Limited number of sources proves that NSAIDs are detected in breast milk at very low concentrations. It is recommended to consider avoiding NSAIDs administration while breastfeeding. Diclotol® should not be used during pregnancy and breastfeeding, unless benefits for mother exceed potential risks for fetus / baby.

Children.
Diclotol® is contraindicated in children.

Peculiarities of use.
Undesirable effects can be minimized by administering the lower effective doses of drug during the shortest possible period necessary for symptoms control (see below the risks of gastrointestinal and cardiovascular disorders). It is recommended to avoid concomitant use of Diclotol® and NSAIDs, including selective cyclooxygenase-2 inhibitors.

Elderly patients
NSAIDs administration in elderly patients is associated with high adverse reactions frequency, namely perforations and gastrointestinal bleedings having lethal outcome.

Respiratory disorders
Diclotol® should be carefully indicated in patients with existing bronchial asthma or that in anamnesis since NSAIDs precipitate bronchospasm.

Cardiovascular system, kidneys and liver disorders
NSAIDs administration can result in dose-dependent reduction of prostaglandin generation and renal failure. High risk of mentioned reaction is typical for patients with kidneys functions disorders, heart failure, liver dysfunction; diuretic administering patients or elderly patients. Mentioned groups should have kidneys functions monitoring.

Kidneys
Prostaglandin importance in renal blood circulation should be taken into account by patients with heart failure or kidneys functions disorders, taking diuretics or recovering after major surgery. Impact on kidneys is generally converse and state goes back to normal upon drug withdrawal.

**Liver**
In case liver function tests remain unsatisfactory or worsen, and liver disease clinical symptoms / signs or other manifestations (eosinophilia, rash) occur, administering of Diclotol® should be stopped. Patients with mild and moderate renal dysfunction require meticulous medical control. Hepatitis without prodromal symptoms may occur. In patients with hepatic porphyria Diclotol® may precipitate disease episodes.

**Cardiovascular and cerebrovascular effect**
Adequate monitoring and corresponding recommendations are necessary for patients with arterial hypertension and/or mild or moderate congestive heart failure in anamnesis since NSAIDs therapy is accompanied by fluid retention and edemas.

Number of sources suggest that some NSAIDs (especially, long-term intake of high doses) may cause slightly increased risk of arterial thrombotic events (namely, myocardial infarct and insult). There is no sufficient data to exclude mentioned risk at aceclofenac use.

Patients with uncontrolled arterial hypertension, congestive heart failure, ischemic heart disease, peripheral arterial diseases and/or cerebrovascular disease should take aceclofenac exceptionally after meticulous clinical analysis. Intensive analysis is also required prior to long-term therapy in patients with risk factors of cardiovascular diseases (namely, arterial hypertension, hyperlipidemia, diabetes mellitus, and smoking).

**Ulcer, perforation, and gastrointestinal bleedings**
Ulcer, perforation, and gastrointestinal bleedings having lethal outcome were associated with administration of all NSAIDs at any treatment stage with or without warning symptoms, including patients with severe gastrointestinal pathology in anamnesis.

Thorough medical examination is critical at suspected gastrointestinal ulcers in anamnesis, for patients with GIT disorders symptoms, ulcerative colitis and Crohn’s disease, hemorrhagic diathesis, or hematologic disorders.

Risk of ulcer, perforation, and gastrointestinal bleedings increases at high NSAIDs doses in patients with ulcer disease in anamnesis, mostly complicated by bleeding or perforation, and in elderly patients. Such patients should begin treatment with the lowest possible doses. Besides, mentioned patients require considering combined therapy with protective agents (namely, misoprostol and proton pump inhibitors), along with patients having necessity in concomitant low dose of acetylsalicylic acid or other drugs causing increase of gastrointestinal complications risk.

Patients with gastrointestinal toxic reactions in anamnesis, mostly elderly ones, should inform of any gastrointestinal symptoms (specifically, GIT bleedings), especially at therapy beginning. Particular attention should be paid to patients concomitantly using drugs causing ulcer and bleeding risks increase, for example peroral corticosteroids, warfarin coagulant, selective serotonin reuptake inhibitors, or acetylsalicylic acid as antiaggregant.

In case ulcer or gastrointestinal bleedings occur in aceclofenac administering patient, therapy should be stopped.

NSAIDs should be carefully prescribed in patients with gastrointestinal disorders in anamnesis (ulcerative colitis, Crohn’s disease) due to exacerbation risk.

**Systemic lupus erythematosus (SLE) and mixed connective tissue diseases**
Patinets with SLE and mixed connective tissues diseases may have increased risk of aseptic meningitis development.

**Dermatology**
Administration of NSAIDs is occasionally associated with severe skin reactions having lethal outcome, such as exfoliative dermatitis, Stevens–Johnson syndrome, and toxic epidermal necrolysis. Therapy should be stopped at first occurrence of skin rash, blennosis, and other hypersensitivity symptoms.
Fertility disorders in women
Diclotol® may suppress fertility in women. This drug is not recommended to pregnancy planning women. Women having trouble getting pregnant or passing sterility examination should stop Diclotol® administration.

Hypersensitivity reactions
Like in case of other NSAIDs administration, allergic reactions, including anaphylactic / anaphylactoid reactions, may occur in patients that do not have experience of using this drug.

Hematologic disorders
Diclotol® may have converse inhibition effect on platelet aggregation (see “Anticoagulating agents” in “Drug interactions and other types of interactions”).

Long-term treatment
All the patients administering NSAIDs should pass proactive examination for timely detection of renal failure, liver dysfunction (increased liver enzymes activity) and hematic picture changing.

Ability to influence reaction rate while driving cars or operating other mechanisms.
Patients should avoid driving cars and operating other mechanisms in case of vertigo, increased fatigability, and other central nervous system disorders occurrence upon NSAIDs administration.

Drug interactions and other types of interactions.

Other analgesic agents including selective cyclooxygenase-2 inhibitors. It is necessary to avoid concomitant use of two or more NSAIDs (including acetylsalicylic acid) since it can lead to increased adverse reactions risk.

Antihypertensive agents. Antihypertensive effect decrease.

Diuretics. Decrease of diuretic effect. Diuretics may increase nephrotoxicity risk at NSAIDs administration. Despite the absence of bendrofluazide effect on arterial blood pressure, interaction with other diuretics should not be excluded. At concomitant use with potassium-sparing diuretics, it is required to control serum potassium level.

Cardiac glycosides. NSAIDs may exacerbate heart failure, reduce glomerular filtration rate, and increase serum glycosides levels.

Lithium drugs. May cause decreased lithium elimination.

Methotrexate. Decreased methotrexate elimination. Special precautions should be taken in case the interval between NSAIDs and methotrexate administration is less than 24 hours since NSAIDs may contribute to serum methotrexate levels increasing, thus causing higher toxicity.

Cyclosporine. Nephrotoxicity risk is increased.

Mifepristone. NSAIDs should not be administered within 8–12 days upon mifepristone intake since mifepristone effect can be decreased.

Corticosteroids. Ulcer and gastrointestinal bleedings risk is increased.

Anticoagulating agents. NSAIDs may increase anticoagulant effect of warfarin. Patients with combined therapy of anticoagulants and Diclotol® should have meticulous control of their state.

Quinolone antibacterial drugs. Animal experiments tests show that NSAIDs may increase risk of convulsions caused by quinolone antibacterial drugs use. Patients administering NSAIDs and quinolones may have increased risk of convulsions development.

Antiplatelet drugs and selective serotonin reuptake inhibitors (SSRI). Increased risk of gastrointestinal bleedings.

Tacrolimus. Concomitant use of NSAIDs and tacrolimus may result in nephrotoxicity risk increase.

Zidovudine. When used concomitantly with NSAIDs may cause higher risk of hematological toxicity. There are proven facts of hemarthrosis and hematomas risks growth in AIDS patients with hemophilia at concomitant use of zidovudine and ibuprofen.

Antidiabetic drugs. It is discovered that diclofenac used concomitantly with oral antidiabetic drugs may influence their clinical efficacy. Yet, there are some reports of hypoglycemic and hyperglycemic effects. Thus, indication of Diclotol® requires adjustment of hypoglycemic agents dose.
Other NSAIDs. Concomitant use with acetylsalicylic acid or other NSAIDs may result in higher frequency of undesirable adverse reactions, including gastrointestinal bleedings risk increase.

**Pharmacological properties.**

**Pharmacodynamics.** Aceclofenac is non-steroid drug causing anti-inflammatory and analgesic effects. Mechanism of action is associated with prostaglandin synthesis inhibition.

**Pharmacokinetics.** 

**Absorption.** Upon oral intake, aceclofenac is rapidly absorbed, its biological availability equals almost 100%. Maximum serum concentration is reached in about 1,25–3 hours after intake. Maximum concentration time ($T_{\text{max}}$) is reduced at concomitant use with food, while it does not influence absorption rate.

**Distribution.** Aceclofenac is significantly bound to serum proteins (>99,7%). Aceclofenac penetrates into synovial fluid where its concentration corresponds to about 60% of serum concentration. Volume of distribution is close to 30 liters.

**Elimination.** Mean elimination half-life is 4–4,3 hours. Clearance is 5 liters per hour. About two-thirds of the administered dose are eliminated via urine, mostly as conjugated hydroxymetabolites. Only 1% of single dose is eliminated unchanged. Aceclofenac is probably metabolized by CYP2C9 into basic metabolite 4-OH-aceclofenac with insignificant clinical effect. Diclofenac and 4-OH-diclofenac were detected among many other metabolites.

**Special groups of patients.** Elderly patients did not have changes in aceclofenac pharmacokinetics. Patients with decreased liver function noticed slower aceclofenac elimination upon single dose intake. Number of clinical trials with multiple daily intakes of 100 mg showed no difference in pharmacokinetic characteristics between patients with mild and moderate cirrhosis and healthy volunteers. Likewise, patients with mild and moderate renal failure did not have any clinically significant differences in pharmacokinetics upon single dose intake.

**Pharmaceutical characteristics.**

**General physical-chemical properties:** round biconvex white film coated tablets.

**Shelf life.**

2 years.

**Storage.**

Store at the temperature not more than 25°C in dry place. Protect from direct sunlight. Keep out of reach of children.

**Package.**

10 tablets in blister, 3 or 10 blisters in carton pack № 30 (10 × 3) or № 100 (10 × 10).
14 tablets in blister, 2 blisters in carton pack № 28 (14 × 2).

**Conditions of supply.**

By prescription.

**Manufacturer.**

KUSUM HEALTHCARE PVT LTD

**Address.**

SP-289 (A), RIICO Industrial area, Chopanki, Bhiwadi, Dist. Alwar (Rajasthan), India.

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