PARDIFEN

Instructions for the medicinal product

Trade name: Pardifen.
International Nonproprietary Name: Paracetamol BP, Diclofenac Sodium BP.
Dosage form: Tablet.
Composition: Each uncoated tablet contains:
Paracetamol BP 500 mg
Diclofenac Sodium BP 50 mg
Pharmacological group: Non-steroidal, anti-inflammatory and anti-rheumatic drugs.
ATC Code: M01AB55
Pharmacologic property:
Pharmacodynamics:
Pardifen is a combined drug with a pronounced anti-inflammatory, analgesic and antipyretic effect. Pharmacological activity of the drug is due to the properties of diclofenac and paracetamol, which are the components of the drug.
Diclofenac sodium has a pronounced anti-inflammatory and analgesic, and a moderate antipyretic effect. Paracetamol has a pronounced analgesic, slight antipyretic and anti-inflammatory effect. The mechanism of action is associated with inhibition of prostaglandin synthesis.
Pharmacokinetics:
After the intake, the drug is rapidly and completely absorbed. Food has no effect on absorption of the drug.
Plasma concentrations of active substances are linearly dependent on the dose; the maximum levels are reached in 60-90 minutes after ingestion.
Binding of diclofenac to plasma proteins (mainly albumin) reaches 99.7%. The expected volume of distribution is 0.12-0.17 L/kg. Diclofenac penetrates into synovial liquid, where its maximum concentration is reached 2-4 hours later than in blood plasma. The half-life for elimination from the synovial fluid is 3-6 hours.
Diclofenac is metabolized by glucuronidation of unchanged molecule and methoxylation, which forms several phenolic metabolites, the biological activity of which is considerably inferior to the activity of the parent substance.
General plasmatic clearance of diclofenac is approximately 300 mL/min. Terminal half-life is 1-2 hours. 60% of the administered dose is excreted in the urine as glucuronic conjugates of unchanged diclofenac; the rest is excreted in the bile and feces.
Paracetamol is metabolized in the liver and is mainly excreted in the urine. After repeated administration of the drug, pharmacokinetic parameters of active substances remain unchanged. No accumulation occurs provided the recommended dosage intervals are observed.
Indications for use:
For the treatment of: Acute Pain (Muscle Pain, Headache, Toothache, Pain Localized in the Spine), Nonarticular Rheumatism, Rheumatoid Arthritis, Ankylosing Spondylitis, Osteoarthrosis, Spondylarthritis, Acute Attacks of Gout, Primary Dysmenorrhea, Adnexitis, Pharyngotonsillitis,
Otitis, Post-Traumatic, Postsurgical Pain Syndrome, Influenza, Feverishness and Feverish colds.
Contraindications:
- Hypersensitivity to Paracetamol, diclofenac, acetylsalicylic acid, other NSAIDs, misoprostol, other prostaglandins, or any other ingredient of the product.
- Active peptic ulcer or gastrointestinal bleeding or perforation,
- Severe hepatic failure (Child-Pugh grade C, cirrhosis or ascites).
- Severe kidney failure (creatinine clearance < 30 mL/min).
- Severe cardiac failure (CH III-IV).
- Patients who respond to diclofenac, paracetamol, aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs) with bronchial asthma ("aspirin asthma"), urticaria or acute rhinitis, nasal polyps, and other allergic symptoms.
- Violation of hematopoiesis of unknown origin.
- Leukopenia.
- Moderate and severe anemia.
- Congenital hyperbilirubinemia.
- Glucose-6-phosphate dehydrogenase deficiency.
- Acute porphyria.
- Alcoholism.
- Asthma, urticaria or acute rhinitis
- Patients who have history of gastrointestinal bleeding or perforation, related to the use of nonsteroidal anti-inflammatory drugs.
- Inflammatory bowel disease (Crohn's disease or ulcerative colitis).
- Established congestive heart failure (NYHA II-IV), ischemic heart disease, peripheral arterial disease and/or cerebrovascular disease.
- Pregnant women and in women planning a pregnancy.
- Treatment of peri-operative pain in the setting of coronary bypass graft (CABG) surgery.
- Children under the age of 14 years.

Pregnancy and Nursing Mother:
The drug is contraindicated during pregnancy or breast-feeding.
Dosage and direction for use:
Oral use only.
The dose is determined by physician individually for each patient, depending on the patient's age, nature and course of the disease, individual tolerance and therapeutic efficacy of the drug.
Adults and children older than 14:
1 tablet 2-3 times per day after meal.
The duration of treatment is not more than 5-7 days, and does not depend on the course of disease.
The maximum daily dose for adults and children older than 14 in not more than 3 tablets.
Side-effects:
Blood and lymphatic system: thrombocytopenia, neutropenia, leukopenia, anemia, including aplastic anemia, hemolytic anemia (especially for patients with glucose-6-phosphate dehydrogenase deficiency), sulfhemoglobinemia and methemoglobinemia (cyanosis, shortness of breath, pain in the heart), agranulocytosis, pancytopenia.
Immune system: hypersensitivity reactions, anaphylactic/anaphylactoid reactions, including hypotension and anaphylactic shock, angioedema (including facial edema).
Mental disorders: disorientation, depression, sleep disturbance, insomnia, nightmares, irritability, restlessness, apprehension, psychotic disorders, confusion, psychomotor agitation.
Nervous system: headache, dizziness, somnolence, paresthesia, sleep disturbance, insomnia, memory impairment, convulsions, anxiety, tremor, aseptic meningitis, dysgeusia, cerebrovascular disease.
Visual organs: visual impairment, blurred vision, diplopia.
Organs of hearing: vertigo, tingling, tinnitus, dysacousia.
Cardiovascular system: palpitation, tachycardia, shortness of breath, pain in the heart, cardiac failure, myocardial infarction, arterial hypertension, vasculitis.
Respiratory system: bronchial asthma (including shortness of breath), bronchospasm (especially in patients sensitive to acetylsalicylic acid), pain in the chest, pneumonitis.
Digestive tract: nausea, vomiting, diarrhea, dyspepsia, abdominal pain, meteorism; gastritis, gastrointestinal bleeding, vomiting with blood, hemorrhagic diarrhea, melena, stomach or intestinal ulcer (with/without bleeding or perforation), colitis (including hemorrhagic colitis and exacerbation of ulcerative colitis or Crohn's disease), constipation, stomatitis, glossitis, disorders of the esophagus, diaphragm-like intestinal strictures, pancreatitis.
Hepatobiliary system: elevated transaminases; hepatic failure, hepatitis, hepatic necrosis, jaundice, hepatic disorders, fulminant hepatitis.
Skin and subcutaneous structures: itching sensation, skin rash, erythema, rash on the mucous membranes, urticaria, bullous rash, eczema, exudative erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome), exfoliative dermatitis, allergic dermatitis, hair loss, photosensitivity reaction, purpura, allergic purpura, pruritus.
Urinary system: acute renal failure, hematuria, proteinuria, nephrotic syndrome, interstitial nephritis, renal papillary necrosis, fluid retention.
General disorders: edema, asthenia, hyperhidrosis, hypoglycemia, even coma.
Diclofenac, especially in high doses (150 mg/day) and in long-term use may increase the risk of arterial thrombembolia (such as myocardial infarction or stroke).
Overdose:
Diclofenac Sodium:
There is no typical clinical presentation characteristic of diclofenac overdose. Overdose may cause vomiting, gastrointestinal bleeding, diarrhea, vertigo, tinnitus and convulsions. Acute renal failure and hepatic damage are possible in case of severe intoxication.
Paracetamol:
Hepatic damage may occur in adults who have taken 10 g paracetamol and more, and in children who have taken more than 150 mg/kg of body weight. In patients with risk factors (long-term use of carbamazepine, phenobarbital, phenytoin, primidone, rifampicin, Hypericum perforatum or other drugs that induce hepatic enzymes, alcohol abuse, insufficiency of glutathione system, e.g. malnutrition, AIDS, starvation, cystic fibrosis, cachexia) intake of paracetamol 5 g or more may bring on hepatic damage.
Symptoms of overdose during the first 24 hours: pallor, nausea, vomiting, anorexia and abdominal pain. Hepatic damage may become apparent within 12-48 hours after the overdose. Impaired glucose metabolism and metabolic acidosis may occur. In severe intoxication, hepatic failure may progress to encephalopathy, hemorrhage, hypoglycemia, coma and result in death. Acute renal failure with acute tubular necrosis may be manifested by back pain, hematuria, and occur even without severe hepatic damage. Cardiac arrhythmia and pancreatitis have also been marked.
In case of prolonged use of large doses, hematopoietic system disorders may occur: aplastic anemia, pancytopenia, agranulocytosis, neutropenia, leukopenia, thrombocytopenia. Large doses may bring on nervous system disorders, such as dizziness, psychomotor agitation, and disorientation, urinary system disorders: nephrotoxicity (renal colic, interstitial nephritis, papillary necrosis), digestive system disorders: hepatonecrosis.
Treatment: urgent measures of supportive and symptomatic therapy.
If the excessive dose has been taken within 1 hour, advisability of use of the activated carbon should be considered. Plasma concentration of paracetamol should be measured 4 hours after the intake or later (earlier concentrations are unreliable). Treatment with N-acetylcysteine may be applied within 24 hours since the drug intake, but maximum protective effect is achieved when using it within 8 hours since the intake. The efficacy of antidote is sharply reduced after this time. If necessary, the patient is given N-acetylcysteine according to the established list of doses. If vomiting is absent, methionine may be used orally as an appropriate alternative in remote areas outside hospital.
Supportive and symptomatic treatment is indicated in case of such complications as arterial hypotension, renal failure, convulsions, gastrointestinal tract disorders and respiratory depression. It is unlikely that forced diuresis, hemodialysis, or hemoperfusion are effective for elimination of nonsteroidal anti-inflammatory drugs (NSAIDs), as the active ingredients of the drug are largely bound to plasma proteins and subjected to intensive metabolism.
Drug interaction:
Paracetamol:
Cholestyramine: The speed of absorption of paracetamol is reduced by cholestyramine. Therefore, the 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 anticoagulant 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: Increased plasma concentration of chloramphenicol.
Diclofenac Sodium:
Lithium: If used concomitantly, diclofenac may raise plasma concentrations of lithium. Monitoring of the serum lithium level is recommended.
Digoxin: If used concomitantly, diclofenac may raise plasma concentrations of digoxin. Monitoring of the serum digoxin level is recommended.
Diuretics and Anti-hypertensive agents: Like other NSAIDs, concomitant use of diclofenac with diuretics or antihypertensive agents (e.g. beta-blockers, angiotensin converting enzyme (ACE) inhibitors) may cause a decrease in their antihypertensive effect via inhibition of vasodilatory prostaglandin synthesis. Therefore, the combination should be administered with caution and patients, especially the elderly, should have their blood pressure periodically monitored. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy and periodically thereafter, particularly for diuretics and ACE inhibitors due to the increased risk of nephrotoxicity.
Drugs known to cause hyperkalemia: Concomitant treatment with potassium-sparing drugs may be associated with increased serum potassium levels, which should therefore be monitored frequently.
Other NSAIDS including cyclo-oxygenase-2selective inhibitors and corticosteroids: Concomitant administration of diclofenac and other systemic NSAIDs or corticosteroids may increase the risk of gastrointestinal bleeding or ulceration. Avoid concomitant use of two or more NSAIDs.
Anticoagulants and anti-platelet agents: Caution is recommended since concomitant administration could increase the risk of bleeding.
Although clinical investigations do not appear to indicate that diclofenac affects the action of anticoagulants, there are reports of an increased risk of haemorrhage in patients receiving diclofenac and anticoagulants concomitantly. Close monitoring of such patients is therefore recommended. As with other NSAIDs, diclofenac in high dose can reversibly inhibit platelet aggregation.
Selective serotonin reuptake inhibitors (SSRIs): Concomitant administration of systemic NSAIDs, including diclofenac, and SSRIs may increase the risk of gastrointestinal bleeding.
Antidiabetics:Clinical studies have shown that diclofenac can be given together with oral antidiabetic agents without influencing their clinical effect. However, there have been isolated reports of both hypoglycaemic and hyperglycaemic effects necessitating changes in the dosage of the antidiabetic agents during treatment with diclofenac. For this reason, monitoring of the blood glucose level is recommended as a precautionary measure during concomitant therapy.
Methotrexate: Diclofenac can inhibit the tubular renal clearance of methotrexate hereby increasing methotrexate levels. Caution is recommended when NSAIDs, including diclofenac, are administered less than 24 hours before or after treatment with methotrexate, since blood concentrations of methotrexate may rise and the toxicity of this substance be increased.
Ciclosporin: Diclofenac, like other NSAIDs, may increase the risk of nephrotoxicity of ciclosporin due to the effect on renal prostaglandins. Therefore, it should be given at doses lower than those that would be used in patients not receiving ciclosporin.
Mifepristone: NSAIDs should not be used for 8-12 days after mifepristone administration as NSAIDs can reduce the effect of mifepristone.
Quinolone antimicrobials: There have been isolated reports of convulsions which may have been due to concomitant use of 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 agents 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.
Potent CYP2C9 inhibitors: “Caution is recommended when co-prescribing diclofenac with potent CYP2C9 inhibitors (such as sulfinpyrazone and voriconazole), which could result in a significant increase in peak plasma concentration and exposure to diclofenac due to inhibition of diclofenac metabolism.
Tacrolimus: Possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus. This might be mediated through renal antiprostaglandin effects of both NSAID and calcineurin.
Cardiac glycosides: Concomitant use of cardiac glycosides and NSAIDs in patients may exacerbate cardiac failure, reduce GFR and increase plasma glycoside levels.
Zidovudine: Increased risk of haematological toxicity when NSAIDs are given with zidovudine. There is evidence of an increased risk of haemarthroses and haematoma in HIV(+) haemophiliacs receiving concurrent treatment with zidovudine and ibuprofen.
Cautions:
General: Concomitant use with other systemic NSAIDs, such as selective COX-2 inhibitors, should be avoided due to the lack of any evidence of synergic effect and because of the possible additive adverse effects.
Caution should be exercised in elderly patients. In particular, it is recommended to use the lowest effective dose in weak elderly patients with low body weight.
Bronchial asthma in anamnesis: In patients with bronchial asthma, seasonal allergic rhinitis, chronic obstructive pulmonary diseases or chronic respiratory tract infections (especially those associated with allergic symptom like rhinitis), such reactions to NSAIDs as exacerbation of asthma (so called intolerance to analgesics/analgesic asthma), Quincke's edema or urticaria occur more often. Therefore, special measures are recommended for such patients (readiness for emergency action), as well as for the patients with allergic reactions, such as rash, itching, urticaria, to other substances.
Effect on digestive tract: As well as when using other NSAIDs, including diclofenac, medical supervision and special caution are obligatory in patients with the symptoms indicating digestive tract (DT) disorders or with the history of gastric or intestinal ulcer, bleeding or perforation. Risk of bleeding in the digestive tract grows with the increasing dose in patients with the history of ulcer, especially with complications, such as bleeding or perforation, and in elderly patients. To decrease the risk of such toxic effect on digestive tract, the treatment should be started and maintained with the lowest effective doses.
For such patients, as well as those requiring concomitant use of drugs containing low doses of acetylsalicylic acid (ASA) or other drugs which are supposed to increase the risk of adverse effect on DT, the use of combined therapy with protective agents (e.g. proton pump inhibitors or misoprostol) should be considered. Patients with the history of gastro-intestinal toxicity, especially elderly patients, should report any unusual abdominal symptoms (especially bleeding in the digestive tract). Caution should also be exercised in patients concomitantly receiving drugs which may increase the risk of ulcer or bleeding, such as systemic corticosteroids, anticoagulants, antithrombotic agents or selective serotonin reuptake inhibitors.
Effect on liver: Careful medical supervision is required when using diclofenac in patients with impaired liver function, as their condition may aggravate.
As well as when using other NSAIDs, including diclofenac, the level of one or several enzymes may increase. The increased enzyme levels as a rule are restored after withdrawal of the drug.
During a long-term drug therapy, regular monitoring of liver function and levels of liver enzymes is prescribed as a precaution. If liver dysfunction persists or aggravates, and clinical manifestations or symptoms may be associated with progressing liver diseases, and there are other manifestations (e.g. eosinophilia, rash) the drug should be withdrawn. The course of diseases, such as hepatitis, may take place without prodromal symptoms. Caution should be exercised in case if the drug is used in patients with hepatic porphyria, due to the likelihood of provoking an attack.
Effect on kidneys: Long-term treatment with high doses of NSAIDs, including diclofenac, often (1-10%) causes edema and arterial hypertension. Special attention should be paid to the patients with the history of impaired cardiac and renal function, arterial hypertension, elderly patients receiving concomitant treatment with diuretics, which have a significant effect on renal function, as well as to the patients with a significant decrease in extracellular fluid volume for any reason, for example, before or after major surgery. In such cases, monitoring of renal function is recommended as a caution. Discontinuation of the therapy results in a return to the condition which preceded the treatment.
Effect on hematological indices: In long-term use of this drug, like other NSAIDs, complete blood count monitoring is recommended.
Like other NSAIDs, the drug may temporarily inhibit platelet aggregation. Patients with impaired hemostasis should be carefully monitored.
Do not exceed the indicated doses.
Take into account that in patients with alcoholic non cirrhotic liver damage the risk of hepatotoxic effect of paracetamol is increased; the drug may affect the results of laboratory tests of blood glucose and uric acid levels.
Do not use the drug concomitantly with other drugs containing paracetamol or diclofenac.
Effects on ability to drive and use machines:
Patients who have visual impairment, dizziness, vertigo, or other central nervous system disorders during treatment should refrain from diving motor transport or operating mechanisms.
Presentation:
10 tablets are packed in Alu/PVC blister. Such 10 blisters are packed in carton along with package insert.
Storage:
Keep in dry place protected from light at a temperature below 30°C. Keep out of reach of children.
Shelf life:
Labeled. Do not use after expiry date.
Distribution condition:
Prescribed medicine.

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