# PARDIFEN ACTIVE

## Instructions for the medicinal product

**Trade name:** Pardifen Active.
**International Nonproprietary Name:** Diclofenac Diethylamine BP, Oleum Lini, Methyl Salicylate BP & Menthol BP.
**Dosage form:** Gel.
**Composition:** Each gm contains:

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| Diclofenac Diethylamine BP Eq. to Diclofenac Sodium | 3% w/w |
| Oleum Lini | 3% w/w |
| Methyl Salicylate BP | 10% w/w |
| Menthol BP | 5% w/w |

**Pharmacotherapeutic group:** Topical products for joint and muscular pain; Antiinflammatory preparations, non-steroids for topical use.
**ATC Code:** M02AA15
**Pharmacologic property:**
*Pharmacodynamics:*
*Mechanism of Action:*
Diclofenac works by blocking the effect of chemicals called cyclo-oxygenase (COX) enzymes. These enzymes help to make other chemicals in the body, called prostaglandins. Some prostaglandins are produced at sites of injury or damage causing pain and inflammation. By blocking the effect of COX enzymes, fewer prostaglandins are produced, which means pain and inflammation are eased.
Methyl salicylate is readily absorbed through the skin and has counter-irritant properties. The linseed oil helps in the penetration of the diclofenac through the skin. Methyl salicylate also acts as an analgesic. Menthol relieves itching, dilates the vessels causing a sensation of coldness followed by an analgesic effect.
*Pharmacokinetics:*
*Absorption:* When Diclofenac gel is applied topically, Diclofenac is absorbed into the epidermis. In a study in patients with com-promised skin (mainly atopic dermatitis and other dermatitis conditions) of the hands, arms or face, approximately 10% of the applied dose (2 grams of 3% gel over 100 cm2) of Diclofenac was absorbed systemically in both normal and compromised epidermis after seven days, with four times daily applications.
After topical application of 2 g Diclofenac gel three times daily for six days to the calf of the leg in healthy subjects, Diclofenac could be detected in plasma. Mean bioavailability parameters were AUC0-t 9±19 ng.hr/mL (mean±SD) with a Cmax of 4±5 ng/mL and a Tmax of 4.5±8 hours. In comparison, a single oral 75 mg dose of diclofenac produced an AUC of 1600 ng.hr/mL. Therefore, the systemic bioavailability after topical application of Diclofenac gel is lower than after oral dosing. Blood drawn at the end of treatment from 60 patients with AK lesions treated with Diclofenac gel in three adequate and well-controlled clinical trials was assayed for Diclofenac levels. Each patient was administered 0.5 g of Diclofenac gel twice a day for up to 105 days. There were up to three 5 cm X 5 cm treatment sites per patient on the face, forehead, hands, forearm, and scalp. Serum concentrations of Diclofenac were, on average, at or below 20 ng/mL. These data indicate that systemic absorption of Diclofenac in patients treated topically with Diclofenac gel is much lower than that occurring after oral daily dosing of Diclofenac sodium. No information is available on the absorption of Diclofenac when Diclofenac gel is used under occlusion.
*Distribution:* Diclofenac binds tightly to serum albumin. The volume of distribution of diclofenac following oral administration is approximately 550 mL/kg.
*Metabolism:* Biotransformation of Diclofenac following oral administration involves conjugation at the carboxyl group of the side chain or single or multiple hydroxylation's resulting in several phenolic metabolites, most of which are converted to glucuronide conjugates. Two of these phenolic metabolites are biologically active, however to a much smaller extent than Diclofenac. Metabolism of Diclofenac following topical administration is thought to be similar to that after oral administration. The small amounts of Diclofenac and its metabolites appearing in the plasma following topical administration makes the quantification of specific metabolites imprecise.
*Elimination:*
Diclofenac and its metabolites are excreted mainly in the urine after oral dosing. Systemic clearance of Diclofenac from plasma is 263±56 mL/min (mean±SD). The terminal plasma half-life is 1-2 hours. Four of the metabolites also have short terminal half-lives of 1-3 hours Systemic exposure (area under the concentration-time curve) and maximum plasma concentrations of Diclofenac are significantly lower with Diclofenac gel than with comparable oral treatment of Diclofenac sodium. Systemic exposure with recommended use of Diclofenac gel (4 x 4 g per day applied to 1 knee) is on average 17 times lower than with oral treatment. (Basis: treatment with Diclofenac gel of 1 knee, 4 times a day versus 50 mg, 3 times a day of oral Diclofenac tablets). The amount of Diclofenac sodium that is systemically absorbed from Diclofenac gel is on average 6% of the systemic exposure from an oral form of Diclofenac sodium. The average peak plasma concentration with recommended use of Diclofenac gel (4 x 4 g per day applied to 1 knee) is 158 times lower than with the oral treatment. The pharmacokinetics of Diclofenac gel has been tested under conditions of moderate heat (application of a heat patch for 15 minutes prior to gel application) and of moderate exercise (first gel application followed by a 20 minutes treadmill exercise). No clinically relevant differences of systemic absorption and of tolerability were found between applications of Diclofenac gel (4 x 4 g per day on 1 knee) with and under the conditions tested. However, the pharmacokinetics of Diclofenac gel was not tested under the condition of heat application following gel application. Therefore, concurrent use of Diclofenac gel and heat is not recommended.
**Indications for use:**
Localised painful inflammatory conditions including sprains, strains, bruises, osteoarthritis of peripheral joints, tenosynovitis, myositis, bursitis, sports injuries, low back pain, localised form of soft tissue rheumatism, traumatic inflammation of tendons, muscles & joints. Mild osteoarthritis, periarthropathy, frozen shoulder, cervical spondylitis. Patients in whom systemic NSAIDs are contraindicated.
**Contraindications:**
This product is contraindicated in the following patients:
- Known hypersensitivity (e.g., anaphylactic reactions and serious skin reactions) to diclofenac or any components of the drug product.
- History of asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs. Severe, sometimes fatal, anaphylactic reactions to NSAIDs have been reported in such patients.
- During the last trimester of pregnancy.

**Fertility, Pregnancy and Lactation:**
*Fertility*
Treatment with this medicine is unlikely to have an adverse effect on fertility because the systemic exposure to diclofenac after application of this medicine is low.
*Pregnancy*
The systemic concentration of diclofenac is lower after topical administration, compared to oral formulations. With reference to experience from treatment with NSAIDs with systemic uptake, the following is recommended: Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/fetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation and gastroschisis after use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk for cardiovascular malformation was increased from less than 1%, up to approximately 1.5 %. The risk is believed to increase with dose and duration of therapy. In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre-and post-implantation loss and embryo-fetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period. During the first and second trimester of pregnancy, diclofenac should not be given unless clearly necessary. If diclofenac is used by a woman attempting to conceive, or during the first and second trimester of pregnancy, the dose should be kept as low and duration of treatment as short as possible. During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the fetus to:
- cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension);
- renal dysfunction, which may progress to renal failure with oligohydroamniosis;
The mother and the neonate, at the end of pregnancy, to:
- possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses.
- inhibition of uterine contractions resulting in delayed or prolonged labour.
Consequently, diclofenac is contraindicated during the third trimester of pregnancy.
*Lactation*
Like other NSAIDs, diclofenac passes into breast milk in small amounts. However, at therapeutic doses of this medicine no effects on the suckling child are anticipated. Because of a lack of controlled studies in lactating women, the product should only be used during lactation under advice from a healthcare professional. Under this circumstance, this medicine should not be applied on the breasts of nursing mothers, nor elsewhere on large areas of skin or for a prolonged period of time.
**Dosage and Direction for use:**
*Adults and children 14 years and over:* The gel should be rubbed gently into the skin. Depending on the size of the affected site to be treated, 2-4g (a circular shaped mass approximately 2.0-2.5 cm in diameter) should be applied 2 times a day (preferably morning and evening). The maximum daily dose is 8 g. Therefore, the maximum weekly dose is 56 g.
The gel can be used for up to 14 days under pharmacy supervision.
After application, the hands should be washed unless they are the site being treated.
If symptoms do not improve by day 7, or if they worsen within the first 7 days, a consultation with a doctor is recommended. Do not use for more than 14 days unless recommended by a doctor.
*Use in the elderly:* The usual adult dosage may be used.
*Children and adolescents:* There are insufficient data on efficacy and safety available for the children and adolescents below 14 years of age. In children aged 14 years and over, if this product is required for more than 7 days for pain relief or if the symptoms worsen the patient/parents of the adolescent is/are advised to consult a doctor.
**Side-effects:**
Undesirable effects include mild and passing skin reactions at the site of application. In very rare instances, allergic reactions may occur.
Adverse reactions are listed below, by system organ class and frequency. Frequencies are defined as: very common (≥ 1/10) common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.
*Infections and infestations:* Very rare: Rash pustular.
*Immune system disorders:* Very rare: Hypersensitivity (including urticaria), angioedema.
*Respiratory, thoracic and mediastinal disorders:* Very rare: Asthma.
*Skin and subcutaneous tissue disorders:* Common: Dermatitis (including contact dermatitis), rash, erythema, eczema, pruritus.Rare: Dermatitis bullous. Very rare: Photosensitivity reaction.
The following additional side-effects have been observed with oral forms of diclofenac.
*Gastro-intestinal tract:* Occasional: Epigastric pain, other gastro-intestinal disorders (e.g. nausea, vomiting, diarrhoea, abdominal cramps, dyspepsia, flatulence, anorexia). *Rare:* Gastro-intestinal bleeding, peptic ulcer (with or without bleeding or perforation), bloody diarrhoea. In isolated cases: Lower gut disorders (e.g. non-specific haemorrhagic colitis and exacerbations of ulcerative colitis or Crohn's proctocolitis, colonic damage and stricture formation), pancreatitis, aphthous stomatitis, glossitis, oesophageal lesions, constipation.
*Central Nervous System:* Occasional: Headache, dizziness, or vertigo. Rare: Drowsiness, tiredness. In isolated cases: Disturbances of sensation, paraesthesia, memory disturbance, disorientation, disturbance of vision (blurred vision, diplopia), impaired hearing. Tinnitus, insomnia, irritability, convulsions, depression, anxiety, nightmares, tremor, psychotic reactions. Taste alteration disorders.
*Skin:* Occasional: Rashes or skin eruptions. Rare: Urticaria. In isolated cases: Eczema, erythema multiforme, Stevens-Johnson syndrome, Lyell's syndrome, (acute toxic epidermolysis), photosensitivity reactions, erythroderma (exfoliative dermatitis), loss of hair, purpura including allergic purpura.
*Kidney:* In isolated cases: Acute renal failure, urinary abnormalities (e.g. haematuria, proteinuria), interstitial nephritis, nephrotic syndrome, papillary necrosis.
*Liver:* Occasional: Elevation of serum aminotransferase enzymes (ALT, AST). Rare: Liver function disorders including hepatitis (in isolated cases fulminant) with or without jaundice.
*Blood:* In isolated cases: Thrombocytopenia, leucopenia, agranulocytosis, haemolytic anaemia, aplastic anaemia.
*Hypersensitivity:* Hypersensitivity reactions have been reported following treatment with NSAIDs. These may consist of rare cases of anaphylactic/anaphylactoid systemic reactions including hypotension, and respiratory tract reactivity comprising asthma, aggravated asthma, bronchospasm or dyspnoea.
*Other organ systems:* Rare: Oedema. Isolated cases: Impotence (association with diclofenac is doubtful), palpitation, chest pain, hypertension.
**Overdose:**
The low systemic absorption of topical diclofenac renders overdose very unlikely.
However undesirable effects, similar to those observed following an overdose of tablets, can be expected if this medicine is inadvertently ingested (e.g. 1 tube of 50 g contains the equivalent of 1 g diclofenac sodium.).
In the event of accidental ingestion, resulting in significant systemic adverse effects, general therapeutic measures normally adopted to treat poisoning with non-steroidal anti-inflammatory medicines should be used. Gastric lavage and the use of activated charcoal should be considered, especially within a short time of ingestion.

**Drug Interactions:**
Systemic absorption of diclofenac from topical application is very low and no drug interactions during treatment with this medicine have been reported, but the following have been observed with oral forms of diclofenac or other NSAIDs.
*Lithium and digoxin:* Diclofenac may increase plasma concentrations of lithium and digoxin.
*Anticoagulants:* Although clinical investigations do not appear to indicate that this medicine has an influence on the effect of anticoagulants, there are isolated reports of an increased risk of haemorrhage with the combined use of diclofenac and anticoagulant therapy. Therefore, to be certain that no change in anticoagulant dosage is required, close monitoring of such patients is required. As with other non-steroidal anti-inflammatory agents, diclofenac in a high dose can reversibly inhibit platelet aggregation.
*Antidiabetic agents:* Clinical studies have shown that this medicine can be given together with oral antidiabetic agents without influencing their clinical effect. However, there have been isolated reports of hypoglycaemic and hyperglycaemic effects which have required adjustment to the dosage of hypoglycaemic agents.
*Ciclosporin:* Cases of nephrotoxicity have been reported in patients receiving concomitant cyclosporin and NSAIDs, including diclofenac. This might be mediated through combined renal antiprostaglandin effects of both the NSAID and cyclosporin.
*Methotrexate:* Cases of serious toxicity have been reported when methotrexate and NSAIDs are given within 24 hours of each other. This interaction is mediated through accumulation of methotrexate resulting from impairment of renal excretion in the presence of the NSAID.
*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.
*Other NSAIDs and steroids:* Co-administration of this medicine with other systemic NSAIDs and steroids may increase the frequency of unwanted effects. Concomitant therapy with aspirin lowers the plasma levels of each, although no clinical significance is known.
*Diuretics:* Various NSAIDs are liable to inhibit the activity of diuretics. Concomitant treatment with potassium-sparing diuretics may be associated with increased serum potassium levels, hence serum potassium should be monitored.
*Mifepristone:* NSAIDs should not be used for 8-12 days after mifepristone administration as NSAIDs can reduce the effects of mifepristone.
*Anti-hypertensives:* Concomitant use of NSAIDs with antihypertensive drugs (i.e. beta-blockers, angiotensin converting enzyme (ACE) inhibitors, diuretics) may cause a decrease in their antihypertensive effect via inhibition of vasodilatory prostaglandin synthesis.
**Special Warnings and precautions for use:**
The possibility of systemic adverse events from application of this medicine cannot be excluded if the preparation is used on large areas of skin and over a prolonged period. This medicine should be applied only to intact, non-diseased skin and not to skin wounds or open injuries. It should not be used with occlusion. It should not be allowed to come into contact with the eyes or mucous membranes, and should never be taken by mouth.
Patients with a history of, or active, peptic ulceration. Some possibility of gastro-intestinal bleeding in those with a significant history of this condition has been reported in isolated cases. Like other drugs that inhibit prostaglandin synthetase activity, diclofenac and other NSAIDs can precipitate bronchospasm if administered to patients suffering from or with a previous history of, bronchial asthma. Discontinue the treatment if a skin rash develops after applying the product.
**Presentation:**
30 g topical gel is filled in printed collapsible lacquer coated aluminium tube provided with sealed nozzle. The tube is closed with a white plastic screw cap, incorporating a moulded feature used to insert, twist and remove the seal before first use. Such one tube is packed in unit 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:**
Non-prescribed medicine.

The holder of Trade Mark and Marketing Authorization:
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