

RUFENAL DS

Emulgel

Composition

Each gram contains 2.32 % Diclofenac diethyl ammonium equivalent to 2% Diclofenac sodium.

Action

Diclofenac is a non-steroidal anti-inflammatory drug (NSAID) with pronounced analgesic, anti-inflammatory and antipyretic properties. Inhibition of prostaglandin synthesis is the primary mechanism of action of diclofenac.

This medicine is an anti-inflammatory and analgesic preparation designed for topical application. In inflammation and pain of traumatic or rheumatic origin, this medicine relieves pain, decreases swelling, and shortens the time to return to normal function.

Pharmacokinetics

Absorption

The quantity of diclofenac absorbed through the skin is proportional to the size of the treated area, and depends on both the total dose applied and the degree of skin hydration. After topical application to approximately 400 cm² of skin, the extent of systemic exposure as determined by plasma concentration of this medicine (2 applications/day) was equivalent to diclofenac 1.16% gel (4 applications/day). The relative bioavailability of diclofenac (AUC ratio) for this medicine versus tablet was 4.5% on day 7 (for equivalent diclofenac sodium dose). Absorption was not modified by a moisture and vapour permeable bandage.

Distribution

Diclofenac concentrations have been measured from plasma, synovial tissue and synovial fluid after application of topical diclofenac to hand and knee joints. Maximum plasma concentrations were approximately 100 times lower than after oral administration of the same quantity of diclofenac. 99.7 % of diclofenac is bound to serum proteins, mainly albumin (99.4 %).

Diclofenac penetrates inflamed areas, preferentially distributing to and persisting in deep inflamed tissues such as joints, where it is found in concentrations up to 20 times higher than in plasma.

Biotransformation

Biotransformation of diclofenac involves partly glucuronidation of the intact molecule, but mainly single and multiple hydroxylation resulting in several phenolic metabolites, most of which are converted to glucuronide conjugates. Two of the phenolic metabolites are biologically active, however, to a much smaller extent than diclofenac.

Elimination

The total systemic clearance of diclofenac from plasma is 263 ± 56 ml/min. The terminal plasma half-life is 1-2 hours. Four of the metabolites, including the two active ones, also have short plasma half-lives of 1-3 hours. One metabolite, 3'-hydroxy-4'-methoxy-diclofenac, has a longer half-life but is virtually inactive. Diclofenac and its metabolites are excreted mainly in the urine.

Characteristics in patients

No accumulation of diclofenac and its metabolites is to be expected in patients suffering from renal impairment. In patients with chronic hepatitis or non-decompensated cirrhosis, the kinetics and metabolism of diclofenac are the same as in patients without liver disease.

Indications

For the local symptomatic relief of pain and inflammation in:

- trauma of the tendons, ligaments, muscles and joints, e.g. due to sprains, strains and bruises
- localized forms of soft tissue rheumatism

Contraindications

- Patients with or without chronic asthma in whom attacks of asthma, urticaria or acute rhinitis are precipitated by aspirin or other non-steroidal anti-inflammatory agents.
- Hypersensitivity to diclofenac, acetylsalicylic acid or other non-steroidal anti-inflammatory drugs.
- Hypersensitivity to any other ingredient of the gel.
- Concomitant use of other products containing diclofenac.
- Concomitant use of oral NSAIDs.
- During the last trimester of pregnancy.

Adverse Reactions

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 ($\geq 1/10$) common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

<u><i>Infections and infestations</i></u> Very rare: Rash pustular
<u><i>Immune system disorders</i></u> Very rare: Hypersensitivity (including urticaria), angioedema
<u><i>Respiratory, thoracic and mediastinal disorders</i></u> Very rare: Asthma
Skin and subcutaneous tissue disorders Common: Dermatitis (including contact dermatitis), rash, erythema, eczema, pruritus. Rare: Dermatitis bullous. Very rare: Photosensitivity reaction

Warnings and Precautions

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.

Pregnancy

Category C

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.

Nursing Mothers

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 Administration

Adults and children 12 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 2.0-2.5cm in diameter) should be applied 2 times a day (preferably morning and evening). The maximum daily dose is 8g. Therefore the maximum weekly dose is 56g.

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 12 years of age. In children aged 12 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.

Presentation

Tube of 30 grams.