APPROVED
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INSTRUCTION
for medical use

DICLOSAFE®

Composition:
active substance: diclofenac diethylamine;
1 g of gel contains 11.6 mg of diclofenac diethylamine, equivalent to diclofenac sodium 10 mg;
excipients: propylene glycol, isopropyl alcohol, carbomer, diethylamine, cocoyl caprylocaprate, oleyl alcohol, polyethylene glycol cetostearyl ether, light mineral oil, butylhydroxytoluene (E 321), purified water.

Pharmaceutical form. Emulsion gel for external use.
Basic physical and chemical properties: white to off-white soft homogeneous gel.

Pharmacotherapeutic group. Agents for topical use for joint and muscular pain. Non-steroidal anti-inflammatory agents for topical use. Diclofenac. ATC Code M02A A15.

Pharmacological properties.
Pharmacodynamics.
Diclosafe® with diclofenac as active ingredient is a highly-efficient non-steroidal anti-inflammatory drug (NSAID) for external use.
Diclofenac is a NSAID that has a pronounced anti-rheumatic, analgesic, anti-inflammatory, and antipyretic effect. The main mechanism of therapeutic action of diclofenac is the inhibition of prostaglandins biosynthesis by cyclooxygenase 2 (COX-2).
In case of inflammation caused by trauma or rheumatic diseases, the diclofenac gel reduces pain, swelling of tissues and shortens the period of renewal of damaged joints, ligaments, tendons and muscles. Clinical data has proven that diclofenac gel reduces acute pain in 1 hour after initial application. The drug reduces pain on movement by 75% within two days. 94% of patients had a positive response to diclofenac gel after 2 days of treatment, compared to 8% of patients who had a positive response to placebo. Overcoming of pain and functional impairment was achieved after 4 days of treatment with diclofenac gel. Thanks to the water-alcohol basis, the diclofenac gel also exhibits local anesthetic and cooling effect.
Pharmacokinetics.
The amount 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 a topical application of 2.5 g of diclofenac gel on the skin area of 500 cm^2, the degree of diclofenac absorption is approximately 6%. Application of occlusion bandage for 10 hours leads to the 3-fold increase in the diclofenac absorption.

After applying diclofenac gel on the skin of hand and knee joints, diclofenac is detected in plasma (where its maximum concentration is approximately 100 times less than after oral administration of the same amount of diclofenac), in the synovial membrane and in synovial fluid. The protein binding of diclofenac is 99.7%.
Diclofenac accumulates in the skin, which serves as a reservoir, where the gradual release of the substance in adjacent tissues occurs. From there, diclofenac predominantly enters deeper inflamed tissues, joints, such as joints, rather than blood plasma. There it continues its action and is determined in concentrations up to 20 times higher than those in plasma.
Diclofenac is metabolized mainly by one- or multiple-step hydroxylation and subsequent glucuronidation or glucuronidation of the entire molecule.
Diclofenac and its metabolites are excreted predominantly in urine. The total systemic plasma clearance of diclofenac is 263 ± 56 ml/min, and the terminal half-life from blood plasma is 1–2 hours on average. Four metabolites, including two active ones, have a short half-life (1–3 hours), and one is slightly longer, but it is practically inactive.
In renal or hepatic insufficiency, metabolism and elimination of diclofenac do not change.

Clinical characteristics.

Indication.

Topical treatment of pain and inflammation of joints, muscles, ligaments and tendons of rheumatic or traumatic origin.

Contraindication.

- Hypersensitivity to diclofenac or to other components of the drug.
- A history of bronchial asthma attacks, angioedema, urticaria, or acute rhinitis precipitated by the intake of acetylsalicylic acid or other NSAIDs.
- The last trimester of pregnancy.
- Children’s age under 14 years.

Interaction with other drugs and other types of interactions.

Since the systemic absorption of diclofenac after topical application of the drug is very low, the probability of interactions is very low. Currently there are no data on the interaction of diclofenac in the case of its topical application. Information on known interactions related to the systemic application of diclofenac is contained in the relevant sources.

Special precautions.

Concomitant use of systemic NSAIDs should be cautioned.
The possibility of the development of systemic side effects (which occur with the use of systemic forms of diclofenac) should be considered when using the drug on larger areas of the skin or for a longer time than recommended. In such cases, the drug should be used with caution in patients with liver, kidney or heart failure, as well as peptic ulcer disease in the active stage.
Caution should be exercised when co-administering diclofenac with oral NSAID, as the incidence of undesirable, especially systemic, side effects may increase (see “Interaction with other drugs and other types of interactions” section).
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.
Diclosafe® gel should be applied only to intact, non-diseased skin and not to inflamed, injured or infected skin. It should not be allowed to come into contact with the eyes or mucous membranes. The drug should not be ingested.
Discontinue the treatment if a skin rash develops after applying the product.

Diclosafe® gel can be used with non-occlusive bandages but should not be used with an airtight occlusive dressing.
Some possibility of gastro-intestinal bleeding in those with a significant history of this condition has been reported in isolated cases when diclofenac has been used topically.
Due to the possibility of photosensitivity, it is necessary to avoid exposure to direct sunlight and visits to the solarium during treatment and for 2 weeks after treatment discontinuation.
It is necessary to advise the patient not to smoke and not to approach open flames, as this is a risk of serious burns. Fabric (clothing, bedding, dressing material) that has come into contact with the product can easily ignite and is a serious fire hazard. Washing clothes and bedding can reduce gel accumulation, but does not remove it completely.
Excipients
Diclosafe® gel contains propylene glycol and butylhydroxytoluene. Propylene glycol may cause skin irritation. Butylhydroxytoluene can cause local skin reactions (e.g., contact dermatitis) or irritation of the eyes and mucous membranes.

Use during pregnancy or breastfeeding.
Pregnancy.
The clinical experience of using Diclosafe® in pregnant women is limited.
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 to take into account.
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 foetus to:
- cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension);
- renal dysfunction, which may progress to renal failure with oligohydroamniosis.

The use of prostaglandin synthesis inhibitors at the end of pregnancy can affect the mother and the neonate as follows:
- prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses are possible;
- inhibition of uterine contractions resulting in delayed or prolonged labour.

Consequently, diclofenac, as other NSAIDs, is contraindicated during the third trimester of pregnancy (see “Contraindications” section).
Breastfeeding.
Like other NSAIDs, diclofenac passes into breast milk in small amounts. However, the use of therapeutic doses of Diclosafe® gel does not provide any effect on breastfeeding. Because of a lack of controlled studies in lactating women, within this period Diclosafe® gel should only be

used by medical prescription. During lactation, the drug should not be applied to the mammary glands or large skin areas; and it should not be used for a long time (see "Special precautions" and "Administration and dosage" sections).
Fertility.
Data on the effects of diclofenac on human fertility when used externally are not available.

Effects on ability to drive and use machines.
The effect of diclofenac is absent when applied externally.

Administration and dosage.
The drug is intended for external use only.
Adults and children aged 14 years and above
Diclosafe® gel should be applied 3–4 times a day, slightly rubbing into the skin at the place of pain localization. The amount of product used depends on the size of the area affected by pain (thus, 2–4 g, about the size of a cherry and a walnut respectively, is sufficient to cover an area of 400–800 cm^2).
After application, the hands should be washed unless they are the site being treated.
Duration of therapy depends on the nature of the disease and the treatment efficacy.
The drug should not be used for more than 14 consecutive days in damages or rheumatism of soft tissues and for longer than 21 days in case of joints pain of arthritic origin, unless otherwise recommended by the physician.
It is necessary to seek medical advice if the symptoms of the disease do not diminish or increase after 7 days of treatment.
Elderly patients
The usual adult dosage may be used.
If large areas of the body are covered with Diclosafe® gel, systemic absorption will be greater and the risk of side-effects increased, especially if the therapy is used frequently.

Children.
Since there is not enough data on the efficacy and safety of diclofenac gel for children aged under 14, the drug is contraindicated for use in children under the age of 14 years (see "Contraindications" section).
When using the product for children above 14 years of age longer than 7 days or if the symptoms of the disease increase, you should seek medical advice.

Overdose
Symptoms
Overdose is unlikely due to the low diclofenac absorption in the systemic bloodstream at the topical application. At the same time, the development of systemic adverse reactions can be observed in the case of accidental ingestion of Diclosafe® gel (it should be noted that 1 tube of 30 g contains an equivalent of 0.3 g of diclofenac sodium).
Treatment
In case of accidental drug ingestion and the occurrence of significant systemic adverse reactions, general therapeutic measures used in the treatment of NSAID poisoning should be taken. Gastric lavage and activated charcoal are recommended, especially when swallowing has occurred recently.
Treatment of NSAID overdose consists in the use of supportive and symptomatic therapy. There is no typical clinical picture caused by overdose of diclofenac gel. Supportive and symptomatic treatment is indicated with such complications as arterial hypotension, renal failure, seizures, gastrointestinal disorders and respiratory depression. It is unlikely that forced diuresis,

hemodialysis or hemoperfusion are useful for NSAID removal because active substances of these drugs are highly bound to plasma proteins and undergo an intensive metabolism.

Adverse reactions.
The category of frequency of adverse reactions is defined as follows: very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1000); very rare (<1/10,000); not known (cannot be estimated from available data).
Infections and invasions: very rare – pustular rash.
Immune system: very rare – hypersensitivity reactions (including urticaria), angioneurotic edema.
Respiratory system, chest and mediastinum: very rare – bronchial asthma.
Skin and subcutaneous tissue: common – rash, itching, eczema, erythema, dermatitis, including contact dermatitis, rare – bullous dermatitis; very rare – photosensitivity reactions; not known – desquamation, skin discoloration, burning sensation of the skin.
In case of adverse reactions, the treatment should be discontinued and a doctor should be consulted.
Reporting of suspected adverse reactions.
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Medical and pharmaceutical workers, as well as patients or their legal representatives are asked to report any suspected adverse reactions and lack of effectiveness of the medicinal product through the Pharmacovigilance Automated Information System at: https://aisf.dec.gov.ua.

Shelf life.
3 years.

Storage conditions.
Store at the temperature below 25°C in original package.
Keep out of reach of children.

Package.
30 g, 50 g, 100 g in tube. 1 tube in a carton package.

Condition of supply.
Without prescription.

Manufacturer.
KUSUM HEALTHCARE PVT LTD.

Location of manufacturer and its address of business activity.
SP-289 (A), RIICO Industrial area, Chopanki, Bhiwadi, Dist. Alwar (Rajasthan), India.

Date of last revision.