SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Diclosafe Forte 2.32% w/w Emulsion Gel

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each gram of emulsion gel contains:
Diclofenac diethylamine BP 23.2 mg equivalent to Diclofenac sodium 20 mg

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

White to off white colour soft homogeneous gel.

4. CLINICAL PARTICULARS

4.1Therapeutic indications

Diclosafe Forte is indicated for local symptomatic relief of pain and inflammation.

4.2 Dosage and mode of administration

Dosage

***Adults*:** Diclosafe Forte should be rubbed gently into the skin. Depending on the size of the affected site to be treated.

Diclosafe Forte Emulsion Gel 2.32% w/w: 2-4 g (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.

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 (see also contraindications section 4.3). 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.

Diclosafe Forte for transmission of ultrasound and may be used as a couplant in combination with ultrasound therapy. If large areas of the body are covered with gel, systemic absorption will be greater and the risk of side effects increased, especially if the therapy is used frequently.

Mode of administration***:*** Topical

4.3 Contraindications

- Patients with or without chronic asthma in whom attacks of asthma, urticaria or acute rhinitis are precipitated by acetylsalicylic acid (aspirin) or other non-steroidal anti-inflammatory drugs (NSAIDs).
- Hypersensitivity to diclofenac or any of the excipients.

- Third trimester of pregnancy.
- The use in children and adolescents aged less than 14 years is contraindicated.

4.4 Special warnings and precautions for use

The possibility of systemic adverse events from application of Diclosafe Forte cannot be excluded if the preparation is used on large areas of skin and over a prolonged period. Diclosafe Forte contains propylene glycol, which may cause mild, localised skin irritation in some people.
Concomitant use of oral NSAID's should be cautioned as the incidence of untoward effects, particularly systemic side effects, may increase.
Diclosafe Forte should not be co-administered with other products containing diclofenac. Diclosafe Forte should be applied only to intact, non-diseased skin and not to skin wounds or open injuries. It should not be allowed to come into contact with the eyes or mucous membranes, and should not be ingested.
Discontinue the treatment if a skin rash develops after applying the product.
Diclosafe Forte 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.

4.5 Interactions with other medicinal products

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 Diclofenac 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 Diclofenac 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 Diclofenac diethylamine 1.16%/2.32% w/w 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.

4.6 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 oligo-hydroamniosis; 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 Diclosafe Forte, 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, Diclosafe Forte should not be applied on the breasts of nursing mothers, or elsewhere on large areas of skin or for a prolonged period of time.

4.7 Effects on ability to drive and use machines

Cutaneous application of Diclosafe Forte has no influence on the ability to drive and use machines.

4.8 Undesirable effects

Adverse reactions are ranked under heading of frequency, the most frequent first, using the following convention: very common (> 1/10) ;common (≥ 1/100, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥ 1/10,000, < 1/1,000); very rare (< 1/10,000), not known: cannot be estimated from the available data.

Immune system disorder
Very rare: Hypersensitivity (including urticaria), angioneurotic oedema.
Infections and infestations
Very rare: Rash pustular
Respiratory, thoracic and mediastinal disorders
Very rare: Asthma
Skin and subcutaneous tissue disorders
Common: Rash, eczema, erythema, dermatitis (including dermatitis contact), 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, and 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. (See also "Skin").

Other organ systems

Rare: Oedema
Isolated cases: Impotence (association with diclofenac is doubtful), palpitation, chest pain, hypertension.

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. Healthcare professionals are asked to report any suspected adverse reactions via EFDA yellow Card Scheme, online at https://primaryreporting.who-umc.org/ET or toll free call 8482 to Ethiopian food and drug authority (EFDA).

4.9 Overdose and treatment

***Signs and Symptoms**:*

The low systemic absorption of Diclosafe Forte renders overdose very unlikely. However, undesirable effects, similar to those observed following an overdose of diclofenac tablets, can be expected if Diclosafe Forte is inadvertently ingested (1 tube of 100 g contains the equivalent of 1000 mg of 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 decontamination and the use of activated charcoal should be considered, especially within a short time of ingestion.

Treatment:

Management of over dosage with NSAIDs essentially consists of supportive and symptomatic measures. There is no typical clinical picture resulting from Diclosafe Forte overdosage. Supportive and symptomatic treatment should be given for complications such as hypotension, renal failure, convulsions, gastrointestinal irritation, and respiratory depression; Specific therapies such as forced diuresis, dialysis or haemoperfusion are probably of no help in eliminating NSAIDs due to their high rate of protein binding and extensive metabolism.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Topical products for joint and muscular pain, anti-inflammatory preparations, non-steroids for topical use.
ATC code: M02AA15

Mechanism of Action:
Diclosafe Forte contains diclofenac sodium which is a non-steroidal anti- inflammatory (NSAID) and analgesic preparation designed for external application. Due to an aqueous-alcoholic base the gel exerts a soothing and cooling effect.

5.2 Pharmacokinetic properties

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.

Metabolism
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.

5.3 Preclinical safety data

None known

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Propylene glycol, isopropyl alcohol, carbomer, diethylamine, cococyl caprylocaprate, oleyl alcohol, polyoxyl-20-cetostearyl ether, light liquid paraffin, butylated hydroxy toluene and purified water.

6.2 Incompatibilities

None known

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at temperature below 30°C. Protect from light. Do not freeze. Keep medicine out of reach of children.

6.5 Nature and contents of container

15 gram laminated tube. Each tube is packed in a carton along with the package insert.
30 gram laminated tube. Each tube is packed in a carton along with the package insert.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Kusum Healthcare Pvt. Ltd.
SP-289(A), RIICO Industrial Area, Chopanki, Bhiwadi, Dist. Alwar (Rajasthan) India

8. MARKETING AUTHORISATION NUMBER(S)

07215/09120/NMR/2021

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORIZATION

21 March 2022

10. DATE OF REVISION OF THE TEXT

08/2023

11.REFERENCES

SmPC published on electronic medicines compendium
https://www.medicines.org.uk/emc#gref

The MHRA published product information
https://products.mhra.gov.uk/

Human medicine European public assessment report
https://www.ema.europa.eu/en/medicines