



## SUMMARY OF PRODUCT CHARACTERISTICS

### 1 NAME OF THE MEDICINAL PRODUCT

DIKLORON 1% Gel

### 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 g gel contains:

**Active Substance:**

Diclofenac diethylammonium.....11.6 mg (equivalent to 10 mg diclofenac sodium)

**Excipient(s) with known effects:**

Methylparaben.....1.5 mg

For the full list of excipients, see section 6.1.

### 3. PHARMACEUTICAL FORM

Gel.

A transparent semi-solid gel with alcohol odor.

### 4. CLINICAL PARTICULARS

#### 4.1 Therapeutic indications

DIKLORON is effective for the local treatment of following diseases as an analgesic and anti-inflammatory drug:

- Rheumatic diseases e.g. osteoarthritis, rheumatoid arthritis, peri-arthritis, tendinitis, tenosynovitis and bursitis.
- Trauma of the soft tissues e.g. due to strains and sprains.
- Musculoskeletal system diseases characterized by pain, inflammation, muscle tightness.

#### 4.2 Posology and method of administration

**Posology**

Adults:

DIKLORON is applied over the affected area 3 or 4 times daily and rubbed gently into the skin. The amount needed depends on the size of the painful area. For example, 2 to 4 g DIKLORON is sufficient to treat an area of approximately 2-2.5 cm in diameter.

DIKLORON Gel can also be used in aid of other pharmaceutical forms of DIKLORON.

**Frequency and duration of administration**

The duration of treatment depends on the indication and clinical response. It should not to be used for more than 14 days for soft tissue injuries or soft tissue rheumatism unless recommended by a doctor, or 21 days for arthritis pain.

Patients should consult their doctor if the condition does not improve within 7 days, or if it gets worse.

**Method of administration**



DIKLORON should be applied over the affected area and rubbed gently into the skin. After application, the hands should be washed (unless it is used to treat arthrosis of finger joints).

#### **Additional information on special populations**

##### **Renal/Hepatic impairment**

No dosage adjustment is needed in patients with renal or hepatic impairment.

##### **Pediatric population**

There are no efficacy and safety data for the use of diclofenac diethylammonium in children and adolescents under 14 years of age (see section 4.3). In children 14 years and older, it is recommended to consult a doctor if used for more than 7 days for pain or if symptoms get worse.

##### **Geriatric population (65 years and older)**

The usual adult dosage of DIKLORON may be used in the elderly.

#### **4.3 Contraindications**

DIKLORON is contraindicated in patients with known hypersensitivity to diclofenac or any of the other ingredients (see section 6.1).

DIKLORON is also contraindicated in patients in whom attacks of asthma, urticaria, or acute rhinitis are precipitated by other NSAIDs drugs like acetylsalicylic acid or ibuprofen.

It is contraindicated in 3<sup>rd</sup> 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 DIKLORON cannot be excluded if the preparation is used on large areas of skin and over a prolonged period. Please refer to the product information on oral forms of diclofenac in case of administration in this way.

DIKLORON should only be applied on undamaged and healthy skin (not on open wounds). It should not come into contact with eyes and mucous membranes and should not be swallowed.

Patients should be warned against excessive exposure to sunlight in order to reduce the incidence of photosensitivity.

If rashes develop, treatment should be stopped.

DIKLORON should not be co-administered with other products containing diclofenac.

DIKLORON can be used with non-occlusive bandages but should not be used with an airtight occlusive dressing.

Concomitant use of oral NSAIDs should be cautioned as the incidence of systemic side effects, may increase.

Isolated cases of systemic reactions resulting in deterioration of renal function have been reported with topically administered NSAIDs. Some possibility of gastro-intestinal bleeding in those with a significant history of this condition has been reported.



Bronchospasm may occur in patients with bronchial asthma or allergic disease.

NSAIDs should be used with caution in elderly patients, as these patients are more prone to side effects.

DIKLORON contains methylparaben, which may cause (possibly delayed) allergic reactions.

#### **4.5 Interaction with other medicinal products and other forms of interaction**

Since systemic absorption of diclofenac is very low following topical application of the gel, no interaction is expected (see section 4.8).

#### **Additional information on special populations**

There are no data on special populations.

#### **Pediatric population**

There are no data on pediatric population.

#### **4.6 Fertility, pregnancy and lactation**

##### **General recommendation**

Pregnancy category is C/D (3<sup>rd</sup> trimester)

##### **Women of child-bearing potential/Contraception**

Although the systemic concentration of topical diclofenac is very low after topical administration; women requiring treatment should use effective methods of contraception, since the effects of active substance on the fetus and newborn are not known exactly.

##### **Pregnancy**

Animal studies are insufficient with respect to effects on pregnancy/and-or/embryonal/fetal development/and-or/parturition/and-or/postnatal development (see section 5.3). The potential risk for humans is unknown.

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. There is an absolute increased risk of cardiovascular malformation from 1% to 1.5%. It is accepted that the risk increases with increasing dose and duration of treatment.

DIKLORON should not be given during the first and second trimester of pregnancy, 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. It should not be used in the third trimester of pregnancy.

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 labor.

Consequently, diclofenac is contraindicated during the third trimester of pregnancy.

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.

The use of DIKLORON during pregnancy is not recommended. It is contraindicated particularly during the third trimester of pregnancy because of possibility of uterus inertia and/or premature closure of the ductus arteriosus.

### **Breast-feeding**

It is not known whether topical diclofenac is excreted in human milk. Therefore; DIKLORON is not recommended for use during breast-feeding. If there are compelling reasons for using it, DIKLORON should not be applied to the breasts or to large areas of skin nor should it be used for a prolonged period.

### **Reproductive ability / Fertility**

Diclofenac had no influence on the fertility in preclinical trials (see section 5.3).

### **4.7 Effects on ability to drive and use machines**

DIKLORON has no influence on the ability to drive and use machines.

### **4.8 Undesirable effects**

The frequencies are defined as follows:

Very common ( $\geq 1/10$ ); common ( $\geq 1/100$ ,  $< 1/10$ ); uncommon ( $\geq 1/1,000$ ,  $< 1/100$ ); rare ( $\geq 1/10,000$ ,  $< 1/1,000$ ); very rare ( $< 1/10,000$ ); not known (cannot be estimated from the available data).

### **Infections and infestations**

Very rare: Rash pustular

### **Immune system disorders**

Very rare: Hypersensitivity (including urticaria), angioedema

### **Respiratory, thoracic and mediastinal disorders**

Rare: Asthma

### **Skin and subcutaneous tissue disorders**



Common: Rash, eczema, erythema, dermatitis (including dermatitis contact), pruritus  
Rare: Dermatitis bullous  
Very rare: Photosensitivity reaction

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorization 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 the national reporting system.

#### **4.9 Overdose**

Signs and symptoms:

Since the systemic absorption of diclofenac with topical application is very low, overdose is not expected.

However, undesirable effects, similar to those observed following an overdose of diclofenac tablets, can be expected if DIKLORON is inadvertently ingested (1 tube of 100 g contains the equivalent of 1000 mg of diclofenac sodium). In the event of accidental ingestion (e.g. in children), resulting in significant systemic adverse effects, general therapeutic measures normally adopted to treat poisoning with nonsteroidal anti-inflammatory medicines (NSAIDs) should be used. Gastric decontamination and the use of activated charcoal should be considered, especially within a short time of ingestion.

Treatment:

Management of overdosage with NSAIDs essentially consists of supportive and symptomatic measures. There is no typical clinical picture resulting from DIKLORON overdosage. Supportive and symptomatic treatment should be given for complications such as hypotension, renal failure, convulsions, gastro-intestinal irritation, and respiratory depression; specific therapies such as forced diuresis, dialysis or hemoperfusion 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: Non-steroidal anti-inflammatory preparations for topical use  
ATC code: M02AA15

DIKLORON is an anti-inflammatory and analgesic preparation designed for external application. Transparent, fat-free, semi-solid gel is absorbed through skin readily. Due to an aqueous-alcoholic base the gel exerts a soothing and cooling effect.

Mechanism of action:

The inhibitory effect of diclofenac on prostaglandin biosynthesis is considered to be an important part of its mechanism of action.

In inflammation and pain of traumatic or rheumatic origin, diclofenac has been shown to relieve pain, decrease swelling, and shorten the time to return to normal function.

Clinical data have demonstrated that diclofenac reduces acute pain one hour after initial application ( $p < 0.0001$  versus placebo gel). Diclofenac provided a 58 mm (75% reduction) reduction in pain from baseline, while placebo gel achieved a 17 mm (23% reduction) from baseline reduction after 2 days



of treatment ( $p < 0.0001$ ). 94% of patients responded to diclofenac after 2 days of treatment versus 8% with placebo gel ( $p < 0.0001$ ). Resolution of both pain and functional impairment were achieved after 4 days of treatment with diclofenac ( $p < 0.0001$  versus placebo gel).

## **5.2 Pharmacokinetic properties**

### **General properties**

#### Absorption:

The amount of diclofenac absorbed through the skin is proportional to the contact time and skin area covered with DIKLORON, and depends on the total topical dose and the hydration of the skin.

Absorption amounts to about 6% of the dose of diclofenac after topical application of 2.5 g DIKLORON per 500 cm<sup>2</sup> skin, determined by reference to the total renal elimination compared with diclofenac tablets. Occlusion over a period of 10 hours leads to a 3-fold increase in the amount of diclofenac absorbed.

#### Distribution:

After topical administration of diclofenac gel to hand and knee joints diclofenac can be measured in plasma, synovial tissue and synovial fluid. Maximum plasma concentrations of diclofenac after topical administration of DIKLORON are about 100 times lower than after oral administration of diclofenac tablets.

99.7% of diclofenac is bound to serum proteins, mainly to albumin (99.4%).

Diclofenac accumulates in the skin, which acts as reservoir from where there is a sustained release of drug into underlying tissues. From there, diclofenac preferentially distributes and persists in deep inflamed tissues, such as the joint, 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 these phenolic metabolites are biologically active, however, to a much smaller extent than diclofenac.

#### Elimination:

The total systemic clearance of diclofenac from the plasma is  $263 \pm 56$  ml/min (mean value  $\pm$  standard deviation). 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 much longer plasma half-life, but is virtually inactive. Diclofenac and its metabolites are excreted mainly in the urine.

### **Characteristics in patients**

No accumulation of diclofenac or its metabolites is to be expected in patients suffering from renal impairment.

The kinetics and metabolism of diclofenac are the same in patients with chronic hepatitis or non-decompensated cirrhosis, as in patients without liver disease.



### **5.3 Preclinical safety data**

Preclinical data from acute and repeated dose toxicity studies, as well as from genotoxicity, mutagenicity, and carcinogenicity studies with diclofenac revealed no specific hazard for humans at the intended therapeutic doses.

There was no evidence that diclofenac had a teratogenic potential in mice, rats or rabbits. Diclofenac had no influence on the fertility of parent animals in rats. The prenatal, perinatal and postnatal development of the offspring was not affected.

Topical diclofenac was well tolerated in a variety of studies. There was no potential for phototoxicity and topical diclofenac gel caused no skin sensitization.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Carbomer 934 P  
Ethyl alcohol  
Triethanolamine  
Methylparaben  
Deionized water

### **6.2 Incompatibilities**

There are no known incompatibilities.

### **6.3 Shelf life**

48 months.

### **6.4 Special precautions for storage**

Store at room temperature below 25°C.

### **6.5 Nature and contents of container**

Aluminum tube closed with a plastic screw cap.  
Each tube contains 50 g gel.

### **6.6 Special precautions for disposal and other handling**

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

## **7. MARKETING AUTHORIZATION HOLDER**

DEVA Holding A.Ş.  
Halkalı Merkez Mah. Basın Ekspres Cad. No:1  
34303 Küçükçekmece - ISTANBUL/TURKEY

## **8. MARKETING AUTHORIZATION NUMBER**

194/58



**9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION**

Date of first authorization : 27.01.2000

Date of last renewal : 10.01.2013

**10. DATE OF REVISION OF THE TEXT**

12.02.2019