SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Almiral 1% gel

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 g of gel contains 10 mg diclofenac sodium as diclofenac diethylamine.
Excipient with known effect: propylene glycol.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Gel
Colourless, transparent, smooth, homogeneous gel with a characteristic peppermint odour.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

For local symptomatic relief of pain and inflammation in:

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

It is recommended that treatment should be reviewed after 14 days in these indications.
These indications should not warrant treatment for more than 6 weeks.

- For the symptomatic treatment of osteoarthritis of superficial joints such as the knee.
- In the symptomatic treatment of osteoarthritis, therapy should be reviewed after 4 weeks.

4.2. Posology and method of administration

Posology

Adults and children 14 years and over:

Almiral 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 3-4 times daily. After application, the hands should be washed unless they are the site being treated.

It is recommended that treatment be reviewed after 14 days. These indications should not warrant treatment for more than 6 weeks.

Elderly:
The usual adult dose may be used.

Paediatric population (Children and adolescents below 14 years):
There are insufficient data on efficacy and safety available for children and adolescents below 14 years of age (see 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.

Method of administration
Topical application.

4.3. Contraindications

Hypersensitivity to diclofenac or to any of the excipients listed in section 6.1.
Patients in who attacks of asthma, urticaria or acute rhinitis are precipitated by acetylsalicylic acid (aspirin) or other non-steroidal anti-inflammatory drugs (NSAIDs).
During the last trimester of pregnancy.
Use in patients hypersensitive to propylene glycol or isopropanol or other components of the gel base.
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 Almiral gel cannot be excluded if the preparation is used at a higher dosage or over a prolonged period. These include gastrointestinal disturbances and bleeding, irritability, fluid retention, rash, hepatitis, renal dysfunction, anaphylaxis and rarely blood dyscrasias, bronchospasm and erythema multiforme.

Discontinue the treatment if a skin rash develops after applying the product.

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

Almiral gel 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.
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.

This product should only be used with great caution in patients with a history of peptic ulcer, gastrointestinal bleeding, hepatic or renal insufficiency, or bleeding diathesis, or intestinal inflammation. Circulating levels of the active drug substance are low but the theoretical risk in these patients should be considered.

Almiral gel contains propylene glycol, which may cause skin irritation.

4.5. Interactions with other medicinal products and other forms of interaction

Since systemic absorption of diclofenac from topical application is very low, such interactions are very unlikely.

4.6. Fertility, pregnancy and lactation

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.

Breastfeeding

Like other NSAIDs, diclofenac passes into breast milk in small amounts. However, at therapeutic doses of diclofenac 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 and if the expected benefit justifies the potential risk to the newborn. Under this circumstance, Almiral gel should not be applied on the breasts of nursing mothers, nor do elsewhere on large areas of skin or for a prolonged period of time (see section 4.4).

4.7. Effects on ability to drive and use machines

Cutaneous application of topical diclofenac has no influence on the ability to drive and use machines.

4.8. Undesirable effects

Adverse reactions (Table 1) are ranked under heading of frequency, the most frequent first, using the following convention: 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), not known: cannot be estimated from the available data. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1

Infections and infestations:	
Very rare:	Rash pustular.
Immune system disorder:	
Very rare:	Hypersensitivity (including urticaria), angioneurotic oedema.

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
Not known:	Burning sensation at the application site Dry skin

Almiral gel is usually well tolerated. Itching, reddening or smarting of the skin, or skin rash, commonly occurs. Photosensitivity reactions have very rarely been observed.

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 the national reporting system.

4.9. Overdose

Signs and symptoms

The low systemic absorption of topical diclofenac renders overdosage unlikely. However, undesirable effects, similar to those observed following an overdose of diclofenac tablets, can be expected if Almiral gel is ingested (1 tube of 100g contains the equivalent of 1000mg 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.

Treatment

Management of overdosage with NSAIDs essentially consists of supportive and symptomatic measures. There is no typical clinical picture resulting from diclofenac 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 haemoperfusion are probably of no help in eliminating NSAIDs due to their high rate of protein binding and extensive metabolism.

Further management should be as clinically indicated or as recommended by the national poisons centres, where available.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

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

Mechanism of action:
Diclofenac is a potent non-steroidal anti-inflammatory (NSAID) with pronounced analgesic, anti-inflammatory and antipyretic properties. Diclofenac exerts its therapeutic effects primarily through inhibition of prostaglandin synthesis by cyclo-oxygenase 2 (COX-2).
Almiral gel is an anti-inflammatory and analgesic preparation designed for topical application. In inflammation and pain of traumatic or rheumatic origin, Almiral gel relieves pain, decreases swelling, and shortens the time to return to normal function.
Clinical data have demonstrated that diclofenac gel reduces acute pain one hour after initial application ($p<0.0001$ versus placebo gel). Ninety-four percent (94%) of patients responded to diclofenac gel 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 gel ($p<0.0001$ versus placebo gel).
Due to an aqueous-alcoholic base it 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. Absorption amounts to about 6% of the applied dose of diclofenac after topical application of 2.5 g diclofenac gel on 500 cm^2 skin, determined by reference to the total renal elimination, compared with diclofenac tablets. A 10-hour occlusion leads to a three-fold increase in the amount of diclofenac absorbed.

Distribution:
Diclofenac concentrations have been measured from plasma, synovial tissue and synovial fluid after topical administration of diclofenac gel to hand and knee joints. Maximum plasma concentrations are 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 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), rather than in the bloodstream. Diclofenac 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.

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.

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

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Propylene glycol
Isopropanol
Carboxypolymethylene (carbopol 940)
Dipropylene glycol monomethylether
Peppermint oil
Purified water

6.2. Incompatibilities

None stated.

6.3. Shelf life

Two (2) years

6.4. Special precautions for storage

Store below 25^{o}C, in the original package.

6.5. Nature and contents of container

Lacquered aluminium tubes sealed with polypropylene screw cap of 25g, 50g and 100g gel.
Polyethylene plastic jars of 250g.
Not all pack sizes may be marketed.

6.6. Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

MEDOCHEMIE LTD, 1-10 Constantinoupoleos street, 3011 Limassol, Cyprus

8. MARKETING AUTHORISATION NUMBER

07438/08278/REN/2021

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 10/12/2013

Date of latest renewal: 28/05/2022

10. DATE OF REVISION OF THE TEXT

10/2022