SUMMARY OF PRODUCT CHARACTERISTICS

DICLORAN GEL

1. NAME OF THE MEDICINAL PRODUCT

Dicloran Gel (Diclofenac Gel BP 1% w/w)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each gram of gel contains:

Diclofenac Diethylamine BP	11.6 mg
equivalent to Diclofenac Sodium	10 mg

3. PHARMACEUTICAL FORM

Dosage form: Gel

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For adults and adolescents aged 14 years and over

For the short-term local, symptomatic treatment of mild to moderate pain in acute strains, sprains or contusions following blunt trauma.

4.2 Posology and method of administration

Posology

Adults and adolescents aged 14 years and over:
The occurrence of undesirable effects can be minimized by using the lowest

possible dose for the shortest duration of treatment necessary to relieve symptoms.
Depending on the size of the affected site to be treated, a cherry to walnut-sized quantity, corresponding to 1 - 4 g of gel (11.6 - 46.4 mg diclofenac diethylamine, corresponding to 10 - 40 mg diclofenac sodium) should be applied 3-4 times daily. This is sufficient to treat of an area of 400 - 800 cm^2.
The maximum daily dose is 16 g of gel corresponding to 185.6 mg of diclofenac, diethylamine salt (corresponding to 160 mg diclofenac sodium).
The duration of use depends on the symptoms and the underlying disease. Dicloran should not be used longer than 1 week without medical advice.
If symptoms worsen or do not improve after 3 - 5 days, a doctor should be consulted.

Special populations

Elderly patients:

No special dose adjustment is required. Because of the potential undesirable-effect profile, elderly people should be carefully monitored.

Patient with renal impairment:

No dose reduction is required in patients with renal impairment.

Patient with hepatic impairment:

No dose reduction is required in patients with hepatic impairment.

Children and adolescents (under 14 years):

There are insufficient data on efficacy and safety in children and adolescents under 14 years of age (see section 4.3).

Method of administration

For cutaneous use.
The gel is applied to the affected parts of the body thinly and rubbed gently into

the skin. The hands should be washed unless they are the site being treated. Before applying a bandage (see section 4.4) the gel should be left to dry for a few minutes on the skin.

4.3 ***Contraindications***

. hypersensitivity to the active substance or to any of the excipients listed in section 6.1
. patients with a history of hypersensitivity reactions, such as asthma, bronchospasmus, urticaria, acute rhinitis or angioedema in response to acetylsalicylic acid or non-steroidal anti- inflammatory drugs (NSAIDs).
. on open injuries, inflammations or infections of the skin as well as on eczema or mucous membranes;
. in the last trimester of pregnancy (see section 4.6);

. in children and adolescents under 14 years of age.

4.4 ***Special warnings and precautions for use***

The possibility of systemic undesirable effects from application of topical diclofenac cannot be excluded if the preparation is used on large areas of skin and over a prolonged period. The gel should therefore be used with caution by patients with reduced renal function, reduced heart function or reduced liver function as well as patients with active peptic ulcers in the stomach or duodenum.
Dicloran must only be applied to intact, not diseased or injured skin. Eyes and mucous membranes must not come into contact with the medicinal product and it must not be taken orally.

Topical diclofenac may be used with a non-occlusive bandage but not with an airtight occlusive dressing (see section 5.2)
If symptoms worsen or do not improve after 3 – 5 days, a doctor should be consulted.
Patients suffering from asthma, hay fever, swelling of nasal mucous membranes

(so-called nasal polyps) or chronic obstructive pulmonary disease, chronic respiratory infections (particularly associated with hay fever-like symptoms), and patients with hypersensitivity to painkillers and anti-rheumatic medicinal products of all kinds are rather at risk to asthma attacks (so called analgesic intolerance / analgesic asthma), to local skin or mucous membrane swelling (so-called quincke edema) or to urticaria - than other patients when treated with Dicloran.
In these patients, Dicloran may only be used under certain precautions (emergency preparedness) and direct medical supervision. The same applies for patients who are also allergic to other substances e.g. with skin reactions, itching or urticaria.
If a skin rash occurs during the treatment with Dicloran, the treatment should be stopped.

Direct sunlight or artificial sun should be avoided during treatment and two weeks after treatment to avoid the risk of photosensitivity.
Preventive measures should be taken so that children do not contact the skin areas to which the gel has been applied.

This medicinal product contains fragrance with benzyl alcohol (0.15 mg/g, E1519), citral, citronellol, coumarin, eugenol, farnesol, geraniol, d-limonene and linalool which may cause allergic reactions.
In addition, benzyl alcohol may cause mild local irritation.

Instruct patients not to smoke or go near naked flames - risk of severe burns. Fabric (clothing, bedding, dressings etc) that has been in contact with this product burns more easily and is a serious fire hazard. Washing clothing and bedding may reduce product build-up but not totally remove it.

4.5 Interaction with other medicinal products and other forms of interaction

Since the systemic absorption of diclofenac is very low with topical application, interactions are very unlikely in use as intended.

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

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:

Pregnancy

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 used 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 hydroamnios;

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.

Breast-feeding

Diclofenac passes into breast milk in small amounts. However, at therapeutic doses of Dicloran no effects on the breast-fed child are anticipated. Because of a lack of controlled studies in breast-feeding women, the medicinal product should only be used during breast-feeding under advice from a healthcare professional. Under this circumstance, Dicloran should not be applied on the breasts of breast-feeding mothers, nor 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

The topical use of diclofenac has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Adverse reactions are listed below, by system organ class and frequency. Frequencies are defined as: 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).

System organ class database	Adverse reactions and frequency
Infections and infestations	*Very rare*: Rash pustular
Immune system disorders	*Very rare*: Hypersensitivity (including urticaria), angioedema
Respiratory, thoracic and mediastinal disorders	Very rare: Asthma

Gastrointestinal disorders	*Very rare:* Gastrointestinal complaints
Skin and subcutaneous tissue disorders	*Common*: Dermatitis (including contact dermatitis), skin rash, erythema, eczema, pruritus *Uncommon*: Scaling, dehydration of the skin, oedema *Rare*: Dermatitis bullous *Very rare*: Photosensitivity reaction
	Not known: Burning sensation at the application site, dry skin.

When the gel is applied on large areas of skin and over a prolonged period, the possibility of systemic undesirable effects (e.g. renal, hepatic or gastrointestinal undesirable effects, systemic hypersensitivity reactions) - as they occur possibly after systemic administration of diclofenac- containing medicinal products cannot be excluded.

4.9 ***Overdose***

Due to the low systemic absorption of diclofenac in limited topical use an overdose is unlikely.

If the recommended dose is significantly exceeded, the gel should be removed from the skin and washed off with water.

Undesirable effects similar to those observed following an overdose of systemic diclofenac can occur if topical diclofenac is inadvertently ingested (1 tube of 100 g contains the equivalent of 1,160 diclofenac diethylamine corresponding to 1,000 mg 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 medicinal products should be used. Gastric lavage and the use of activated charcoal should be considered, especially within a short time of ingestion.

A specific antidote does not exist.

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

Diclofenac is a potent non-steroidal anti-inflammatory drug. It develops its therapeutic efficacy mainly via inhibition of prostaglandin synthesis by cyclooxygenase 2 (COX-2). Diclofenac has proven to be effective via the prostaglandin synthesis inhibition in the conventional animal- experiment inflammation models. In humans, diclofenac reduces inflammatory-related pain, swellings and fever. Furthermore, diclofenac inhibits reversibly the ADP and the collagen- induced thrombocyte aggregation.

5.2 Pharmacokinetic properties

Absorption

The quantity of diclofenac absorbed through the skin is proportional to the duration of the skin contact and the size of the treated area, and depends on both the total dose applied and the degree of skin hydration. After local application of Dicloran to hand and knee joints, the active substance is absorbed through the skin and detectable in the plasma as well as the tissue in varying quantities – depending on the diffusion range – beneath the application site.
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 measuring total renal elimination of diclofenac and its hydroxylated metabolites, compared with the oral administration of diclofenac sodium. Due to a depot-effect in the skin, there is a delayed and prolonged release of active substance into the underlying tissue and the plasma. Under occlusive conditions (10 hours), percutaneous absorption of diclofenac in adults can be increased three-fold (serum concentration).

Distribution

99.7 % of diclofenac is bound to serum proteins, mainly albumin (99.4 %). Plasma levels after application of diclofenac gel are not sufficient to explain the observed therapeutic efficacy; this is more likely due to the presence of significantly higher active substance concentrations beneath the application site. Due to its properties (such as short plasma half-life, low pKa value, small distribution volume and high protein binding), diclofenac has an affinity to inflamed tissue.
Diclofenac preferentially distributes and persists in inflamed tissue. 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.

5.3 Preclinical safety data

Based on conventional studies on safety pharmacology, genotoxicty and carcinogenic potential, the preclinical data do not reveal any specific hazards for humans, apart from those already described in other sections of the SPC. In animal studies, the chronic toxicity of diclofenac following systemic application mainly manifested as gastrointestinal lesions and ulcers. In a 2- year toxicity study, a dose-dependent increase in the incidence of thrombosis of the heart was observed in diclofenac-treated rats.

In animal studies on reproductive toxicity, systemically administered diclofenac caused inhibition of ovulation in rabbits and impairment of implantation and early embryonic development in rats. Gestation and duration of parturition were prolonged by diclofenac. The embryotoxic potential of diclofenac was investigated in three animal species (rat, mouse, rabbit). Fetal death and growth retardation occurred at materno-toxic dose levels. Based on the available non-clinical data,

diclofenac is regarded as being non-teratogenic. Doses below the maternotoxic threshold had no impact on the postnatal development of the offspring.
Diclofenac poses a risk to the aquatic environment (see section 6.6).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Carbomer
Cocoyl Caprylocaprate
Macrogol
Cetostearyl
ether Paraffin
Liquid Diethylamine
Isopropyl alcohol
Propylene glycol (E1520)
Fragrance (contains citronellol, geraniol, benzyl alcohol (E1519), linalool, limonene, citral, farnesol, coumarin, eugenol)
Purified water

6.2 Incompatibilities

None known.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store in the original tube in order to protect from light.

This medicinal product does not require any special temperature storage conditions.

6.5 Nature and contents of container

Tube of 20 gm in a carton along with leaflet.

6.6 Special precautions for disposal

7. MARKETING AUTHORIZATION HOLDER AND MANUFACTURING SITE ADDRESSES

Unique Pharmaceutical Laboratories

(A division of J.B. Chemicals & Pharmaceuticals

Ltd) Neelam Centre, B wing, 4th floor, Hind Cycle

Road, Worli, Mumbai - 400030.India.

8. MARKETING AUTHORIZATION NUMBER

12066

9. DATE OF FIRST / RENEWAL OF THE REGISTRATION

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10. DATE OF REVISION OF THE TEXT

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