For the use of only a Registered Medical Practitioner or a Hospital or a Laboratory

Not to be sold by retail without the prescription of a Registered Medical Practitioner

Prescribing Information

1. Generic Name

Diclofenac, Linseed Oil, Methyl Salicylate & Menthol Gel

DICLOTAL®+ Gel

WARNING: RISK OF SERIOUS CARDIOVASCULAR AND GASTROINTESTINAL EVENTS

- Non-steroidal anti-inflammatory drugs (NSAIDs) cause an increased risk of serious cardiovascular thrombotic events, including myocardial infarction and stroke, which can be fatal. This risk may occur early in treatment and may increase with duration of use.
- DICLOTAL+ Gel is contraindicated in the setting of coronary artery bypass graft (CABG) surgery.
- NSAIDs cause an increased risk of serious gastrointestinal (GI) adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients and patients with a prior history of peptic ulcer disease and/or GI bleeding are at greater risk for serious GI events.

2. Qualitative and Quantitative Composition

Diclofenac Diethylamine IP ……... 1.16% w/w
(equivalent to Diclofenac Sodium 1% w/w)
Linseed Oil BP ……..... 3% w/w
Methyl Salicylate IP …….……..... 10% w/w
Menthol IP ..... 5% w/w
Benzyl Alcohol IP ……..……... 1% w/w
(As Preservative)
Gel Base ……..… q.s.

3. Dosage Form and Strength

Dosage Form: Topical Gel.

Topical Strength: Diclofenac diethylamine 1.16%, linseed oil 3%, methyl salicylate 10%, and menthol 5%.

4. Clinical Particulars

4.1 Therapeutic Indication

DICLOTAL+ Gel is indicated for the relief of pain and inflammation in:

- Muscular and joint pain, muscle cramps, stiff neck/neck pain.
- Pain associated with arthritis (knee pain), neuralgia, sprains and strains, lumbago (low back pain), and fibrositis.

4.2Posology and Method of Administration

For topical administration.

Adults and children above 14 years of age: Gel should be rubbed gently into the skin. Depending on the area of the affected site, 2 to 4 gram of gel should be applied 3 to 4 times daily. Total dose of diclofenac-containing topical preparation should not exceed 32 gram per day. After application, the hands should be washed unless they are the site being treated.

In the treatment of osteoarthritis, therapy should be reviewed after 4 weeks while in other indications, it is recommended that the treatment be reviewed after 14 days.

Or, as prescribed by the physician.

4.3Contraindications

DICLOTAL+ Gel is contraindicated in the following:

- Known or suspected hypersensitivity to diclofenac or aspirin or other NSAIDs, linseed oil, methyl salicylate, menthol or to any other component of the formulation.
- Concomitant use of oral diclofenac or other NSAIDs/aspirin.
- In patients with aspirin or salicylate idiosyncrasy.
- Patients in whom attacks of asthma, urticaria, or acute rhinitis are precipitated by acetylsalicylic acid or other NSAIDs.
- In the setting of coronary artery bypass graft (CABG) surgery.

4.4Special Warnings and Precautions for Use

Warnings

The possibility of systemic adverse events from application of this topical therapy cannot be excluded if this product is used on large areas of skin and over a prolonged period of time.

Concomitant Use of Oral NSAIDs: Concomitant use of oral NSAIDs with DICLOTAL+ Gel should be best avoided, as incidence of adverse effects of NSAIDs may increase, particularly systemic side effects.

Skin Reactions: NSAIDs, including diclofenac, can cause serious skin adverse events such as exfoliative dermatitis, Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. These serious events may occur without warning. Patients should be informed about the signs and symptoms of serious skin manifestations, and the use of the drug should be discontinued at the first appearance of skin rash or any other signs of hypersensitivity.

Sun Exposure: Patients should minimize or avoid exposure to natural or artificial sunlight on treated areas because studies in animals indicated topical diclofenac treatment resulted in an earlier onset of ultraviolet light-induced skin tumors. The potential effects of diclofenac gels on skin response to ultraviolet damage in humans are not known.

Precautions

- FOR EXTERNAL USE ONLY.
- NOT FOR VETERINARY USE.
- Discontinue the treatment if a skin rash develops after applying this product.
- Avoid showering/bathing for at least 1 hour after the application.
- Avoid wearing of clothing or gloves for at least 10 minutes after applying the gel.
- Do not apply gel to open skin injuries/wounds, irritated skin, infections, skin abrasions.
- Avoid contact of gel with eyes and mucous membranes.
- Do not apply external heat and/or occlusive dressings to treated joints.
- Avoid exposure of the treated joint(s) to natural or artificial sunlight.
- Avoid concomitant use of gel on the treated skin site with other topical products, including sunscreens, cosmetics, lotions, moisturizers, insect repellants, or other topical medications.
- Should not be co-administered with other products containing diclofenac.
- Convulsions have been reported rarely with methyl salicylate, thus, use of this product should be avoided in such cases.

4.5Drug Interactions

Since systemic absorption of diclofenac from topical application of the gel is very low, drug interactions are very unlikely. The following drug interactions have been observed rarely.

Oral NSAIDs: Concomitant administration of DICLOTAL+ Gel with oral diclofenac or other NSAIDs/aspirin is generally not recommended because of the potential for increased risk of GI events including ulceration, bleeding, and perforation.

Anticoagulants: Concomitant use of anticoagulants and diclofenac has a risk of serious GI bleeding higher than use of either drug alone.

4.6Use in Special Populations

Pregnant Women

The systemic concentration of diclofenac is lower after topical administration, compared to oral formulations. But, due to lack of safety data in pregnant women and fetus, use of diclofenac-containing topical preparations are not indicated during pregnancy. This applies in particular to the third trimester of pregnancy, owing to the possibility of uterine inertia and/or premature closure of the ductus arteriosus.

Lactating Women

Like other non-steroidal anti-inflammatory drugs (NSAIDs), diclofenac passes into breast milk in small amounts. However, at therapeutic doses no effects on the breast-feeding infants are anticipated. Because of a lack of controlled studies in lactating women, this product should be used during lactation only if clearly needed and under medical supervision. Even if it is used, gel should neither be applied on the breasts of nursing mothers nor elsewhere on large areas of the skin or for a prolonged period of time.

Paediatric Patients
Safety and effectiveness of DICLOTAL+ Gel in children below 14 years of age have not been established.

Geriatric Patients
No overall differences in effectiveness or safety have been observed between the elderly population and younger subjects, but greater sensitivity to the effect of NSAIDs in some older individuals cannot be ruled out.

4.7Effect on Ability to Drive and Use Machines
Topical application of DICLOTAL+ Gel has no influence on the ability to drive and use machines.

4.8Undesirable Effects
Local: This preparation is usually well tolerated. Commonly/occasionally reported adverse reactions are application site reactions, including skin irritation, rash, dermatitis, pruritus, erythema, paresthesia, vesicles, papules, redness or swelling, burning or stinging sensation.
Skin photosensitivity, desquamation, discolouration and bullous or vesicular eruptions have been reported in isolated cases. Patients should be warned against excessive exposure to sunlight in order to reduce the incidence of photosensitivity.
This product may cause hypersensitivity/allergic reactions in some individuals with sensitive skin. If hypersensitivity/allergic reactions develop or if any of the above effects/reactions persist or worsen, discontinue use of the drug and seek immediate medical attention.
General: The possibility of systemic adverse events from topical application of this product cannot be excluded if the preparation is used (either accidently or deliberately) on large areas of skin and over a prolonged period which is usually not recommended. Asthma has been reported, *albeit* rarely, in patients using topical NSAID preparations.

4.9Overdose
Symptoms: Overdose with DICLOTAL+ Gel is very unlikely, due to its low systemic absorption. No event of accidental ingestion has been reported in the literature. However, as it contains diclofenac, undesirable effects similar to those observed following an overdose of diclofenac tablets can be expected if it is inadvertently ingested. Symptoms following acute oral NSAID overdose are usually limited to lethargy, drowsiness, nausea, vomiting, and epigastric pain, which

are generally reversible with supportive care. GI bleeding, hypertension, acute renal failure, respiratory depression, and coma may occur. Anaphylactic reactions have been reported with therapeutic intake of NSAIDs, and may occur after an overdose.

When accidentally ingested by oral route large doses of linseed oil may cause loose stools and diarrhea.

Salicylate intoxication can occur after ingestion or topical application of methyl salicylate. Mild chronic salicylate intoxication or salicylism usually occurs only after repeated use of large doses. Salicylism can also occur following excessive topical application of salicylates.

Ingestion of significant quantities of menthol is reported to cause symptoms such as severe abdominal pain, nausea, vomiting, vertigo, ataxia, drowsiness, and coma.

Treatment: Management of overdose essentially consists of supportive and symptomatic measures. Supportive and symptomatic treatment should be given for complications such as hypotension, renal failure, convulsions, GI irritation, and respiratory depression. Gastric decontamination and the use of activated charcoal should be considered, especially within a short time of ingestion. 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 Mechanism of Action

Diclofenac

Mechanism of action of diclofenac is similar to that of other NSAIDs. Diclofenac inhibits the enzyme cyclooxygenase (COX), an early component of the arachidonic acid cascade, resulting in the reduced formation of prostaglandins, thromboxanes and prostacylin.

Linseed Oil

Linseed oil produces anti-inflammatory and analgesic effects because of its α-linolenic acid (omega-3 fatty acid) content. The linseed oil inhibits prostaglandin E2, leukotriene B4, histamine and bradykinin-induced inflammation. The linseed oil also inhibits arachidonic acid-induced inflammation. It shows inhibition of both cyclooxygenase and lipoxygenase pathways of arachidonic acid metabolism. Linseed oil also softens the skin and thus soothes skin irritation.

Methyl Salicylate

Methyl salicylate inhibit COX enzyme, thereby reducing the formation of prostaglandins and block the inflammatory process and pain. Methyl salicylate produces rubefacient effect by reddening of the skin by dilatation of the blood vessels and gives a soothing feeling of warmth. Methyl salicylate also produces counterirritant effect by causing irritation of the sensory nerve endings which alters pain in the underlying muscle or joints that are served by the same nerves.

Menthol

When menthol is rubbed on the skin, it acts as a rubefacient and causes localized vasodilatation; which gives feelings of comfort and warmth. Menthol produces counter-irritant effect by imparting a cooling effect and by initially stimulating nociceptors and then desensitizing them.

5.2Pharmacodynamic Properties

Diclofenac

Diclofenac, an NSAID, exhibits anti-inflammatory and anti-nociceptive/analgesic effects.

Linseed Oil

Linseed oil (flaxseed oil) has anti-inflammatory, analgesic, antioxidant, and anesthetic properties.

Methyl Salicylate

Methyl salicylate is a salicylic acid derivative thus, shares the actions of salicylates. Methyl salicylate has analgesic, anti-inflammatory, and rubefacient properties. Methyl salicylate also produces counterirritant effects. Upon topical application, methyl salicylate relieves pain in arthritic conditions and painful musculoskeletal disorders.

Menthol

Menthol has rubefacient effect. When applied gently on the skin, menthol acts as an anti-pruritic agent and creates a feeling of coolness, and a mild local anesthetic effect. Menthol has good soothing effect. Menthol also acts as a penetration enhancer, increasing the penetration of topically-applied drugs and providing a faster onset of action.

5.3Pharmacokinetic Properties

Diclofenac

When DICLOTAL+ Gel is applied locally, diclofenac sodium is absorbed through the skin. In healthy volunteers, approximately 6% of the applied dose is absorbed as determined by urinary excretion of diclofenac and its hydroxylated metabolites. Following local application of gel, diclofenac penetrates into the inflamed areas. After topical administration of gel to hand and knee joints, diclofenac can be measured in plasma, synovial tissue, and synovial fluid. Maximum plasma concentration of diclofenac is about 100 times lower than following oral administration of diclofenac.

Linseed Oil

Pharmacokinetic properties of linseed oil after topical application are not known.

Methyl Salicylate

The absorption of topical salicylates is proportional to the surface area involved, duration of exposure, concentration and skin integrity. Per-cutaneous absorption is enhanced by exercise, heat, occlusion, or disruption of the integrity of the skin or application to large areas of skin. Both the

rate and extent of absorption increases after repeated application, increasing the bioavailability. Methyl salicylate is extensively metabolized to salicylic acid in the dermal and subcutaneous tissues after topical application. At therapeutic levels, the half-life of salicylates is 2 to 4 hours. As salicylate level reaches the toxic range, the half-life can be greater than 18 hours.

Menthol

After absorption, menthol is excreted in the urine and bile as a glucuronide.

6. Nonclinical Properties

6.1 Animal Toxicology

Diclofenac

Carcinogenesis: Carcinogenicity studies in mice and rats administered diclofenac sodium as a dietary constituent for 2 years at doses up to 2 mg/kg/day resulted in no significant increases in tumor incidence. In a dermal carcinogenicity study conducted in albino mice, daily topical applications of a diclofenac sodium gel product for two years at concentrations up to 0.035% diclofenac sodium did not increase neoplasm incidence.

Mutagenesis: Diclofenac was not mutagenic in genotoxicity tests that included the bacterial reverse mutation assay, in vitro mouse lymphoma point mutation assay, chromosomal aberration studies in Chinese hamster ovarian cells *in vitro* and *in vivo* rat chromosomal aberration assay of bone marrow cells.

Impairment of Fertility: Diclofenac did not affect male or female fertility in rats at doses up to 4 mg/kg/day.

Reproductive and Developmental Toxicity: Studies in animals demonstrated that diclofenac sodium administration during organogenesis did not produce teratogenicity despite the induction of maternal toxicity and fetal toxicity in mice at oral doses up to 20 mg/kg/day, and in rats and rabbits at oral doses up to 10 mg/kg/day.

Linseed Oil

No acute or sub-chronic toxicity data for linseed oil was found. In 90 day oral toxicity in rodents (rats), no adverse effects observed at 10% of diet over 130 days.

Prenatal developmental toxicity study in rats: Higher than normal mortality when fed boiled linseed oil. Survivors had atrophied livers. Linseed oil is not identified as a carcinogen by the International Agency for Research on Cancer.

Reproduction/development toxicity screening test in chickens: Reduced growth when fed boiled linseed oil.

Methyl Salicylate

Acute dermal LD50 of > 2 g/kg were reported when rats were exposed dermally to methyl salicylate. A single dermal application of neat methyl salicylate at 5 g/kg was applied to 4 rabbits (strain not stated) for 24 h under occlusion. Six animals were observed for a 14-day period. None

of the animals died, and no clinical signs were observed. The dermal LD50 in rabbits exceeded 5 g/kg.
Methyl salicylate was applied (at 7 days 9 h of gestation) to dorsal skin of timed-pregnant LVG hamsters, at doses of 350 and 525 mg/100 g. Few embryos from the high-dose group survived beyond 12 days of gestation, but, of the 19 litters produced in this group, there were 53% neural tube defects. Of the 6 litters produced in the lower dose group, 6% of the fetuses had neural tube defects.

Menthol

Menthol show low acute oral toxicity with LD50 values normally greater than 2000 mg/kg body weight (rats and mice). Only limited studies are available investigating dermal toxicity. In one study the LD50 of menthol in rabbits was above 5000 mg/kg body weight. In a second investigation a dermal dose of 34500 mg menthol liquid / kg body weight was lethal to a mouse.
Menthol was not mutagenic in the Ames test with the standard tester strains *Salmonella typhimurium* TA 92, TA 94, TA 98, TA 100, TA 1535, TA 1537, TA 2637 with and without metabolic activation and including cytotoxic concentrations.
Menthol was tested in a well performed study for carcinogenicity (103 weeks) in doses of 3750 and 7500 ppm in the feed in F344 rats and of 2000 and 4000 ppm in the feed in B6C3F1 mice. In male and female rats the survival rate was not affected by treatment and no carcinogenic effects of menthol were found in any organ.
There is no evidence indicating a potential of menthol to interfere adversely with reproduction. Histopathological examinations of the reproduction organs of rats and mice showed no changes in repeated dose toxicity studies with menthol and also in carcinogenicity studies with menthol.

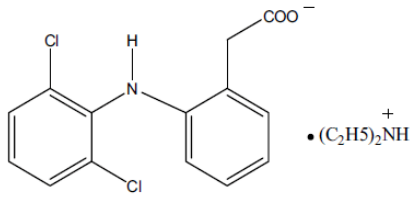
7. Description

DICLOTAL+ Gel is an off white coloured smooth gel with uniform consistency and free from gritty particles and foreign matter. This is packed in printed lamitube with white coloured cap.

DICLOTAL+ Gel contains active ingredients such as diclofenac diethylamine, linseed oil, methyl salicylate, and menthol for topical use in adults and children above 14 years of age.

Diclofenac Diethylamine

Diclofenac diethylamine is a white to light beige crystalline powder, sparingly soluble in water and acetone, freely soluble in ethanol and methanol. It is commonly used as an analgesic and anti-inflammatory agent.
Chemical Name: 2-[2-(2,6-dichloroanilino)phenyl]acetic acid; N-ethylethanamine.
Molecular Weight: 369.3 g/mol.
Molecular Formula: C18H22Cl2N2O2.
Structural Formula:



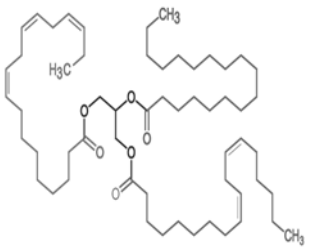
Linseed Oil

Linseed oil is golden yellow, amber, or brown drying oil with a peculiar odor and bland taste. Chief constituents of linseed oil are glycerides of linolenic, linoleic, and oleic acid. Molecular formulas are as follows:

- Linolenic acid: C18H30O2.
- Linoleic Acid: C18H32O2.
- Oleic Acid: C18H34O2.

Molecular Weight: 282.46.

Structural Formula:



Methyl Salicylate

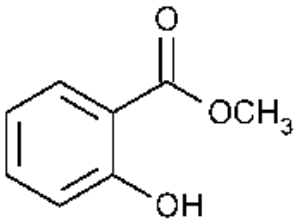
Methyl salicylate appears as colorless yellowish or reddish liquid with odor of wintergreen. Methyl salicylate is a benzoate ester that is the methyl ester of salicylic acid.

Chemical Name: Methyl 2-hydroxybenzoate.

Molecular Weight: 152.15 g/mol.

Molecular Formula: C8H8O3.

Structural Formula:



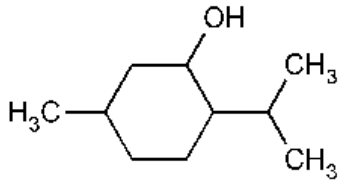
Menthol

Chemical Name: Cyclohexanol, 5-methyl-2-(1-methylethyl).

Molecular Weight: 156.27 g/mol

Molecular Formula: C10H20O.

Structural Formula:



Inactive ingredients (excipients) of DICLOTAL+ Gel contain Purified Water, Disodium EDTA, Carbomer, Propylene Glycol, Polyethylene Glycol, Tween 80, Povidone K-30, Benzyl Alcohol, and Diethylamine.

8. Pharmaceutical Particulars

8.1 Incompatibilities

None known.

8.2Shelf-life

18 Months.

8.3Packaging Information

Lami tube of 30 gram.

8.4Storage and Handling Instructions

Store below 25°C. Do not freeze. Replace the cap tightly after each use.
Keep away from children.

9. Patient Counseling Information

Administration Instructions

Instruct patients to:

- Use this product only on external surfaces, but, not to apply on open skin injuries/wounds, irritated skin, infections, skin abrasions.
- Discontinue the treatment if a skin rash develops after applying this product.
- Avoid showering/bathing for at least 1 hour after the application.
- Avoid contact of gel with eyes and mucous membranes.
- Avoid use of DICLOTAL+ Gel in pregnant women especially in the last 3 months of pregnancy and use it with caution during breastfeeding.

10. Details of Manufacturer

Blue Cross Laboratories Pvt Ltd.

L-17, Verna Industrial Estate, Verna - Goa 403 702.

11. Details of Permission or License Number with Date

Mfg. Lic. No. 271.
Date of FDA Product Permission: 03/05/2019.

12. Date of Revision

March 2021.

MADE IN INDIA BY
BLUE CROSS LABORATORIES PVT LTD.
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