SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Capsifenac Gel (Capsaicin, Diclofenac Diethylamine, Levomenthol and Methyl Salicylate Gel)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Capsaicin	USP	0.025% w/w (as Capsicum Oleoresin)
Diclofenac Diethylamine	BP	1.160% w/w
Levomenthol	BP	1.000% w/w
Methyl Salicylate	BP	3.000% w/w
Gel base	q.s.	

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

White to off-white coloured semi-solid mass with pungent odour.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Capsifenac Gel is indicated for the quick and comfortable relief from pain and inflammation associated with musculoskeletal disorders such as sprains, strains, tendonitis, bursitis, head, neck and shoulder pain, sciatica, muscle stiffness, joint pain and backache.

4.2 Posology and Method of Administration

Recommended Posology

Adults

Capsifenac Gel is applied locally to the skin 3 or 4 times daily. The amount needed depends on the size of the painful site. For example, 2 to 4 g Capsifenac Gel (a quantity ranging in size from a cherry to a walnut) is sufficient to apply to an area of about 400 - 800 cm^2. After application, the hands should be washed, unless they are the site being treated. The duration

of treatment depends on the indication and the response obtained. Treatment beyond two weeks' duration is not recommended and therapy should be reviewed after this time.

Children

Dosage recommendations and indications for the use of Capsifenac Gel in children have not been established. Keep out of reach of children

Route of administration: Topical

4.3 Contraindications

Capsifenac Gel is contraindicated in those individuals with known hypersensitivity to Diclofenac, Capsaicin, Levomenthol or Methyl Salicylate as well as propylene glycol, isopropyl alcohol, or the other ingredients in the gel. Capsifenac Gel is also contra indicated in patients in whom attacks of asthma, urticaria, or acute rhinitis are precipitated by aspirin or other non-steroidal anti- inflammatory drugs (NSAID's).

4.4 Special Warnings and Precautions for Use

Capsifenac Gel should be applied only to intact, healthy skin and not to skin wounds, infections, exudative dermatoses or open injuries. It should not be allowed to come into contact with the eyes or mucous membranes, and should never be taken by mouth.

Capsifenac Gel is "For external use only". Avoid getting in eyes or on broken or irritated skin. If condition worsens, or if symptoms persist for more than 28 days in the case of arthritis (14 days with post-herpetic neuralgia), or clear up and occur again within a few days, discontinue use of this product and consult your doctor. Keep out of reach of children. The likelihood of systemic side effects occurring following topical diclofenac is small compared with the frequency of side effects following oral diclofenac. However, when Capsifenac Gel is applied to relatively large areas of skin and over a prolonged period of time, the possibility of systemic side effects cannot be excluded. In general, topical NSAID's should be used with caution in those patients with a history of (or active) gastro-intestinal ulceration or bleeding, or severe renal

impairment.

4.5 Interaction with Other Medicinal Products and Other Forms of Interaction The concurrent use of NSAID's and warfarin has been associated with severe, sometimes fatal, haemorrhage. The exact mechanism of the interaction between NSAID's and warfarin is unknown, but may involve enhanced bleeding from NSAID- induced gastrointestinal ulceration or an additive effect of anticoagulation by warfarin and inhibition of platelet function by NSAID's. Systemic reactions are unlikely to occur when Capsifenac Gel is used as recommended. Nevertheless, the possibility of such an interaction should be borne in mind.

4.6 Pregnancy and Lactation

Usage in Pregnancy

Non-steroidal anti-inflammatory drugs inhibit prostaglandin synthesis and, when given during the latter part of pregnancy, may cause closure of the fetal ductus arteriosus, fetal renal impairment, inhibition of platelet aggregation, and delay labour and birth. Continuous treatment with NSAID's during the last trimester of pregnancy should only be given on sound indications. During the last few days before expected birth, agents with an inhibitory effect on prostaglandin synthesis should be avoided.

Safety of diclofenac in pregnancy has not been established. Therefore Capsifenac Gel should not be used in pregnant women or those likely to become pregnant unless the expected benefits are likely to outweigh any possible risk.

No measurable amounts of active substance are to be expected in the breast milk of nursing mothers. However, since no experience has been acquired with Capsifenac Gel during lactation, it is not recommended for use in this circumstance. Reproduction studies have been performed in mice given diclofenac sodium (up to 20 mg/kg/day or 60 mg/m2/day) and in rats and rabbits given diclofenac sodium (up to 10 mg/kg/day or 60 mg/m2/day for rats, and 80 mg/m2/day for rabbits), and have revealed no evidence of teratogenicity despite the induction of maternal toxicity and fetal toxicity. In rats, maternally toxic doses were associated with dystocia, prolonged

gestation, reduced fetal weights and growth, and induced fetal survival. Diclofenac has been shown to cross the placental barrier in mice and rats.

Usage in Lactation:

Safety and efficacy of this formulation in lactating mothers have not been established.

4.7 Effects on Ability to Drive and Use Machines

Application of Capsifenac Gel was not found to have any effect on the ability to drive and use machines.

4.8 Undesirable Effects

Local Reactions

Occasional: allergic or non-allergic contact dermatitis (with symptoms and signs such as itching, reddening, edema, papules, vesicles, bullae, or scaling of the skin).

Systemic Reactions

In isolated cases: generalized skin rash; hypersensitivity reactions (e.g. asthmatic attack, angioedema), or Photosensitivity reactions.

The concurrent use of NSAID's and warfarin has been associated with severe, sometimes fatal, hemorrhage. The exact mechanism of the interaction between NSAID's and warfarin is unknown, but may involve enhanced bleeding from NSAID- induced gastrointestinal ulceration or an additive effect of anticoagulation by warfarin and inhibition of platelet function by NSAID's. Systemic reactions are unlikely to occur when Capsifenac Gel is used as recommended. Nevertheless, the possibility of such an interaction should be borne in mind.

Reporting of suspected adverse reactions: Healthcare professionals are asked to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org

4.9 Overdose

The low systemic absorption of ingredients in Capsifenac Gel renders

overdosage extremely unlikely. In the event of accidental ingestion, resulting in significant systemic side-effects, general therapeutic measures normally adopted to treat poisoning with non-steroidal anti-inflammatory drugs should be used.

Management of overdosage essentially consists of supportive and symptomatic measures. There is no typical clinical picture resulting from Capsifenac Gel overdosage. Supportive and symptomatic treatment should be given for complications such as hypotension, renal failure, convulsions, gastro-intestinal irritation and respiratory depression.

Generally, ingestion /of salicylates at/ doses larger than 150 mg/kg (or 70 mg/lb) can produce toxic symptoms such as tinnitus, nausea, and vomiting. Serious toxicity can be seen with ingestions greater than 400 mg/kg (approximately 180 mg/lb), with severe vomiting, hyperventilation, hyperthermia, confusion, coma, convulsions, hyper-or hypoglycemia, and acid-base disturbances such as respiratory alkalosis or metabolic acidosis. In severe cases, the clinical course may progress to pulmonary edema, hemorrhage, acute renal failure, or death. It is important to note that the salicylate-overdose patient can progress to a more serious condition over time as additional drug is absorbed from the gastrointestinal tract. Chronic salicylism presents clinically in a similar fashion to the acute situation, although it is often associated with a higher morbidity and mortality as well as more pronounced hyperventilation, dehydration, coma seizures, and acidosis /Salicylates.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: M02AB -Topical products for joint and muscular pain -

Capsaicin and similar agents

5.1 Pharmacodynamic Properties

Capsifenac Gel is an anti-inflammatory and analgesic preparation designed for external application. Due to an aqueous-alcoholic base, it exerts a soothing and cooling effect. The active ingredients of Capsifenac Gel are Diclofenac Diethylamine, Capsaicin, Menthol & Methyl Salicylate and the

pharmacological actions of the gel are the result of the pharmacodynamics of these 4 active ingredients.

Diclofenac

As with other NSAID's, its mode of action is not known; however, its ability to inhibit prostaglandin synthesis may be involved in the anti-inflammatory effect. Diclofenac has both hydrophilic and hydrophobic properties to achieve good penetration through the skin and achieve topical effect.

Diclofenac is a well characterized, potent, non-steroidal anti-inflammatory drug (NSAID) with clinically proven anti-inflammatory, analgesic, and antipyretic properties. NSAIDs, including diclofenac, reduce pain principally by inhibiting formation of prostaglandins, leukotrienes, and free oxygen radicals.

All non-aspirin NSAIDs reversibly block cyclo-oxygenase (COX) activity, which is responsible for converting arachidonic acid to prostaglandins. Diclofenac is a potent,

non-selective inhibitor of COX-1 and COX-2 (preferentially COX-2), which may underlie both its therapeutic efficacy and potential side effects.

In addition, diclofenac, when compared to NSAIDs such as ibuprofen, also blocks the lipoxygenase pathway of the arachidonic acid cascade, thereby inhibiting the formation of leukotriene B4 (LTB4), which is a known pain mediator and has been shown to stimulate pain receptors in the peripheral nerves. The inhibition of lipoxygenase also prevents the pro-inflammatory and gastrointestinal damaging effects of leukotrienes. Prostaglandins, along with thromboxanes and LTB4, are responsible for several inflammatory effects. The lipoxygenase inhibition produced by diclofenac may therefore play a significant role in its efficacy as an analgesic and anti- inflammatory agent.

Diclofenac competes with Arachidonic acid for binding to cyclooxygenase resulting in decreased formation of prostaglandins. The drug has both analgesic and antipyretic activities. It has been advocated for use in painful

and inflammatory rheumatic and certain non-rheumatic conditions. The Diethylammonium salt of Diclofenac-Diclofenac Diethylammonium has been documented to be effective in the short-term management of musculoskeletal disorders and non-articular rheumatism.

Capsaicin

Capsaicin is the major pungent principle of hot peppers from the plat genus Capsicum, the members of which are used extensively in food. Although the precise mechanism of action of capsaicin is not fully understood, current evidences suggest that capsaicin renders the applied area insensitive to pain by depleting Substance-P a neuropeptide which transmits the pain impulses from the peripheral neurons to the central nervous system. Pain relief is obtained after Substance P is totally depleted. Capsaicin is a counter-irritant used as a topical analgesic in painful skin conditions.

Menthol

Menthol, an alcohol obtained from diverse mint oils in low concentrations stimulates the sensory nerve endings for cold and hence causes a sensation of coolness. Local analgesic effect also accompanies this effect. In addition menthol has been shown to

enhance the skin penetration of methyl Salicylate and to inhibit the in vivo and in vitro hydrolysis of methyl Salicylate to salicylic acid

Methyl Salicylate

Methyl Salicylate is a counter irritant. It has been shown that esterases present in the skin rapidly hydrolyze Salicylate esters to release the active Salicylate in both the epidermis and dermis. Methyl Salicylate produces a paradoxical pain relieving effect by producing a sensation that counters more intense feeling of pain (gate control theory). The pleasant smell of methyl Salicylate is always associated with pain relief.

5.2 Pharmacokinetic

Properties Absorption

When Diclofenac Diethylamine is applied locally, the active substance is absorbed through the skin. The amount of diclofenac absorbed through intact skin is proportional to the contact time and skin area covered with Diclofenac Diethylamine 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 2.5g of gel per 500 cm^2 skin, determined by reference to the total renal elimination
compared with diclofenac tablets. Occlusion over a period of 10 hours leads to a three- fold increase in the amount of diclofenac absorbed. No information is available on the clinical effects and consequences of use under occlusion.

Distribution

After topical administration of Diclofenac Diethylamine 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 are about 100 times lower than after oral administration. 99.7% of diclofenac binds to serum proteins, chiefly to albumin (99.4%).

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. Metabolism of diclofenac following percutaneous and oral administration is similar.

Elimination

The total systemic clearance of diclofenac from plasma is 263 ± 56 mL/min (mean value ± SD). The terminal plasma half-life is 1 to 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. However, this metabolite is virtually inactive. Diclofenac and its metabolites are excreted mainly in the urine.
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 Toxicity &

Carcinogenicity:

Toxicological studies have not been performed. Percutaneous absorption of active ingredients of topical formulations like Capsifenac Gel occurs in sufficient amounts to achieve therapeutic levels in target tissues only and hence concentration in plasma to cause systemic toxicity and thereby other serious adverse effects is comparably low. Established side-effects include local irritation with erythema or dermatitis, and urticarial reactions can occur with all preparations.

Systemic reactions, particularly gastrointestinal disturbance and asthma are quite rare. In general the extensive studies of efficacy and toxicity of drugs by the topical route are very limited.

Capsaicin is not generally recognized as safe and effective by the U.S. Food and Drug Administration for fever blister and cold sore treatment, but is considered to be safe and effective as an external analgesic counterirritant.

Human Toxicity Excerpts:

When ingested, the highly concentrated liquid methyl salicylate in the form of wintergreen oil, as with other volatile oils, can induce vomiting and is a notorious source for severe, often fatal poisonings.

Methyl salicylate was found to be negative when tested for mutagenicity using the Salmonella/microsome preincubation assay, using the standard protocol approved by the National Toxicology Program (NTP). Methyl salicylate was tested in as many as 5 Salmonella typhimurium strains (TA1535, TA1537, TA97, TA98, and TA100) in the presence and absence of rat and hamster liver S-9, at doses of 1,000, 3, 300, 10,000, 33,300, 100,000, and 333,300 ug/plate. The highest ineffective dose tested in any Salmonella typhimurium strain was 333,000 ug/plate.

[Mortelmans K et al; Environ Mutagen 8: 1-119 (1986)]**PEER REVIEWED**

Methyl salicylate (MS) is teratogenic in animals and can be absorbed in toxic quantities by the dermal route. Consequently the dermal absorption and teratogenic potential of a petroleum-based grease (PBG) manufactured using methyl salicylate (3%) was assessed.
The test material (petroleum based grease/methyl salicylate) was dermally applied at doses of either 0, 1, 3, or 6 g/kg/day to groups (N greater than or equal to 12) of pregnant rats on gestational days 6-15. Undiluted methyl salicylate was applied to the positive control group at a dose of 2 g/kg/day and was reduced to 1 g/kg/day on gestational days 10-15 due to maternal toxicity (ie, 25% mortality and severe dermal irritation). Positive control animals evidenced a 100% incidence of total resorptions. Urinalysis revealed very high concentrations of salicylic acid in the positive controls and that a significant proportion of the available methyl salicylate was absorbed from the petroleum based grease/methyl salicylate test material. However, the urinary concentrations of salicylic acid in petroleum based grease/methyl salicylate treated animals were far below the toxic levels observed in methyl salicylate treated animals. Despite the high doses of petroleum based grease/methyl salicylate, there were no signs of maternal toxicity (as measured by food consumption and body weight parameters or clinical signs) and no alterations in reproductive parameters. Fetal external and visceral examinations revealed no malformations or variations that were related to petroleum based grease/methyl salicylate treatment. These findings confirm the developmental toxicity of methyl salicylate and indicate that petroleum based grease/methyl salicylate was not a teratogenic hazard under these test conditions. The maternal and developmental No-Observable-Adverse-Effect-Level for petroleum based grease/methyl salicylate was greater than 6 g/kg/day.
[Infurna R et al; Teratology 41 (5): 566 (1990)]**PEER REVIEWED**

Prenatal exposures to methyl salicylate on kidney function in rats were studied. Pregnant female Sprague Dawley rats were treated with methyl salicylate by intraperitoneal injections between gestational days 10 and 14. Functional assessments of renal toxicity included baseline urinary parameters, urine concentrating ability and in-vitro determination of the

transport function of the renal cortex. Methyl salicylate exposure was teratogenic and embryotoxic.

Prenatal exposure decreased fetal weight and increased the number of resorptions, fetal mortality, and the incidence of fetal malformations including ectopic kidneys. The primary postnatal renal defect associated with prenatal methyl salicylate treatment was a decreased urine concentrating ability in weanlings.]
[Daston GP et al; Fundam and Appl Toxicol 11 (3): 381-400 (1988)]**PEER REVIEWED**

Methyl salicylate was administered topically to pregnant hamsters at 7 day 9 hr and the teratogenic results were compared with those obtained following oral treatment with the same compound. Both treatments produced the same defect in embryos recovered at day 9: failure of fusion of the neural tube, especially in the area of the developing brain. Analysis of serum salicylate levels following both treatments produced similar curves and indicated that teratogenic levels of salicylate can reach the maternal circulation after topical exposure.
[Overman DO, White JA; Teratology 28 (3): 421-6 (1983)]**PEER REVIEWED** Three bacterial assay studies showed no mutagenic activity for methyl salicylate unless administered in very high doses were (>5,000 µg/plate) (MRID44213012 and 13). This limited information (carcinogenicity data from one species and genotoxicity studies from microorganisms) suggests no carcinogenic potential for methyl salicylate.

Dermal absorption
According to the findings in a single dose developmental toxicity study with hamsters, plasma salicylate levels reached a peak of 125 mg/100ml at 2 hours after oral treatment with 1750 mg/kg and returned to control levels during the next 8-10 hours. Peak plasma concentrations of 50/mg/100ml were observed 5-6 hours following dermal application of 1750 mg of methyl salicylate/kg, and these plasma levels were similar to oral control values, several hours following dermal treatment. In a study increasing the dermal

dose to approximately 8750 mg/kg, results in a peak plasma salicylate level of 120 mg/100ml (similar to that following oral treatment).
However, the higher dose was difficult to apply and too stressful for the animals to continue being treated, and moreover, it is a dose that is well in excess of the limit dose for an acute dermal toxicity study (>5,000 mg/kg).
There is no evidence that moderate therapeutic doses of salicylates cause fetal damage in human beings; however, babies born to women who ingest salicylates for long periods may have significantly reduced weights at birth. In addition, there is an increase in perinatal mortality, anemia, antepartum and postpartum hemorrhage, prolonged gestation, and complicated deliveries. /Salicylates/ [Gilman, A.G., T.W. Rall, A.S. Nies and P. Taylor (eds.). Goodman and Gilman's The Pharmacological Basis of Therapeutics. 8th ed. New York, NY. Pergamon Press, 1990. 649]**PEER REVIEWED**
The average lethal dose /SRP: 95-98% **methyl salicylate/** for children is 10 ml, and for adults, 30 ml or 0.5 g/kg. [Clayton, G. D. and F. E. Clayton (eds.). Patty's Industrial Hygiene and Toxicology: Volume 2A, 2B, 2C: Toxicology. 3rd ed. New York: John Wiley Sons, 1981-1982. 2309]**PEER REVIEWED**
The acute toxicity of the active substance, **diclofenac diethylamine**, was examined in a comparative study together with diclofenac sodium. Single-dose experiments in mice, rats, rabbits, and dogs indicated an acute intravenous LD50 in the region of 100 mg/kg and an oral LD50 nearer 200 mg/kg. An oral study in baboons suggests significantly greater tolerance with a probable oral LD50 of more than 600 mg/kg. Following intravenous administration, death was usually attributed to respiratory or cardiac failure, while death following oral treatment usually took several days and involved gastrointestinal ulceration.

Genotoxicity/ Mutagenicity

No studies of potential genetic toxicity were carried out with diclofenac diethylamine. Genotoxicity studies carried out with diclofenac sodium, which could also be relevant for the diethylamine salt, did not show any evidence of genotoxic or mutagenic potential.

Carcinogenicity

No studies of the carcinogenic potential of diclofenac diethylamine were

conducted. Three previous long-term studies with diclofenac sodium in rats and mice, which could also be relevant for the diethylamine salt, did not suggest any potential to induce tumours.

Reproductive and Developmental Toxicity

No reproductive or developmental toxicity studies were conducted with diclofenac diethylamine. However, reproductive toxicity has been assessed in a series of pre-ICH design studies, including Segment I and III studies in rats and a variety of Segment II studies in mice, rats, and rabbits. Almost all studies included treatment at toxic doses, and death of the dams, usually attributed to peritonitis, was a common finding.

Percutaneous absorption of topical formulations like CAPSIFENAC GEL occurs in sufficient amounts to achieve therapeutic levels in target tissues only and hence concentration in plasma to cause systemic toxicity and thereby other effects on the reproductive system is comparably low to cause any teratogenic effects

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Benzyl Alcohol, Carbomer 940, Propylene Glycol, Isopropyl Alcohol, Polysorbate 80, Disodium Edetate, Sodium Hydroxide and Purified water. .

6.2 Incompatibilities

None.

6.3 Shelf Life

24 months

6.4 Special Precaution for Storage

Do not store above 30°C. Protected from light. Do not freeze. Keep the tube tightly closed after use.

6.5 Nature and Contents of Container

Tube of 10 /20 g packed in carton with pack insert.

6.6 Special Precautions for Disposal

None.

7. APPICANT/SUPPLIER:

PRISMA PHARMA FZE

P.O.Box 17269

Jebel Ali Free Zone

Dubai

U.A.E

8. Marketing authorization number

H2008/19799/686/R1

9. Date of first registration / renewal of the registration

22/01/2026

10. DATE OF REVISION OF THE TEXT:

January 2025, 18th August 2026