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

Methyl Salicylate, Menthol & Camphor Cream
(Brand Name: MEFTAL-FORTE® Topical Cream)

2. Qualitative and Quantitative Composition

Methyl Salicylate IP …….. 30% w/w
Menthol IP ……..….... 10% w/w
Camphor USP …… 4% w/w
Cream Base ……. q.s.

3. Dosage Form and Strength

Dosage Form: Cream.
Dosage Strength: Methyl salicylate 30%, menthol 10%, and camphor 4%.

4. Clinical Particulars

4.1 Therapeutic Indication

MEFTAL-FORTE Topical Cream is indicated for:

- Symptomatic relief from mild to moderate muscle and joint aches and pains, muscle cramps, shoulder aches, and stiff neck.
- Relief of pain associated with rheumatism, arthritis, neuralgia, sprains and strains, lumbago, and fibrositis.

4.2Posology and Method of Administration

For topical administration.
Adults and children over 6 years: Apply a thin layer of cream to the affected area of skin not more than 3 to 4 times a day. Rub in gently and thoroughly. For muscular strains and stiffness it is recommended to use cream after a hot bath.
Or, as prescribed by the physician.

4.3Contraindications

MEFTAL-FORTE Topical Cream is contraindicated in patients with known hypersensitivity to methyl salicylate or to menthol or to camphor or to any component of the formulation. Do not use in patients with aspirin or salicylate idiosyncrasy.

4.4Special Warnings and Precautions for Use

Warnings

- Topical analgesic preparations containing methyl salicylate should be used with caution in patients at increased risk of developing salicylate adverse effects.
- Children suffering from flu, chickenpox, or fever should avoid using this product because salicylates may induce Reye's syndrome.
- Convulsions were reported rarely, thus, use of this product should be avoided in such cases.
- Do not apply to skin abrasions.
- Do not apply to irritated skin.
- Avoid direct application into nostrils.
- Not recommended for children under 6 years.

Precautions

- For external use only.
- Use sparingly on tender skin and do not cover immediately after application.
- Do not apply to open lesions or damaged skin.
- Avoid contact with the eyes and mucous membranes.
- Do not apply over large areas of the body or bandage or use with heating pads.
- If skin irritation develops, discontinue its use and consult a doctor.
- It is dangerous to place any camphor containing product into the nostril of children.
- Replace cap tightly after use.

4.5Drug Interactions

Topical salicylates may potentiate the anticoagulant effects of warfarin (increase the chances of bleeding). Concomitant use with other topical products, including topical medications, sunscreens, lotions, moisturizers and cosmetics, on the same skin site has not been tested and should be avoided because of the potential to alter local tolerability and absorption.

4.6Use in Special Populations

Pregnant Women

There is inadequate evidence of safety in human pregnancy. As a precautionary measure, this product should be used only when clearly needed and when there is no safer alternative available.

Lactating Women

It is not known whether this product passes into breast milk. Caution should be exercised while administration of this product to nursing mother.

Paediatric Patients

Safety and effectiveness of this topical formulation has not been established in children below 6 years of age.

Geriatric Patients

Elderly patients may be given the same dose as recommended for adults.

4.7Effect on Ability to Drive and Use Machines

Topical application of MEFTAL-FORTE Cream has no influence on the ability to drive and use machines.

4.8Undesirable Effects

This product can cause convulsions. Headache, dizziness, nausea and vomiting, skin irritation, contact dermatitis, rash, itching, redness or swelling, burning or stinging sensation may occur. It may cause hypersensitivity/allergic reactions in some individuals with sensitive skin. If any of these effects persist or worsen, discontinue the use of drug immediately and seek immediate medical attention.

4.9Overdose

When used externally as directed, overdose is unlikely. This medication may be harmful if swallowed orally.

Symptoms of Methyl Salicylate Overdose: 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. Symptoms include dizziness, tinnitus, deafness, sweating, nausea, vomiting, headache, confusion, and may be controlled by reducing the dosage. Symptoms of more severe intoxication or of acute poisoning following overdose include hyperventilation, fever, restlessness, ketosis, respiratory alkalosis, and metabolic acidosis. Depression of the CNS may lead to coma; cardiovascular collapse and respiratory failure may also occur.

Symptoms of Menthol and Camphor Overdose: Ingestion of significant quantities is reported to cause symptoms such as severe abdominal pain, nausea, vomiting, vertigo, ataxia, drowsiness, and coma. Instant collapse in infants has been reported after the local application of menthol/camphor to their nostrils. Seizures may be the first clinical sign of severe toxicity of camphor; however, seizures are usually self-limited. Severe toxicity of camphor can result in delirium, visual hallucinations, cerebral edema, and status epilepticus. Systemic toxicity may include hypotension, tachycardia, respiratory failure, and death.

Treatment: The stomach should be emptied by gastric lavage or administration of oral activated charcoal. Fluid and electrolyte management is the mainstay of treatment with the immediate aim of correction of acidosis, hyperpyrexia, hypokalaemia, and dehydration, if present. Any convulsions must be controlled first through supportive care including anticonvulsant therapy.

5. Pharmacological Properties

5.1 Mechanism of Action

Methyl Salicylate

Methyl salicylate inhibit cyclooxygenase (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.

Camphor

Camphor exerts an analgesic action when applied topically by producing a warm sensation. It excites and desensitizes sensory nerves by activating heat-sensitive TRP vanilloid subtype 1 (TRPV1) and TRPV3 receptors. TRPV3 cation channels are molecular sensors that play a role in nociception and thermosensation by inducing thermal sensation and heat-induced hyperalgesia. Camphor interacts with TRPV3 channels via pore-region cysteine residues 3, leading to channel activation and a rise in intracellular calcium levels.

Camphor also activates cold-sensitive transient receptor potential melastatin 8 (TRPM8) and sensitizes cold-induced calcium transients. By this mechanism, camphor produces cooling effect following topical application.

5.2Pharmacodynamic 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.

Camphor

Camphor is a stimulant, rubefacient, anti-pruritic, and mild antiseptic agent. Camphor produces counterirritant effect by activating and then desensitizing epidermal nociceptors. When camphor used in combination with other ingredients like menthol and methyl salicylate, it becomes more effective for neuralgia and other types of neuropathic pain.

5.3Pharmacokinetic Properties

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.

Camphor

Camphor is well absorbed after dermal exposure. It is hydroxylated in the liver to yield hydroxyl-camphor metabolites which are then conjugated with glucuronic acid and excreted in the urine. Camphor crosses the placenta.

6. Nonclinical Properties

6.1 Animal Toxicology

Methyl Salicylate

Acute dermal LD_{50} 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 LD_{50} 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 LD_{50} values normally greater than 2000 mg/kg body weight (rats and mice). Only limited studies are available investigating dermal toxicity. In one study the LD_{50} 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.

Camphor

Camphor appears to have moderate acute oral toxicity, with an LD_{50} of 1310 mg/kg in mice. It demonstrated moderate to high toxicity in acute inhalation studies (450 mg/m^3 (72 ppm) in mice and 500 mg/m^3 (80 ppm) in rats). In sub-chronic studies, inhaled camphor resulted in emphysema in mice at 210 mg/m^3 (33 ppm) and rabbits at 33 mg/m^3 (5 ppm). In 13-week subchronic dermal studies, camphor had the no-observed-adverse-effect levels (NOAELs) of 1000 mg/kg/day in mice and 250 mg/kg /day in rats.
The International Programme on Chemical Safety (IPCS) reported negative results in carcinogenicity tests for camphor. In addition, camphor was negative for genotoxicity in a microsome mutagenesis test, and a peripheral blood micronucleus assay. Reproductive toxicity studies were not available for camphor, however, in developmental toxicity studies, camphor demonstrated no fetal toxicity (with NOAELs ≥800 mg/kg/day in rats) at dose levels that resulted in maternal toxicity.

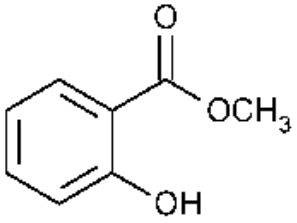
7. Description

MEFTAL-FORTE Topical Cream is White to off white coloured smooth cream with uniform consistency, free from gritty particles & foreign matter.

MEFTAL-FORTE Topical Cream contains 30% of methyl salicylate, 10% of menthol, and 4% of camphor for external use in adults and children above 6 years of age.

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.
Molecular Weight: 152.15 g/mol.
Chemical Name: Methyl 2-hydroxybenzoate.
Molecular Formula: C8H8O3.
Structural Formula:



Menthol

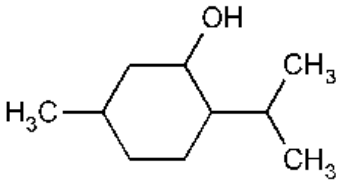
Menthol is an organic compound obtained from peppermint or mint oils with flavoring and local anesthetic properties.

Molecular Weight: 156.27 g/mol

Chemical Name: 5-methyl-2-propan-2-ylcyclohexan-1-ol.

Molecular Formula: C10H20O.

Structural Formula:



Camphor

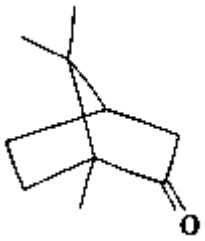
Camphor appears as a colorless or white colored crystalline powder with a strong mothball-like odor.

Molecular Weight: 152.23 g/mol

Chemical Name: 1,7,7-trimethylbicyclo[2.2.1]heptan-2-one.

Molecular Formula: C10H16O.

Structural Formula:



Inactive ingredients: Purified Water, Disodium Adetate, Imidurea, Carbomer 940, Trolamine, Glyceryl Monostearate, Cetamacrogol 1000, Cetostearyl Alcohol, Anhydrous Lanolin, polysorbate 80 & Polyoxyl 40 Hydrogenated Castor Oil.

8. Pharmaceutical Particulars

8.1 Incompatibilities

None known.

8.2Shelf-life

24 Months

8.3Packaging Information

Available in 50 gram lami-tube.

8.4Storage and Handling Instructions

Store below 30°C. Do not freeze.
Keep out of reach of children.

9. Patient Counseling Information

Instructions to patients:

- Use this product only on external surfaces, and 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 cream with eyes and mucous membranes.
- Avoid direct application into nostrils. It is dangerous if this medicine (as it contains camphor) come in contact with the nostril of a child.
- This medicine is not recommended for use in children below 6 years of age.

10. Details of Manufacturer

Blue Cross Laboratories Pvt Ltd.
L – 17, Verna Industrial Estate, Verna, Goa – 403722.

11. Details of Permission or License Number with Date

Mfg. Lic. No. : 271, Date of FDA Product Permission: 23/02/2019

12. Date of Revision

March 2021.

MADE IN INDIA BY
BLUE CROSS LABORATORIES PVT LTD.
A-12, M.I.D.C., NASHIK-422 010.
Regd. Off.: Peninsula Chambers, G. K. Marg, Mumbai-400 013.