SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
THERMO-EFAMAT 10%+1% cream

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Active substance:
Each 1 g cream contains 100 mg etofenamate and 10 mg benzyl nicotinate as active ingredients.
Excipients:
Cetyl alcohol.....……10 mg/g
Benzyl alcohol……15 mg/g

See section 6.1 for excipients

3. PHARMACEUTICAL FORM
Cream.
White or whitish cream with a homogeneous appearance.

4. CLINICAL PARTICULARS
4.1. Therapeutic indications
Subacute and chronic rheumatic diseases of the soft tissues of the musculoskeletal system.
- Muscular rheumatism
- Muscle stiffness associated with frozen shoulder (periarthritis of the shoulder region)
- Lumbago
- Sciatalgia
- Tenosynovitis
- Bursitis
- Diseases of the spine or joints due to overstrain and erosion (spondylosis, osteoarthritis)

4.2. Posology and method of administration
Frequency and duration of administration
THERMO-EFAMAT can be applied up to 2 g (the size of a hazelnut) several times a day (3-4 times) depending on the size of the painful area.

Treatment can be continued for up to 2 weeks. If symptoms persist, a doctor should be consulted to determine whether further treatment is required.

Method of administration

For topical use.
Using the massage nozzle of THERMO-EFAMAT, apply the cream into the skin with light pressure and circular movements.

Additional information on special populations
Renal/hepatic impairment:
No dosage adjustment is required.

Pediatric population:
Experience with use in children is limited. THERMO-EFAMAT is not recommended for use in children.

Geriatric population:
No dose adjustment is required.

4.3. Contraindications
THERMO-EFAMAT is contraindicated in the following cases.
- Hypersensitivity to etofenamate, flufenamic acid, benzyl nicotinate, any substance contained in THERMO-EFAMAT or other non-steroidal anti-inflammatory agents.
- Last trimester of pregnancy.
- Breastfeeding period.
- In children, as clinical experience is not yet sufficient.

4.4. Special warnings and precautions for use
THERMO-EFAMAT should not be applied to damaged or eczematous inflamed skin.
THERMO-EFAMAT should not come into contact with mucous membranes or eyes.
THERMO-EFAMAT contains cetyl alcohol. This substance may cause local skin reactions (such as contact dermatitis).
This medicinal product contains benzyl alcohol. However, it does not require any warning due to the way it is used.

4.5. Interactions with other medicinal products and other forms of interaction
THERMO-EFAMAT has no known interaction when used topically as recommended.

4.6. Pregnancy and lactation
General advice
Pregnancy Category: C/D (3rd trimester).

Women of childbearing potential/ Birth control (Contraception)
It is not recommended for women planning to become pregnant. If THERMO-EFAMAT is to be used, effective contraception should be used.

Data on the use of etofenamate/benzyl nicotinate in pregnant women are not available. Animal studies are insufficient in terms of effects on pregnancy /and-or/ embryonal/fetal development /and-or/ parturition /and-or/ postnatal development. The potential risk to humans is not known.

Pregnancy
Inhibition of prostaglandin synthesis may adversely affect pregnancy and/or embryo/fetal development. Data from epidemiologic studies suggest an increased risk of miscarriage, cardiac malformations and congenital abdominal wall defects after the use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk increase for cardiovascular malformation is less than 1% and is approximately 1.5%. This risk is thought to increase with dose and duration of treatment.

Animal experiments have shown that prostaglandin synthesis inhibitor administration leads to increased pre- and post-implantation loss and embryo/fetus lethality. In addition, an increased incidence of various malformations, including cardiovascular malformations, has been reported in animals given prostaglandin synthesis inhibitors during the organogenesis stage.

Ethophenamate should not be given during the first and second trimesters of pregnancy unless clearly necessary. If etofenamate is to be used in childbearing women or during the first or second trimester of pregnancy, the dose of etofenamate should be as low as possible and the duration of treatment should be short.

With all prostaglandin synthesis inhibitors during the third trimester of pregnancy;
- Possible effects on the fetus:
  - cardiopulmonary toxicity (premature closure of the ductus arteriosus and pulmonary hypertension);
  - renal dysfunction (may progress to renal failure with oligohydramnios)
- In the mother and newborn, at the end of pregnancy:
  - possible prolongation of bleeding time, anti-aggregant effect that can occur even at very low doses.
  - inhibition of uterine contractions, resulting in prolongation or delay of labor.

Consequently, etofenamate is contraindicated in the third trimester of pregnancy.

Lactation

THERMO-EFAMAT may only be used in small areas and for a short time in nursing mothers.

Reproductive ability / Fertility
Since the use of etofenamate may impair fertility in women, THERMO-EFAMAT is not recommended in women planning to become pregnant. Discontinuation of THERMO-EFAMAT treatment should be considered in women who have problems getting pregnant or who are being investigated for infertility.

4.7. Effects on driving and using machines
Not known.

4.8. Undesirable effects
Terms and frequency ratings used for undesirable effects:
Very common (≥1/10); common (≥1/100 to < 1/10); uncommon (≥1/1000 to <1/100); rare (≥1/10,000 to <1/1000); very rare (<1/10,000); unknown (cannot be estimated based on available data)

Skin and subcutaneous tissue disorders:

Uncommon:	Skin redness and mild burning are part of the desired therapeutic effect and resolve rapidly when the drug is discontinued.
Very rare:	Very rarely allergic skin reactions may occur, which disappear rapidly when the drug is discontinued.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization 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
If THERMO-EFAMAT is applied to the skin more than the recommended dose, the gel should be removed and the skin washed with water.

In case of misuse, headache, dizziness or epigastric pain may occur when a tube of THERMO-EFAMAT or more is applied over a large body surface in a short period of time.

Recommended treatment:
Excessive amounts of THERMO-EFAMAT applied to the body surface should be washed off

with water.

Because of its taste, toxicologically significant doses cannot usually be swallowed orally, but gastric lavage is performed when this occurs.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Non-steroidal anti-inflammatory / analgesic drugs
ATC Code: M02AA06

Etofenamate is a non-steroidal anti-inflammatory drug with analgesic properties. Its pronounced antifilogistic effect, proven by several animal experiments and demonstrated by several studies in humans, is based on its many different actions. Ethofenamate acts at various points of the inflammatory process: in addition to inhibition of prostaglandin synthesis, inhibition of histamine release, antagonistic effects on bradykinin and serotonin, inhibition of complement activity and inhibition of hyaluronidase release have been demonstrated.

Membrane stabilizing properties inhibit the release of proteolytic enzymes. As a result, it inhibits exudative and proliferative inflammatory events and reduces anaphylactic and foreign body reactions.

5.2. Pharmacokinetic properties

Absorption:
After administration of 300 mg etofenamate in THERMO-EFAMAT cream form, maximum plasma flufenamic levels are reached approximately 12 to 24 hours later.

There is considerable inter- and intra-individual variability, depending on the site of application, skin moisture status and other factors. Following dermal administration, its relative bioavailability is within the limits of other ethophenamate products (up to 20%).

Distribution:
Binds 98-99% to plasma proteins.

Biotransformation:
Ethophenamate is metabolized in the liver by hydroxylation, ether and ester cleavage.

Elimination:
Ethophenamate is excreted via the kidneys and feces as a large number of metabolites

(hydroxylation, ether and ester cleavage) and their conjugates.

5.3. Preclinical safety data

When etofenomate is applied topically, the rate of absorption should be kept in mind when evaluating toxicological data.

Acute toxicity:

Acute toxicity studies of etofenomate have been performed in rats, mice, guinea pigs and rabbits by different routes of administration.

Subchronic and chronic toxicity:

Subchronic toxicity has been investigated in various animal species. One-year studies with oral administration were performed in rats (7, 27, 100 mg/kg/day) and primates (7, 26, 100 mg/kg/day). Rats given 100 mg/kg per body weight developed gastrointestinal bleeding and ulcers followed by peritonitis and increased mortality. High doses resulted in decreased body weight, thymus gland weight and hemoglobin in primates.

Mutagenicity and carcinogenicity

In vitro and in vivo gene and chromosome mutation induction studies have yielded negative results. The possibility of mutagenicity has been excluded with sufficient reliability. Long-term studies involving oral administration to rats (7, 21, 63 mg/kg/day) and mice (15, 45, 140 mg/kg/day) did not provide evidence of any tumorigenic potential of etofenamate.

Reproductive toxicity:

Ethofenamate crosses the placental barrier.

There is no experience of administration in humans. In animal studies, the embryotoxic dose was lower than the maternal toxic dose. In rats, there was an increased incidence of renal pelvic enlargement at a dose of 21 mg/kg orally administered and an increased incidence of 14 rib pairs at a dose of 7 mg/kg orally in offspring whose mothers had received treatment.

6. PHARMACEUTICAL PROPERTIES

6.1. List of excipients

Benzyl alcohol
Cetyl alcohol
Citrate buffer
Glyceryl monostearate
Macrogol stearate

Isopropyl myristate
Deionized water

6.2. Incompatibilities
There are no known incompatibilities.

6.3. Shelf life
36 months.

6.4. Special precautions for storage
Store at room temperature below 25°C.

6.5. Nature and contents of the container
In box, in Alu tube with pink HDPE screw cap and white HDPE massage cap, 50 g.

6.6. Special precautions for disposal and other handling
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORIZATION NUMBER
2015/226

9. DATE OF FIRST AUTHORIZATION / RENEWAL OF THE AUTHORIZATION
Date of first authorization: 03.03.2015
Date of last renewal:

10. DATE OF REVISION OF THE TEXT