

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Etoflam 5% w/w Gel

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

The gel contains 5% w/w etofenamate.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Gel

A nearly transparent yellowish gel.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the treatment of inflammatory disorders of the musculo-skeletal system.

4.2 Posology and method of administration

Recommended dosage:

Adults (including the elderly):

Etoflam 5% w/w gel is applied topically. A 5-10cm strip of gel (according to the area affected) should be rubbed in gently. This may be repeated up to 4 times daily.

Clinical studies in patients with impaired renal function or undergoing anti-coagulant therapy have not indicated a need to change the recommended dosage in these patients.

Children and infants:

The use of Etoflam 5% w/w gel is not recommended in children or infants.

It is recommended that treatment should be reviewed after 14 days. Treatment should not extend beyond 6 weeks. In symptomatic treatment of osteoarthritis, therapy should be reviewed after 4 weeks.

4.3 Contraindications

1. Etoflam 5% w/w gel contains alcohol and should not be applied to broken skin.
2. Use with occlusive dressings.
3. Use in patients hypersensitive to any of the ingredients or to non-steroidal anti-inflammatory agents including aspirin.
4. Use simultaneously to the same site with any other topical preparation.
5. Use in the presence of local infection.

4.4 Special warnings and precautions for use

1. Etoflam 5% w/w gel contains alcohol and therefore contact with the eyes or the mucous membranes should be avoided.
2. Hands should be thoroughly washed after use of this product.
3. This product should not be applied to irritated or broken skin. If skin irritation develops, use of the product should be discontinued.
4. If there is no improvement or the condition is aggravated, the doctor should be consulted.

4.5 Interaction with other medicinal products and other forms of interaction

None known.

4.6 Fertility, pregnancy and lactation

Etoflam 5% w/w gel is not recommended for use during pregnancy and lactation.

Etofenamate and some of its metabolites have been shown to cross the placenta in rats (oral and cutaneous) and rabbits (cutaneous). After 10, 30 and 100mg/kg BW per day (rabbits up to the 18th day of gestation) the concentrations in the placentas, uteri, foetuses, organs and bile decreased rapidly after stopping administration; they were below the per mille limit.

Elimination with the milk has been studied in goats and humans. After 65 mg/kg BW i.m., goats excreted 20-60 microg of etofenamate plus metabolites per litre of milk. After oral administration of 300 mg etofenamate the milk of lactating women contained no etofenamate but only main metabolite flufenamic acid. In total 1-14 microg flufenamic acid was excreted within 2 days. These concentrations have no practical meaning, since they are orders of magnitude below the therapeutic dose.

No teratogenic effects have been found in laboratory studies but the safety of etofenamate absorbed from Etoflam 5% w/w gel to the foetus, if used during pregnancy, or to the suckling infant if used during lactation, has not been established.

4.7 Effects on ability to drive and use machines

Not applicable.

4.8 Undesirable effects

The following undesirable effects have been reported through post-marketing use.

Undesirable effects listed in the table are grouped by MedDRA System Organ Classes and are ranked under heading of frequency, using the following convention, when applicable: very common ($\geq 1/10$); common ($\geq 1/100$ to $<1/10$); uncommon ($\geq 1/1,000$ to $<1/100$); rare ($\geq 1/10,000$ to $<1/1000$); very rare ($<1/10,000$); not known (cannot be estimated from the available data).

System Organ class	Adverse reaction	Frequency
Skin and subcutaneous tissue disorder		
	Contact dermatitis	Rare

4.9 Overdose

In view of the topical route of administration overdosage is not considered a practical possibility.

5 PHARMACOLOGICAL PROPERTIES**5.1 Pharmacodynamic properties**Pharmacotherapeutic group:

Anti-inflammatory/analgesic for the treatment of inflammatory musculoskeletal system disorder.

Mechanism of action:

Interactions with the arachidonic acid cascade (inhibition of prostaglandin synthesis) is postulated as the main action mechanism of nonsteroidal anti-inflammatories.

Pharmacodynamic Effect:

In vitro studies have clearly shown that etofenamate inhibits both the lipoxigenase pathway and the cyclooxygenase pathway of arachidonic acid metabolism. The IC_{50} is 1.2×10^5 M for inhibition of leukotriene B_4 biosynthesis in polymorphonuclear

leucocytes and 2.8×10^7 M for inhibition of PGE₂ release from macrophages. These values show that etofenamate has anti-inflammatory/analgesic activity.

Etofenamate is a flufenamic acid derivative, which is readily transported through the skin and concentrated in inflamed tissue, where it exerts anti-inflammatory and analgesic effects by inhibiting the release of histamine, lysosomal enzymes and prostaglandin.

5.2 Pharmacokinetic properties

In human studies plasma levels after a single topical application of gel were found to be low. Levels were similar in patients with impaired kidney function. Levels are broadly independent of kidney function.

In long term study (20 or 40g gel/week for 10-36 weeks) plasma levels of up to 184 microg/l (40g dose) in serum and dose-proportional levels up to 170 microg/l in the synovial fluid of the knee were found.

Etofenamate, like other xenobiotics, is metabolised by the liver by oxidation and conjugation. The only active metabolite is flufenamic acid. All other degradation compounds are inactive. A change in the metabolism of etofenamate in patients with pre-existing liver damage is very unlikely because of considerable excess capacity for two main metabolisation pathways: oxidation and conjugation.

If drug metabolism were slowed, elevation and prolongation of the activity would be conceivable. The etofenamate plasma level found in these patients however are in roughly the same region as those of rheumatic patients without liver disease.

Etofenamate is excreted renally and faecally in the form of its metabolites (hydroxylations, ether cleavage, ester cleavage) and their conjugates.

Renal function has been shown not to limit etofenamate elimination during cutaneous application. In studies even in the most severe forms of renal insufficiency there were no signs of active ingredient accumulation.

5.3 Preclinical safety data

Animal studies have shown no evidence of an embryotoxic or carcinogenic effect. In vitro and in vivo studies of the induction of gene and chromosome mutations were negative. A mutagenic effect appears to be adequately ruled out.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

ethoxylated cetyl-/oleyl alcohol
ethoxylated partially unsaturated fatty alcohol
Isopropyl alcohol
Macrogol 400
Carbomer
Sodium hydroxide
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Collapsible aluminium tube with an internal coating with polyethylene screw cap. Tubes contain either 20g or 100g of gel product.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

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Clonee
Co. Meath.
Ireland

8 MARKETING AUTHORISATION NUMBER

PA1113/002/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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