SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

EFAMAT 1 g/2 mL Solution for IM Injection

Cardiovascular Risk:
NSAI drugs may cause an increased risk of stroke, MI and serious cardiovascular thrombotic events, which can be fatal. This risk may increase with the duration of use. Patients with cardiovascular disease or at risk of cardiovascular disease may be at increased risk, (see section 4.4)
EFAMAT I.M. is contraindicated for the treatment of peri-operative pain in preparation for coronary artery by-pass graft surgery (see section 4.4).

Gastrointestinal Risk:
NSAI drugs cause an increased risk of serious gastrointestinal side effects such as perforation, ulceration and bleeding in the stomach or intestinal tract, which can be fatal. These side effects can occur at any time during treatment and without warning symptoms. The risk of serious gastrointestinal events is higher in elderly patients (see section 4.4).

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ampoule,
Active substance:
Contains 1 g of etofenamate in 2 ml of injection solution.

Excipients:
For the full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

Ampoule (Solution for injection)
Light yellow, clear oily solution for intramuscular (i.m.) administration.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

It is indicated for the treatment of signs and symptoms of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis, as well as acute gouty arthritis, acute musculoskeletal pain, postoperative pain and dysmenorrhea.

Note: The solution for injection is indicated only when topical application of etofenamate is not useful or not appropriate. As a rule, treatment should be limited to a single injection.

EFAMAT I.M. is not suitable for the initiation of treatment in diseases requiring rapid onset of action due to the slow release of the active substance.
Due to the slow release of the active substance from the oily formulation, the duration of action after EFAMAT I.M. administration may be prolonged up to 24 hours.

4.2 Posology and method of administration

Frequency and duration of administration:
In adults, a single deep intramuscular injection of 2 ml of EFAMAT I.M. solution for

injection (1 ampoule is equivalent to 1000 mg etofenamate) is usually sufficient.

Method of administration:
For intramuscular administration.
Due to the possibility of anaphylactic reactions including shock, the patient should be monitored for at least 1 hour after EFAMAT I.M. injection. An emergency kit must be available. The patient is informed about this measure.

After breaking the ampoule, the solution for injection is drawn into a syringe and injected deeply into the muscle (usually the gluteus muscle) with a sufficiently long injection needle. Before injecting the solution, the plunger of the syringe is retracted very slightly to ensure that no blood vessels are damaged.

Additional information on special populations:
Renal / Hepatic impairment:
It should not be used in patients with impaired liver or kidney function.

Paediatric population:
Experience in children is limited. EFAMAT I.M. is not recommended for use in children and adolescents.

Geriatric population:
Caution should be exercised during use in elderly patients due to possible side effects (see section 4.4).

4.3 Contraindications

EFAMAT I.M. is contraindicated in the following cases.

- Those who are hypersensitive to etofenamate, other non-steroidal anti-inflammatory (NSAI) drugs or any substance contained in EFAMAT I.M.
- History of bronchospasm, asthma, rhinitis, urticaria or allergic-type reactions to acetylsalicylic acid (aspirin) or other non-steroidal anti-inflammatory (NSAI) drugs.
- Peri-operative pain management in preparation for coronary artery by-pass surgery.
- Patients with a history of gastrointestinal bleeding or perforation previously associated with NSAI drugs.
- Active or past history of peptic ulcer/haemorrhage (one or two proven bleeding or ulcer attacks).
- Those with severe heart failure.
- Treated with anticoagulants or platelet aggregation inhibitors.
- Those with impaired liver or kidney function.
- Last trimester of pregnancy.

4.4 Special warnings and precautions for use

Warnings:
Cardiovascular (CV) effects:
Cardiovascular thrombotic events:
Clinical trials of various COX-2 selective and non-selective NSAI drugs of up to three years duration have shown an increased risk of serious cardiovascular thrombotic events, myocardial infarction (MI) and stroke, which can be fatal. All COX-2 selective or non-

selective NSAI drugs have similar risks. Patients with known CV disease or CV risk factors are at increased risk. There is insufficient information to exclude these risks for etofenamate. In patients treated with NSAI drugs, the lowest effective dose should be used for the shortest possible duration to minimise potential CV risk. Physicians and patients should remain alert for the development of such events, even in the absence of previous CV symptoms. Patients should be informed about serious CV signs and/or symptoms and what to do if they occur.

There is no consistent evidence that aspirin use reduces the increased risk of serious CV thrombotic events associated with NSAI drug use. Concomitant use of aspirin and NSAI drugs increases the risk of serious GI events.

In two large, controlled clinical trials of COX-2 selective NSAI drugs for the treatment of pain in the first 10-14 days after coronary artery bypass surgery, an increased risk of MI and stroke was found (see section 4.3).

Hypertension:
NSAI drugs, including EFAMAT I.M., may lead to the development of new hypertension or worsening of existing hypertension, which may have implications in increasing the risk of CV events.

In patients using thiazide or loop diuretics, inadequate response to these drugs may develop due to NSAI drug intake.

NSAI drugs including EFAMAT I.M. should be used with caution in patients with hypertension. Blood pressure should be carefully monitored at the beginning and during NSAI drug treatment.

EFAMAT I.M. should be used after careful medical evaluation in patients with hypertension, immediately after major surgical interventions.

Congestive heart failure and oedema:
Fluid load and oedema were observed due to the use of NSAI drugs. EFAMAT I.M. should be used with caution in patients with fluid overload and heart failure.

In patients with uncontrolled hypertension, heart failure, acute ischaemic heart disease, peripheral arterial occlusive disease and/or cerebrovascular disease, NSAI drugs should be used only after careful evaluation of the indication. Similar assessment is also required before initiation of long-term therapy in patients with risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking).

Gastrointestinal effects:
For gastrointestinal safety, EFAMAT I.M. should be avoided in combination with NSAI drugs, including cyclooxygenase-2 selective inhibitors (COX-2 inhibitors).

Elderly patients have an increased incidence of adverse events observed with NSAI drugs, especially gastrointestinal bleeding and perforations, which can be fatal. (see section 4.3)

Gastrointestinal effects – risk of ulceration, bleeding and perforation:
NSAI drugs, including EFAMAT I.M., can cause serious gastrointestinal (GI) adverse events

such as inflammation, bleeding, ulceration and perforation of the stomach, small intestine and large intestine, which can be fatal. These serious adverse events can occur without warning at any time in patients treated with NSAI drugs. Only one in five patients with upper gastrointestinal adverse events due to NSAI drugs was symptomatic. Upper GI ulcers, major bleeding and perforation caused by NSAI drugs occur in approximately 1% of patients treated for 3-6 months and in approximately 2-4% of patients treated for 1 year. This increasing trend continues with prolonged use, increasing the chance of developing serious GI events at any time during treatment. However, even short-term treatment is not without risk.

NSAI drugs should be prescribed with extreme caution in patients with a history of ulcer and gastrointestinal bleeding. The risk of developing GI bleeding in *patients with a history of peptic ulcer and/or gastrointestinal bleeding* and prior NSAI drug use is 10 times higher than in patients without any of these risk factors. Other risk factors that increase the risk of GI bleeding in patients treated with NSAI drugs are concomitant use of oral corticosteroids or anti-coagulants, long-term use of NSAI drugs, smoking, alcohol use, advanced age, and impaired general condition. Most spontaneous reports of fatal GI events have occurred in elderly or debilitated patients and therefore particular caution should be exercised in the treatment of this patient population.

In patients treated with NSAI drugs, the lowest effective dose should be used in the shortest possible time to minimise the risk of potential GI events. Physicians and patients should be prepared for signs and symptoms of GI bleeding and ulceration that may develop during the use of NSAI drug, and if serious GI side effects are suspected, additional evaluation and treatment should be initiated immediately. In this case, NSAI drugs should be discontinued until a serious GI adverse event is excluded. Alternative non- NSAI treatments should be considered for high-risk patients.

Combination therapy with prophylactic agents (e.g. misoprostol or proton pump inhibitors) should be recommended in patients with a history of serious gastrointestinal events, in elderly patients, as well as in patients who should be taking low-dose aspirin or other drugs that increase gastrointestinal risks. (see section 4.5)

Caution should be exercised in patients taking medicines that increase the risk of ulceration or bleeding, including oral corticosteroids, anticoagulants such as warfarin, selective serotonin reuptake inhibitors or anti-thrombotic agents such as aspirin. (see section 4.5)

Caution should be exercised when giving NSAI drugs to patients with a history of gastrointestinal disease (ulcerative colitis, Crohn's disease) as their condition may worsen. (see section 4.8)

Renal Effects:
Long-term use of NSAI drugs has resulted in renal papillary necrosis and other kidney damage. Renal toxicity has also been observed in patients with compensatory activity of prostaglandins in maintaining renal perfusion. The use of NSAI drug in these patients may cause a dose-dependent decrease in the production of prostaglandins and a secondary decrease in renal blood flow, which may predispose to significant renal failure. The risk of this reaction is higher in patients with inadequate renal function, heart failure, liver failure, those taking diuretics and ACE inhibitors and elderly patients. Following discontinuation of NSAI drug treatment, the pretreatment state is usually restored.

Advanced renal disease:
There are no controlled clinical trial data on the use of EFAMAT I.M. in patients with advanced renal disease. Therefore, EFAMAT I.M. is not recommended in patients with advanced kidney disease. If EFAMAT I.M. is to be used, close monitoring of renal function is recommended.

Anaphylactoid reactions:
Like other NSAI drugs, anaphylactoid reactions may occur in patients with unknown previous exposure to EFAMAT I.M. EFAMAT I.M. should not be given to patients with aspirin triad. This symptom complex typically occurs in patients with asthma who have rhinitis with or without nasal polyps or who frequently experience severe, potentially fatal bronchospasm after taking aspirin or other NSAI drugs (see section 4.3). In cases of anaphylactoid reaction, emergency help should be sought.

Skin reactions:
NSAI drugs, including EFAMAT I.M., can cause serious skin reactions such as exfoliative dermatitis, Stevens-Johnson Syndrome (SJS) and toxic epidermal necrosis (TEN), which can be fatal (see section 4.8). These serious events can occur without warning symptoms. In the majority of cases, the development of reactions is in the first month of treatment. Patients should be informed about the signs and symptoms of serious dermatological conditions and EFAMAT I.M. should be discontinued at the first appearance of skin rash, mucosal lesions or any signs of hypersensitivity.

EFAMAT I.M. should be used in patients with inducible porphyria after careful evaluation of the risk-benefit ratio.

Precautions:
EFAMAT I.M. cannot be expected to replace corticosteroids or treat corticosteroid insufficiency. Sudden discontinuation of corticosteroids may lead to exacerbation of the disease. In patients who have been using corticosteroids for a long time, if treatment is to be discontinued, it should be gradually and slowly reduced.

The pharmacological activity of EFAMAT I.M. in reducing inflammation may reduce the specificity of diagnostic findings in the detection of complications of non-infectious, painful conditions.

Hepatic effects:
In 15% of patients receiving NSAI drugs, including EFAMAT I.M., one or more of the liver tests may be borderline elevated. These laboratory abnormalities may progress during treatment, may remain unchanged or may be transient if treatment is continued. In clinical trials with NSAI drugs, significant ALT and AST elevations (three or more times normal values) have been reported in approximately 1% of patients. In addition, rare serious liver reactions have been reported, including jaundice and fatal fulminant hepatitis, liver necrosis and liver failure, some of which may result in death.

If a patient develops symptoms and/or signs of impaired liver function or if liver tests are abnormal during treatment with EFAMAT I.M., investigations for the development of more serious liver reactions should be performed. EFAMAT I.M. treatment should be discontinued

if clinical signs and symptoms compatible with liver disease develop or if systemic clinical findings (eosinophilia, skin rash, etc.) occur.

Hematological effects:
Anaemia may sometimes be observed in patients receiving NSAI drugs including EFAMAT I.M. This may be due to fluid retention, obvious or massive GI blood loss or an incompletely defined effect on erythropoiesis. If any signs and symptoms of anaemia are observed in patients receiving long-term NSAI drugs including EFAMAT I.M., haemoglobin and haematocrit values should be checked. NSAI drugs inhibit platelet aggregation and have been shown to prolong bleeding time in some patients. Unlike aspirin, its effects on platelet function are quantitatively small, short-term and reversible.

Patients receiving EFAMAT I.M. who may be adversely affected by changes in platelet function, such as patients with coagulation disorders or patients receiving anticoagulants, should be carefully monitored.

Patients with asthma:
Patients with asthma may have aspirin-sensitive asthma. Aspirin use in patients with aspirin-sensitised asthma may cause severe bronchospasm, which can be fatal. Since cross-reactions including bronchospasm have been reported between aspirin and other NSAI drugs in such aspirin-sensitive patients, EFAMAT I.M. should not be administered to such aspirin-sensitive patients and should be used with caution in patients with asthma.

Patients should be given the following information before starting NSAI drug treatment and periodically during treatment:

1. EFAMAT I.M. can cause serious cardiovascular (CV) side effects, such as myocardial infarction or stroke, which may lead to hospitalisation or even death. Since serious CV events may occur without any warning symptoms, patients should be alert for signs or symptoms such as chest pain, shortness of breath, weakness, difficulty in speaking and should seek medical advice if such signs or symptoms occur. Patients should be informed about the importance of this follow-up.
2. Like other NSAI drugs, EFAMAT I.M. can cause GI discomfort and, rarely, serious GI side effects such as ulcers and bleeding that may lead to hospitalisation or death. Since serious GI tract ulceration and haemorrhage may occur without any warning symptoms, patients should be alert for signs and symptoms of ulceration and haemorrhage and seek medical advice if signs and symptoms such as epigastric pain, dyspepsia, melena and haematemesis develop.
3. EFAMAT I.M., like other NSAIDs, may cause serious dermatological side effects such as exfoliative dermatitis, SJS and TEN, which may lead to hospitalisation and death. Although many skin reactions occur without warning, patients should be alert for other hypersensitivity reactions such as skin rash, wheals, fever or itching and should seek medical advice if these signs or symptoms develop. If patients develop any skin rash, treatment should be discontinued and patients should contact their doctor as soon as possible.
4. Patients should report signs and symptoms such as unexpected weight gain or oedema to their doctor.
5. Patients should be informed about the signs and symptoms of hepatotoxicity (such as nausea, weakness, lethargy, pruritus, jaundice, right upper quadrant tenderness and

flu-like symptoms). When these symptoms occur, the patient should stop taking the medicine and be referred to medical treatment immediately.

6. Patients should be warned about signs of anaphylactoid reactions (such as difficulty breathing, swelling of the face and neck). When these symptoms occur, the patient should be referred to emergency care immediately.
7. Since it may cause premature closure of the ductus arteriosus in late pregnancy, EFAMAT I.M. should be avoided like other NSAI drugs.

Laboratory tests:
Since severe GI tract ulceration and haemorrhage may develop without signs and symptoms, physicians should monitor for signs and symptoms of GI bleeding. Complete blood count and biochemistry tests should be performed periodically in patients receiving long-term NSAI drug. EFAMAT I.M. treatment should be discontinued if clinical signs and symptoms are compatible with the development of hepatic and renal insufficiency, if symptoms specific to systemic disease develop (eosinophilia, skin rash, etc.) or if elevated liver tests persist or worsen.

4.5 Interaction with other medicinal products and other forms of interaction

Angiotensin-converting enzyme (ACE) inhibitors:
Reports suggest that NSAI drugs may reduce the antihypertensive efficacy of ACE-inhibitors. This interaction should be considered in patients taking ACE-inhibitors together with NSAI drug.

Aspirin:
Like other NSAI drugs, concomitant use of etofenamate with aspirin is generally not recommended as it may increase side effects.

Furosemide:
Clinical studies and post-marketing observations have shown that etofenamate reduces the natriuretic effect of furosemide and thiazides in some patients. This effect has been attributed to inhibition of renal prostaglandin synthesis. During concomitant use with NSAI drugs, patients should be closely monitored to ensure that the diuretic effect is achieved and for signs of renal impairment (see section 4.4).

Lithium:
NSAI drugs cause an increase in plasma lithium level and a decrease in renal lithium clearance. The mean minimum lithium concentration increases by 15% and renal clearance decreases by approximately 20%. These effects have been attributed to the inhibition of renal prostaglandin synthesis by NSAI drugs. Therefore, when NSAI drugs and lithium are used together, patients should be carefully monitored for signs of lithium toxicity.
Lithium excretion from the kidneys should be monitored.

Methotrexate:
NSAI drugs have been reported to competitively inhibit the accumulation of methotrexate in rabbit kidney sections. This may indicate that they could enhance the toxicity of methotrexate. Caution should be exercised when NSAI drugs are used together with methotrexate.

Warfarin and anticoagulants:
The effects of warfarin and NSAI drugs on GI bleeding are synergistic. Therefore, those who

use these drugs together have a higher risk of serious GI bleeding than those who use them separately.

Corticoids or other non-steroidal anti-inflammatory agents:
Increased risk of gastrointestinal bleeding.

Probenecid or sulphinpyrazone:
Slowing of etofenamate elimination

Alcohol:
Increased risk of gastrointestinal bleeding.

Digoxin:
Digoxin serum levels are likely to be elevated.

Phenytoin:
An increase in phenytoin serum levels is possible.

Diuretics and other antihypertensive agents:
Decrease in diuretic or antihypertensive possible effect.

Potassium-sparing diuretics:
Development of hyperkalaemia is possible. Therefore, potassium values should be checked.

Cyclosporin:
Increased renal toxicity of cyclosporine is possible.

Antidiabetic agents:
In isolated cases, an interaction in blood glucose levels with the administration of non-steroidal anti-phylogistic agents has been described, requiring adjustment in the dose of anti-diabetic therapy. It is therefore recommended to take precautions to control blood glucose levels in concomitant treatment with these agents.

Selective serotonin reuptake inhibitors:
Increased risk of gastrointestinal bleeding

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

Women with childbearing potential / Birth control (Contraception)
It is not recommended for use in women planning to become pregnant. If EFAMAT I.M. is to be used, an effective contraceptive method should be applied.
Etofenamate has harmful pharmacological effects on pregnancy and/or fetus/newborn.

Pregnancy
Inhibition of prostaglandin synthesis may adversely affect pregnancy and/or embryo/fetal development. Data from epidemiological 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. This risk is thought to increase with the 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 frequency of various malformations, including cardiovascular malformations, has been reported in animals given prostaglandin synthesis inhibitors during the organogenesis stage.

In the first and second trimester of pregnancy, etofenamate should not be given 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 foetus:
  - cardiopulmonary toxicity (premature closure of the ductus arteriosus and pulmonary hypertension);
  - impaired renal function, (may progress to renal failure with oligohydramnios)
- In the mother and the child in late pregnancy
  - possible prolongation of bleeding time, anti-aggregant effect, which can occur even at very low doses.
  - inhibition of uterine contractions, resulting in prolonged or delayed labour.

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

Breastfeeding
Since etofenamate can pass into breast milk, EFAMAT I.M. should not be used during lactation.

Fertility
EFAMAT I.M. is not recommended in women planning to become pregnant as administration of etofenamate - similar to the use of other drugs that inhibit cyclooxygenase/prostaglandin synthesis - may impair fertility.

4.7 Effects on ability to drive and use machines
Even if used correctly, EFAMAT I.M. can alter the reaction speed in a way that impairs the ability to drive a car or operate machinery. This is especially important when used in combination with alcohol.
Patients should not drive and use machines while using EFAMAT I.M.

4.8 Undesirable effects
It should be borne in mind that the following undesirable effects are dose-dependent and may vary from individual to individual.

In general, the most common side effects are gastrointestinal. Peptic ulcer, perforation or gastrointestinal bleeding, sometimes fatal, may occur, especially in the elderly (see section 4.4.). Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melena, haematemesis, ulcerative stomatitis, colitis and exacerbation of Crohn's disease have been reported following administration (see section 4.4.). Less frequently, inflammation in

the stomach is observed. In general, the risk of gastrointestinal bleeding depends on the duration of treatment with NSAI drugs and the dose range used.

Oedema, hypertension and cardiac failure associated with NSAI drug treatment have been reported.

Clinical studies and epidemiological data suggest that the use of some NSAI drugs (particularly at high doses and long-term use) may be associated with a small increase in the risk of arterial thrombotic events (e.g. myocardial infarction or stroke) (see section 4.4).

Terms used for undesirable effects and their frequency:
Very common (≥1/10), common (≥1/100, < 1/10), uncommon (≥1/1,000, < 1/100), rare (≥ 1/10,000, < 1/1,000), very rare (< 1/10,000), unknown (cannot be estimated from the available data).

Undesirable effects reported for EFAMAT I.M:
Infections and infestations:
Very rare: Increased inflammation caused by infections (e.g. development of necrotising fasciitis)

Blood and lymphatic system disorders:
Rare: Haematopoiesis disorders (anaemia, leukopenia, agranulocytosis, thrombocytopenia)
Very rare: Haemolytic anaemia

Immune system disorders:
Unknown: Severe hypersensitivity reactions, swelling of the face and tongue, oedema of the larynx and contraction of the airways, difficulty breathing. Allergic vasculitis and pneumonia.

Endocrine disorders:
Very rare: Pancreatitis

Psychiatric disorders:
Very rare: Anxiety, nightmares, depression and psychotic reactions

Nervous system disorders:
Uncommon: Headache, agitation, irritability, fatigue, drowsiness and dizziness
Very rare: Impaired perception, taste disturbances, memory impairment, disorientation, spasms, tremor.

Eye disorders:
Very rare: Visual disturbances (blurred vision, diplopia)

Ear and labyrinth disorders:
Very rare: Tinnitus and conductive hearing disorders

Cardiac disorders:
Very rare: Palpitations, chest pain, hypertension, oedema.
Unknown: Cardiac failure may develop in isolated cases.

Gastrointestinal disorders:
Common: Gastrointestinal complaints such as nausea, vomiting, diarrhoea and mild gastrointestinal blood loss, which may cause anaemia in exceptional cases.
Uncommon: Dyspepsia, flatulence, abdominal spasm, anorexia, gastrointestinal ulcers (possible bleeding and perforation)
Rare: Haematemesis, melanoma or haemorrhagic diarrhoea
Very rare: Stomatitis, glossitis, oesophageal lesions, lower abdominal complaints (e.g. haemorrhagic colitis or exacerbation of Crohn's disease/ulcerative colitis) and constipation.

Hepatobiliary disorders:
Uncommon: Increased serum transaminase levels
Rare: Liver damage (hepatitis with or without jaundice, fulminant course in isolated cases, rarely without prodromal symptoms)

Skin and subcutaneous tissue disorders:
Uncommon: Hypersensitivity reactions such as cutaneous rash and itching
Rare: Urticaria, alopecia
Very rare: Bullous exanthema, eczema, erythema, photosensitisation, purpura (also allergic purpura) and severe forms of skin reaction (Stevens-Johnson syndrome, Lyell syndrome)

Kidney and urinary tract diseases:
Very rare: Renal tissue damage (interstitial nephritis, papillary necrosis), proteinuria and/or haematuria, which may be accompanied by acute renal failure.
Unknown: Nephritic syndrome may develop in isolated cases.

General disorders and administration site conditions:
Rare: Peripheral oedema (in patients with hypertension or renal failure)
Very rare: Burning sensation at the injection site or formation of a sterile abscess, oily tissue or skin necrosis (drug-induced skin embolism)

4.9 Overdose
Central nervous system disorders such as headache, dizziness, drowsiness and confusion may be symptoms of overdose. In addition, abdominal pain, nausea and vomiting may occur. Liver and kidney disorders and gastrointestinal haemorrhage may also occur.

Recommended treatment:
No specific antidote is available. In case of overdose, contact with the Poison Advisory Centre is recommended.

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Non-steroidal anti-inflammatory/ analgesic drugs
ATC Code: M02AA06

Etofenamate is a non-steroidal antiphlogistic drug with analgesic and anti-inflammatory properties. Its pronounced antifilogenic effect, proven by various animal experiments and shown by various studies on humans, is based on many different effects. Etofenamate acts at various points in the inflammatory process: In addition to inhibition of prostaglandin synthesis, inhibition of histamine release, antagonistic effect on bradykinin and serotonin,

inhibition of complement activity and inhibition of hyaluronidase release have been shown.

Membrane stabilising properties prevent the release of proteolytic enzymes. As a result, it prevents exudative and proliferative inflammatory events and reduces anaphylactic and foreign body reactions.

5.2 Pharmacokinetic properties

Absorption:
The release of etofenamate from the oily formulation of etofenamate occurs at a slow rate, thus showing a longer duration of action than water-soluble injectable forms of similar substances.
The plasma curves of etofenamate from etofenamate injection in the elderly and young are similar.
The relative bioavailability of intramuscularly injected etofenamate (EFAMAT I.M.) is 91% compared with orally administered flufenamic acid (tablets).
The maximum plasma levels of etofenamate (Cmax = 0.633 µmol/l + 0.232 µmol/l) are reached on average 5.67 hours (5.67±2.66 hours) after administration of etofenamate. Area under the curve is 8.95 ± 3.51 µmol*h/l.

Distribution:
It binds 98-99% to plasma proteins.

Biotransformation:
Etofenamate is metabolised in the liver by hydroxylation, ether and ester cleavages. May participate in the enterohepatic circulation.

Elimination:
Etofenamate is excreted in the form of various metabolites (hydroxylations, ether, ester decomposition) and their conjugates, mainly in bile and faeces and 35% through the kidneys.

5.3 Preclinical safety data

There is no indication of reproductive toxicity.
The tolerability of etofenamate has been investigated in acute and chronic toxicity studies in various animal species.

Acute toxicity.
The LD50 in rats after intravenous administration is 140 mg/kg and after oral administration is 292 mg/kg.

Chronic toxicity:
Of particular importance are the chronic studies in rats (7, 27, l00 mg/kg) and monkeys (7, 26, l00 mg/kg) by daily oral administration for 1 year. Doses of 27 mg/kg (in rats) and 26.0 mg/kg (in monkeys), which showed no adverse effects, are considerably higher than the daily therapeutic doses in humans.

Mutagenic and tumourogenic potential:
As shown in various studies, there is no evidence of any embryotoxic, mutagenic or carcinogenic effects.

Reproductive toxicity:
In rats (oral and cutaneous administration) and rabbits (cutaneous administration), etofenamate and some of its metabolites have been shown to cross the placenta. Rabbits were administered 10, 30 and 100 mg/kg per day until the 18th day of gestation. Levels in the placenta, uterus, foetus, organs and bile decreased rapidly after discontinuation of the drug.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Medium-chain triglyceride

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
24 months

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

6.5 Nature and contents of container
Colourless 2 ml colourless ring ampoule made of Type I glass (high strength borosilicate glass) with imprint.
EFAMAT I.M. 2 ml in boxes of 1 or 3 ampoules.

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 AUTHORISATION NUMBER(S)
231/80

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10. DATE OF REVISION OF THE TEXT