

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

FLEXO 1 G/2 ML IM SOLUTION FOR INJECTION

Cardiovascular Risk:

NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk (see section 4.4)

FLEXO is contraindicated for treatment of peri-operative pain in the setting of coronary artery bypass graft surgery (see section 4.4)

Gastrointestinal Risk:

NSAIDs cause an increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events (see section 4.4)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance:

Each 2 ml ampoule contains 1 g of etofenamate.

Excipients:

Medium-chain triglycerides.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

Clear and viscous solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Indicated for the treatment of the signs and symptoms of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis, and for the treatment of acute gouty arthritis, acute musculoskeletal pain, postoperative pain and dysmenorrhea.

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

Due to slow release of its active ingredient, FLEXO is not suitable for initiation of treatment in conditions requiring a rapid onset of action.

Due to slow release of the active ingredient from the oily formulation, the duration of action may be extended up to 24 hours after FLEXO administration.

4.2 Posology and method of administration

Posology / frequency and duration of administration:

In adults, a single deep intramuscular injection of 2 ml of FLEXO solution for injection (1 ampoule, equivalent to 1000 mg etofenamate) is usually sufficient.

Method of administration:

For intramuscular administration.

Due to the likelihood of the development of anaphylactic reactions including shock, the patient should be monitored for at least 1 hour after FLEXO injection. An emergency kit should be readily available. The patient should be informed about this measure.

After breaking the ampoule, the solution for injection is withdrawn into a syringe and is injected deeply into the muscle (usually gluteal muscle) with a sufficiently long injection needle. Before injecting the solution, the plunger of the syringe is withdrawn slightly to ensure that a blood vessel has not been entered.

Additional information on special populations

Kidney/Liver impairment:

It should not be used in patients with impaired liver or kidney function.

Pediatric population:

Experience with the use on children is limited. FLEXO is not recommended for use in children and adolescents.

Geriatric population:

Because of possible side effects (see section 4.4) caution should be exercised during use in elderly patients.

4.3 Contraindications

FLEXO is contraindicated in the following situations:

- Patients with hypersensitivity to etofenamate, other non-steroidal anti-inflammatory drugs (NSAIDs) or to any of the ingredients of FLEXO.
- Patients with a previous history of bronchospasm, asthma, rhinitis, urticaria, or allergic-type reactions associated with the use of acetylsalicylic acid (aspirin) or other non-steroidal anti-inflammatory drug (NSAIDs).
- For treatment of peri-operative pain in the setting of coronary artery bypass graft surgery.
- Patients with a previous history of gastrointestinal bleeding or perforation associated with NSAIDs.
- Patients with active or previous history of peptic ulcer/hemorrhage (one or two episodes of proven ulceration or bleeding).
- Patients with severe heart failure.
- Patients on anticoagulants or platelet aggregation inhibitors.
- Patients 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 up to 3 years' duration with several COX-2 selective and non-selective NSAIDs showed an increased risk of serious cardiovascular thrombotic events, myocardial infarction (MI), and stroke, which can be fatal. All COX-2 selective or non-selective NSAIDs have similar risks. Patients with CV disease or risk factors for CV disease are at greater risk. There is insufficient information for etofenamate to exclude these risks. To minimize the potential risk for an adverse CV event in patients treated with NSAIDs, the lowest effective dose should be used for the shortest duration possible. 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 the signs and/or symptoms of serious CV events and the steps to take if they occur.

There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious CV thrombotic events associated with NSAID use. The concurrent use of aspirin and an NSAID does increase the risk of serious GI events.

Two large, controlled, clinical trials of a COX-2 selective NSAID for the treatment of pain in the first 10 to 14 days following coronary artery bypass graft surgery found an increased incidence of myocardial infarction and stroke (see section 4.3).

Hypertension:

NSAIDs including FLEXO, can lead to onset of new hypertension or worsening of pre-existing hypertension, either of which may contribute to the increased incidence of CV events.

Patients taking thiazides or loop diuretics may have impaired response to these therapies when taking NSAIDs.

NSAIDs, including FLEXO, should be used with caution in patients with hypertension. Blood pressure should be monitored closely during the initiation of NSAID treatment and throughout the course of therapy.

FLEXO should be used after careful medical evaluation in hypertensive patients immediately after major surgical interventions.

Congestive heart failure and edema:

Fluid retention and edema have been observed in some patients taking NSAIDs. FLEXO should be used with caution in patients with fluid retention, hypertension, or heart failure.

NSAIDs should only be used after careful assessment of the indication in patients with uncontrolled hypertension, heart failure, acute ischemic heart disease, peripheral arterial occlusive disease and/or cerebrovascular disease. Similar consideration should be made before initiating treatment of patients with risk factors for cardiovascular disease (e.g. hypertension, hyperlipidemia, diabetes mellitus, and smoking).

Gastrointestinal effects:

For gastrointestinal safety, concomitant administration of FLEXO with NSAIDs including selective inhibitors of cyclooxygenase-2 (COX-2 inhibitors) should be avoided.

The elderly have an increased frequency of adverse reactions, to NSAIDs, especially gastrointestinal bleeding and perforation which may be fatal (see section 4.3)

Gastrointestinal effects - risk of ulceration, bleeding, and perforation:

NSAIDs, including FLE XO, can cause serious gastrointestinal (GI) adverse events including inflammation, bleeding, ulceration, and perforation of the stomach, small intestine, or large intestine, which can be fatal. These serious adverse events can occur at any time, with or without warning symptoms, in patients treated with NSAIDs. Only one in five patients, who develop a serious upper gastrointestinal adverse event on NSAID therapy, is symptomatic. Upper GI ulcers, gross bleeding, or perforation caused by NSAIDs occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year. These trends continue with longer duration of use, increasing the likelihood of developing a serious GI event at some time during the course of therapy. However, even short-term therapy is not without risk.

NSAIDs should be prescribed with extreme caution in those with a prior history of ulcer disease or gastrointestinal bleeding. *Patients with a prior history of peptic ulcer disease and/or gastrointestinal bleeding* who use NSAIDs have a greater than 10-fold increased risk for developing a GI bleed compared to patients treated with neither of these risk factors. Other factors that increase the risk of GI bleeding in patients treated with NSAIDs include concomitant use of oral corticosteroids or anticoagulants, longer duration of NSAID therapy, smoking, use of alcohol, older age, and poor general health status. Most spontaneous reports of fatal GI events are in elderly or debilitated patients and therefore, special care should be taken in treating this population.

To minimize the potential risk for an adverse GI event in patients treated with NSAIDs, the lowest effective dose should be used for the shortest duration possible. Patients and physicians should remain alert for signs and symptoms of GI ulcerations and bleeding during NSAID therapy and promptly initiate additional evaluation and treatment if a serious GI event is suspected. This should include discontinuation of the NSAID until a serious GI adverse event is ruled out. For high-risk patients, alternate therapies that do not involve NSAIDs should be considered.

Combination therapy with protective agents (e.g., misoprostol or proton pump inhibitors) should be considered for patients with a history of serious gastrointestinal events, for elderly patients, and also for patients requiring concomitant low dose aspirin or other drugs likely to increase gastrointestinal risk (see section 4.5)

Caution should be advised in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin, selective serotonin-reuptake inhibitors or anti-platelet agents such as aspirin (see section 4.5).

NSAIDs should be given with care to patients with a history of inflammatory bowel disease (ulcerative colitis, Crohn's disease) as their condition may be exacerbated (see section 4.8)

Undesirable Effects:

Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of a NSAID may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state.

Advanced renal disease:

No information is available from controlled clinical studies regarding the use of etofenamate in patients with advanced renal disease. Therefore, treatment with FLEXO is not recommended in these patients with advanced renal disease. If FLEXO therapy must be initiated, close monitoring of the patients renal function is advisable.

Anaphylactic reactions:

As with other NSAIDs, anaphylactoid reactions may occur in patients without known prior exposure to FLEXO. FLEXO should not be given to patients with the aspirin triad. This symptom complex typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking aspirin or other NSAIDs (see section 4.3). Emergency help should be sought in cases where an anaphylactoid reaction occurs.

Skin reactions:

NSAIDs, including FLEXO, can cause serious skin adverse events such as exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal (see section 4.8). These serious events may occur without warning symptoms. In most cases the reactions occur in the first month of treatment. Patients should be informed about the signs and symptoms of serious skin manifestations and FLEXO should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.

FLEXO should be used after careful evaluation of risk-benefit ratio in patients with induced porphyria.

Precautions:

FLEXO[®] cannot be expected to substitute for corticosteroids or to treat corticosteroid insufficiency. Abrupt discontinuation of corticosteroids may lead to disease exacerbation. Patients on prolonged corticosteroid therapy should have their therapy tapered slowly if a decision is made to discontinue corticosteroids.

The pharmacological activity of FLEXO in reducing inflammation may diminish the utility of these diagnostic signs in detecting complications of presumed noninfectious, painful conditions.

Hepatic effects:

Borderline elevations of one or more liver tests may occur in up to 15% of patients taking NSAIDs, including FLEXO. These laboratory abnormalities may progress, may remain unchanged, or may be transient with continuing therapy. Notable elevations of ALT or AST (approximately three or more times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials with NSAIDs. In addition, rare cases of severe hepatic reactions, including jaundice, fulminant hepatitis, liver necrosis, and hepatic failure, some of them with fatal outcomes have been reported.

A patient with symptoms and/or signs suggesting liver dysfunction, or with abnormal liver test values, should be evaluated for evidence of the development of a more severe hepatic reaction while on therapy with FLEXO. If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), FLEXO should be discontinued.

Hematological effects:

Anemia is sometimes seen in patients receiving NSAIDs, including FLEXO. This may be due to fluid retention, occult or gross GI blood loss, or an incompletely described effect upon erythropoiesis. Patients on long-term treatment with NSAIDs, including FLEXO, should have their hemoglobin or hematocrit checked if they exhibit any signs or symptoms of anemia. NSAIDs inhibit platelet aggregation and have been shown to prolong bleeding time in some patients. Unlike aspirin, their effect on platelet function is quantitatively less, of shorter duration, and reversible.

Patients receiving FLEXO who may be adversely affected by alterations in platelet function, such as those with coagulation disorders or patients receiving anticoagulants should be carefully monitored.

Patients with asthma:

Patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin-sensitive asthma may cause severe bronchospasm, which can be fatal. Since cross reactivity, including bronchospasm, between aspirin and NSAIDs has been reported in such aspirin-sensitive patients, FLEXO should not be administered to patients with this form of aspirin sensitivity and should be used with caution in patients with preexisting asthma.

Patients should be informed of the following information before initiating therapy with an NSAID and periodically during the course of ongoing therapy:

1. FLEXO® may cause serious cardiovascular (CV) side effects, such as myocardial infarction (MI) or stroke, which may result in hospitalization and even death. Although serious CV events can occur without warning symptoms, patients should be alert for the signs and symptoms of chest pain, shortness of breath, weakness, slurring of speech, and should ask for medical advice when observing any indicative sign or symptoms. Patients should be apprised of the importance of this follow-up.
2. FLEXO, like other NSAIDs, can cause GI discomfort and, rarely, serious GI side effects, such as ulcers and bleeding, which may result in hospitalization and even death. Although serious GI tract ulcerations and bleeding can occur without warning symptoms, patients should be alert for the signs and symptoms of ulcerations and bleeding, and should ask for medical advice when observing any indicative signs or symptoms including epigastric pain, dyspepsia, melena, and hematemesis.
3. FLEXO, like other NSAIDs, can cause serious dermatological side effects such as exfoliative dermatitis, SJS and TEN, which may result in hospitalization and even death. Although serious skin reactions may occur without warning, patients should be alert for the signs and symptoms of skin rash and blisters, fever, or other signs hypersensitivity such as itching, and should ask for medical advice when observing any indicative sign or symptoms. Patients should be advised to stop the drug immediately if they develop any type of rash and contact their physicians as soon as possible.
4. Patients should promptly report signs or symptoms of unexplained weight gain or edema to their physicians.
5. Patients should be informed of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, pruritus, jaundice, right upper quadrant tenderness and flu-like symptoms). If these occur, patients should be instructed to stop therapy and seek immediate medical therapy.
6. Patients should be informed of the signs of an anaphylactoid reaction (e.g. difficulty breathing, swelling of the face or throat). If these occur, patients should be instructed to seek immediate emergency help.
7. In late pregnancy, as with other NSAIDs, FLEXO should be avoided because it may cause premature closure of the ductus arteriosus.

Laboratory tests:

Because serious GI tract ulcerations and bleeding can occur without warning symptoms, physicians should monitor for signs or symptoms of GI bleeding. Patients on long-term treatment with NSAIDs should have their complete blood count and chemistry profile checked periodically. If clinical signs and symptoms consistent with liver or renal disease develop, systemic manifestations occur (e.g., eosinophilia, rash etc.), or abnormal liver tests persist or worsen, FLEXO should be discontinued.

4.5 Interaction with other medicinal products and other forms of interaction

Angiotensin converting enzyme (ACE) inhibitors:

Reports suggest that NSAIDs may diminish the antihypertensive effect of ACE-inhibitors. This interaction should be given consideration in patients taking NSAIDs concomitantly with ACE-inhibitors.

Aspirin:

As with other NSAIDs, concomitant administration of etofenamate and aspirin is not generally recommended because of the potential for increased adverse effects.

Furosemide:

Clinical studies, as well as post marketing observations, have shown that NSAIDs can reduce the natriuretic effect of furosemide and thiazides in some patients. This response has been attributed to inhibition of renal prostaglandin synthesis. During concomitant therapy with NSAIDs, the patient should be observed closely for signs of renal failure, as well as to assure diuretic efficacy (see section 4.4).

Lithium:

NSAIDs lead to an elevation of plasma lithium levels and a reduction in renal lithium clearance. The mean minimum lithium concentration is increased by 15% and the renal clearance of lithium is decreased by 19%. This effect has been attributed to inhibition of renal prostaglandin synthesis by NSAIDs. Thus, when NSAIDs and lithium are administered concurrently, patients should be observed carefully for signs of lithium toxicity.

Renal excretion of lithium should be monitored.

Methotrexate:

NSAIDs have been reported to competitively inhibit methotrexate accumulation in rabbit kidney slices. Therefore, NSAIDs may the toxicity of methotrexate. Caution should be used when NSAIDs are administered concomitantly with methotrexate.

Warfarin and anticoagulants:

The effects of warfarin and NSAIDs on GI bleeding are synergistic. Therefore, users of both drugs together have a risk of serious GI bleeding higher than users of either drug alone.

Corticoids or other non-steroidal anti-inflammatory agents:

Increased risk of gastrointestinal bleeding.

Probenecid or sulfinpyrazone:

Deceleration in etofenamate elimination.

Alcohol:

Increased risk of gastrointestinal bleeding.

Digoxin:

Elevation in serum levels of digoxin is likely.

Phenytoin:

Elevation in serum levels of phenytoin is likely.

Diuretics and other antihypertensive agents:

Possible reduction in diuretic or antihypertensive effect.

Potassium-sparing diuretics:

Hyperkalemia development is likely. Therefore, potassium levels should be checked.

Cyclosporine:

Increase in cyclosporine's nephrotoxicity is likely.

Antidiabetic agents:

There have been isolated reports of both hypoglycemic and hyperglycemic effects necessitating changes in the dosage of the antidiabetic agents during treatment with NSAIDs. For this reason, monitoring of the blood glucose level is recommended as a precautionary measure during concomitant therapy.

Selective serotonin reuptake inhibitors:

Increased risk of gastrointestinal bleeding

Additional information for special populations

There are no interaction studies on special populations.

Pediatric population:

There are no interaction studies on pediatric populations.

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 use in women who plan to become pregnant. If FLEXO is to be used, an effective birth control method should be applied.

Etofenamate has no harmful pharmacological effects on pregnancy and/or fetus/neonate.

Pregnancy

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/fetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation and gastroschisis after use of a prostaglandin synthesis inhibitor in early pregnancy. The risk is believed to increase with dose and duration of therapy.

In animal experiments, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation loss and embryo-fetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period.

During the first and second trimester of pregnancy, etofenamate should not be given unless clearly necessary. If etofenamate is used by a woman attempting to conceive, or during the first and second trimester of pregnancy, the dose should be kept as low and duration of treatment as short as possible.

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose;

- The fetus to:
 - cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension);

- renal dysfunction, which may progress to renal failure with oligo-hydroamniosis.
- The mother and the neonate, at the end of pregnancy, to:
 - possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses.
 - inhibition of uterine contractions resulting in delayed or prolonged labor.

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

Lactation

As etofenamate can pass into the breast milk, FLEXO should not be used during breastfeeding.

Reproductive ability/Fertility

As etofenamate administration - like other cyclooxygenase/prostaglandin synthesis inhibitors - may impair female fertility, FLEXO is not recommended in women attempting to conceive.

4.7 Effects on ability to drive and use machines

Even when used correctly, FLEXO can change the reaction rate to such an extent that ability to drive or using machines may be impaired. This is particularly important when used concomitantly with alcohol. Patients should refrain from driving or using machines while using FLEXO.

4.8 Undesirable effects

It should be kept in mind that the following undesirable effects are dose-dependent and may vary from person to person.

The most commonly observed adverse events are gastrointestinal in nature. Peptic ulcers, ulcer, perforation or GI bleeding, sometimes fatal, particularly in the elderly, may occur (see section 4.4). Nausea, vomiting diarrhea, flatulence, constipation dyspepsia, abdominal pain, melena, hematemesis, stomatitis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease have been reported following administration (see section 4.4). Less frequently, inflammation in the stomach has been observed. Generally the risk for gastrointestinal bleeding is dependent on the duration of treatment with NSAIDs and the dose range used.

Edema, hypertension and cardiac failure associated with NSAIDs treatment have been reported.

Clinical trial and epidemiological data suggest that use of some NSAIDs(particularly at high doses and for long term) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke) (see section 4.4).

The terms and frequency rating used for undesirable effects:

Very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1000$ to $< 1/100$); rare ($\geq 1/10.000$ to $< 1/1000$); very rare ($< 1/10.000$); not known (cannot be estimated from the data available).

Undesirable effects reported for intramuscular etofenamate:

Infections and infestations

Very rare: Increased inflammation caused by infections (e.g., development of necrotizing fasciitis)

Blood and lymphatic system disorders

Rare: Hematopoiesis disorders (pancytopenia, anemia, leukopenia, neutropenia, agranulocytosis, thrombocytopenia)

Very rare: Hemolytic anemia

Unknown: Aplastic anemia

Immune system disorders

Uncommon: Hypersensitivity reactions (swelling of the face and tongue, oedema of the larynx and contraction of the airways, difficulty breathing)

Metabolism and nutrition disorders

Uncommon: Loss of appetite

Psychiatric disorders

Uncommon: Excitation

Very rare: Disorientation, anxiety, nightmares, depression, and other psychotic reactions

Nervous system disorders

Uncommon: Headache, fatigue, drowsiness, and dizziness

Very rare: Impaired perception, taste disturbances, memory impairment, tremor.

Eye disorders

Very rare: Visual disturbances (blurred vision, diplopia)

Ear and labyrinth disorders

Very rare: Tinnitus and temporary hearing problems

Cardiac disorders

Very rare: Palpitations, chest pain

Cardiac failure may develop in isolated cases.

Vascular disorders

Very rare: Hypertension

Respiration, pulmonary disorders, and mediastinal diseases

Very rare: Pneumonia

Gastrointestinal disorders

Common: Gastrointestinal complaints such as nausea, vomiting, diarrhea and mild gastrointestinal blood loss, which in exceptional cases may cause anemia.

Uncommon: Dyspepsia, flatulence, abdominal spasm, gastrointestinal ulcers (possible bleeding and perforation)

Rare: Gastritis, hematemesis, melana, or hemorrhagic diarrhea

If such symptoms appear, the patient should be instructed to stop taking the medication and immediately contact the emergency department of the nearest hospital.

Very rare: Stomatitis, glossitis, esophageal lesions, lower abdominal complaints (e.g. hemorrhagic colitis or exacerbation of Crohn's disease/ulcerative colitis), constipation and pelvic pain.

Hepatobiliary Disorders

Rare: Liver damage (hepatitis with or without jaundice, fulminant course in isolated cases, rarely without prodromal symptoms)

Cutaneous and subcutaneous tissue disorders

Uncommon: Hypersensitivity reactions such as cutaneous rash and itching

Rare: Urticaria, alopecia

Very rare: Bullous exanthema, eczema, erythema, purpura (also allergic purpura) and severe forms of skin reaction (Stevens-Johnson syndrome, Lyell syndrome), allergic vasculitis (leukocytoclastic vasculitis)

Not known: Photosensitivity

Musculoskeletal and connective tissue disorders

Very rare: Muscle cramps

Kidney and urinary tract disorders

Rare: Edema (especially in patients with hypertension or renal failure).

Very rare: Renal tissue damage that may be accompanied by acute renal failure (interstitial nephritis, papillary necrosis), proteinuria and/or hematuria.

Not known: Nephritic syndrome may develop in isolated cases.

General disorders and administration site conditions

Uncommon: Irritability, fatigue

If administered intramuscularly, burning sensation or sterile abscess formation, fatty tissue or skin necrosis (drug-induced skin embolism) may occur at the injection site.

Investigations

Uncommon: Increased serum transaminase

Description of selected adverse effects

Infection-related inflammation (e.g., development of necrotizing fasciitis) may temporarily worsen following systemic use of non-steroidal anti-inflammatory drugs. This may be related to the mechanism of action of non-steroidal anti-inflammatory drugs. Therefore, if symptoms of infection appear or worsen during the administration of FLEXO®, the patient is advised to seek medical attention immediately. The necessity of anti-infective/antibiotic treatment should be evaluated.

Hypersensitivity reactions have been reported following systemic use of non-steroidal anti-inflammatory drugs. These may include a) non-specific allergic reactions and anaphylaxis, b) respiratory reactivity consisting of asthma, worsening asthma, bronchospasm or dyspnea, or c) a variety of skin disorders including different types of rashes, itching, urticaria, purpura, angioedema and, less commonly, exfoliative and bullous skin disease (including toxic epidermal necrolysis, Steven-Johnson syndrome and erythema multiforme). Immediate medical attention is required if you experience any of these symptoms, which may occur soon after the first use.

In patients with autoimmune diseases (systemic erythematous lupus, mixed connective tissue disease), there have been reports of symptoms of aseptic meningitis with neck stiffness, headache, nausea, vomiting, fever, or confusion during the use of non-steroidal anti-inflammatory drugs.

4.9 Overdose and management

Symptoms of overdose may include central nervous system disorders including headache, dizziness, drowsiness and loss of consciousness. In addition, abdominal pain, nausea and vomiting may occur. Liver and kidney disorders, and gastrointestinal hemorrhage may also occur.

Recommended treatment:

There is no specific antidote. It is recommended that the Poison Information Center should be contacted in case of overdose.

5. PHARMACOLOGICAL PARTICULARS

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 and antipyretic properties. Its antiphlogistic effect as evidenced by several animal experiments and demonstrated by various studies in humans is based on many different effects. Etofenamate exerts its effects on several points of the inflammatory process: These effects include inhibition of prostaglandin synthesis as well as inhibition of histamine release, antagonizing bradykinin and serotonin, inhibition of complement activity and inhibition of hyaluronidase release.

Membrane-stabilizing properties inhibit release of proteolytic enzymes. Consequently, exudative and proliferative inflammatory processes are inhibited and anaphylactic and foreign body reactions decreased.

5.2 Pharmacokinetic properties

Absorption:

Intramuscular etofenamate is released from the oily formulation at a slower rate, and thus it confers a longer duration of action compared to that of similar substances released from the water-soluble injectable forms.

After intramuscular injection of etofenamate, the plasma curves for young and elderly patients are similar.

The relative bioavailability of intramuscularly injected etofenamate is 91% compared to orally administered flufenamic acid (tablets).

Etofenamate maximum plasma levels ($C_{max} = 0.633 \mu\text{mol/l} + 0.232 \mu\text{mol/l}$) are reached 5.67 hours (5.67 ± 2.66 hours) after intramuscular administration. The area under the curve is $8.95 \pm 3.51 \mu\text{mol} \cdot \text{h/l}$.

Distribution:

Etofenamate binds to proteins at a rate of 98-99%.

Biotransformation:

Etofenamate is metabolized in the liver by hydroxylation, cleavage of ether and ester. It enters into enterohepatic circulation.

Elimination:

Etofenamate is excreted as various metabolites (such as hydroxylations, cleavage of ether, ester) and as conjugates thereof, mainly in the bile and feces, and via the kidneys at a rate of 35% .

5.3 Preclinical safety data

Subchronic and chronic toxicity:

Subchronic toxicity has been investigated in several animal species. One-year studies of oral administration were performed in rats (7, 27, 100 mg/kg/day) and primates (7, 26, 100 mg/kg/day). In rats given 100 mg/kg body weight, gastrointestinal bleeding and ulcers followed by peritonitis developed and mortality was increased.

In primates, high doses led to decreases in body weight, thymus gland weight and hemoglobin.

Mutagenic and tumorigenic potential:

In vitro and in vivo gene and chromosome mutation induction studies have shown negative results. The likelihood of mutagenicity has been excluded with sufficient reliability.

Long-term studies in rats and mice involving oral administration did not provide any evidence of tumorigenic potential of etofenamate.

Reproduction toxicity:

Etofenamate crosses the placental barrier.

In animal studies, the embryotoxic dose was lower than the maternal toxic dose. In rats, an oral dose of 21 mg/kg/day resulted in an increased incidence of renal pelvic enlargement and an oral dose of 7 mg/kg/day resulted in an increased incidence of 14 rib pairs in offspring whose mothers had received treatment.

Etofenamate is excreted in breast milk as flufenamic acid.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Medium-chain triglycerides

6.2 Incompatibilities

Not applicable

6.3 Shelf life

48 months.

6.4 Special precautions for storage

Store at room temperature below 25°C, in the original package. Protect from light.

6.5 Nature and contents of packaging

FLEXO® is available in colorless glass ampoules containing 2 mL of clear viscous solution, in boxes of 1 or 3 ampoules with the package leaflet.

6.6 Disposal of waste materials derived from the medicinal product and other special precautions

Unused medicinal products or waste materials must be disposed of in accordance with the “Regulations on Control of Medical Waste” and “Regulations on Control of Package and Package Waste”.

7. MARKETING AUTHORIZATION HOLDER

Santa Farma Ilac San. A.S.
H.Edip Adıvar, Boru Çiçeği Sok. No: 16
Sisli - ISTANBUL
0212 220 64 00
0212 222 57 59

8. MARKETING AUTHORIZATION NUMBER(S)

181/11

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Date of first authorization: 20.01.1997

Date of renewal of authorization: 20.01.2007

10. DATE OF REVISION OF THE TEXT
