1.3 Product Information

1.3.1 Summary of product characterization

1. Name of the Medicinal Product

(a) Product Name : Fexona Piroxicam Injection 20 mg/ml
(Piroxicam Injection 20 mg/ml)

(b) Strength : 20mg/ml

(c) Pharmaceutical Dosage Form : Injection

2. Quality and Quantitative Composition

(a) Qualitative Declaration, the active substance should be declared by its recommended INN. Accompanied by its salt or hydrate form if relevant.

Composition:

Each ml contains:

Piroxicam U.S.P 20 mg

Benzyl Alcohol B.P. 2% w/v

(as preservative)

Water for injection B.P q.s.

(b) Quantitative Declaration, the quantity of the active substance must be expressed per dosage unit

S. No.	Active Ingredients	Specification	Label Claim	Overages (%)	Quantity (mg/vial)
1	Piroxicam	USP	20 mg	2%	20.4 mg

3. Pharmaceutical Form Visual description of the appearance of the product (colour, markings, etc.) e.g.:

Pale yellow colour solution filled in amber glass ampules.

4. Clinical Particulars,

4.1 Therapeutic Indications:

Piroxicam is indicated for the symptomatic treatment of osteoarthritis, rheumatoid arthritis or ankylosing spondylitis. Because of its safety profile, piroxicam should not be used in first-line treatment when a NSAID is indicated. The decision to prescribe a drug containing piroxicam should be based on an assessment of the individual patient's overall risks.

4.2 Posology and method of administration:

Intra-muscular route

Posology

The prescription of products containing piroxicam should be initiated by physicians with experience in the diagnosis and treatment of patients with inflammatory or degenerative rheumatic diseases. The maximum recommended daily dose is 20 mg (one ampoule). Adverse effects may be minimised by using the minimum effective dose for the shortest duration necessary to control symptoms. The benefit and safety of the treatment should be reassessed within 14 days. If continued treatment is necessary, it must be accompanied by frequent revaluations.

Given that piroxicam has been shown to be associated with an increased risk of gastrointestinal complications, the need for possible combination therapy with gastro-protective agents (e.g., misoprostol or proton pump inhibitors) should be carefully considered, in particular for elderly patients.

Frequency of administration

The duration of the treatment is 2 to 3 days (this time allowing, if necessary, the switch of the therapy to the oral or rectal route). The piroxicam injectable route is administered only when the oral or rectal route could not be used.

CYP2C9 poor metabolizers

The risk of dose-related adverse events is higher, piroxicam should be administered with caution to patients known or suspected to be CYP2C9 poor metabolizers based on genotyping or history/previous experiences with other substrates CYP2C9. A dose reduction should be considered.

Method of administration

This product can be injected either with a glass syringe or with a single-use syringe (polypropylene). Injections must be performed in a strictly aseptic way in the external part of the top external quadrant of the buttock, deeply and slowly. When repeated, it is recommended to change side at each injection. It is important to aspire before injecting, in order to ensure that the point of the needle is not in a vessel. In case of severe pain, the injection must be stopped immediately. In case of hip prosthesis, the injection must be performed on the opposite side.

4.3 Contraindications:

This medicinal product is contraindicated in the following cases:

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1,

- Pregnancy, from the start of the 6th month (beyond 24 weeks of amenorrhoea) ,
- History of allergy or asthma triggered by taking piroxicam or substances with similar activity such as other NSAIDs, aspirin,
- History of all types of serious allergic drug reactions, in particular skin reactions such as polymorphic erythema, Stevens-Johnson syndrome, and toxic epidermal necrolysis (Lyell syndrome),

- Concomitant use of acitretin
- History of gastrointestinal ulcer, bleeding or perforation,
- Patients presenting with a history of gastrointestinal disorders that predispose them to bleeding disorders such as ulcerative colitis, Crohn's disease, gastrointestinal cancers or diverticulitis,
- Patients presenting with a progressive peptic ulcer, an inflammatory gastrointestinal disorder or gastrointestinal bleeding,
- Severe hepato-cellular insufficiency,
- Severe uncontrolled heart failure,
- Severe renal insufficiency,
- Children under 15 years of age,
- Haemostasis symptoms or concomitant anticoagulant treatment (contra indication due to the Intra Muscular route),
- In preterm and term newborns, due to the presence of benzyl alcohol and propylene glycol
- Aorto-coronary bypass,
- A combination with mifamurtide

4.4 Special warning and precautions for use:

Warnings and Precautions:

The concomitant use of piroxicam with other NSAIDs, including selective cyclooxygenase-2 (COX-2) inhibitors, should be avoided. The onset of undesirable effects may be minimised by using the minimum effective dose for the shortest duration necessary to relieve the symptoms (see section 4.2 and paragraphs "Gastrointestinal effects" and "Cardiovascular and cerebrovascular effects" below). The clinical benefit and tolerability should be re-evaluated periodically and treatment should be immediately discontinued at the first appearance of cutaneous reactions or relevant gastrointestinal events. Patients with asthma combined with a chronic rhinitis, chronic sinusitis and/or nasal polyposis have a higher risk of allergic reaction when they take aspirin and/or NSAIDs compared to the general population. The administration of this medicine may lead in an asthma crisis, particularly in some patients allergic to aspirin or NSAIDs.

Gastrointestinal (GI) Effects: risk of GI Ulceration, Bleeding, and Perforation

NSAIDs, including piroxicam, can cause serious gastrointestinal events including bleeding, ulceration, and perforation of the stomach, small intestine or large intestine, which can be fatal. The administration of doses greater than 20 mg per day increases the risk of adverse gastrointestinal reactions. Observational studies suggest that piroxicam may be associated with an increased risk of serious gastrointestinal toxicity as compared to other NSAIDs. These serious adverse events can occur at any

time, with or without warning symptoms, in patients treated with NSAIDs. NSAID exposures of both short and long duration have an increased risk of serious GI event. Patients with significant risk factors for serious GI events should be treated with piroxicam only after careful evaluation of benefit/risk ratio. The possible need for combination therapy with gastro-protective agents should be carefully considered.

Serious GI Complications

Identification of at-risk subjects

The risk for developing serious GI complications increases with age. Age over 70 years is associated with high risk of complications. The administration to patients over 80 years should be avoided. Patients taking concomitant oral corticosteroids, selective serotonin reuptake inhibitors (SSRIs) or antiplatelet agents such as low-dose acetylsalicylic acid are at increased risk of serious GI complications (see below and section 4.5), as well as patients who consume alcohol. As with other NSAIDs, the use of piroxicam in combination with protective agents (e.g., misoprostol or proton pump inhibitors) must be considered for these at-risk patients. Patients and physicians should remain alerted for signs and symptoms of GI ulceration and/or bleeding during piroxicam treatment. Patients should be asked to report any new or unusual abdominal symptom during treatment. If a gastrointestinal complication is suspected during treatment, piroxicam should be discontinued immediately and additional clinical evaluation and treatment should be considered.

Cardiovascular (CV) and cerebrovascular effects

Appropriate monitoring and advice are required for patients with a history of hypertension and/or mild to moderate congestive heart failure as fluid retention and oedema have been reported in association with NSAID therapy. Clinical trial and epidemiological data suggest that use of some NSAIDs (particularly at high doses and in long term treatment) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke) that are potentially fatal. A relative increase in the risk seems to be similar in all patients, whether they present with known CV disease or risk factors for CV that could lead to a higher risk in terms of absolute incidence, due to the higher risk that they present with from the start. There are insufficient data to exclude such a risk for piroxicam. Patients with uncontrolled hypertension, congestive heart failure, ischaemic heart disease, peripheral arterial disease and/or a history of cerebrovascular disease (including a transitory ischaemic accident) should only be treated with piroxicam after a careful evaluation of the benefit/risk ratio. Patients suffering from a CV disease may present with an increased risk of the aggravation of cardiac insufficiency: doctors and patients must be warned of this risk, even in the absence of past CV symptoms. Patients must, moreover, be informed of the signs and symptoms of serious cardiac toxicity

and the actions to take if they occur. Similar consideration should be made before initiating longer-term treatment of patients with risk factors for CV events.

Hypertension

As with all NSAIDs, piroxicam may lead to the onset of arterial hypertension or the increase in preexisting hypertension, which could contribute to an increase in the incidence of CV effects. NSAIDs, including piroxicam, should be used with caution in patients with hypertension. Blood pressure should be closely monitored at the start and for the entire period of treatment.

Hepatic effects

Severe hepatic involvement (jaundice, serious or fatal hepatitis) have rarely been reported with piroxicam. If liver function abnormalities persist or worsen or if clinical signs of liver failure of general signs (eosinophilia, rash) appear, piroxicam should be stopped.

Skin reactions

Serious skin reactions, some of which have fatal outcomes, including drug reaction with eosinophilia and systemic symptoms (DRESS syndrome), exfoliative dermatitis, Stevens-Johnson syndrome and toxic epidermal necrolysis (Lyell syndrome) have very rarely been reported during treatment with NSAIDs (see section 4.8). Cases of fixed drug eruption (FDE) have been reported with piroxicam. Piroxicam should not be reintroduced in patients with history of piroxicam-related FDE. Potential cross reactivity might occur with other oxicams. Studies have suggested that piroxicam may be associated with a higher risk of serious skin reactions compared with other non-oxicam NSAIDs. The incidence of these adverse effects appears to be more significant at the start of treatment with the latency period in most cases during the first month of treatment. Treatment with piroxicam should be stopped at the first appearance of a skin rash, mucosal lesions or any other sign of hypersensitivity.

Functional renal impairment

NSAIDs, by inhibiting the vasodilatory action of renal prostaglandins, are likely to cause functional renal impairment by decreasing glomerular filtration.

At the start of treatment, monitoring of diuresis and renal function is recommended in all patients presenting with the following risk factors:

- elderly subjects,
- associated drugs such as ACE inhibitors, sartans and diuretics (see section 4.5),
- hypovolaemia irrespective of the cause,
- cardiac insufficiency,
- chronic renal impairment,
- nephrotic syndrome,

- lupus nephropathy,
- decompensated liver cirrhosis.

Special attention should be paid when starting treatment with piroxicam in patients presenting with severe dehydration. Monitoring is also recommended in patients with kidney failure.

Due to the significant elimination of piroxicam and its biotransformation products via the renal route, the administration of lower doses of piroxicam should be considered in patients with altered kidney function, and should be closely monitored.

Use with oral anticoagulants

The concomitant use of NSAIDs, including piroxicam, with oral anticoagulants increases the risk of gastrointestinal and non-gastrointestinal bleeding, and should be avoided. Oral anticoagulants include warfarin/coumarin anticoagulants and direct oral anticoagulants (for example, apixaban, dabigatran, rivaroxaban). Anticoagulation/INR should be monitored in patients during anticoagulant treatment with warfarin/coumarin.

Fluid retention

Fluid retention with possible oedema, hypertension or increased hypertension, and worsened cardiac insufficiency. Clinical monitoring is necessary at the start of treatment in the case of hypertension or cardiac insufficiency. A decreased effect in anti-hypertensive drugs is possible.

Hyperkalaemia

Hyperkalaemia contributed by diabetes or treatment with hyperkalaemia-inducing medication.

Blood potassium levels should be regularly monitored in these circumstances.

Elderly subjects

Elderly subjects present with an increased risk of undesirable effects from NSAIDs, in particular, gastrointestinal haemorrhages and perforations that could be fatal.

When prescribing, the physician must take into account the fact that cases of secondary anovulatory infertility by non-rupture of De Graaf follicles, reversible upon discontinuation of treatment have been reported in patients treated chronically by some inhibitor's synthesis of prostaglandins.

The drug product contains 20 mg/ ampoule of benzyl alcohol per Ampoule. Benzyl alcohol can lead to allergic reactions. Benzyl alcohol, a preservative, is linked with the risk of severe side effects including breathing problems (called "gasping syndrome" and death in young children. While at the usual therapeutic doses, the quantities of benzyl alcohol delivered are considerably less than doses at the origin of "gasping syndrome", the minimum quantity of benzyl alcohol at which toxicity may occur is not known. The risk of benzyl alcohol-induced toxicity depends on the quantity administered and the hepatic detoxification capacity of the product. In particular, there is an increased risk due to

accumulation in young children. Premature infants and infants with a low birth weight have a greater risk of presenting with toxicity. Benzyl alcohol may also cause toxic reactions and anaphylactoid reactions in infants and children up to 3 years old. FELDENE is contraindicated in children less than 15 years old . High volumes should be used with caution and only if necessary, especially in subjects with liver or kidney impairment because of the risk of accumulation and toxicity (metabolic acidosis). High volumes should be used with caution and only if necessary, especially in pregnant women because of the risk of accumulation and toxicity (metabolic acidosis). This medicine contains 400 mg of propylene glycol per vial and can lead to similar symptoms to those caused by alcohol.

Precautions for use

This medicine is presented in several dose strength which might be more appropriate. The occurrence of asthma crisis in some patients might be related to an aspirin or NSAID allergy.

Particular attention should be given to patients with a history of hypertension and/or heart failure, cases of fluid retention and oedema have been reported in association with NSAID therapy.

Slow CYP2C9 substrate metabolisers

Precaution should be taken with patients who are known or suspected to be slow metabolisers of CYP2C9, based on the history of other CYP2C9 substrates, since there could be abnormally elevated plasma concentrations of piroxicam due to a decrease in metabolism.

4.5 Interaction with other medicinal products and other forms of interactions:

Simultaneous administration of piroxicam with the following products requires careful monitoring of patient clinical and biological status.

Contraindicated associations

+ Mifamurtide At high doses of NSAIDs, risk of less effective mifamurtide.

Inadvisable combinations

+ Acetylsalicylic acid (at anti-inflammatory doses (≥ 1 g per dose and/or ≥ 3 g per day) or at analgesic or antipyretic doses (500 mg per dose and/or < 3 g per day) increased risk of digestive ulcers and bleeding.

+ Oral anticoagulants

NSAIDs, including piroxicam, are likely to enhance the effects of anticoagulants, such as coumarin-type derivatives (warfarin) and direct oral anticoagulants (for example, apixaban, dabigatran, rivaroxaban). Increase in the risk of haemorrhage from oral anticoagulant (aggression of the gastroduodenal mucosa by non-steroidal anti-inflammatories). Consequently, the concomitant use of

piroxicam and anticoagulants should be avoided. If the association cannot be avoided, carry out close clinical, or even biological, monitoring.

+ Other non-steroidal anti-inflammatories (including aspirin and other salicylates)

With other non-steroidal anti-inflammatories: increased risk of digestive ulcers and bleeding. As with all NSAIDs, the use of piroxicam combined with acetylsalicylic acid or other NSAIDs, and the combination of several proprietary medicinal products containing piroxicam, must be avoided. No data has made it possible to demonstrate the benefit of these combinations compared with piroxicam alone, and therefore the incidence of adverse effects is increased (see section 4.4). Human studies have highlighted a reduced piroxicam plasma concentration of approximately 80% of the usual value during the concomitant administration of piroxicam and acetylsalicylic acid.

+ Low-molecular-weight heparins and related agents (curative doses and/or elderly subjects)

Increase in the risk of haemorrhage (aggression of the gastroduodenal mucosa by non-steroidal antiinflammatories). If the combination cannot be avoided, close clinical monitoring.

Increase in the risk of haemorrhage (aggression of the gastroduodenal mucosa by non-steroidal antiinflammatories). If the combination cannot be avoided, close clinical monitoring.

+ Unfractionated heparins (curative doses and/or elderly subjects)

Increase in the risk of haemorrhage (aggression of the gastroduodenal mucosa by non-steroidal antiinflammatories). If the combination cannot be avoided, close clinical monitoring.

+ Lithium

Increase of lithium plasma level, which might reach the toxic threshold (decrease of renal lithium excretion). If the combination cannot be avoided, close monitoring of the lithium plasma levels and adaptation, during the combination and after the non-steroidal anti-inflammatory withdrawal, of the lithium doses.

+ Methotrexate, used at doses upper than 20 mg/week

Increase of the methotrexate particularly haematologic toxicity (decrease of its renal clearance by antiinflammatory drugs).

+ Nicorandil Increased risk of digestive ulcers and bleeding.

+ Pemetrexed (in patients with weak to moderate renal function) Risk of increased toxicity of pemetrexed (decreased its renal clearance due to NSAIDs).

Combinations to be used with caution

+ Angiotensin II receptor antagonists

Acute renal failure in at-risk patients (elderly, dehydration, concomitant treatment with diuretics, renal function impairment), by decreasing glomerular filtration (inhibition of renal prostaglandins. These effects are usually reversible. Moreover, the antihypertensive effect is decreased. Hydrate the patient and monitor the renal function at treatment initiation and regularly during the combination.

+ Cyclosporin

Risk of additive nephrotoxic effects, particularly in elderly subjects.

Renal function should be monitored at the beginning of treatment with NSAIDs.

+ Diuretics

Risk of acute renal failure in at risk patients (elderly, dehydrated, on diuretics, with impaired renal function) by decrease of the glomerular filtration secondary to a decrease in synthesis of renal prostaglandins. These effects are usually reversible. Moreover, the antihypertensive effect is decreased. Hydrate the patient and monitor the renal function at treatment initiation and regularly during the combination.

+ Converting-enzyme inhibitors

Acute kidney failure in at-risk patients (elderly, dehydrated, on diuretics, with altered kidney function), from a decrease in glomerular filtration secondary to a decrease in synthesis of renal prostaglandins. These effects are generally reversible. Moreover, the antihypertensive effect is decreased. Hydrate the patient and monitor the renal function at treatment initiation and regularly during the combination.

+ Methotrexate, at low doses (lower than or equal to 20 mg/week)

Increase of the haematological toxicity of methotrexate (decrease of its renal clearance by antiinflammatory drugs).

Weekly blood monitoring during the first weeks following the association initiation. Close monitoring in case of renal impairment, even mild, and when administered to elderly subjects.

+ Pemetrexed (in patients with normal renal function)

Risk of increased toxicity of pemetrexed (decreased itsrenal clearance due to NSAIDs). Monitoring of renal function parameters.

+ Tacrolimus

Risk of additive nephrotoxic effects, particularly in elderly subjects.

Renal function should be monitored at the beginning of treatment with NSAIDs.

+ Tenofovir disoproxil

Increased risk of nephrotoxicity of tenofovir, notably with elevated doses of anti-inflammatories or in the presence of risk factors of kidney failure. In the case of a combination, monitor kidney function.

Combinations to take into account

+ Acetyl salicylic acid at anti-aggregate doses (from 50 mg to 375 mg daily taken once or several times)

Increased risk of digestive ulcer and bleeding.

Piroxicam, like other NSAIDs, decreases platelet aggregation and prolongs bleeding time. This effect must be considered when determining bleeding time. Piroxicam interferes with the antiplatelet effect of aspirin at low doses and may, therefore, interfere in the prophylactic action of aspirin in treating CV diseases.

+ Platelet anti-aggregants

Increased risk of bleeding, especially gastrointestinal.

+ Other potassium-sparing agents

Potentially fatal risk of increased hyperkalaemia.

Risks related to hyperkalaemia

Some medicinal products or therapeutic groups can favour the development of hyperkalaemia: potassium salts, potassium-sparing diuretics, angiotensin converting enzyme inhibitors, angiotensin II antagonists, non-steroidal anti-inflammatory drugs, heparins (low molecular weight or unfractionated), immunosuppressive drugs such as cyclosporine and tacrolimus, and trimethoprim. This drug combination increases the risk of hyperkalaemia. This risk is especially important with potassium-sparing diuretics, particularly when combined or with potassium salts, while the combination of an ACE inhibitor and an NSAID, for example, is safer if the recommended

precautions are implemented. To know the risks and levels of constraints specific to potassium sparing drugs, refer to the interactions related to each substance. However, some substances, such as trimethoprim, are not subject to specific interactions with regard to this risk. However, they can act as enabling factors when combined with other drugs such as those mentioned above. The onset of hyperkalaemia may depend on the existence of co-related factors.

+ Beta-blockers (except esmolol) (including eye drops)

Reduction of the antihypertensive effect (inhibition of vasodilator prostaglandins by the non-steroidal anti-inflammatories).

+ Deferasirox

Increased risk of digestive ulcers and bleeding.

+ Gluco-corticosteroids (except hydrocortisone)

Increased risk of gastrointestinal ulcer and bleeding.

+ Non-fractionated heparins and low molecular weight heparins and related agents (preventive doses)

Increased risk of bleeding.

+ Selective serotonin re-uptake inhibitors (SSRI)

Higher risk of bleeding (see section 4.4).

+ Mixed adrenergic-serotonergic drugs

Increased haemorrhagic risk.

4.6 Pregnancy and lactation:

Pregnancy

Inhibition of prostaglandin synthesis by NSAIDs may affect the course of pregnancy and/or the development of the embryo or foetus.

Risks related to the use during the 1st trimester

Data of epidemiological studies suggests an increase in the risk of miscarriage, heart malformations and gastroschisis, after treatment by a prostaglandin synthesis inhibitor at the start of pregnancy. The absolute risk of cardiovascular malformations went from less than 1% in general population to approximately 1.5% in people exposed to NSAIDs. The risk appears to increase with dose and treatment duration. In animals, it has been shown that the administration of a prostaglandin synthesis inhibitor

causes an increased risk of pre- and post-implant loss and a rise in embryo-foetal fatality. Moreover, a higher incidence of certain malformations, including cardiovascular malformations, has been reported in animals who received a prostaglandin synthesis inhibitor during the organogenesis phase of gestation.

Risks related to the use from the 12th week of amenorrhoea and until birth:

- From the 12th week of amenorrhoea and until birth, all NSAIDs, by inhibition of prostaglandin synthesis, may expose the foetus to renal function disorder:
- in utero observed from 12 weeks of amenorrhoea (start of foetal diuresis): oligoamnios (usually reversible after discontinuation of treatment), or anamnios, especially after extended exposure.
- at birth, renal impairment (reversible or irreversible) can persist, particularly in case of late and prolonged exposure (with a risk of severe delayed hyperkalaemia).

Risks related to the use from the 24th week of amenorrhoea and until birth:

From the 24th week of amenorrhea, NSAIDs may expose the foetus to cardiopulmonary toxicity (premature closure of the ductus arteriosus and pulmonary arterial hypertension). Constriction of the arterial canal may arise from the beginning of the 6 th month (beyond the 24th week of amenorrhoea), and can lead to foetal or neonatal right heart failure or foetal death in utero. This risk is greater the closer administration is to delivery (less reversibility). This effect occurs even with occasional administration.

At the end of pregnancy, the mother and newborn may have:

- increased bleeding time due to an anti-aggregating action, which may arise even after the administration of very small doses of the medicinal product;
- an inhibition of uterine contractions, resulting in a delay in term or prolonged delivery.

Consequently:

Unless absolutely necessary, this medicinal product must not be prescribed in a woman considering pregnancy or during the first 5 months of pregnancy (first 24 weeks of amenorrhoea). If this medicinal product is administered to a woman intending to get pregnant or who is less than 6 months pregnant, the dose should be as low as possible and the duration of treatment as short as possible. Prolonged use is highly inadvisable. The health care professionals should consider ultrasound monitoring of amniotic fluid if NSAID treatment extends beyond 48 hours and discontinue the NSAID if oligohydramnios is found.

From the beginning of the 6 th month (after 24 weeks of amenorrhoea): any ongoing administration, however brief, is contraindicated. An inadvertent use from this date requires cardiac and renal

monitoring of the foetus or neonate, depending on the date of exposure. The duration of this monitoring depends on the elimination half-life of the molecule. Benzyl alcohol may cross the placental barrier

Breast-feeding

Because NSAIDs pass into breast milk, this medicinal product is not recommended for use by breastfeeding women.

Fertility

Like all NSAIDs, the use of this medicinal product may temporary affect female fertility by acting on ovulation. It is therefore not recommended for women wishing to conceive a child. In women having difficulty conceiving or undergoing fertility tests, discontinuation of treatment should be considered.

4.7. Effects on ability to drive and use machines

Patients must be warned about the possible occurrence of dizziness and sleepiness.

4.8. Undesirable effects

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

Gastro-intestinal effects are the most commonly encountered side effects. Peptic ulcers, perforation or gastrointestinal bleeding, sometimes fatal, can occur, especially in the elderly (see section 4.4). Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, ulcerative stomatitis, abdominal pain, melena, hematemesis, exacerbation of ulcerative colitis or Crohn's disease (see section 4.4) have been reported following administration of NSAIDs. Less frequently, gastritis was observed. Oedema, hypertension, and cardiac failure have been reported in association with NSAID treatment.

Gastrointestinal effects

Gastrointestinal effects have been reported, such as anorexia, epigastric heaviness, nausea, vomiting, constipation, abdominal pain, flatulence, diarrhoea, ulcers, perforations, occult or non-occult digestive haemorrhages, abdominal pain, anorectal reaction during the administration of a suppository, characterised by local pain, burning, itching and tenesmus and occasional rectal bleeding, epigastric pain, gastritis, gastrointestinal bleeding (including hematemesis and melena), indigestion. These are more common with high doses.

Hypersensitivity reactions

- Dermatologic: eruption, rash, pruritus, worsening of chronic urticaria, alopecia,

- Respiratory: the occurrence of an asthma attack, bronchospasm and dyspnoea have been noted in some subjects, particularly those allergic to aspirin and other NSAIDs,
- General: epistaxis, anaphylaxis, angio-oedema, vasculitis, hypertension, serum sickness have rarely been reported.

Side effects on the central nervous system

- Headache, somnolence, vertigo, infectious meningitis, vertigo sensations, paraesthesia have been reported, as well as tinnitus,
- Anecdotal cases of hearing impairment have been reported,
- No evidence of ocular changes has been reported on routine ophthalmoscopy and slit-lamp examination (blurred vision, ocular irritation, ocular swelling).

Cutaneo-mucous reactions

- Stomatitis,
- Rash, itching, rare cases of photosensitisation,
- Rare cases of bullous skin reactions, such as erythema multiforme, erosive pluriorificialis or epidermal necrolysis (Stevens-Johnson, Lyell syndrome), angio-oedema, exfoliative dermatitis, multiforme erythema, onycholysis, DRESS syndrome, fixed drug eruption have been reportedfrequency unknown.

Renal and urinary effects

- Functional acute renal failure (ARF) in patients presenting with risk factors
- Organic renal damage that could develop into ARF: isolated cases of interstitial nephritis, acute tubular necrosis, nephrotic syndrome, glomerulonephritis and papillary necrosis have been reported.

Others

- Oedema, mainly leg oedema, local adverse reactions (burning sensation) or tissue lesions (formation of sterile abscess, necrosis of the adipose tissue) at the injection site, dizziness, temporary pain during the injection,
- Fluid retention, hyperkalaemia,
- Exceptional cases of pancreatitis.

Some rare changes in clinical laboratory parameters have been observed:

- Renal: Reversible increase in BUN and creatinine.
- Haematologic:
    - Reduction in platelet aggregation and increase in bleeding time, reduction in haemoglobin and haematocrit not associated with obvious gastro-intestinal bleeding.

- Exceptional cases of haemolytic anaemia,
- Thrombocytopenia and non-thrombocytopenic purpura (Henoch-Schönlein) leucopoenia and eosinophilia,
- Rare cases of aplastic anaemia.

• Hepatic: There have been some cases of changes - most transitory or reversible - in hepatic function tests (serum transaminase, bilirubin). More important liver damage (jaundice, severe or fatal hepatitis) have been exceptionally reported with the piroxicam. In case of persistence or aggravation of liver anomalies, or occurrence of clinical symptoms of hepatic impairment or general symptoms such as eosinophilia or rash, the piroxicam should be stopped.

• Investigation for positive anti-nuclear antibodies: some rare anecdotal cases have been reported.

- Metabolism and nutrition disorders: hyperglycaemia, hypoglycaemia, fluid retention.

• Cardiac disorders: palpitations.

• Reproductive disorders, decreased fertility in women.

Undesirable effects related to the method of administration

• Rare cases of minimal, temporary pain at the injection site have been reported;

• Local reactions (burning sensation, tissue alterations) may appear occasionally

4.9 Overdose:

• Immediate transfer to a hospital.

• Symptomatic treatment

5. Pharmacological Properties

5.1 Pharmacodynamic Properties:

Pharmacotherapeutic group:

NON-STEROIDAL ANTI-INFLAMMATORY DRUG, ATC code: M01AC01

Piroxicam is a non-steroidal anti-inflammatory agent of the oxicam group. It has the following actions:

• analgesic action,

• antipyretic action,

• anti-inflammatory action,

• inhibiting action on platelet aggregation.

These whole actions are linked to the inhibition of the prostaglandin synthesis

5.2 Pharmacokinetic Properties:

Piroxicam pharmacokinetic is linear. Various studies showed no pharmacokinetics difference according to the age.

Absorption

A comparative study of the bioavailability of the injectable form with the oral form has shown:

- After intramuscular administration of piroxicam plasma levels are significantly higher than those obtained after ingestion of capsules during the 45 minutes following the administration the first day and during thirty minutes the second day.
- A bioequivalence between the two forms.

Distribution

Plasma elimination half-life: about 50 hours. After intramuscular injection of 40 mg of piroxicam, a Cmax of 3.80 µg/mL is reached in 45 minutes (Tmax).

Binding to plasma protein is high: about 99 per cent.

Piroxicam rapidly crosses the synovial membrane: synovial levels are on average, 45 to 50% of blood levels.

Binding to synovial fluid protein is the same as that seen in the plasma.

A preliminary study showed that piroxicam is present in maternal milk (about 1 to 3% of plasma levels).

Biotransformation – Elimination

The piroxicam is slowly eliminated. It is almost totally metabolised. Less than 5% of the ingested dose is eliminated unchanged in the urine and faeces. Piroxicam metabolism is predominantly mediated via cytochrome P450 CYP 2C9 in the liver. One of the main metabolic way is the hydroxylation of the pyridine nucleus of the lateral chain followed by a glucuronide conjugation and urinary elimination. Serum levels verified a year after continuous oral administration of 20 mg per day are the same as those when the initial state of equilibrium is reached. A study evaluated the pharmacokinetics of piroxicam administered at a single dose of 20 mg to healthy volunteers with genotype CYP2C9 *1/*1, CYP2C9 *1/*2 or CYP2C9 *1/*3. During the latter, it was observed for subjects with genotype CYP2C9 *1/*2 or CYP2C9 *1/*3, an increase of ASC0-∞ and a decrease in oral clearance of piroxicam. It was also observed an increase in the inhibition of cyclooxygenase I by piroxicam for these patients. Patients who are known or suspected to be poor CYP2C9 metabolizers based on previous history/experience with

other CYP2C9 substrates should be administered piroxicam with caution as they may have abnormally high plasma levels due to reduced metabolic clearance.

Pharmacogenetics

The activity of CYP2C9 is reduced in people presenting with genetic polymorphisms, such as CYP2C9*2 and CYP2C9*3 polymorphism. Limited data from two published reports show that subjects presenting with heterozygous genotypes CYP2C9*1/*2 (n = 9), heterozygotes CYP2C9*1/*3 (n = 9) and homozygotes CYP2C9*3/*3 (n = 1) had, respectively, systemic levels of piroxicam 1.7, 1.7 and 5.3 times greater than in subjects with a genotype CYP2C9*1/*1 (n = 17, metaboliser genotype) following the administration of a single dose via the oral route. The mean half-life elimination values of piroxicam in subjects presenting with CYP2C9*1/*3 (n = 9) and CYP2C9*3/*3 (n = 1) genotypes were, respectively, 1.7 and 8.8 times greater than those in subjects presenting with a CYP2C9*1/*1 (n = 17) genotype. We estimate that the frequency of the homozygote genotype *3/*3 ranges from 0% to 5.7% in different ethnic groups.

5.3 Preclinical Safety Data:

NA

6.0 Pharmaceutical Particulars

6.1 List of excipients:

Benzyl Alcohol, EDTA DI Sodium, Sodium Metabisulphate, Sodium Hydroxide Pellets & L- Arginine

6.2 Incompatibilities:

Piroxicam Injection for infusion should not be mixed with other medicinal products than those mentioned.

6.3 Shelf life: 24 Months

6.4 Special precautions for storage:

Store protected from light & moisture below 30ºC.

6.5 Nature and contents of container:

1 ml amber colour glass ampoule

6.6 Instructions for use and handling

Not applicable.

7.0 Marketing Authorization Holder

Name :

Address :

Phone :

Fax :

E-mail :

8.0 Marketing Authorization Numbers

9.0 Date of first authorization/renewal of the authorization

10.0 Date of revision of the text