Feldene*

Piroxicam

20 mg/ml solution for IM injection

Reference market: Belgium

AfME Markets using same as LPD: Egypt

SUMMARY OF PRODUCT CHARACTERISTICS

The injection form of this product (Feldene 20 mg/ml IM) Contains benzyl alcohol, Not for use in neonates and infants

1. NAME OF THE MEDICINAL PRODUCT

Feldene 20 mg/ml IM injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Solution for injection 20 mg/ml: each ampoule contains 20 mg piroxicam.

Excipient(s) with known effect:

Each 1 ml ampoule of Feldene IM solution for injection contains 100 mg anhydrous ethanol (alcohol), 20 mg benzyl alcohol and 400 mg propylene glycol.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Clear greenish yellow solution for IM injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Piroxicam is indicated for the symptomatic treatment of osteoarthritis, rheumatoid polyarthritis and ankylosing spondylitis in children over 16 years, adults and elderly patients less than 80 years. Due to its tolerability profile (see sections 4.2, 4.3 and 4.4), piroxicam should not be used as a first line treatment when NSAID treatment is indicated.
The decision to prescribe a medicinal product containing piroxicam should be based on an assessment of all the risks specific to each patient (see sections 4.3 and 4.4).

4.2 Posology and method of administration

Medicinal products containing piroxicam should be prescribed by doctors with experience in diagnosing and treating patients with inflammatory and degenerative rheumatic diseases.

Posology

The maximum recommended daily dose is 20 mg.
Undesirable effects can be minimised by using the lowest possible dose to relieve the symptoms during the shortest treatment period. The treatment's benefit and the safety of use should be reassessed within 14 days. If continuation of treatment is required, then treatment should be frequently reassessed.
Since piroxicam has been associated with an increased risk of gastrointestinal complications, the option of using a treatment to protect the gastric mucosa (such as misoprostol or a proton pump inhibitor) should be seriously considered, particularly in elderly patients.

General recommendation / Use in elderly patients over 60 years

As with all NSAIDs, titration for minimal effective dose and evaluation of the opportunity to pursue treatment in time are recommended, especially in case of long-term therapy. Such rational therapeutic approach often helps minimize the implications of undesirable effects. This is especially true when treating elderly patients over 60 years and/or patients in poor health who represent a population at risk that may present with a pathology predisposing to complications, notably of the digestive system. In elderly patients, the lowest effective dosage should be used. Therapy should be initiated with a dose of 10 mg daily. A dosage regimen of 20 mg daily is only acceptable if the response to the 10 mg dose is insufficient and has to be limited to a short-term treatment because of the higher risk for haemorrhages and GI ulcers.
Piroxicam should not be used in elderly patients over 80 years of age.

Renal Impairment
Lower doses of piroxicam should be considered in patients with impaired renal function, and they should be carefully monitored (see sections 4.3, 4.4 and 5.2).

Paediatric population
Dosage recommendations and indications for use in children under age 16 have not been established. Dosage recommendations for children over 16 years are the same as for adults.

Combined use

The combined total daily dosage of piroxicam administered as hard capsules, dispersible tablets, Flash tablets, suppositories and solution for injection should not exceed the maximum recommended daily dosage as indicated above.

Method of administration

Intramuscular use: Feldene IM 20 mg/ml Solution for injection

Feldene IM 20 mg/ml Solution for injection (ampoules) is suitable for initial treatment of acute inflammatory conditions and acute exacerbations of chronic inflammatory conditions. For continuation of treatment, oral or rectal forms (hard capsules, dispersible tablets, Flash tablets or suppositories) should be utilized. The recommended dosage of Feldene IM 20 mg/ml Solution for injection (ampoules) is identical with the dosage of piroxicam, hard capsules. Intramuscular injection of Feldene IM 20 mg/ml Solution for injection (ampoules) should be made using aseptic technique into a large muscle. The preferred site is the upper outer quadrant of the buttock. Before the injection, a slight aspiration is necessary to help avoid direct injection into a blood vessel.

4.3 Contraindications

- Hypersensitivity to the active substance, and history of cutaneous reaction (regardless of severity) to piroxicam, other NSAIDs, acetylsalicylic acid or other drugs or to any of the excipients listed in section 6.1.
- Antecedents of symptoms of asthma, nasal polyps, angioedema further a treatment with piroxicam, other NSAIDs or acetylsalicylic acid.
- Antecedents of any type of severe allergic drug reaction, particularly cutaneous reactions such as erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis (Lyell's syndrome).
- History of gastrointestinal ulcer, haemorrhage or perforation.
- Patients presenting a history of gastrointestinal disorders predisposing them to haemorrhagic problems such as ulcerative colitis, Crohn's disease, gastrointestinal cancers or diverticulitis.

- Patients presenting progressive peptic ulcer, an inflammatory gastrointestinal disorder or gastrointestinal haemorrhage.
- Concomitant use of other NSAIDS, including COX-2 selective inhibitors and acetylsalicylic acid, at analgesic doses.
- Concomitant use of anticoagulants (see sections 4.4 and 4.5).
- Patients with severe heart failure.
- Patients with severe renal failure.
- Patients with severe hepatic failure.
- Treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery
- During the first and third trimesters of pregnancy.

4.4 Special warnings and precautions for use

Undesirable effects can be minimised by using the lowest possible dose to relieve the symptoms during the shortest treatment period.
Clinical benefit and safety of use should be reassessed periodically. Treatment should be immediately stopped if there is any sign of cutaneous reaction or symptomatic gastrointestinal events.

Gastrointestinal (GI) signs: risk of GI ulcers, haemorrhage and perforations.
NSAIDs, including piroxicam, can cause serious undesirable GI effects, notably haemorrhage, ulceration and perforation of the stomach, the small intestine and the large intestine. Some of these effects can be fatal. These serious undesirable effects can occur at any time, without there necessarily being any warning signs, in any patient treated with NSAIDs.

Any NSAID treatment, whether of short or long duration, leads to an increased risk of serious undesirable GI effects. Administration of doses of greater than 20 mg per day carries an increased risk of gastrointestinal side effects. Studies have suggested that piroxicam may be associated with a higher risk of serious GI toxicity compared to other NSAIDs.

Patients presenting risk factors for serious undesirable GI effects should only be treated with piroxicam after a careful risk-benefit analysis (see section 4.3 and below).
The option of using a treatment to protect the gastric mucosa (e.g. misoprostol or a proton pump inhibitor) should be seriously considered (see section 4.2).

Serious GI complications
Identifying at-risk subjects
Incidence of serious GI complications increases with age. Beyond 70 years of age, there is a higher risk of complications. Piroxicam should not be administered to patients over the age of 80.
Patients receiving associated treatments, such as oral corticosteroids, selective serotonin reuptake inhibitors (SSRIs), patients ingesting alcohol and platelet antiaggregants such as low dose acetylsalicylic acid, run a higher risk of serious GI complications (see below and section 4.5). As with other NSAIDs, the use of a treatment to protect the gastric mucosa (e.g. misoprostol or a proton pump inhibitor) alongside piroxicam should be considered for these at-risk patients.

Prior to initiating therapy with an agent of this class a detailed history should be obtained in this respect. In case of previous or active digestive disorder, caution should be exercised when starting and monitoring treatment with NSAIDs. It may be useful to systematically examine patient's stools for the presence of occult blood.
Vigilance is essential for both patients and doctors in order to detect potential signs and symptoms of digestive ulcer and/or haemorrhage during treatment with piroxicam. It is advisable to ask patients to report any new or unusual abdominal symptoms during treatment. If a GI complication is suspected during treatment, piroxicam should be stopped immediately. An additional clinical assessment, as well as a therapeutic alternative, should be considered.

Cutaneous reactions
Life-threatening cutaneous reactions including drug reaction with eosinophilia and systemic symptoms (DRESS Syndrome), Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported with the use of Feldene. Patients should be advised of the signs and symptoms and monitored closely for skin reactions. The highest risk for occurrence of DRESS, SJS or TEN is within the first weeks of treatment. If symptoms or signs of DRESS, SJS or TEN (e.g. progressive skin rash often with blisters or mucosal lesions) are present, Feldene treatment should be discontinued. The best results in managing DRESS, SJS and TEN come from early diagnosis and immediate discontinuation of any suspect drug. Early withdrawal is associated with a better prognosis. If the patient has developed DRESS, SJS or TEN with the use of Feldene, Feldene must not be re-started in this patient at any time.

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.

Renal effects
In rare instances NSAIDs may cause acute interstitial nephritis, glomerulitis, papillary necrosis and the nephrotic syndrome. NSAIDs inhibit prostaglandin synthesis and are therefore responsible of a decrease in renal function, which has chiefly been observed in patients with previously impaired renal circulation, as is the case in severe heart insufficiency, dehydration, nephrotic syndrome, liver cirrhosis or overt renal disease. In these patients, administration of an NSAID may precipitate overt renal decompensation, which is typically followed by recovery to pretreatment state upon discontinuation of NSAID therapy.

Caution should be used when initiating treatment with piroxicam in patients with severe dehydration. Caution is also recommended in patients with kidney disease (see section 4.3).
Because of extensive renal excretion of piroxicam and its biotransformation products lower doses of piroxicam should be considered in patients with impaired renal function, and they should be carefully monitored (see sections 4.3 and 5.2).

Hepatic Effects
Piroxicam can cause fatal hepatitis and jaundice. Although such reactions are rare, if abnormal liver function tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g. eosinophilia, rash, etc), piroxicam should be discontinued.

Cardiovascular and cerebrovascular effects
Like all NSAIDs, piroxicam can cause new hypertension to appear or aggravate existing hypertension. These two conditions can increase the risk of cardiovascular events. NSAIDs, including piroxicam, should be used cautiously in patients with hypertension. Blood pressure should be very carefully monitored at the beginning of treatment and during the entire duration of treatment with piroxicam.

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 and stroke)),which can be fatal. The relative increase of this risk appears to be similar in those with or without known cardiovascular disease or cardiovascular risk factors. However, patients with known cardiovascular disease or cardiovascular risk factors may be at greater risk in terms of absolute incidence, due to their increased rate at baseline. There are insufficient data to exclude such a risk for piroxicam.

Patients with uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease and/or cerebrovascular disease should only be treated with piroxicam after careful consideration.
Similar consideration should be made before initiating longer-term treatment of patients with risk factors for cardiovascular disease (e.g. hypertension, hyperlipidaemia, diabetes mellitus and smoking).

Ophthalmologic effects
Because of reports of eye disorders with NSAIDs, it is recommended that patients who develop visual complaints during treatment with piroxicam have ophthalmic evaluation.

Use with oral anticoagulants
The concomitant use of NSAIDs, including piroxicam, with oral anticoagulants increases the risk of GI and non-GI bleeding and should be avoided. Oral anticoagulants include warfarin/coumarin-type and novel oral anticoagulants (e.g. apixaban, dabigatran, rivaroxaban). Anticoagulation/INR should be monitored in patients taking a warfarin/coumarin-type anticoagulant (see sections 4.3 and 4.5).

General
Liver and kidney function tests should be performed regularly in patients with a history of hepatic and renal disorders, during treatment with piroxicam. These periodic function tests during treatment are especially recommended in elderly patients who often exhibit a gradual deterioration of such functions with aging (see above « renal / hepatic effects »).

Piroxicam, like other non-steroidal anti-inflammatory agents, decreases platelet aggregation and prolongs bleeding time. This effect should be kept in mind when bleeding times are determined. Piroxicam should be used with caution when pre-existing blood coagulation disorders are present.

Due to their antipyretic and analgesic activities, NSAIDs may partially obscure the symptomatology of a number of infectious diseases, thereby creating a risk that their adequate diagnosis and treatment may be delayed.

Poor Metabolizers of CYP2C9 Substrates
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 (See section 5.2,).

Warnings: The NSAIDs, including salicylates, may only be used with optimal doses. They may only exceptionally be combined with another agent of the same class, since the benefits of such combinations do not compensate for their drawbacks.

Excipient information

Feldene IM 20 mg/ml Solution for injection

Feldene IM solution for injection contains benzyl alcohol, propylene glycol and ethanol (see section 2).

Feldene IM solution for injection contains 20 mg of benzyl alcohol in each 1 ml ampoule which is potentially toxic when administered locally to neural tissue.

This product is contraindicated for use in premature infants because the formulation contains benzyl alcohol.

Benzyl alcohol may cause allergic reactions. Intravenous administration of benzyl alcohol has been associated with serious adverse events and death in neonates (“gasping syndrome”). The minimum amount of benzyl alcohol at which toxicity may occur is not known. Benzyl alcohol containing formulations should not be used for more than 1 week in children under 3 years of age unless necessary.

If use of a benzyl alcohol-containing formulation of Feldene IM Solution for injection is necessary, it is important to consider the combined daily metabolic load of benzyl alcohol from all sources, especially in patients with liver or kidney impairment, as well as in pregnant or breast-feeding women or epilepsy, because of the risk of accumulation and toxicity (metabolic acidosis).

This medicine contains 400 mg propylene glycol in each 1 ml ampoule. A 1 ml ampoule of Feldene IM solution for injection administered to an adult weighing 70 kg would result in a propylene glycol exposure of 5.72 mg/kg/day. Co-administration with any substrate for alcohol dehydrogenase such as ethanol may induce serious adverse effects in neonates.

Each 1 ml ampoule of Feldene IM solution for injection contains 100 mg ethanol (alcohol), which is equivalent to less than 3 ml beer or 1 ml of wine. The small amount of alcohol in this medicine will not have any noticeable effects.

Feldene IM solution for injection contains less than 1 mmol sodium (23 mg) per ampoule, that is to say essentially 'sodium free'.

4.5 Interaction with other medicinal products and other forms of interaction

Acetylsalicylic acid and other NSAIDs: as with all NSAIDs, piroxicam should not be combined with acetylsalicylic acid or other NSAIDs, and patients should not take more than one medicinal product containing piroxicam. There are no data to demonstrate that such combinations are better than piroxicam alone. Furthermore, the incidence of undesirable effects is increased (see section 4.4). Studies in humans have shown a reduction of around 80% in the plasma concentration of piroxicam compared to the usual value when piroxicam is given in combination with acetylsalicylic acid.

Piroxicam interferes with the antiplatelet effect of low-dose aspirin, and thus may interfere with aspirin's prophylactic treatment of cardiovascular disease.

Corticosteroids: an increased risk of GI ulceration and haemorrhage (see section 4.4).

Anticoagulants: NSAIDs, including piroxicam, are likely to increase the effects of anticoagulants such as warfarin. NSAIDs including piroxicam have an antiaggregant effect on blood platelets. When these agents are administered in combination with coumarin-type anticoagulants an increased risk of haemorrhage may ensue, particularly in cases of digestive mucosal lesions. Concomitant use of piroxicam and anticoagulants such as warfarin should therefore be avoided (see section 4.3).

Platelet antiaggregants and selective serotonin reuptake inhibitors (SSRIs): increased risk of GI haemorrhage (see section 4.4).

Anti-hypertensives including diuretics, angiotensin-converting enzyme (ACE) inhibitors and angiotensin II antagonists (AIIA) and beta-blockers: NSAIDs can reduce the efficacy of diuretics and other anti-hypertensive drugs including ACE inhibitors, AIIA and beta-blockers: NSAIDs may cause sodium retention and oedema, which decrease the effect of any antihypertensive therapy; NSAIDs interfere with the natriuretic action of diuretic agents, especially with loop diuretics.
In patients with impaired renal function (e.g. dehydrated patients or elderly patients with the renal function compromised), the co-administration of an ACE inhibitor or an AIIA and/or diuretics with a cyclo-oxygenase inhibitor can increase the deterioration of the renal function, including the possibility of acute renal failure, which is usually reversible.
The occurrence of these interactions should be considered in patients taking piroxicam with an ACE inhibitor or an AIIA and/or diuretics. Therefore, the concomitant administration of these drugs should be done with caution, especially in elderly patients. Patients should be adequately hydrated and the need to monitor the renal function should be assessed in the beginning of the concomitant treatment and periodically thereafter.

Lithium and other protein-bound agents: Piroxicam is highly serum protein bound, and therefore might be expected to displace other protein-bound drugs from their links. The physician should therefore closely monitor patients for change in dosage requirements when administering piroxicam to patients on highly protein-bound drugs. NSAIDs, including piroxicam, can increase steady state lithium serum levels. It is therefore recommended that these levels be monitored when initiating, adjusting and discontinuing administration of piroxicam.

Cimetidine: The results of two different studies show that absorption of piroxicam is slightly increased after administration of cimetidine, while elimination parameters remain unchanged. With cimetidine, AUC (at 0 to 120 hours) and piroxicam maximum concentrations increase by about 13-15 per cent. Elimination constants and serum half-life show no significant differences. The slight, but significant, increase in absorption does not appear to have any clinical relevance.

Cholestyramine: Cholestyramine has been shown to enhance the oral clearance and decrease the half-life of piroxicam. To minimize this interaction, it is prudent to administer piroxicam at least 2 hours before or 6 hours after cholestyramine

Antacids: Concomitant administration of antacids had no effect on piroxicam blood levels.

Digoxin and Digitoxin: NSAIDs may exacerbate cardiac failure, reduce glomerular filtration rate (GFR) and increase plasma glycoside levels.
Concomitant administration of piroxicam and digoxin or piroxicam and digitoxin had no effect on blood levels of either drug.

Methotrexate:
When methotrexate is administered concurrently with NSAIDs, including piroxicam, NSAIDs may decrease elimination of methotrexate resulting in increased plasma levels of methotrexate. This may result in methotrexate toxicity (leukopenia, thrombocytopenia, anaemia, nephrotoxicity and mucosal ulcerations). Caution is advised, especially in patients receiving high doses of methotrexate. Patients should be closely monitored when concomitant administration of these two products is necessary.

Potentially nephrotoxic drugs: The renal function should be monitored when piroxicam and potentially nephrotoxic drugs (ex. Tacrolimus, cyclosporine...) are concomitantly administered.

4.6 Fertility, pregnancy and lactation

Fertility
Based on the mechanism of action, the use of NSAIDs, including piroxicam, may delay or prevent rupture of ovarian follicles, which has been associated with reversible infertility in some women. In women who have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of NSAIDs, including piroxicam, should be considered.

Pregnancy
Pregnancy, Nursing mothers and Paediatric use:
Do not administer injections preserved with benzyl alcohol to neonates, infants, pregnant women or nursing mothers. Benzyl alcohol has been associated with serious adverse events and death, particularly in paediatric patients. Injections preservatives free should be used in these populations.

The use of Feldene during pregnancy is not recommended; it is contraindicated during the first and third trimesters.

Piroxicam inhibits prostaglandin synthesis and release by an effect on prostaglandin biosynthetase. Studies in animals have shown reproductive toxicity (see section 5.3).

NSAI agents may delay the beginning of labour in pregnant women, or unfavourably influence the course of parturition. Their use in the final stages of pregnancy may be associated with a risk of haemorrhage in the newborn.

In addition, NSAIDs are also known to induce premature closure of the ductus arteriosus.

Inhibition of prostaglandin synthesis might adversely affect pregnancy. Data from epidemiological studies suggest an increased risk of spontaneous abortion after use of prostaglandin synthesis inhibitors in early pregnancy.

If used during second or third trimester of pregnancy, NSAIDs may cause fetal renal dysfunction which may result in reduction of amniotic fluid volume or oligohydramnios in severe cases. Such effects may occur shortly after treatment initiation and are usually reversible. Pregnant women on piroxicam should be closely monitored for amniotic fluid volume.

The following statement applies only for *Feldene IM 20 mg/ml Solution for injection*: Benzyl alcohol can cross the placenta (see section 4.4).

Breastfeeding
The presence of piroxicam has been established in maternal milk following short-term and long-term (52 days) therapy in a concentration of approximately 1 to 3 % of maternal plasma concentrations. Piroxicam does not accumulate in breast milk at the same ratio as it achieves plasma levels during treatment.

There is insufficient data on the effects of piroxicam on newborn/infants

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Feldene therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman

4.7 Effects on ability to drive and use machines

No studies on the effect of piroxicam on the ability to drive and use machines have been performed.

4.8 Undesirable effects

The following events have been reported in patients receiving piroxicam with:
Frequency categories: Very common ≥1/10; Common ≥1/100 to <1/10; Uncommon ≥1/1000 to <1/100; Rare ≥1/10000 to <1/1000; Very rare <1/10000; Not known (cannot be estimated from available data).

MedDRASystem Organ Class	Very Common	Common	Uncommon	Rare	Very Rare	Not Known (cannot be estimated from available data)
Blood and lymphatic system disorders		Anaemia Eosinophilia Leucopenia Thrombocytopenia				Aplastic anaemia Haemolytic anaemia
Immune system disorders						Anaphylaxis Serum sickness

MedDRASystem Organ Class	Very Common	Common	Uncommon	Rare	Very Rare	Not Known (cannot be estimated from available data)
Metabolism and nutrition disorders		Anorexia Hyperglycaemia	Hypoglycaemia			Fluid retention
Psychiatric disorders						Depression Dream abnormalities Hallucinations Insomnia Mental confusion Mood alterations Nervousness
Nervous system disorders		Dizziness Headache Somnolence Vertigo				Aseptic meningitis Paresthesia Tremor
Eye disorders			Blurred vision			Eye irritations Swollen eyelids
Ear and labyrinth disorders		Tinnitus				Hearing impairment Surdity
Cardiac disorders			Palpitations			Heart failure (**)
Vascular disorders						Vasculitis Hypertension (**) Arterial thrombotic events (**)
Respiratory, thoracic and mediastinal disorders						Bronchospasm Dyspnoea Epistaxis
Gastrointestinal disorders (*)		Abdominal discomfort Abdominal pain Constipation Diarrhoea Epigastric distress Indigestion Flatulence Nausea Vomiting	Stomatitis			Gastritis Gastrointestinal bleeding (including occult blood loss, hematemesis and melena) Pancreatitis Perforation Ulceration
Hepatobiliary disorders						Fatal hepatitis (***) Jaundice (***)

MedDRASystem Organ Class	Very Common	Common	Uncommon	Rare	Very Rare	Not Known (cannot be estimated from available data)
Skin and subcutaneous tissue disorders		Pruritis Skin rash			Stevens-Johnson syndrome Toxic epidermal necrolysis (Lyell's disease)	Alopecia Angioedema Dermatitis exfoliative Erythema multiforme DRESS Syndrome Non-thrombocytopenic purpura (Henoch-Schoenlein) Onycholysis Photoallergic reactions Urticaria Vesiculo bullous reactions Fixed drug eruption (see section 4.4)
Renal and urinary disorders						Nephrotic syndrome Glomerulonephritis Interstitial nephritis (****), Renal failure
Reproductive system and breast disorders						Female fertility decreased
General disorders and administration site conditions		Oedema (mainly of the ankle) (**)				Local adverse reactions (burning sensations) or tissue damage (sterile abscess formation, fatty tissue necrosis) at the site of injection Malaise Transient pain upon injection Fatigue

MedDRASystem Organ Class	Very Common	Common	Uncommon	Rare	Very Rare	Not Known (cannot be estimated from available data)
Investigations		Reversible elevations of BUN Increased serum transaminase levels (***), Weight increase	Reversible elevations of creatinine			Positive ANA Weight decrease Hemogram changes Decreases in hemoglobin and hematocrit unassociated with obvious gastro-intestinal bleeding

(*) Gastrointestinal symptoms are the most commonly encountered undesirable effects.
(**) Oedema, hypertension and heart failure have been reported in association with NSAID treatment. Clinical studies and epidemiological data suggest that the use of certain NSAIDs (especially when they are used at high doses and for a long period of time) can be associated with a slight increase in the risk of arterial thrombotic events (e.g. myocardial infarction and stroke) (see section 4.4).

(***) Changes in different liver function parameters have been observed. As with most other non-steroidal anti-inflammatory agents, some patients may develop increased serum transaminase levels during treatment with piroxicam (see section 4.4).

(****) In rare instances NSAIDs may cause acute interstitial nephritis. NSAIDs inhibit prostaglandin synthesis and are therefore responsible of a decrease in renal function, which has chiefly been observed in patients with previously impaired renal circulation, as is the case in severe heart insufficiency, dehydration, nephrotic syndrome, liver cirrhosis or overt renal disease.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after marketing authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions according to their local country requirements.

To report any side effect(s):

Pharmacovigilance center, Pfizer Pharmaceutical Company: EGY.AEReporting@pfizer.com
Egyptian Pharmacovigilance center (EPVC), EDA: pv.report@edaegypt.gov.eg

4.9 Overdose

In the event of overdosage with piroxicam supportive and symptomatic therapy is indicated. Preliminary studies indicate that administration of activated charcoal may reduce absorption and intestinal reabsorption of piroxicam thus reducing the total amount of active drug available.

Although there are no studies to date, haemodialysis is probably not useful in enhancing elimination of piroxicam since the drug is highly protein-bound.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-inflammatory and antirheumatic products, non-steroids, oxicams.
ATC Code: M01AC01.

Feldene IM brand of piroxicam belong to the chemical class of non-steroidal anti-inflammatory agents, N-heterocyclic carboxamides of 1,2-benzothiazine-1,1-dioxide. Piroxicam is an amphoteric compound.

Mechanism of action

Piroxicam is a non-steroidal anti-inflammatory agent, which possesses analgesic and antipyretic properties. While its mode of action is not fully understood, independent studies in vitro as well as in vivo have nevertheless shown that piroxicam interacts at several steps in the immune and inflammation responses through:

- Inhibition of prostanoid synthesis, including prostaglandins, through a reversible inhibition of the cyclooxygenase enzyme.
- Inhibition of aggregation of neutrophiles.
- Inhibition of polymorphonuclear cell and monocyte migration to the area of inflammation.
- Inhibition of lysosomal enzyme release by stimulated leucocytes.
- Inhibition of superoxide anion generation by the neutrophiles.
- Reduction of both systemic and synovial fluid rheumatoid factor production in patients with seropositive rheumatoid polyarthritis.

It is established that piroxicam does not act by pituitary-adrenal axis stimulation. In-vitro studies have neither revealed any negative effects on cartilage metabolism.

5.2 Pharmacokinetic properties

Absorption and Distribution

Piroxicam is well absorbed following oral and rectal administration. With food there is a slight delay in the rate but no extent of absorption following oral administration of piroxicam. As with any drug dosed in suppository form, individual drug absorption depends on the condition of the rectal ampulla and of the length of useful contact between the suppository and the rectal mucosa. Passing stools too soon after administering a suppository may impair therapeutic effect.

Stable plasma concentrations are maintained throughout the day on once-daily dosage. Plasma protein binding approximates 99%.

Continuous treatment with 20 mg/day for periods of 1 year produces similar serum levels to those seen once initial steady state is achieved. Plasma concentrations are proportional for 10 and 20 mg doses after oral administration and generally peak within three to five hours after administration. A single 20 mg dose generally produces peak plasma levels of 1.5 to 2 mcg/ml while concentrations, after repeated daily ingestion of 20 mg piroxicam, usually stabilize at 3 to 8 mcg/ml.

A multiple dose comparative study of the bioavailability of the intramuscular form with the oral form has shown on the one hand that after intramuscular administration of piroxicam, plasma levels are significantly higher during the 45 minutes following administration the first day, during 30 minutes the second day and 15 minutes the seventh day, and on the other hand that the two dosage forms are bioequivalent.

A multiple dose comparative study of the pharmacokinetics and the bioavailability of Feldene Flash with the oral hard capsule has shown that after one daily administration during 14 days, the plasma piroxicam concentration time were nearly superimposable. There were no significant differences between the mean steady state C_{max} values, C_{min} values, $T_{1/2}$ or T_{max} values. This study concluded that Feldene Flash is bioequivalent to the hard capsule after once daily dosing. Single dose studies have also demonstrated bioequivalence whether the tablet is taken with or without water.

Biotransformation and Elimination

Piroxicam is extensively metabolized and less than 5 % of the daily dose is excreted unchanged in urine and faeces. Piroxicam metabolism is predominantly mediated via cytochrome P450 CYP2C9 in the liver. One important metabolic pathway is hydroxylation of the pyridyl ring of the piroxicam side chain, followed by conjugation with glucuronic acid and urinary elimination.
The plasma half-life is approximately 50 hours in man.

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 (See section 4.4).

Pharmacogenetics:
CYP2C9 activity is reduced in individuals with genetic polymorphisms, such as the CYP2C9*2 and CYP2C9*3 polymorphisms. Limited data from two published reports showed that subjects with heterozygous CYP2C9*1/*2 (n=9), heterozygous CYP2C9*1/*3 (n=9), and homozygous CYP2C9*3/*3 (n=1) genotypes showed 1.7-, 1.7-, and 5.3-fold higher piroxicam systemic levels, respectively, than the subjects with CYP2C9*1/*1 (n=17, normal metabolizer genotype) following administration of an oral single dose. The mean elimination half life values of piroxicam for subjects with CYP2C9*1/*3 (n=9) and CYP2C9*3/*3 (n=1) genotypes were 1.7- and 8.8-fold higher than subjects with CYP2C9*1/*1 (n=17). It is estimated that the frequency of the homozygous*3/*3 genotype is 0% to 5.7% in various ethnic groups.

5.3 Preclinical safety data

Non-clinical data show effects typical of a non cox-selective NSAID; namely, renal papillary necrosis and gastrointestinal lesions. In reproductive toxicity studies, piroxicam increases the incidence of dystocia and delayed parturition in animals, when drug administration is continued during pregnancy. Administration of prostaglandin synthesis inhibitors has also been shown to result in increased pre- and post-implantation loss.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Feldene IM 20 mg/ml Solution for injection:
Solution for IM injection contains sodium dihydrogen phosphate dihydrate, nicotinamide, propylene glycol (E1520)*, ethanol absolute*, benzyl alcohol (E1519)*, sodium hydroxide, concentrated hydrochloric acid and water for injection.

* See also section 4.4 "Excipient information".

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Shelf life: 3 years.

Do not use Feldene after the expiry date which is stated on the carton label after EXP:. The expiry date refers to the last day of that month.

6.4 Special precautions for storage

Store at temperature not exceeding 30°C.

6.5. Nature and contents of container

carton box contains 1 or 2 trays, each of 3 ampoules each of 1 ml and an inner leaflet.

6.6. Special precautions for disposal and other handling

Keep out of sight and reach of children.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

7. FURTHER INFORMATION

7. MARKETING AUTHORISATION HOLDER

Pfizer Inc. USA

MANUFACUTRED, PACKED & RELEASED BY:

Global pharmaceutical industries (2), Egypt under license of Pfizer USA

8. DATE OF REVISION OF THE TEXT

July 2021

THIS IS A MEDICAMENT

- Medicament is a product which affects your health and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use and the instructions of the Pharmacist who sold the medicament.
- The doctor and the Pharmacist are experts in medicines, their benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed.
- Do not repeat the same prescription without consulting your doctor.

Keep all medicaments out of reach and sight of children

Council of Arab Health Ministers
Union of Arabic Pharmacists