Pfizer

فیلڈین

# FELDENE®

## (PIROXICAM)

(پائراکسیکیم)

**1. NAMES OF MEDICINAL PRODUCT**
**FELDENE®**

**2. QUALITATIVE AND QUANTITATIVE COMPOSITION**
Piroxicam contains as its active ingredient piroxicam 10 mg and 20 mg as capsules, 10 mg and 20 mg as dispersible tablets. 20 mg as fast dissolving dosage forms, and as a 20 mg/ml solution for intramuscular use.

**3. PHARMACEUTICAL FORM**
Capsule, dispersible tablet, fast dissolving tablet-like dosage form, solution for intramuscular use.

**4. CLINICAL PARTICULARS**
**4.1 Therapeutic indications**
Piroxicam is a nonsteroidal anti-inflammatory drug (NSAID) indicated for a variety of conditions requiring anti-inflammatory and/or analgesic activity, such as rheumatoid arthritis, juvenile rheumatoid arthritis, osteoarthritis (arthritis, degenerative joint disease), ankylosing spondylitis, acute trauma, for the treatment of primary dysmenorrhea in patients 12 years of age or older, and for the relief of fever and pain associated with acute upper respiratory tract inflammation.

**4.2 Posology and method of administration**
Undesirable effects may be minimize by using the minimum effective dose for the shortest duration necessary to control symptoms.
*Dosage*
*Rheumatoid Arthritis, Osteoarthritis (Arthrosis, Degenerative Joint Disease), Ankylosing Spondylitis*
The recommended starting dose is 20 mg given as a single daily dose. The majority of patients will be maintained on 20 mg daily. A relatively small group of patients may be maintained on 10 mg daily. Some patients may require up to 30 mg daily given in single or divided doses. Long-term administration of doses 30 mg or higher carries an increased risk of gastrointestinal side effects **(See section 4.4 Special warning and precautions for use, Gastrointestinal (GI) Effects).**
*Acute Gout*
Therapy should be initiated by a single dose of 40 mg, followed on the next 4 to 6 days with 40 mg daily, given in single or divided doses/Piroxicam is not indicated for the long-term management of gout.
*Acute Musculoskeletal Disorders*
Therapy should be initiated with 40 mg daily for the first two days given in single or divided doses. For the remainder of the 7 to 14 days treatment period, the dose should be reduced to 20 mg daily.
*Postoperative an Posttraumatic Pain*
The recommended starting dose is 20 mg, given as a single daily dose. In case where a more rapid onset of action is divided doses. For the remainder of the treatment period, the dose should be reduced to 20 mg daily.
*Dismenorrhea*
The treatment of primary dysmenorrhea is initiated at the earliest onset of symptoms with a recommended starting dose of 40 mg given as a single daily dose for the first two days. Treatment may be continued thereafter with a single daily dose of 20 mg for the next one to three days as necessary.
*Upper Respiratory Tract Inflammation*
The usual adult dosage is 10 or 20 mg orally once daily. In cases where a more rapid onset of action is desired, therapy should be initiated with 40 mg once daily for the first two days, followed by 10 or 20 mg daily for three to five days.
*Use in Children*
*Juvenile Rheumatoid Arthritis (JRA)*
The recommended dosages for children with JRA are base on body weight as follows:

| Weight (kg) | Dosage mg |
|---|---|
| less than 15 | 5 |
| 16 to 25 | 10 |
| 26 to 45 | 15 |
| greater than 46 | 20 |

The drug should be taken once daily. The dispersible tablet may be used to obtain the exact dose required.
*Administration*
*Oral (Capsules, Dispersible Tablets, Fast Dissolving Dosage Form).* Piroxicam dispersible tablets can be swallowed whole with fluid, or may be dispersed in a minimum of 50 ml of water and then swallowed. Piroxicam FDDF (Fast Dissolving Dosage Form) may be swallowed with water, or placed on the tongue to disperse and then swallowed with salvia or water as a suspension. Piroxicam FDDF dissolving almost instantly in the mouth in the presence of water or salvia.
*Intramuscular*
Piroxicam intramuscular is suitable for initial treatment of acute conditions and acute exacerbations of chronic conditions.
For continuation of treatment, oral (capsules, tablets or fast dissolving dosage form) or suppository dosage forms should be utilized. Dosage of intramuscular piroxicam is identical with the dosage of piroxicam oral. Intramuscular injection of piroxicam should be made using aseptic technique into a relative large muscle. The preferred site is the upper outer quadrant of the buttock (i.e. gluteus maximus). As with all intramuscular injections, aspiration is necessary to help avoid inadvertent injection into a blood vessel.
*Combined Administration*
The total daily dosage of piroxicam administered as capsules, dispersible tablets, fast dissolving dosage form, and intramuscular injection should not exceed the maximum recommended daily dosage as indicated above.

**4.3 Contraindications**
Piroxicam with active peptic ulcerations.
Patients with known hypersensitivity to piroxicam or to any of the excipients. The potential exists for cross sensitivity to aspirin and other NSAIDs. Piroxicam should not be given to patients in whom aspirin and other NSAIDs induce the symptoms of asthma, nasal polyps, angioedema or urticaria.
Treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery.
Patients with severe renal and hepatic failure.
Patients with severe heart failure.

**4.4 Special warnings and precautions for use**
The use of piroxicam with concomitant NSADIs including COX-2 inhibitors should be avoided.
**Cardiovascular Effects**
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 know cardiovascular disease may be at greater risk. To minimize the potential risk for an adverse cardiovascular event in patients treated with piroxicam, the lowest effective dose should remain alert for the development of such events, even in the absence of pervious cardiovascular symptoms. Patients should be inform about the signs and/or symptoms of serious cardiovascular toxicity and the steps to take if they occur (See section **4.3 Contraindications**).
**Fluid Retention and Edema**
As with other drugs known to inhibit prostaglandin synthesis, fluid retention and edema have been observed in some patients taking NSAIDs, including piroxicam. Therefore, piroxicam should be used with caution in patients with compromised cardiac function and other conditions predisposing to, or worsened by, fluid retention. Patients with pre-existing congestive heart failure or hypertension should be closely monitored.
**Gastrointestinal (GI) Effects**
NSAIDs, including piroxicam, 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. When GI bleeding or ulceration occurs in patients receiving piroxicam, the treatment should be withdrawn. Patients most at risk of developing these types of GI complications with NSAIDs are the elderly, patients with cardiovascular disease, patients using concomitant aspirin, or patients with a prior history of, or active, gastrointestinal disease, such as ulceration, GI bleeding or inflammatory conditions.
Therefore piroxicam should be used with caution in these patients (See section **4.3 Contraindications**).
**Renal Effects**
In rare cases NASIDs may cause interstitial nephritis, glomerulitis, papillary necrosis and the nephrotic syndrome. NSAIDs inhibit the synthesis of renal prostaglandin which plays a supportive role in the maintenance of renal perfusion in patients whose renal blood flow and blood volume are decreased. In these patients, administration of an NSAID may precipitate overt renal compensation, which is typically followed by recovery to pretreatment state upon discontinuation of NSAID therapy.
Patients at greatest risk of such a reaction are those with congestive heart failure, liver cirrhosis, nephrotic syndrome and overt renal disease. Such patients should be carefully monitored while receiving 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 Contraindications**).
Because of extensive renal excertion 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 section **4.3 Contraindications** and section **5.2 Pharmacokinetic** properties).
**Skin Reactions**
Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported very rarely in association with the use of NSAIDs, including piroxicam. Patients appear to be at highest risk for these events early in the course of therapy, the onset of the event occuring in the majority if cases within the first month of treatment.
Piroxicam should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign if hypersensitivity.
**Ophthalmologic Effects**
Because or reports of adverse eye finding with NSAID, it is recommended that patients who develop visual complaints during treatment with piroxicam have an ophthalmic evaluation.
**General**
For patients with phenylketonuria: because of its aspartame content, piroxicam FDDF contains phenylalanine 0.070 mg and 0.140 mg per 10 mg dose and 20 mg dose respectively.
When used for the relief of pain and inflammation in upper respiratory tract inflammation, it should be remained that NSAIDs are only a symptomatic therapy. When given to patients with such conditions, appropriate concomitant antibacterial therapy should be considered.

**4.5 Interaction with other medical products and other forms of interaction**
*Acetylsalicylic Acid:*
As with other NSAIDs, the use of piroxicam in conjuction with acetylsalicylic acid or the concomitant use of two NSAIDs is not recommended because data are inadequate to demonstrate that the combination produces greater improvement than that achieved with the drug alone and the potential for adverse reactions is increased.
Studies in man have shown that the concomitant administration of piroxicam and acetylsalicylic acid resulted in a reduction of plasma levels of priroxicam to about 80% of the normal values.
*Anti-coagulants:*
Bleeding has been reported rarely when piroxicam has been administered to patients on coumarin type anti-coagulants. Patients should be kept in mind when bleeding times are determined.
*Antacids:*
Concomitant administration of antacids had no effect on piroxicam plasma levels.
*Anti-hypertrnsives including diuretic, angiotensinconverting enzyme (ACE) inhibitors and angiotensin ii antagonist (ALLA):*
Nsaids can reduce the efficacy of diuretics and other anti-hypertensive drugs.
In patients with impaired renal function (e.g. dehydrated patients or elderly patients with the renal function compromised), the coadministration of an ACE inhibitor or an ALLA with 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 be patients taking piroxicam with a diuretic, an ACE inhibitor or an AIIA. Therefore, the concomitant administration of these rugs should be done with caution, especially in elderly patients. Patients should be adequately hydrated and the need to monitor the renal function should be assesse in the beginning of the concomitant treatment and perioically thereafter.
*Cardiac glycosided (digoxin and digitoxin):*
NASID may exacerbate cardiac failure, reduce glomerular filtration rate (GPR) and increase plasma glycoside levels.
Concomitant administration of digoxin or digitoxin had no effect on the plasm levels of piroxicam or either drug.
*Cimetidine:*
Results of two separate studies indicate a slight increase in absorption of piroxicam following cimetidine administration but no significant changes in elimination parameters. Cimetidine increases the area under the curve ($AUC_{0\text{-}120hrs}$) and $C_{max}$ of piroxicam by approximately 13% to 15%. Elimination rate constants and halflife show no significant differences. The small but signficant increase inabsorption is unlikely to be clinically significant.
*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.
*Corticosteroids:*
Increased risk of gastrointestinal ulceration or bleeding.
*Cyclosporine:*
increased risk of nephrotoxicity.
*Lithium and other protein-bound agents:*
Piroxicam is highly protein-bound, and therefore might be expected to displace other proteinbound drugs. The physician should closely monitor patients for change in dosage

requirements when administering piroxicam to patients on highly protein-bound drugs. NSAIDs including piroxicam, have been reported to increase steady state plasma lithium levels. It is recommended that these levels be monitored when initiating, adjusting and discontinuing piroxicam.

*Methotrexate:*

Decreased elimination of methotrexate.

*Tacrolimus:*

possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus.

**4.6 Pregnancy and lactation**

*Pregnancy*

Although no teratogenic effects were seen in animal testing, the use of piroxicam during pregnancy is not recommended. Piroxicam inhibits prostaglandin synthesis and release through a reversible inhibition of the cyclooxygenase enzyme. This effect, as with other NSAID have been associated with an increased incidence of dystocia and delayed parturition in pregnant animals when drug administration was continued into late pregnancy. NSAIDs are also known to induce premature cliurse of the ducts arterious in infants.

*Lactation*

The presence of piroxicam in breast milk has been determined during initial and long term dosing conditions (52 days). Piroxicam appeared in breast milk at about 1% to 3% of the maternal plasma concentration. No accumulation of piroxicam occured in milk relative to that in plasma during treatment. Piroxiam is not recommended for use in nursing mothers as the clinical safety has not been established.

**4.7 Effects on ability to rive and use machines**

The effect of piroxicam on the ability to drive or operate machinery has not been studied.

**4.8 Undesirable effects**

Piroxicam is generally well tolerate.

Gastrointestinal symptoms are the most commonly encountered side effects (See section **4.4 Special warnings an precautions for use, Gastrointestinal (GI) Effects).**

Objective evaluations of gastric mucosal appearances and intestinal blood loss show that 20 mg/day of piroxicam administered either in single or divided daily doses is significantly less irritating to the gastrointestinal tract than acetylsalicylic acid.

*Blood and lymphatic system disorders:* Anemia, aplastic anemia, eosinophilia, hemolytic anemia, leucopenia, thrombocytopenia

*Immune system disorders:* Anaphylaxis, serum sickness

*Metabolism and nutrition disorders:* Anorexia, hyperglycemia, hypoglycemia

*Psychiatric disorders:* Depression, dream abnormalities, hallucinations, insomnia, mental confusion, mood alterations, nervourness

*Nervous system disorders:* Aseptic menigitis, dizzness, headche, paresthesia, spmnolence, vertigo

*Eye disorders:* Blurredd vision, eye irritations, swollen eyes

*Ear an labyrinth disorders:* Hearing impairment tinnitus

*Cardiac disorders:* Palpitations

*Vascular disorders:* Vasculitis

*Respiratory, thoracic and mediastinal disorders:* Bronchospasm, dyspnea, epistaxis

*Gastrointestinal disorders:* Abdominal discomfort, abdominal pain, ano-rectal reactions to suppositories presenting as local pain, burning, pruritus and tenesmus and rare instances of rectal bleeding, constipation, diarrhea, epigastric distress, flatulence, gastriti, gatrointestinal bleeding (including **hematemesis** and melena), indigestion, nausea, pancreatitis, perforation, stomatitis, ulceration, vomiting (See section **4.4 Special warnings and precautions for use, Gastrointestinal (GI) Effects)**

*Hepatobiliary disorders:* Fatal hepatitis jaundice. Although such reaction are rare, if abnormal liver function tests persist or worsen, if clinical signs and symptoms constant with liver diseases develop, or if systemic manifestations occur (e.g. eosinophilia, rash etc, piroxicam should be discontinued.

*Skin and subcutaneous tissue disorders:* Alopecia, angioedema, dermatitis exfoliative erythema multiforme, non-thrombocytopenic purpura (Henoch-Schoenlein, onycholysis, photollergic reactions, pruritus, skin rash, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's disease), urticaria, vesiculo bullous reactions ( See section **4.4 Special warnings and precautions for use, Skin Reactions)**

*General disorder and administration site conditions:* Edema (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

*Investigations:* Positive ANA, reversible elevations of BUN and creatinine, decreases in hemoglobin and hematocrit unassociated with obvious gastro-intestinal bleeding, increased serum transaminase levels, weight decrease, weight increase

**4.9 Overdose**

In the event of overdosage with piroxicam, supportive and symptomatic therapy is Indicated. Studies indicate that administration of activated charcoal may result in reduced absorption and re-absorption and reabsorption of piroxiccam thus reducing the total amount of active drug available.

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

## 5. PHARMACOLOGICAL PROPERTIES

**5.1 Pharmacodynamic properties**

Piroxicam is a nonsteroidal anti-inflammatory agent, which also possesses analgesic and antipyretic properties. Edema, erythema, tissue proliferation, fever, an pain can all be inhibited in laboratory animals by the administration of piroxicam. It is effective regardless of the etiology of the inflammation. While its mode of action is not fully understood, indepenent studies *in vitro* as well as *in vivo* have shown that piroxicam interacts at several steps in the immune an inflammation responses through:

- Inhibition of prostanoid sunthesis, including prostaglanins, through a reversible inhibition of the cyclooxygenase enzyme.
- Inhibition of polymorphonuclear cell and monocyte migration to the area of inflammation.
- Inhibition of lysosomal enzyme release from stimulate leucocytes.
- Inhibition of superoxie anion generation by the neutrophil.
- Reduction of both systemic an synovial fluid rheumatoid factor production in patients with seropositive rheumatoid arthiritis.

In clinical studies piroxicam has been found effective as an analgesic in pain of various etiologies (post-traumatic pain, post-episiotomy pain an post-operative pain).

The onset of analgesia is prompt.

In primary dysmenorrhea the increased levels of endometrial prostaglanins cause uterine hypercontractility resulting in uterine ischemia and pain. Piroxicam , as a potent inhibitor of prostaglandin synthesis, has been shown to reduce uterine hypercontractility an to be ffective in the treatment of pirmary dysmenorrhea.

**5.2 Pharmacokinetic properties**

*Absorption and Distribution*

Piroxicam is well absorbed following oral administration. With food there is a slight delay in the rate but not the extent of absorption following oral administration. Stable plasma concentrations are maintained throughout the day on one-daily dosage. Continuous treatment with 20 mg/day for periods of 1 year produces similar blood levels to those seen once steady state is first achieved.

Drug plasma concentrations are proportional for 10 mg and 20 mg and doses and generally peak within three to five hours after administration.

A single 20 mg dose generally produces peak piroxicam plasma levels of 1.5 to 2 mcg/ml while maximum drug plasma concentrations, after repeated daily ingestion of 20 mg piroxicam, usually stabilize at 3 to 8 mcg/ml. Most patients approximate steady state plasma levels within 7 to 12 days.

Treatment with a loading dose regimen of 40 mg daily for the first two days followed by 20 mg daily thereafter allows a high percentage (approximately 76%) of steady state levels to be achieved immediately following the second dose. Steady state levels, are under the curves and elimination half-life are similar to that following a 20 mg daily dose regimen.

A multiple dose comparative study of the bioavailability of the injectable form with the oral capsule has shown that after intramuscular administration of prioxicam, plasma levels are significantly higher than those obtained after ingestion of capsules during the 45 minutes following administration the first day, during 30 minutes the second day and 15 minutes the seventh day. Bioequivalence exists between the two dosage forms.

A multiple dose comparative study of the pharmacokinetics and the bioavailability of piroxicam FDDF with the oral capsule has shown that after once daily administration for 14 days, the mean plasma piroxicam concentration time profiles for capsules and piroxicam FDDF were nearly superimposable. There were no significant differences between the mean steady state C values, c values, to values. This study concluded that piroxicam FDDF (fast dissolving dosage form) is bioequivalent to the capsule after once daily dosing. Single dose studies have demonstrated bioequivalence as well when the tablet is taken with or without water.

*Metabolism and Elimination*

Piroxicam is extensively metabolized and less than 5% of the daily dose is excreted unchanged in urine and feces. One important metabolic pathway is hydroxylation of the pyridyl ring of the piroxicam side chain, followed by conjunction with glucuronic acid and urinary elimination. The plasma half-life is approximately 50 hours in man.

**5.3 Preclinical safety data**

Subacute and chronic toxicity studies have been carried out in rats, mice, dogs, and monkeys, using doses which ranged from 0.3 mg/kg/day to 25 mg/kg/day. The latter dose is approximately 90 times the recommended human dose level. The only pathology seen was that characteristically associated with the animal toxicology of nonsteroidal antiinflammatory agents; namely, renal papillary necrosis and gastrointestinal lesions. With regard to the latter, the monkey proved to be quite resistant to this effect and the dog unusually sensitive.

## 6. PHARMACEUTICAL PARTICULARS

**6.1 List of excipients**

**Capsules**

Corn Strach
Hard Gelatin Capsules
Lactose
Magnesium Stearate
Sodium Lauryl Sulfate

**Dispersible Tablets**

Hydroxypropyle Cellulose
Lactose
Microcrystalline Cellulose
Sodium Steary Fumarate

**Fast Dissolving Dosage Form**

Aspartame
Citric Acid
Gelatin
Mannitol
Sodium Methyl Paraben
Sodium Propy Paraben
Purified

**Intramuscular Solution**

Benzyl Alcohol
Ethanol
Hydrochloride Acid
Nicotinamide
Propylene Glycol
Sodium Dihydrogen Phosphate
Sodium Hydroxide
Water

**6.2 Incompatibilities**

Solution for intramuscular use should not be mixed other medicines.

**6.3 Shelf life**

Capsules: 24 months, dispersible tablets 24 months, solution for intramuscular use 36 months.

Fast Dissolving Dosage Form: 24 months

**6.4 Special precautions for storage**

Capsules dispersible tablets solution for intramuscular use: Store in a dry place at room temperature.

FDDF store below 30°C in a dry place.

**6.5 Nature and contents of container**

Capsules dispersible tablets, solution for intramuscular use:

*Capsules & dispersible tablets:* PVDS blister Film: 250 micron PVDC, clear
Film: 250 micron hard temperature aluminum foil, heat-sealeds.

*Solution for intramuscular use:*

1 ml ampoule of brown fiolax glass with break ring and light blue color ring.

*Fast Dissolving Dosage Form:* The primary pack is blister pack. The base material is a moisture barrier laminate comprising 200 µm opacified polyvinycloride (PVC) coated with 40 gsm polyvinylidene chloride (PVdC) the blister foil lacquer laminated to 20 µm polyethylence teraphthalate, lacquer laminated to 40 calendared bleach kraft paper.

**6.6 Instructions for use and handling and disposal**

Due to the physical nature of the freeze dried tablet, the blister pack is not a traditional push through type, the heat seal lacquer has been specially developed to allow the lidding material to be peeled to expose the tablet individual FDDF are exposed in this manner. The fast dissolving dosage from may be swallowed with water, or placed on the tongue to disperse and then swallowed with the salvia.

The fast dissolving dosage from dissolves almost instantly in the mouth in the presence of water or saliva.

خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔
تاکید: صرف میڈیکل پریکٹشنر کے نسخہ پر فروخت کریں۔
دوا کو تیس ڈگری سینٹی گریڈ سے کم درجہ حرارت پر خشک جگہ میں رکھیں۔
گرمی اور دھوپ سے بچائیں۔
تمام دوائیں بچوں کی پہنچ سے دور رکھیں۔

**Feldene Capsules & Dispersible Tablets**
Manufactured by:
**Parke-Davis & Co., Ltd. Karachi.**
For Pfizer Lab. Ltd. Karachi-Pakistan.

**Feldene Intramuscular**
Manufactured by:
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For Pfizer Lab. Ltd. Karachi-Pakistan.

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