1. NAMES OF MEDICINAL PRODUCT
FELDENE® (PIROXICAM) باربيكاسم

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Piroxicam contains 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
Combination of fast dissolving tablet-like dosage form, solution for intramuscular use.

4. CLINICAL PARTICULARS
Piroxicam is a nonsteroidal anti-inflammatory drug (NSAID) indicated for a variety of conditions including 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
The posology and method of administration should be minimized by using the minimum effective dose for the shortest duration of treatment to control symptoms of:

- Arthritis
- Arthritis, Osteoarthritis (Arthritis, Degenerative Joint Disease), Ankylosing Spondylitis
- Trauma

The recommended starting dose is 20 mg given as a single daily dose. The majority of patients can be maintained on 10 mg daily, and a relatively small group of patients may be maintained on 5 mg daily. Some patients may benefit from a single daily dose of 40 mg or divided doses.

4.3. Contraindications
Contraindications are absolute or relative contraindications, or conditions that should be avoided.

- Allergy to or a history of hypersensitivity to piroxicam or any of its excipients.
- History of peptic ulceration or hemorrhage.

Because of extensive renal excretion of piroxicam and its metabolites, lower doses of piroxicam should be considered in patients with impaired renal function, and the duration of therapy should be minimized.

4.3. Contraindications and section 6. Pharmacokinetic properties
- Skin Reactions
- Serious skin reactions, some of them fatal, have been reported with the use of NSAIDs, including piroxicam.

4.4. Special warnings and precautions for use
The use of piroxicam with concomitant NSAIDs including COX-2 inhibitors should be avoided.

4.5. Cardiovascular Effects
NSAIDs may increase the risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with known cardiovascular disease may be at greater risk.

5.2. Acute Musculoskeletal Disorders
Therapy should be initiated with 40 mg daily for the first two days given as a single daily dose or divided doses. For the remainder of the 7 to 14-day treatment period, the recommended dose should be reduced to 20 mg daily.

6.3. Gastrointestinal (GI) Effects
NSAIDs, including piroxicam, can cause serious gastrointestinal (GI) adverse events including bleeding, ulceration, and perforation, which may be fatal. Patients who are predisposed to these adverse effects should be closely monitored.

6.4. Concomitant use of piroxicam with glucocorticoids, anticoagulants, or drugs with a high risk of interstitial lung disease (e.g., azathioprine, cyclosporine, or penicillamine) may increase the risk of interstitial lung disease.

8.2. Use in Children
Juvema Rheumatoid Arthritis (JRA)
The use of piroxicam in children is based on weight. The dosage should be based on weight as follows:

<table>
<thead>
<tr>
<th>Weight</th>
<th>Doseage</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;15 kg</td>
<td>5 mg/day</td>
</tr>
<tr>
<td>15-24 kg</td>
<td>10 mg/day</td>
</tr>
<tr>
<td>&gt;25 kg</td>
<td>15 mg/day</td>
</tr>
</tbody>
</table>

If long-term treatment is required, the dose should be decreased when the growth rate decreases.

8.3. Special information (including serious warnings and precautions for use)
Because of extensive renal excretion of piroxicam and its metabolites, lower doses of piroxicam should be considered in patients with impaired renal function, and the duration of therapy should be minimized.

13.4. Contraindications
- Skin Reactions
- Serious skin reactions, some of them fatal, have been reported with the use of NSAIDs, including piroxicam.

13.4. Special warnings and precautions for use
The use of piroxicam with concomitant NSAIDs including COX-2 inhibitors should be avoided.

13.5. Cardiovascular Effects
NSAIDs may increase the risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with known cardiovascular disease may be at greater risk.

13.6. Acute Musculoskeletal Disorders
Therapy should be initiated with 40 mg daily for the first two days given as a single daily dose or divided doses. For the remainder of the 7 to 14-day treatment period, the recommended dose should be reduced to 20 mg daily.

13.7. Gastrointestinal (GI) Effects
NSAIDs, including piroxicam, can cause serious gastrointestinal (GI) adverse events including bleeding, ulceration, and perforation, which may be fatal. Patients who are predisposed to these adverse effects should be closely monitored.

13.8. Concomitant use of piroxicam with glucocorticoids, anticoagulants, or drugs with a high risk of interstitial lung disease (e.g., azathioprine, cyclosporine, or penicillamine) may increase the risk of interstitial lung disease.
requirements when administering proxicam to patients on highly protein-bound drugs. NSAIDs including proxicam, have been reported to increase the steady state level of lithium. It is recommended that these medications should be administered with food. 

Metabolism: 

Disposition and elimination of metotrexate. 

Talcum: 

Possible increase risk of nephrotoxicity when NSAIDs are given with talcums.

4.6 Pregnancy and lactation 

Pregnancy: 

Although no teratogenic effects were seen in animal studies, there is no well-controlled study in humans. Proxicam is not recommended during pregnancy. Proxicam inhibits prostaglandin synthesis and release, blocks the synthesis of the cyclooxygenase enzyme. This effect, as with other NSAIDs, may result in an increased incidence of dystocia and delayed parturition in pregnant women when drug administration is continued during pregnancy. NSAIDs are also known to induce premature closure of the ducts aerius in infants. 

Lactation: 

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

4.7 Effects on ability to ride and use machines 

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

4.8 Undesirable effects 

Proxicam is generally well tolerated. Gastrointestinal disorders are the most commonly encountered side effects (See section 5.2 for details on the use for, Gastrointestinal (GI) Effects).

Objective evaluations of gastric mucosal adverse effects showed that 20 mg/day of proxicam administered in a single dose or divided doses significantly less irritating to the gastrointestinal tract than acetylsalicylic acid.

Blood and lymphatic system disorders: Anemia, aplastic anemia, eosinophilia, hemolytic anemia, leukemia, thrombocytopenia, lymphadenopathy, leukopenia, thrombocytosis, hemolytic-uremic syndrome.

Metabolic and nutritional disorders: Anorexia, hyperglycemia, hypoglycemia.

Psychiatric disorders: Depression, drowsiness, nervousness, panic disorder, psychic effects, psychoses, insomnia, nervousness.

Neurological disorders: Convulsion, nervousness.

Dermatological disorders: Urticaria, rash, pruritus, sweating, skin eruptions, increased sweating.

Eye disorders: Blurred vision, eye irritation.

Ear and labyrinth disorders: Hearing impairment, tinnitus.

Cardiac disorders: Palpitations, arrhythmias.

Respiratory, thoracic and mediastinal disorders: Asthma, bronchitis, respiratory infections.

Gastrointestinal disorders: Abdominal discomfort, abdominal pain, anorectal reflux, constipation, diarrhea, dyspepsia, flatulence, nausea, pain, pruritus and tenesmus and related disorders, abdominal distention, anorexia, anorexia nervosa, aspiration, constipation, diarrhea, epigastric distress, flatulence, gastritis, gastrointestinal bleeding (including anemia), hemorrhage, idiopathic, nausea, pancreatitis, perforation, spontaneous pneumothorax, vomiting.

4.9 Special warnings and precautions for use, Gastrointestinal (GI) Effects 

Hepatitis, jaundice: Any jaundice.

Although such reaction are rare, if abnormal liver function tests occur or if symptoms or signs and symptoms consistent with liver diseases develop, or if systemic manifestations occur (e.g. fever, pruritus) that should be discontinued.

Sensitivity reaction: Sensitivity skin tissue disorders: Alopecia, angioedema, dermatitis exfoliative erythema multiforme, non-thrombocytopenic purpura (Henoch-Schönlein), photoreactions, pruritus, skin rash. Stevens-Johnson syndrome.

Blood and lymphatic system disorders: Anemia, aplastic anemia, eosinophilia, hemolytic anemia, leukemia, lymphadenopathy, leukopenia, thrombocytosis, neoplasms (lymphoma, leukemia), urticaria, vesicle bullous reactions (See section 4.4 Special warnings and precautions for use, Gastrointestinal (GI) Effects).

4.10 Overdose 

In the overdose setting with proxicam, supportive and symptomatic therapy is indicated. Studies indicate that administration of activated charcoal may result in reduced absorption and re-absorption and resorption of proxicam thereby reducing the total amount of active drug available. 

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

5. PHARMACOLOGICAL PROPERTIES 

5.1 Pharmacodynamic properties 

Proxicam is a nonsteroidal anti-inflammatory agent, which also possesses analgesic and antipyretic properties, Edema, erythema, tissue proliferation, fever, an pain. 

Inhibited in laboratory animals by the administration of proxicam. It is effective regardless of the efficacy of the inflammatory response. Proxicam inhibits the release of prostaglandins and thromboxane A2, which are involved in the mediation of the inflammatory response through the following:

- Inhibition of prostaglandin synthesis, including prostaglandins 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 leukocytes.
- Inhibition of superoxide anion generation by the neutrophils.
- Reduction of both systemic an inflammatory fluid and heat production in patients with septicemia rheumatoid arthritis.

In clinical studies proxicam has been found effective as an analgesic in pain and inflammatory (post-traumatic pain, post-eosinophilia joint pain, post-perioperative pain).

The onset of analgesia is prompt. 

In primary dysmenorrhea the increased levels of endometrial prostaglandins cause uterine hypercontractility resulting in uterine nociception and sensation. 

As a prodrug of proxicam, prostaglandin synthesis, has been shown to reduce uterine hypercontractility an to be effective in the treatment of primary dysmenorrhea.

5.2 Pharmacokinetic properties 

Absorption and Distribution 

Proxicam is well absorbed following oral administration. 

With food there is a delay in the rate but not the extent of absorption following oral administration. 

Steady state concentrations are maintained throughout the day on one-daily dosage. 

Continuous treatment with 20 mg daily for periods of 1 year produces similar blood levels to those seen once steady state is first achieved.

Drug plasma concentrations are proportional for both 20 mg and 2 mg daily doses 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 mg/ml depending on the maximum plasma concentration after repeated daily ingestion of 20 mg proxicam, usually stable at 3 to 8 mg/ml. 

Most patients achieve maximum steady state plasma levels within 7 to 12 days.

Treatment with the usual dose regimen of 40 mg daily for the first two days followed by 20 mg daily thereafter allows a high percentage (87%) to be steady state levels by the third day, achieving immediately following the second dose steady state levels, are, under the drug, and elimination half-life is 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 proxicam capsule showed that after intramuscular administration of proxicam, plasma levels are significantly higher than those attained after ingestion of capsules during the 45 minutes following administration and first day, during minutes the second day and 15 minutes the seventh day. Bioavailability exists between the two dosage forms and should be discontinued.

A multiple dose comparative study of the pharmacokinetic parameters, the bioavailability of proxicam FDCD with the oral capsule has shown that after once daily administration for 14 days, the maximum plasma concentration time profiles for capsules and proxicam FDCD were nearly superimposable. 

There were no significant differences between the mean steady state C values, C values at steady state levels, these studies concluded that proxicam FDCD (fast dissolving dosage form) bioequivalent to the capsules on once daily dosing. Single dose studies have demonstrated bioequivalence as well when the tablet taken with or without water.

Metabolism and Elimination 

Pharmacokinetics, are 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 proxicam side chain, followed by conjugation with glucuronic acid and urinary elimination. 

The plasma half-life is approximately 50 hours in man.

Clinical studies: 

On the clinical study 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 about 20 times the recommended human dose level. The only pathology seen was that characteristicly associated with the antiphlogistic toxicity of nonsteroidal anti-inflammatory agents, namely, renal papillary necrosis and gastrointestinal lesions with hemorrhage. In addition, the monkey proved to be quite resistant to this effect and the dog unusually sensitive.

6. PHARMACOThERAPIC PARTICULARS 

6.1 Shelf life 

Capsules: 

Capsules are stable for at least 30 months. The plastic material is a moisture barrier laminate comprising 200 μm opacified polyethylene (COV) coated with 40 gmp polyvinylidine chloride (PVC) the blister for lacquer laminated to 20 μm polyethylene, polyethylene, laminated to 40 calendared baleed craft paper.

6.2 Incompatibilities for intramuscular use should not be 

mixed with other medicines. 

6.3 Administration 

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

6.4 Special precautions for storage 

Capsules dispensible tablets: PVC/PE blister Film: 250 micron PVC, clear, 250 micron hard temperature resistant aluminum blister film.

Solution for intramuscular use: 

1. Dissolve the single dose in an oxal glass with beak ring and light blue color ring.

Fast Dissolving Dosage Form: The primary pack is a paperboard laminate comprising 200 μm opacified polyethylene (COV) coated with 40 gmp polyvinylidine chloride (PVC) the blister for lacquer laminated to 20 μm polyethylene, polyethylene, laminated to 40 calendared baleed craft paper.

6.5 Instructions for use and handling and disposal 

Due to the physical nature of the freeze dried tablets, to take prior to use the push through type, the heat seal lacquer has been developed to allow the litter material to be peeled off the tablet. 

Individual FDCD are exposed in this manner. The tablet should be swallowed with or without water, then placed on the tongue and then swallowed with the saliva.

The fast dissolving dosage from dissolves almost immediately 30 times the time the powdered water or saliva.

Feldene Capsules & Dispersible Tablets 

Manufactured by: Pfizer Italia S.r.l., Italy. 

For Pfizer Lab. Ltd. Karachi-Pakistan. 

Feldene Intramuscular 

Manufactured by: Pfizer Italia S.r.l., Italy. 

For Pfizer Lab. Ltd. Karachi-Pakistan. 

Feldene Flush 

Manufactured by: Catalent Pharma Solutions, Inc. U.K. 

Packaged by: Pfizer Italia S.r.l., Italy. 

For Pfizer Lab. Ltd. Karachi-Pakistan.