Piroxicam Dispersible Tablets, Piroxicam Injection (Intramuscular Solution)

DOLONEX® DT/DOLONEX® IM

1. GENERIC NAME

Piroxicam Dispersible Tablets 20 mg,

Piroxicam Injection Intramuscular Solution 20 mg/ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Dispersible Tablets:
Each uncoated dispersible tablet contains Piroxicam I.P. 20 mg.

Injection (*Intramuscular Solution):*
Each ml contains Piroxicam I.P. 20 mg
Benzyl Alcohol IP (as preservative) 20 mg
Ethanol Content ……12.6 % v/v

All strengths/presentations mentioned in this document might not be available in the market.

List of excipients:

Dispersible Tablets: Dibasic calcium phosphate I.P., Lactose I.P. (Tablettose)., Microcrystalline cellulose I.P. (Avicel 102, Vivapur 102), Hydroxy propyl cellulose NF (LH 11, Low substituted), and sodium stearyl fumarate NF.

Injection (Intramuscular Solution): Sodium dihydrogen phosphate dihydrate I.P., Niacinamide I.P., Propylene glycol I.P., Ethanol (95%) I.P., Benzyl alcohol I.P., sodium hydroxide I.P., hydrochloric acid I.P., and water for injection I.P.

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3. DOSAGE FORM AND STRENGTH

Uncoated Dispersible Tablets 20 mg, Parenteral- Solution for Intramuscular use 20 mg/ml.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Piroxicam Dispersible Tablets:
Anti-inflammatory Agent – Indicated in the treatment of pain and inflammation associated with conditions like rheumatoid arthritis, juvenile rheumatoid arthritis, osteoarthritis, other musculoskeletal disorders, tendinitis, bursitis, post traumatic disorders, post operative pain, primary dysmenorrhea, ankylosing spondylitis, cervical spondylitis and for the relief of fever and pain associated with acute upper respiratory tract inflammation.

Piroxicam Intramuscular Injection:
Indicated in the treatment of musculoskeletal disorders, acute gout, pain after operative intervention following acute trauma, and in primary dysmenorrhea (12 years age or older).

4.2 Posology and Method of Administration

Undesirable effects may be minimized 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 (see section **4.4 Special Warnings and Precautions for Use, Gastrointestinal [GI] Effects**).

Acute Gout
Because of its GI safety profile (see sections **4.3 Contraindications** and **4.4 Special Warnings and Precautions for Use**), piroxicam should not be used in first-line treatment for acute gout when an NSAID is indicated. For the same reason, it should not be used to treat acute gout in patients most at risk of developing serious GI adverse events (see section **4.4 Special Warnings and Precautions for Use**). 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
Because of its GI safety profile (see sections **4.3 Contraindications** and **4.4 Special Warnings and Precautions for Use**), piroxicam should not be used in first-line treatment for acute musculoskeletal disorders when an NSAID is indicated. For the same reason, it should not be used to treat acute musculoskeletal disorders in patients most at risk of developing serious GI adverse events (see section **4.4 Special Warnings and Precautions for Use)**. 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 day treatment period, the dose should be reduced to 20 mg daily.

Post-operative and Post-traumatic Pain
The recommended dose is 20 mg, given as a single daily dose.

Dysmenorrhea
Because of its GI safety profile (see sections **4.3 Contraindications** and **4.4 Special Warnings and Precautions for Use**), piroxicam should not be used in first-line treatment for dysmenorrhea when an NSAID is indicated. For the same reason, it should not be used to treat dysmenorrhea in patients most at risk of developing serious GI adverse events (see section 4.4 **Special** W**arnings and Precautions for Use**). 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 adult dosage is 10 mg or 20 mg orally once daily for five to seven days.

Use in Children

Juvenile Rheumatoid Arthritis (JRA)
The recommended dosages for children with JRA are based on body weight as follows:

Weight (kg)	Dose (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

Dispersible Tablets
Piroxicam dispersible tablets can be swallowed whole with fluid, or may be dispersed in a minimum of 50 ml of water and then swallowed.

Intramuscular
Piroxicam intramuscular injection is suitable for initial treatment of acute conditions and acute exacerbations of chronic conditions. Dosage of intramuscular piroxicam is identical with the dosage of piroxicam oral.
Intramuscular injection of piroxicam should be given using aseptic technique into a relatively 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 dispersible tablets, and intramuscular injection should not exceed the maximum recommended daily dosage as indicated above.

4.3 Contraindications

Piroxicam is contraindicated in:

Patients with a history of gastro-intestinal ulceration, bleeding or perforation.

Patients 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 systemic non-aspirin NSAIDs including cyclooxygenase-2 (COX-2) inhibitors should be avoided. Concomitant use of a systemic NSAID and another systemic NSAID may increase frequency of gastrointestinal ulcers and bleeding.

Cardiovascular Effects

NSAIDs may cause an increased risk of serious cardiovascular (CV) thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. The relative increase of this risk appears to be similar in those with or without known CV

disease or CV risk factors. However, patients with known CV disease or CV risk factors may be at greater risk in terms of absolute incidence, due to their increased rate at baseline. To minimize the potential risk for an adverse CV event in patients treated with piroxicam, the lowest effective dose should be used for the shortest duration possible. Physicians and patients should remain alert for the development of such events, even in the absence of previous CV symptoms. Patients should be informed about the signs and/or symptoms of serious CV toxicity and the steps to take if they occur (see section **4.3 Contraindications**).

Hypertension

As with all NSAIDs, piroxicam can lead to the onset of new hypertension or worsening of pre-existing hypertension, either of which may contribute to the increased incidence of CV events. NSAIDs, including piroxicam, should be used with caution in patients with hypertension. Blood pressure should be monitored closely during the initiation of therapy with piroxicam and throughout the course of therapy.

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. Administration of doses of greater than 20 mg per day carries an increased risk of gastrointestinal side effects. Evidence from observational studies suggests that piroxicam may be associated with a high risk of serious gastrointestinal toxicity, relative to other NSAIDs. 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 CV disease, patients using concomitant corticosteroids, antiplatelet drugs (such as aspirin), selective serotonin reuptake inhibitors, patients ingesting alcohol 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 sections **4.2 Posology and Method of Administration** and **4.3 Contraindications**).

Renal Effects

In rare cases, NSAIDs 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 decompensation, which is typically followed by recovery to pre-treatment 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 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 Contraindications** and **5.3 Pharmacokinetic Properties**).

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.

Skin Reactions

Serious skin reactions, some of them fatal, including drug reaction with eosinophilia and systemic symptoms (DRESS syndrome), 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 occurring in the majority of cases within the first month of treatment. Piroxicam should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

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 (see section **4.8 Undesirable Effects**).

Ophthalmologic Effects

Because of reports of adverse eye findings with NSAIDs, it is recommended that patients who develop visual complaints during treatment with piroxicam have an ophthalmic evaluation.

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 **5.3 Pharmacokinetic Properties,** *Pharmacogenetics*).

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 given with caution. 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 section **4.5 Drugs Interactions**).

General

When used for the relief of pain and inflammation in upper respiratory tract inflammation, it should be remembered that NSAIDs are only a symptomatic therapy. When given to patients with such conditions, appropriate concomitant antibacterial therapy should be considered.

The following statement applies only when benzyl alcohol is included in the formulation:
Piroxicam solution for intramuscular use contains benzyl alcohol. The preservative benzyl alcohol has been associated with serious adverse events, including the "gasping syndrome", and death in pediatric patients. Although normal therapeutic doses of this product ordinarily deliver amounts of benzyl alcohol that are substantially lower than those reported in association with the "gasping syndrome", the minimum amount of benzyl alcohol at which toxicity may occur is not known. The risk of benzyl alcohol toxicity depends on the quantity administered and the liver and kidneys' capacity to detoxify the chemical. Premature and low-birth weight infants may be more likely to develop toxicity.

The amount of benzyl alcohol in the diluent per each mL is 20 mg.

4.5 Drugs Interactions

Acetylsalicylic acid:
As with other NSAIDs, the use of piroxicam in conjunction 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 piroxicam to about 80% of the normal values.

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

Anti-coagulants:
Bleeding has been reported rarely when piroxicam has been administered to patients on coumarin type anti-coagulants. Patients should be monitored closely if piroxicam and oral anticoagulants are administered together.

Piroxicam, like other NSAIDs, decreases platelet aggregation and prolongs bleeding time. This effect should be kept in mind when bleeding times are determined.

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

Anti-hypertensives including diuretics, angiotensin-converting enzyme (ACE) inhibitors, 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.

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.

Cardiac glycosides (digoxin and digitoxin):
NSAIDs may exacerbate cardiac failure, reduce glomerular filtration rate (GFR) and increase plasma glycoside levels. Concomitant administration of digoxin or digitoxin had no effect on the plasma 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 half-life show no significant differences. The small but significant increase in absorption 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 protein-bound 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:
When methotrexate is administered concurrently with NSAIDs, including piroxicam, NSAIDs may decrease elimination of methotrexate resulting in increased plasma levels of methotrexate. Caution is advised, especially in patients receiving high doses of methotrexate.

Tacrolimus:
Possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus.

4.6 Use in Special Populations

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
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 cyclo-oxygenase enzyme. This effect, as with other NSAIDs has 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 closure of the ductus arteriosus in infants. Therefore, piroxicam should be avoided during the third trimester of pregnancy.

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. In animals, administration of prostaglandin synthesis inhibitors has been shown to result in increased pre- and post-implantation loss.

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 upon discontinuation. Pregnant women on piroxicam should be closely monitored for amniotic fluid volume.

The following statement applies only when benzyl alcohol is included in the formulation: Benzyl alcohol can cross the placenta (see section **4.4 Special Warnings and Precautions for Use**).

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 occurred in milk relative to that in plasma during treatment. Piroxicam is not recommended for use in nursing mothers as the clinical safety has not been established.

4.7 Effects on Ability to Drive 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 tolerated. Gastrointestinal symptoms are the most commonly encountered side effects but in most instances do not interfere with the course of therapy.

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.

The following table lists adverse drug reactions (ADRs) within each standard System Organ Class (SOC) by decreasing order of medical seriousness or clinical importance.

Table 1. Adverse Drug Reactions

System Organ Class	Adverse Drug Reactions
Blood and lymphatic system disorders	Aplastic anaemia*, haemolytic anaemia*, anaemia*, eosinophilia*, leucopenia*, thrombocytopenia*
Immune system disorders	Anaphylaxis*, serum sickness*
Metabolism and nutrition disorders	Hyperglycaemia*, hypoglycaemia*, anorexia, fluid retention*
Psychiatric disorders	Depression*, hallucinations*, mental

	confusion*, mood alterations*, insomnia*, nervousness*, dream abnormalities*
Nervous system disorders	Aseptic meningitis*, paraesthesia*, headache, dizziness, somnolence, vertigo
Eye disorders	Blurred vision, eye irritation*, swollen eyes*
Ear and labyrinth disorders	Hearing impairment*, tinnitus
Cardiac disorders	Palpitations
Vascular disorders	Vasculitis*, hypertension*
Respiratory, thoracic and mediastinal disorders	Bronchospasm*, dyspnoea*, epistaxis*
Gastrointestinal disorders[a]	Perforation*, ulceration*, pancreatitis*, gastrointestinal bleeding (including hematemesis and melena)*, gastritis*, epigastric distress, nausea, constipation, abdominal discomfort, flatulence, abdominal pain, diarrhoea, vomiting, indigestion, stomatitis, ano-rectal reactions to suppositories presenting as local pain, burning, pruritus and tenesmus and rare instances of rectal bleeding*
Hepatobiliary disorders	Fatal hepatitis*, jaundice*
Skin and subcutaneous tissue disorders[b]	Angioedema*, Stevens-Johnson syndrome*, toxic epidermal necrolysis (Lyell's disease)*, drug reaction with eosinophilia and systemic symptoms (DRESS syndrome)*, vesiculo bullous reactions*, dermatitis exfoliative*, erythema multiforme*, photoallergic reactions*, fixed drug eruption*, non-thrombocytopenic purpura (Henoch-Schoenlein)*, onycholysis*, alopecia*, skin rash, urticaria*, pruritus
Renal and urinary disorders	Renal failure*, nephrotic syndrome*, glomerulonephritis*, interstitial nephritis*
Reproductive system and breast disorders	Female fertility decreased*
General disorders and administration site conditions	Local adverse reactions (burning sensations) or tissue damage (sterile abscess formation, fatty tissue necrosis) at the site of injection*, malaise*, edema (mainly of the ankle), transient pain upon injection*
Investigations	Reversible elevations of BUN, reversible elevations of creatinine, decreases in hemoglobin and hematocrit unassociated with obvious gastro-intestinal bleeding*, increased serum transaminase level, positive ANA*,

	weight increase, weight decrease*

* Adverse Drug Reaction (ADR) identified post-marketing.
[a] see section 4.4 **Special warnings and precautions for use, Gastrointestinal (GI) Effects**
[b] see section 4.4 **Special warnings and precautions for use, Skin Reactions**
Abbreviations: BUN = blood urea nitrogen; ANA = antinuclear antibody.

4.9 Overdose

For oral formulations (Dispersible Tablets):

In the event of acute overdosage with piroxicam, supportive and symptomatic therapy is indicated. There are no specific antidotes. Emesis and/or gastric lavage and/or activated charcoal may be considered dependent upon amount ingested and time since ingestion. Studies indicate that administration of activated charcoal may result in reduced absorption and re-absorption of piroxicam thus reducing the total amount of active drug available.

For injectable formulations:

In the event of acute overdosage with piroxicam, supportive and symptomatic therapy is indicated. There are no specific antidotes.

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 Mechanism of Action

Piroxicam is a non-steroidal anti-inflammatory agent, which also possesses analgesic and antipyretic properties. Edema, erythema, tissue proliferation, fever, and 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, independent studies *in vitro* as well as *in vivo* have 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 cyclo-oxygenase enzyme.
-Inhibition of neutrophil aggregation.
-Inhibition of polymorphonuclear cell and monocyte migration to the area of inflammation.
-Inhibition of lysosomal enzyme release from stimulated leucocytes.

-Inhibition of superoxide anion generation by the neutrophil.
-Reduction of both systemic and synovial fluid rheumatoid factor production in patients with seropositive rheumatoid arthritis.

It is established that piroxicam does not act by pituitary-adrenal axis stimulation. *In vitro* studies have not revealed any negative effects on cartilage metabolism.

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

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

5.2 Pharmacodynamic Properties

Piroxicam is a non-steroidal anti-inflammatory agent, which also possesses analgesic and antipyretic properties. Edema, erythema, tissue proliferation, fever, and pain can all be inhibited in laboratory animals by the administration of piroxicam. It is effective regardless of the etiology of the inflammation.

5.3 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 once-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 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, area 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 piroxicam, 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.

Metabolism and Elimination

Piroxicam is extensively metabolized and less than 5% of the daily dose is excreted unchanged in urine and feces. Piroxicam metabolism is predominantly mediated via cytochrome P450 CYP 2C9 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 Special Warnings and Precaution for Use, Poor Metabolizers of CYP2C9 Substrates**).

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.

6. NONCLINICAL PROPERTIES

6.1 Animal Toxicology or Pharmacology

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 non-steroidal anti-inflammatory 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.

7. DESCRIPTION

Piroxicam Dispersible Tablets:
White to off-white, oblong tablet with a break line and “DOL 20”engraved on the same side and plain on the other side

Piroxicam Injection (Intramuscular Solution):
Clear greenish- yellow colored solution

8. PHARMACEUTICAL PARTICULARS

8.1 Incompatibilities

Solution for intramuscular use should not be mixed with other medications.

8.2 Shelf-life

Dispersible Tablets: 36 Months.
Intramuscular Solution: 36 Months.

8.3 Packaging Information

Dispersible Tablets (20 mg): 15 tablets per blister strip, 3 strips per combistrip, 10 combistrips per carton.

Injection (Intramuscular Solution) (20 mg/ml): 1 ml and 2 ml in amber coloured ampoules.
5 ampoules in a blister strip. 20 blister in a carton.

8.4 Storage and Handling Instructions

Dispersible Tablets: Store in a dry place at a temperature not exceeding 40°C.

Injection (Intramuscular Solution): Store protected from warm temperature and light.

9. PATIENT COUNSELLING INFORMATION

Advise the patient to read the Package insert leaflet that accompanies each prescription dispensed.

Inform patients, families, or their caregivers of the following information before initiating therapy with piroxicam and periodically during the course of ongoing therapy.

Cardiovascular Thrombotic Events:
Advise patients to be alert for the symptoms of cardiovascular thrombotic events, including chest pain, shortness of breath, weakness, or slurring of speech, and to report any of these symptoms to their health care provider immediately.

Gastrointestinal Bleeding, Ulceration, and Perforation:
Advise patients to report symptoms of ulcerations and bleeding, including epigastric pain, dyspepsia, melena, and hematemesis to their health care provider.

In the setting of concomitant use of low-dose aspirin for cardiac prophylaxis, inform patients of the increased risk for and the signs and symptoms of GI bleeding.

Hepatotoxicity:
Inform patients of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, pruritus, diarrhea, jaundice, right upper quadrant tenderness, and "flu-like" symptoms). If these occur, instruct patients to stop piroxicam and seek immediate medical therapy.

Heart Failure and Edema:
Advise patients to be alert for the symptoms of congestive heart failure including shortness of breath, unexplained weight gain, or edema and to contact their healthcare provider if such symptoms occur.

Anaphylactic Reactions:
Inform patients of the signs of an anaphylactic reaction (e.g., difficulty breathing, swelling of the face or throat). Instruct patients to seek immediate emergency help if these occur.

Serious Skin Reactions, including DRESS:
Advise patients to stop taking piroxicam immediately if they develop any type of rash or fever and to contact their healthcare provider as soon as possible.

Female Fertility:
Advise females of reproductive potential who desire pregnancy that NSAIDs, including piroxicam, may be associated with a reversible delay in ovulation.

Fetal Toxicity:
Inform pregnant women to avoid use of piroxicam and other NSAIDs starting at 30 weeks gestation because of the risk of the premature closing of the fetal ductus arteriosus. If treatment with piroxicam is needed for a pregnant woman between about 20 to 30 weeks gestation, advise her that she may need to be monitored for oligohydramnios, if treatment continues for longer than 48 hours.

Avoid Concomitant Use of NSAIDs:

Inform patients that the concomitant use of piroxicam with other NSAIDs or salicylates (e.g., diflunisal, salsalate) is not recommended due to the increased risk of gastrointestinal toxicity, and little or no increase in efficacy. Alert patients that NSAIDs may be present in "over the counter" medications for treatment of colds, fever, or insomnia.

Use of NSAIDS and Low-Dose Aspirin:
Inform patients not to use low-dose aspirin concomitantly with piroxicam until they talk to their healthcare provider.

10. DETAILS OF MANUFACTURER

Piroxicam Dispersible Tablets 20 mg:

Pfizer Limited
Plot No. L-137, Phase III-A, Verna Industrial Estate,
Verna, Goa- 403 722

Piroxicam Injection (Intramuscular Solution) 20 mg/ml:

Sovereign Pharma Pvt. Limited,
Survey No.46/1-4, Kadaiya Village, Nani Daman- 396 210
For Pfizer limited, Mumbai-400051, India

Marketed by:

CIPLA LTD
Cipla House, Peninsula Business Park,
Ganpatrao Kadam Marg, Lower Parel,
Mumbai· 400 013, INDIA

11. DETAILS OF PERMISSION OR LICENCE NUMBER WITH DATE

Piroxicam Dispersible Tablets 20 mg:
Mfg. Lic. No. 544 dated 11/03/2020*(*The license is renewed every 5 years as per regulations)

Piroxicam Injection (Intramuscular Solution) 20 mg/ml:
Mfg. Lic. No. DD/449 dated 11/11/2019*(*The license is renewed every 5 years as per regulations)

12. DATE OF REVISION

April, 2026