PRODUCT MONOGRAPH

PENTA–PIROXICAM

(Piroxicam)

10 mg and 20 mg Capsules

U.S.P.

Anti–inflammatory Agent with Analgesic Properties

Pentapharm Limited,
Scarborough, Canada
M1S 5G3
#052291

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July 28, 97
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PHARMACOLOGICAL CLASSIFICATION

Anti–inflammatory Agent with Analgesic Properties

ACTIONS AND CLINICAL PHARMACOLOGY

PENTA–PIROXICAM (piroxicam) is a nonsteroidal anti–inflammatory agent possessing both analgesic and antipyretic properties. The mode of action of piroxicam is not fully established at this time, however as a result of piroxicam's inhibition of prostaglandin synthetase, prostaglandin biosynthesis is decreased. This may explain, in part, its anti–inflammatory action. It is known that pituitary–adrenal stimulation is not a mechanism of action of piroxicam.

A 20 mg dose of piroxicam daily has been shown to have similar efficacy to 4.5 g of ASA daily in the treatment of rheumatoid arthritis.

Piroxicam is well absorbed when given orally. Neither food nor antacids affect the rate or extent of absorption. Peak plasma concentrations of piroxicam are achieved in about 4 hours following a single 20 mg oral dose. In man, the plasma half–life is approximately 38 hours. When administered daily, plasma concentrations of piroxicam increase for five to eight days to reach a steady state level.

A single dose (20 mg) bioavailability study was performed by Richardson et al in order to evaluate age and sex–related differences in the pharmacokinetics of piroxicam. It was found that elderly

women (62 to 75 years) had 33% lower piroxicam clearance than young women (20 to 31 years), a difference that was reflected in the significantly different half–life of 61.7 and 44.9 hours, respectively. No significant difference of the clearance rate was found between young men and elderly men. The predicted steady state plasma concentrations were found to be 5.7, 5.4 and 5.7 µg/mL in young women, young men and elderly men, compared with 9.3 µg/mL in elderly women. These results are at variance with the finds of Hobbs et al and Woolf et al, who concluded that age had no or negligible effect on piroxicam clearance and steady state plasma levels.

A comparative two–way, single dose bioavailability study was performed on Penta–Piroxicam 20 mg Capsules and Feldene 20 mg Capsules. The pharmacokinetic data (mean ± standard deviation) calculated for the Penta–Piroxicam and Feldene Capsule formulations is tabulated below:

Pharmacokinetic Indices for Piroxicam

	Penta–Piroxicam	Feldene
Area Under the Curve: (µg–hours/mL); 0–144 hours	135.99 ± 43.95	139.90 ± 47.28
Peak Plasma Concentration: Cmax (µg/mL)	2.18 ± 0.31	2.24 ± 0.39
Time of Peak Plasma Level: Tmax (hours)	1.34 ± 0.60	1.25 ± 0.55
Plasma Half–Life: t–1/2 (hours)	56.35 ± 33.21	56.11 ± 41.84
Elimination Rate Constant: Kel ($hour^{-1}$)	0.019 ± 0.021	0.023 ± 0.024

Piroxicam undergoes extensive hepatic metabolism with less than 5% excreted unchanged in the urine or feces. Hydroxylation of the pyridyl ring constitutes the major pathway of metabolism after which the metabolite is conjugated with glucuronic acid and excreted as such in the urine and feces.

Studies have shown that subjects had significantly lower average daily fecal blood loss over a 4 day period when given piroxicam 20 mg daily (in single or divided doses) than when given aspirin 3.9 g daily.

INDICATIONS AND CLINICAL USE

PENTA–PIROXICAM (piroxicam) is indicated for the treatment of symptoms related to rheumatoid arthritis, osteoarthritis (degenerative joint disease) and ankylosing spondylitis.

CONTRAINDICATIONS

PENTA–PIROXICAM (piroxicam) should not be administered to patients with, or with a recent or recurrent history of, peptic ulcer disease or active gastrointestinal inflammatory disease.

PENTA–PIROXICAM is contraindicated in patients that have shown hypersensitivity to piroxicam. It should not be administered to patients in whom ASA or other nonsteroidal anti–inflammatory agents have precipitated acute asthmatic attacks, urticaria, rhinitis or other allergic manifestations because of the possibility of cross–sensitivity. Fatal anaphylactoid reactions have occurred in such individuals.

WARNINGS

Gastrointestinal bleeding, peptic ulceration and perforation have been observed during therapy with piroxicam. These side effects were sometimes severe and, in some instances, fatal. If piroxicam must be used in patients prone to gastrointestinal tract irritation, particularly those with a history of peptic ulcer, diverticulosis or other inflammatory disease of the gastrointestinal tract, this should be done with great caution and under close supervision. In these cases, the physician

must weigh the benefits of treatment against the possible hazards. The use of doses higher than the recommended dose, 20 mg daily, is associated with an increase in the incidence of gastrointestinal irritation and ulcers. Patients taking any NSAID, including piroxicam, should be instructed to contact a physician immediately if they experience symptoms or signs suggestive of peptic ulceration or gastrointestinal bleeding. These reactions can occur without warning symptoms or signs and at any time during the treatment.

Use in Elderly, Frail or Debilitated Patients:

Since gastrointestinal side effects and ulceration from piroxicam are dose related, persons with a decreased ability to eliminate the drug may be more susceptible to adverse effects. Therefore, treatment in elderly, frail or debilitated patients, especially those aged 65 and over, should be started with 10 mg a day and increased to 20 mg a day if necessary. Careful monitoring of these patients is essential. See PRECAUTIONS for further advice.

Use in Pregnant or Lactating Women:

The safety of piroxicam has not been established in these conditions and therefore, the use of PENTA–PIROXICAM (piroxicam) is not recommended during pregnancy or lactation. It has not been determined whether piroxicam crosses the placenta. Piroxicam was present in human milk in a concentration of approximately 1% of that reached in plasma.

Animal reproductive studies have not demonstrated any teratogenic effects. Pregnant rats and rabbits receiving piroxicam have shown an increased frequency of dystocia and delayed parturition. Suppression of lactation has been observed in rats receiving piroxicam.

Gastrointestinal tract toxicity was increased in pregnant females in the last trimester of pregnancy compared to nonpregnant females or females in earlier trimesters of pregnancy.

Use in Children:

PENTA–PIROXICAM is not recommended for use in children under 16 years of age. Dose and indications for pediatric patients have not been established.

PRECAUTIONS

Gastrointestinal System:

PENTA–PIROXICAM (piroxicam) should be discontinued if peptic ulceration is suspected or confirmed, or if gastrointestinal bleeding or perforation occurs. An appropriate treatment should be instituted and the patient monitored closely.

There is no evidence that the concurrent administration of H_2 antagonists or antacids will either prevent the occurrence of gastrointestinal side effects or allow continuation of piroxicam therapy when and if these adverse reactions appear.

Renal Function:

PENTA–PIROXICAM should be used cautiously in patients with decreased renal function. Because of the extensive renal excretion of piroxicam and its biotransformation products (less than 5% of the daily dose excreted unchanged), lower doses of piroxicam should be anticipated in patients with impaired renal function and they should be carefully monitored. Acute renal failure and hyperkalemia as well as reversible elevations of BUN and serum creatinine have been reported with piroxicam. In addition to reversible changes in renal function, interstitial nephritis, hematuria, proteinuria, glomerulitis, papillary necrosis and the nephrotic syndrome have been reported with piroxicam. A second form of renal toxicity has been seen in patients with prerenal conditions leading to the reduction in renal blood flow or blood volume, where the renal prostaglandins have a supportive role in the maintenance of renal perfusion. Administration of a nonsteroidal anti–inflammatory drug to these patients may cause a dose–dependent reduction in

prostaglandin formation and may precipitate overt renal decompensation. Discontinuation of nonsteroidal anti–inflammatory therapy is usually followed by recovery to pre–treatment state. Patients with impaired renal function, congestive heart failure, cirrhosis with ascites or those on diuretics, as well as elderly patients are at the greatest risk. Patients on long term therapy with piroxicam, especially those in the high risk categories, should have blood chemistry and kidney function tests monitored periodically. If renal function deterioration commences, PENTA–PIROXICAM administration should be stopped.

Hepatic Function:

PENTA–PIROXICAM should be used cautiously in patients with decreased hepatic function. Borderline elevations of one or more liver tests may occur in patients taking piroxicam. These abnormalities may progress, remain essentially unchanged or may be transient with continued therapy. Any patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of more severe hepatic reaction while receiving piroxicam therapy. Severe hepatic reactions, including jaundice and cases of fatal hepatitis, have been reported with piroxicam. Although such reactions are rare, if abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g. eosinophilia, rash, etc.), PENTA–PIROXICAM should be discontinued (see also ADVERSE REACTIONS). All patients on long term piroxicam therapy should have periodic liver function tests.

Hematology:

Piroxicam, like other nonsteroidal anti–inflammatory agents, inhibits prostaglandin biosynthesis and therefore interferes with platelet function, partly due to a decrease in platelet aggregation. Therefore, patients who may be adversely affected by such an action should be carefully observed during PENTA–PIROXICAM administration. Although blood dyscrasias associated with the use of nonsteroidal anti–inflammatory drugs are rare, they could have severe consequences.

Although at the recommended dose of 20 mg/day of piroxicam increased fecal blood loss due to gastrointestinal irritation did not occur, in about 4% of the patients treated with piroxicam alone or concomitantly with ASA, reductions in hemoglobin and hematocrit values were observed. Therefore, these values should be checked periodically.

Ophthalmology:

There have been reports of blurred and/or diminished vision with the use of piroxicam and other nonsteroidal anti–inflammatory drugs. If such symptoms develop, piroxicam should be discontinued and an ophthalmologic examination performed. In any patient receiving this drug for an extended period of time, ophthalmologic examinations should be carried out at periodic intervals.

Fluid and Electrolyte Balance:

Approximately 2% of patients treated with piroxicam experienced peripheral edema. Therefore PENTA–PIROXICAM should be used with caution in patients with heart failure, hypertension or other conditions predisposing to fluid retention, since its use may be associated with a worsening of these conditions. Congestive heart failure may be precipitated in the elderly and in patients with compromised cardiac function. Serum electrolytes should be monitored periodically during long term therapy, especially in those patients at risk.

Hypersensitivity Reactions:

Patients should be monitored for a combination of dermatological and/or allergic signs and symptoms of serum sickness which have occasionally occurred in conjunction with the use of piroxicam. These include arthralgias, pruritus, fever, fatigue and rash including vesiculo bullous reactions and exfoliative dermatitis.

Infection:

Because of the drug's anti–inflammatory activity, PENTA–PIROXICAM may mask the usual signs of infection.

Drug Interactions:

Protein–bound Drugs:

Piroxicam is highly bound to plasma proteins and may displace or may be displaced by other protein–bound agents such as oral anticoagulants, salicylates and sulfonylureas. Patients being treated with coumarin anticoagulants or other highly protein–bound drugs should have their dosage requirements monitored closely and be observed for adverse effects during concomitant PENTA–PIROXICAM administration.

Antacids:

Concomitant administration of antacids has no effect on piroxicam plasma levels, however, plasma levels are depressed to approximately 80% of their normal values when piroxicam is administered in conjunction with acetylsalicylic acid (3.9 g/day).

Other Nonsteroidal Anti–inflammatory Drugs:

The use of PENTA–PIROXICAM in conjunction with acetylsalicylic acid or another nonsteroidal anti–inflammatory agent is not recommended since data are not available demonstrating that the combination produces greater improvement than that achieved with either drug alone, and the potential for adverse reactions is increased.

Lithium:

Nonsteroidal anti–inflammatory agents, including piroxicam, have been reported to increase steady state plasma lithium levels. When initiating, adjusting or discontinuing PENTA–PIROXICAM, it is recommended that plasma lithium levels be monitored.

ADVERSE REACTIONS

Approximately 30% of all patients receiving daily doses of 20 mg of piroxicam experienced side effects.

The most frequent side effects occurring in patients receiving piroxicam (20% of patients) have been gastrointestinal in origin. Approximately 4% of patients have been required to discontinue piroxicam treatment due to gastrointestinal complaints. The most severe adverse reactions are peptic ulceration and gastrointestinal bleeding.

The following adverse reactions, with approximate incidences, have been reported:

Gastrointestinal:

Abdominal discomfort	5.7%
Flatulence	5.2%
Nausea	4.8%
Abdominal pain	4.7%
Epigastric distress	4.1%
Constipation	3.8%
Diarrhea	3.2%
Peptic ulceration	1.8%
Stomatitis	1–3%
Anorexia	2.0%
Vomiting	1.0%
Indigestion	0.7%
Gastrointestinal bleeding	0.1%

Liver function abnormalities, jaundice, hepatitis, hematemesis, melena and dry mouth were seen in less than 1% of patients.

Central Nervous System:

Dizziness	4.1%
Headache	4.1%
Drowsiness/Sedation	2.1%

Amnesia, anxiety, depression, hallucinations, insomnia, nervousness, paresthesia, personality change, tremors, and vertigo were seen in less than 1% of patients.

Dermatologic:

Rash	2.4%
Pruritus	1.1%

Alopecia, sweating, erythema, bruising, desquamation, exfoliative dermatitis, erythema multiforme, toxic epidermal necrolysis, Stevens – Johnson syndrome, vesiculo–bullous reaction, and photoallergic reactions were seen in less than 1% of patients.

Genito–Urinary:

Edema	2.7%
BUN elevation	1–3%
Creatinine elevation	1–3%

Dysuria, urinary frequency, hematuria, oliguria, proteinuria, interstitial nephritis, renal failure, hyperkalemia, glomerulitis, papillary necrosis, nephrotic syndrome and menorrhagia were seen in less than 1% of patients.

EENT:

Blurred vision, eye irritation/swelling, deafness, tinnitus, epistaxis, and glossitis were seen in less than 1% of patients.

Hematological:

Decreases in hemoglobin and hematocrit	3–9%
Anemia	1–3%
Leukopenia	1–3%
Eosinophilia	1–3%

Thrombocytopenia, petechial rash, ecchymosis, bone marrow depression including aplastic anemia, and epistaxis were seen in less than 1% of patients.

Cardiovascular/Respiratory:

Hypertension, worsening of congestive heart failure, exacerbation of angina, palpitations, tachycardia, and breathlessness were seen in less than 1% of patients.

Metabolic:

Hypoglycemia, hyperglycemia, weight increase, and weight decrease were seen in less than 1% of patients.

Hypersensitivity:

Bronchospasm, anaphylaxis, angioedema, vasculitis, and serum sickness were seen in less than 1% of patients.

Miscellaneous:

Pain (colic), fever, flu–like syndrome, thirst, chills, flushing, and increased appetite were seen in less than 1% of patients.

SYMPTOMS AND TREATMENT OF OVERDOSE

A few cases of overdoses (up to 1800 mg) have been reported. Recovery was complete. Symptoms and signs included nausea, abdominal pain, multiple superficial gastric and duodenal ulcers, and gastrointestinal tract bleeding.

No specific antidote is known to piroxicam. The usual supportive and symptomatic treatment is recommended. In animals, the use of activated charcoal has been shown to reduce the absorption of piroxicam.

DOSAGE AND ADMINISTRATION

In the symptomatic treatment of rheumatoid arthritis and ankylosing spondylitis, the recommended starting dose of PENTA–PIROXICAM (piroxicam) is a single daily dose of 20 mg or, if desired, 10 mg twice daily. The majority of patients will require a maintenance dose of 20 mg daily although some may be maintained on 10 mg daily.

The recommended dosage of PENTA–PIROXICAM for the initiation of treatment of osteoarthritis is 20 mg once daily or, if desired, 10 mg twice daily. Usual maintenance therapy is 10–20 mg daily.

Because of increased risk of toxicity to elderly, debilitated and frail patients or patients with impaired renal function, a starting dose of 10 mg/day is recommended. The dose may be increased to 20 mg/day, if necessary (see WARNINGS and PRECAUTIONS).

Because of an increased frequency of gastrointestinal side effects, piroxicam dosage should not exceed 20 mg daily.

Because of the length of time required to attain steady–state plasma concentrations on once per day dosing (5–8 days), the full effect of treatment should not be assessed for two weeks.

AVAILABILITY

PENTA–PIROXICAM (piroxicam) capsules are available in bottles of 100 and 500.

Each No. 2 maroon/blue opaque hard gelatin capsule contains: 10 mg piroxicam.

Each No. 2 maroon opaque hard gelatin capsule contains: 20 mg piroxicam.

PHARMACEUTICAL INFORMATION

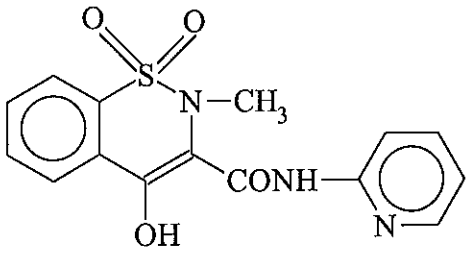
Trade Name: PENTA–PIROXICAM

Proper Name: Piroxicam

Structural Formula and Chemistry:

Piroxicam belongs to the chemical class of N–heterocyclic carboxamides of 1,2–benzothiazine–1,1–dioxide(oxicams). An amphoteric compound, piroxicam has a weakly acidic 4–hydroxy proton (pKa 5.1) and a weakly basic pyridyl nitrogen (pKa 1.5) as determined by ultraviolet absorption spectrophotometry in methanol–water (2.5/97.5, v/v) solvent medium. Its chemical name is 2H–1,2–

benzothiazine–3–carboxamide,4 hydroxy–2–methyl–N–2–pyridinyl–,1,1–dioxide and it has the following structural formula:



Molecular Formula: $C_{15}H_{13}N_3O_4S$ Molecular Weight: 331.35

Description:

Piroxicam is a white, crystalline, hygroscopic solid. Melting point is 196–200°C. It is poorly soluble in water, dilute acid and most organic solvents and slightly soluble in alcohols and aqueous alkaline solution.

STORAGE RECOMMENDATIONS

PENTA–PIROXICAM (piroxicam) capsules should be protected from light and stored at room temperature (15–30°C).

PHARMACOLOGY

The anti–inflammatory activity of oral doses of piroxicam has been shown in rats, guinea pigs and dogs. A 50% inhibition of carogeenan induced foot edema was produced after a 4.0 mg/kg dose was given to rats. Adjuvant induced arthritis in rats was inhibited by piroxicam in doses of 0.3 – 3.3 mg/kg. Inhibition of cotton string induced granuloma formation in rats was observed after doses of 10 and 18 mg/kg. Guinea pigs given a 0.3 mg/kg dose of piroxicam showed a 50%

inhibition of ultraviolet light induced erythema. Piroxicam given intravenously to dogs in a dose of 5 mg/kg inhibited the inflammatory response to urate induced synovitis in knee joints.

Analgesic activity of piroxicam has been demonstrated in mice given 1.85 mg/kg orally, using the phenylquinone induced writhing test. Oral doses of 1 to 2 mg/kg of piroxicam were effective in elevating the threshold to pressure in edematous rat paws. Doses up to 100 mg/kg orally were inactive in hot–plate and tail–flick tests.

Antipyretic activity of piroxicam given orally to rats at 10 mg/kg has been demonstrated in a model of hyperpyrexia induced by intramuscular injections of E. coli lipopolysaccharide.

Prostaglandin biosynthesis is reduced by piroxicam due to inhibition of prostaglandin synthetase. Collagen induced aggregation of platelets is also inhibited. Anti–inflammatory activity in adrenalectomized rats demonstrated the independence of piroxicam's anti–inflammatory activity from adrenal stimulation.

Piroxicam has been shown not to have significant cardiovascular or central nervous system activity in animals.

TOXICOLOGY

Acute Toxicity:

Oral LD_{50} mg/kg (95% Confidence Limits)

Mice: 395 (255–612)

Rats: 320 (244–419)

Toxic effects observed in mice and rats included apathy, decreased motor activity, depression, dyspnea, ataxia, ptosis and prostration. Necropsy of these animals revealed internal hemorrhage of the stomach wall, adjacent small intestine and adrenals, congested adrenal glands, livers and lungs and partial thickening of the stomach wall.

The oral LD_{50} in dogs has been reported to be greater than 500 mg/kg.

Subacute and Chronic Toxicity:

Beagle dogs, given piroxicam 1.0 mg/kg/day orally for 12 months, showed signs of both gastrointestinal and renal toxicity. The former included emesis, diarrhea, gastric and duodenal erosions and ulceration, fecal occult blood loss and anemia. Renal damage was demonstrated by proteinuria, hematuria, papillary necrosis and a single case of pyelonephritis. Other effects considered to be manifestations of drug toxicity were leukocytosis, decreased serum calcium and integumental signs.

A rhesus monkey study in which oral doses of 2.5, 5.0 and 10.0 mg/kg/day for 12 months were given, revealed epithelial casts within the collecting ducts of the kidneys of 67% of the females receiving 10 mg/kg daily. No gastrointestinal toxicity was observed in any of the monkeys. Another study in rhesus monkeys was conducted over 90 days at the same dose levels. Occasional erosions of the gastrointestinal mucosa were observed only in the animals receiving the highest dose. However, one female monkey receiving 2.5 mg/kg/day did develop an acute gastric ulcer.

Papillary necrosis, elevated blood urea nitrogen and necrotizing gastrointestinal lesions were noted in an 18 month study of rats receiving oral piroxicam doses of 0.3, 1.0 and 3.0 mg/kg daily. The toxicity was dose and duration related. More females than males developed gastrointestinal

lesions and papillary necrosis at a 3.0 mg/kg daily dose. In males, a dose related anemia was observed.

Mice were given daily oral doses of 2, 4 and 8 mg/kg for 18 months in one study, resulting in increased mortality at 8 mg/kg. Renal papillary necrosis with secondary chronic diffuse interstitial nephritis was dose related. Other observed adverse effects were elevated blood urea nitrogen and necrotizing gastrointestinal lesions.

Reproduction and Teratology Studies:

Piroxicam, like other prostaglandin inhibitors, prolongs the gestational period in rats. This effect is dose and duration dependent.

Pregnant rats were given piroxicam in oral daily doses of 2, 5 and 10 mg/kg from day 15 post coitum. An increase in mortality and prolongation of gestation and parturition were dose related. Complete inhibition of parturition occurred when piroxicam was given for 8 days at 10 mg/kg. This dystocia, along with gastrointestinal toxicity, resulted in weakness and death of the females and their offspring. Deaths and prolonged parturition occurred even when drug administration was discontinued after 5 days.

Pregnant rats that received piroxicam orally at 10 mg/kg daily from day 1 post coitum to 16–20 post coitum displayed prolonged gestational periods. This prolongation of gestation was increased with increasing durations of treatment. Parturition was prolonged and there was an elevation in the mortality rate of the offspring. Suppression of lactation was observed to be dose related.

Rats of both sexes were given piroxicam orally in doses of 2, 5 and 10 mg/kg daily for 81 days (males) and 14 days (females) before mating. Females continued to receive the drug for 6 days

post coitum. Sexual behaviour was unaltered in either sex, nor was there a decrease in fertility. Normal fetal development ensued. Offspring were comparable to controls both in viability and growth. No drug induced abnormalities were observed.

Pregnant rats and rabbits, dosed with piroxicam orally at 2, 5 and 10 mg/kg/day during the critical period of organogenesis had offspring that displayed no teratogenic effects. No embryotoxicity was observed.

A dose related suppression of lactation occurred on days 1–12 of the lactation period in female rats which resulted in decreased postnatal weight gain in their offspring. Oral daily doses of 2, 5 and 10 mg/kg of piroxicam were studied.

Mutagenicity:

None of the studies demonstrated any mutagenic activity of piroxicam.

Carcinogenicity:

In a 24 month rat study, piroxicam, administered in the diet to provide doses of 0.3 and 1.0 mg/kg, induced the same spectrum as in the 18 month rat study, but there was a higher incidence at 1 mg/kg of non–neoplastic lesions. The principal drug induced pathologic changes consisted of renal papillary necrosis, suppurative pyelonephritis and pyloric ulceration. Except for suppurative pyelonephritis, females were more often affected than males.

INFORMATION FOR THE CONSUMER

The following information will be dispensed with this drug:

PATIENT INFORMATION LEAFLET

PENTA–PIROXICAM

Brand of Piroxicam Capsules

10 mg and 20 mg

Piroxicam, which has been prescribed to you by your doctor, is one of a large group of nonsteroidal anti–inflammatory drugs (NSAID's) and is used to treat the symptoms of certain types of arthritis (rheumatism). It helps to relieve joint pain, swelling, stiffness and fever by reducing the production of certain substances (prostaglandins) and helping to control inflammation and other body reactions.

You should take piroxicam only as directed by your doctor. Do not take more of it, do not take it more often and do not take it for a longer period of time than your doctor ordered.

Be sure to take piroxicam regularly as prescribed. In some types of arthritis, up to two weeks may pass before you feel the full effects of this medicine. During treatment, your doctor may decide to adjust the dosage according to your response to the medication.

To lessen stomach upset, take this medicine immediately after a meal or with food or milk. If stomach upset (indigestion, nausea, vomiting, stomach pain or diarrhea) occurs and continues, contact your doctor.

This medicine is available only with your doctor's prescription. Remember:

- This medicine has been prescribed for your current medical problem only. It must

not be given to other people or used for other problems unless you are otherwise directed by your doctor.

PROPER USE OF THIS MEDICINE

Do not take ASA (acetylsalicylic acid), ASA–containing compounds or other drugs used to relieve symptoms of arthritis while taking piroxicam unless directed to do so by your physician.

If you are prescribed this medication for use over a long period of time, your doctor will check your health during regular visits to assess your progress and to ensure that this medication is not causing unwanted effects.

SIDE EFFECTS OF THIS MEDICINE

Along with its beneficial effects, piroxicam, like other NSAID drugs, may cause some undesirable reactions. Elderly, frail or debilitated patients often seem to experience more frequent or more severe side effects. Although not all of these side effects are common, when they do occur they may require medical attention. Check with your doctor immediately if any of the following are noted:

- Bloody or black tarry stools
- Shortness of breath, wheezing, any trouble in breathing or tightness in the chest
- Skin rash, swelling, hives or itching
- Indigestion, nausea, vomiting, stomach pain or diarrhea
- Yellow discolouration of the skin or eyes, with or without fatigue
- Any changes in the amount or colour of your urine (such as dark, red or brown)
- Swelling of the feet or lower legs

- Blurred vision or any visual disturbance
- Mental confusion, depression, dizziness, lightheadedness
- Hearing problems

ALWAYS REMEMBER

Before taking this medication tell your doctor and pharmacists if you:

- are allergic to piroxicam or other related medicines of the NSAID group such as acetylsalicylic acid, diflunisal, fenoprofen, flurbiprofen, diclofenac, indomethacin, ketoprofen, mefenamic acid, ibuprofen, sulindac, tiaprofenic acid or tolmetin
- have a history of stomach upset, ulcers, or liver or kidney disease
- are pregnant or intend to become pregnant while taking this medication
- are breast feeding
- are taking any other medication (either prescription or nonprescription)
- have any other medical problem(s)

While taking this medication:

- Tell any other doctor, dentist or pharmacist that you consult or see, that you are taking this medication.
- Be cautious about driving or participating in activities that require alertness if you are drowsy, dizzy or lightheaded after taking this medication. Tranquilizers, sleeping pills and certain antihistamines (anti–allergic) may increase the frequency and/or severity of these side effects.
- Check with your doctor if you are not getting any relief or if any problems develop.
- Report any untoward reactions to your doctor. This is very important as it will aid in the early detection and prevention of potential complications.
- Your regular medical checkups are essential.

- If you want more information about this medicine, ask your doctor or pharmacist.

Pentapharm Limited,

Scarborough, Canada.

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