PRODUCT MONOGRAPH

RHO®-PIROXICAM

(piroxicam)

10 and 20 mg Capsules

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#030614

DATE OF PREPARATION

November 30, 1994

PRODUCT MONOGRAPH

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(piroxicam)

10 and 20 mg Capsules

PHARMACOLOGICAL CLASSIFICATION

Anti-inflammatory agent with analgesic properties.

ACTIONS AND CLINICAL PHARMACOLOGY

RHO-PIROXICAM (piroxicam) is a nonsteroidal anti-inflammatory agent with analgesic and antipyretic properties. Its mechanism of action is incompletely known. **RHO-PIROXICAM** inhibits the activity of prostaglandin synthetase. The resulting decrease in prostaglandin biosynthesis may partially explain its anti-inflammatory action. **RHO-PIROXICAM** does not act by pituitary-adrenal stimulation.

In rheumatoid arthritis the efficacy of **RHO-PIROXICAM** 20 mg daily has been found to be similar to 4.5 g daily of ASA.

Piroxicam is well absorbed following oral or rectal administration. After a single oral dose of 20 mg, peak plasma levels of piroxicam are achieved in

about 4 hours. When the drug is administered daily, plasma concentrations increase for seven to twelve days during which a steady state is reached. Concentrations attained are not exceeded following further constant daily drug intake. The plasma half-life is approximately 50 hours in man. The extent and rate of absorption are not influenced by administration with food or antacids.

After a single rectal dose of 20 mg, the pharmacokinetics are similar to that obtained after oral administration except for peak plasma levels which are achieved at about 10 hours.

Piroxicam is extensively metabolized and less than 5% of the daily dose is excreted unchanged in urine and feces. The main metabolic pathway is hydroxylation of the pyridyl ring, followed by conjugation with glucuronic acid and urinary elimination. Approximately 5% of the dose is metabolized to and excreted as saccharin.

Over a four day period of observation, twenty healthy men, taking piroxicam 20 mg daily in single or divided doses, showed significantly less mean daily fecal blood loss than did ten healthy male controls taking 3.9 g of ASA daily.

The effects of age and sex on the pharmacokinetics of piroxicam have been examined in three single-dose, three multiple dose, and five therapeutic drug monitoring studies. Although not consistent across all studies, some indicated a tendency towards a modest decrease in total body clearances and an increase in elimination half-life and steady-state plasma concentrations in the elderly, particularly elderly females. Irrespective of age, some patients had plasma concentration levels that are substantially greater than the mean.

INDICATIONS AND CLINICAL USE

RHO-PIROXICAM (piroxicam) is indicated for the symptomatic treatment of rheumatoid arthritis, osteoarthritis (degenerative joint disease) and ankylosing spondylitis and primary dysmenorrhea.

CONTRAINDICATIONS

1. Peptic ulcer or active inflammatory disease of the gastrointestinal system, or patients with a recent or recurrent history of these conditions.

2. Known or suspected hypersensitivity to the drug. **RHO-PIROXICAM** (piroxicam) should not be used in patients in whom

acute asthmatic attacks or symptoms of asthma, urticaria, rhinitis (nasal polyps), angioedema or other allergic manifestations are precipitated by ASA or other nonsteroidal anti-inflammatory agents since cross-sensitivity exists. Fatal anaphylactoid reactions have occurred in such individuals.

WARNINGS

- Peptic ulceration, perforation and gastrointestinal bleeding, sometimes severe, and occasionally fatal, have been reported during therapy with nonsteroidal anti-inflammatory drugs (NSAID's) including piroxicam.

- **RHO-PIROXICAM** should be given under close medical supervision to patients prone to gastrointestinal tract irritation particularly those with a history of peptic ulcer, diverticulosis or other inflammatory disease of the gastrointestinal tract. In these cases the physician must weigh the benefits of treatment against the possible hazards.

- Patients taking any NSAID including this drug 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.

- Elderly, frail and debilitated patients appear to be at higher risk from a variety of adverse reactions from nonsteroidal anti-inflammatory drugs (NSAID's). For such patients, consideration should be given to a starting dose lower than usual, with individual adjustment when necessary and under close supervision. See "Precautions" for further advice.

- Gastro-intestinal side effects are dose-related and doses of **RHO-PIROXICAM** greater than 20 mg daily should not be used. The minimum maintenance dose needed to control symptoms is recommended.

Use in Pregnancy and Lactation:

- The use of **RHO-PIROXICAM** (piroxicam) during pregnancy or lactation is not recommended as its safety in these conditions has not been established. 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.

No teratogenic effects have been observed in animal reproductive studies. Rats and rabbits receiving piroxicam during pregnancy have shown an increased frequency of dystocia and delayed parturition. Rats have exhibited suppression of lactation.

PRECAUTIONS

Gastro-intestinal System:

If peptic ulceration is suspected or confirmed, or if gastrointestinal bleeding or perforation occurs **RHO-PIROXICAM** (piroxicam) should be discontinued, an appropriate treatment instituted and patient closely monitored.

There is no definitive evidence that the concomitant administration of histamine H_2-receptor antagonists and/or antacids will either prevent the occurrence of gastro-intestinal side effects or allow continuation of **RHO-PIROXICAM** therapy when and if these adverse reactions appear. (Also see Drug Interactions section).

Renal Function:

As with other nonsteroidal anti-inflammatory drugs, long term administration of piroxicam to animals has resulted in renal papillary necrosis and other abnormal renal pathology. In humans, there have been reports of acute interstitial nephritis with hematuria, proteinuria, and occasionally nephrotic syndrome.

Acute renal failure and hyperkalemia as well as reversible elevations of BUN and serum creatinine have been reported with piroxicam. The effect is thought to result from inhibition of renal prostaglandin synthesis resulting in a change in medullary and deep cortical blood flow with an attendant effect on renal function. Patients with impaired renal function or on diuretics, as well as elderly patients and those with congestive heart failure or liver cirrhosis with ascites, are more at risk. 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.

During long-term therapy kidney function should be monitored periodically.

Hepatic Function:

As with other nonsteroidal anti-inflammatory drugs, borderline elevations of one of more liver tests may occur. These abnormalities may progress, may remain essentially unchanged, or may be transient with continued therapy. The SGPT (ALT) test is probably the most sensitive indicator of liver dysfunction.

Meaningful (3 times the upper limit of normal) elevations of SGPT or SGOT (AST) occurred in controlled clinical trials in less than 1% of patients. A 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 on therapy with this drug. Severe hepatic reactions including jaundice and cases of fatal hepatitis have been reported with this drug as with other nonsteroidal anti-inflammatory drugs. 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.), this drug should be discontinued (see also **ADVERSE REACTIONS**).

During long-term therapy, liver function tests should be monitored periodically. If this drug is to be used in the presence of impaired liver function, it must be done under strict observation.

Fluid and Electrolyte Balance:

Fluid retention and edema have been observed in patients treated with piroxicam. Therefore, as with many other nonsteroidal anti-inflammatory drugs, the possibility of precipitating congestive heart failure in elderly patients or those with compromised cardiac function should be borne in mind. **RHO-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 worsening of these conditions.

Serum electrolytes should be monitored periodically during long-term therapy, especially in those patients at risk.

Hematology:

Drugs inhibiting prostaglandin biosynthesis do interfere with platelet function to some degree; therefore, patients who may be adversely affected by such an action should be carefully observed when **RHO-PIROXICAM** is administered.

At the recommended dose of 20 mg/day of piroxicam increased fecal blood loss due to gastrointestinal irritation did not occur, but 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 determined periodically.

Blood dyscrasia associated with the use of nonsteroidal anti-inflammatory drugs are rare, but could be with severe consequences.

Infection:

In common with other anti-inflammatory drugs, **RHO-PIROXICAM** may mask the usual signs of infection.

Dermatological and/or allergic:

A combination of dermatological and/or allergic signs and symptoms suggestive of serum sickness have occasionally occurred in conjunction with the use of piroxicam. These include arthralgia, pruritus, fever, fatigue, and rash including vesiculo bullous reactions and exfoliative dermatitis.

Ophthalmology:

Blurred and/or diminished vision has been reported with the use of piroxicam and other nonsteroidal anti-inflammatory drugs. If such symptoms develop this drug should be discontinued and an ophthalmologic examination performed; ophthalmic examination should be performed at periodic intervals in any patient receiving this drug for an extended period of time.

Use in Children:

RHO-PIROXICAM (piroxicam) is not recommended for use in children under 16 years of age as the dose and indications have not been established.

Drug Interactions:

Acetylsalicylic Acid (ASA) or other NSAID's

Plasma concentrations of piroxicam are reduced to approximately 80% of their normal concentrations when piroxicam is administered in conjunction with acetylsalicylic acid (3900 mg/day). The use of **RHO-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.

Anticoagulants

RHO-PIROXICAM (piroxicam) is highly protein-bound, and therefore, might be expected to displace other protein-bound drugs. The physician should closely monitor dosage requirements of coumarin anticoagulants and other drugs that are highly protein-bound when these are administered concomitantly with **RHO-PIROXICAM**.

Lithium

Nonsteroidal anti-inflammatory agents, including piroxicam, have been reported to increase steady state plasma lithium concentrations. It is recommended that these concentrations are monitored when initiating, adjusting and discontinuing **RHO-PIROXICAM** treatment.

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 clinical significance of this small but significant increase in absorption is yet unknown.

Digoxin or Digitoxin

Concurrent therapy with piroxicam and digoxin and/or piroxicam and digitoxin did not affect the plasma levels of either drug.

Antacids

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

Diuretics

Nonsteroidal anti-inflammatory drugs, including **RHO-PIROXICAM** (piroxicam) may cause sodium and fluid retention, and may interfere with the natriuretic action of diuretic agents. These properties should be kept in mind when treating patients with compromised cardiac function or hypertension since they may be responsible for a worsening of those conditions.

Methotrexate

Although up to date there have been no reports of an interaction with piroxicam, isolated cases indicate that the concomitant use of some NSAIDs in patients receiving methotrexate may be associated with severe or sometimes fatal methotrexate toxicity.

Until more information is available on this interaction, caution should be used if **RHO-PIROXICAM** as well as other NSAIDs, are administered concomitantly with methotrexate, particularly in patients with pre-existing renal impairment, who may be more susceptible.

Beta-adrenergic Blockers

As with other nonsteroidal anti-inflammatory drugs, concomitant administration of **RHO-PIROXICAM** (piroxicam) with propranolol can reduce the hypotensive effect. Patients should be monitored for altered

antihypertensive or antianginal response to beta-blockers when **RHO-PIROXICAM** is initiated or discontinued.

Cholestyramine

Preliminary study indicates that in healthy subjects co-administration of cholestyramine to piroxicam results in enhanced elimination of piroxicam (i.e. reduction in half-life by 40% and increase in clearance by 52%). Although the magnitude of these changes in piroxicam disposition appear sufficient to inhibit its therapeutic effects, studies in patients are needed to confirm this. It is suggested that the doses of piroxicam and cholestyramine be separated as much as possible, and that the patients be monitored for inadequate response to **RHO-PIROXICAM** therapy. If an inadequate anti-inflammatory response appears to be related to the concomitant use of cholestyramine, consideration should be given to the use of alternative hypolipidemic therapy.

ADVERSE REACTIONS

The most common adverse reactions encountered with nonsteroidal anti-inflammatory drugs are gastrointestinal, of which peptic ulcer, with or without bleeding is the most severe. Fatalities have occurred on occasion, particularly in the elderly.

In approximately 2300 patients receiving a daily dose of 20 mg or less of piroxicam in clinical trials, the most frequent side effects observed have been gastrointestinal (approximately 20% of the patients). Of the patients experiencing gastrointestinal side effects, approximately 5% discontinued therapy with an overall incidence of peptic ulceration of about 1% and gastrointestinal bleeding of approximately 0.1%. The incidence of adverse reactions is summarized below.

Gastrointestinal (17.4%): epigastric distress (6.4%), nausea (4.1%), constipation (2.4%), abdominal discomfort (2.2%), flatulence (2.1%), diarrhea (1.8%), abdominal pain (1.5%), indigestion (1.3%), anorexia (1.2%), peptic ulceration (about 1%); stomatitis, vomiting, hematemesis, melena, perforation, dry mouth, pancreatitis, each in less than 1% of patients.

Allergic (<1%): anaphylaxis, bronchospasm, urticaria/angioedema, vasculitis, serum sickness (see **PRECAUTIONS**), each in less than 1% of patients.

Central Nervous System (5.0%): headache (1.8%), malaise (1.0%); dizziness, drowsiness/sedation (somnolence), vertigo, depression, hallucinations, insomnia, nervousness, paresthesia, personality change, dream abnormalities, mental confusion, each in less than 1% of patients.

Dermatologic (2.0%): rash (2.0%); pruritus, erythema, bruising, desquamation, exfoliative dermatitis, erythema multiforme, toxic epidermal necrolysis (Lyell's Disease), vesiculo bullous reaction, onycholysis, Stevens-Johnson syndrome, photoallergic skin reactions, each in less than 1% of patients.

Cardiovascular (<1%): hypertension, palpitations, worsening of congestive heart failure (see PRECAUTIONS), exacerbation of angina, each in less than 1% of patients.

Special Senses: Eyes, ears, nose and throat reactions (<1%): tinnitus (about 1%); blurred vision, eye irritation/swelling, each in less than 1% of patients.

Hematologic (15.0%): decreases in hemoglobin (4.6%) and hematocrit (4.2%) (see **PRECAUTIONS**), thrombocytopenia (2.4%), eosinophilia (1.8%), leukocytosis (1.7%), basophilia (1.7%), leukopenia (1.4%); petechial rash, ecchymosis, bone marrow depression including aplastic anemia, epistaxis, each in less than 1% of patients.

Renal (1.0%): edema (1.6%) (see **PRECAUTIONS**); dysuria, hematuria, proteinuria, interstitial nephritis, renal failure, hyperkalemia, glomerulitis, nephrotic syndrome (see **PRECAUTIONS**), each in less than 1% of patients.

Hepatic (<1%): jaundice, hepatitis (see PRECAUTIONS), each in less than 1% of patients.

Respiratory (<1%): dyspnea.

Metabolic (<1%): hypoglycemia, hyperglycemia, weight increase/decrease, each in less than 1% of patients.

Miscellaneous (<1%): sweating, pain (colic), fever, flu-like syndrome (see **PRECAUTIONS**), weakness, each in less than 1% of patients.

Primary Dysmenorrhea: In primary dysmenorrhea the side effect profile of piroxicam is similar in nature to that observed in rheumatic diseases.

Laboratory Parameters:

Changes in laboratory parameters observed during piroxicam therapy have included an elevation of BUN, creatinine (see **PRECAUTIONS**), uric acid and liver enzymes LDH, SGOT, SGPT and alkaline phosphatase.

Other:

Since market introduction, isolated reports have included delayed wound healing, thrombophlebitis, pemphigus, alopecia, mastodynia, reduction or

loss of libido, impotence, urinary frequency, oliguria, menorrhagia, amnesia, anxiety, tremor, hearing impairment, deafness, thirst, chills, increased appetite, akathisia, tachycardia, flushing, tooth discoloration, glossitis, chest pain, anemia, hemolytic anemia, pancreatitis, and positive antinuclear factor (ANA); a causal relationship has not been established for those rarely reported events.

SYMPTOMS AND TREATMENT OF OVERDOSE

In the event treatment for overdosage is required the long plasma half-life (see **CLINICAL PHARMACOLOGY**) of piroxicam should be considered. The absence of experience with acute overdosage precludes characterization of sequelae and recommendation of specific antidotal efficacy at this time. It is reasonable to assume, however, that the standard measures of gastric evacuation and general supportive therapy would apply. In addition to supportive measure, the use of activated charcoal may effectively reduce the absorption and reabsorption of piroxicam. Experiments in dogs have demonstrated that the use of multiple-dose treatments with activated charcoal could reduce the half-life of piroxicam elimination from 27 hours (without charcoal) to 11 hours and reduce the systemic bioavailability of piroxicam by as much as 37% when activated charcoal is given as late as 6 hours after administration of piroxicam.

DOSAGE AND ADMINISTRATION

ADULTS:

In rheumatoid arthritis and ankylosing spondylitis it is recommended that therapy with **RHO-PIROXICAM** (piroxicam) capsules be initiated as a single daily dose of 20 mg. If desired, this dose may be given as 10 mg b.i.d. Most patients will be maintained on 20 mg daily. A relatively small number of patients may be maintained on 10 mg daily.

In osteoarthritis the recommended starting dosage of **RHO-PIROXICAM** is 20 mg once daily. If desired, this dose may be given as 10 mg b.i.d. The usual maintenance dose is 10-20 mg daily.

RHO-PIROXICAM should not be given in doses greater than 20 mg daily owing to an increased incidence of gastrointestinal side effects.

Elderly and debilitated:

As elderly patients appear to be at higher risk from a variety of adverse reactions from nonsteroidal anti-inflammatory drugs and as elderly, frail or debilitated patients tolerate gastrointestinal side effects less well, consideration should be given to a starting dose that is lower than usual and

to an increase of the dose only if symptoms remain uncontrolled. Such patients must be very carefully supervised.

In primary dysmenorrhea the treatment is initiated at the earliest onset of symptoms with a recommended starting dose of 40 mg given as a single daily dose on the first day. For the remainder of the treatment period (usually 2 to 4 days), the dose should be reduced to 20 mg daily.

AVAILABILITY

RHO-PIROXICAM 10 mg: # 2 marron/blue opaque hard gelatin capsules printed with "RHO" and "PIR 10". Each capsule contains 10 mg of piroxicam. Available in bottles of 100. Store at 15 - 30°C.

RHO-PIROXICAM 25 mg: # 2 marron opaque hard gelatin capsules printed with "RHO" and "PIR 20". Each capsule contains 20 mg of piroxicam. Available in bottles of 100. Store at 15 - 30°C.

INFORMATION TO THE PATIENT

RHO-PIROXICAM (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. 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 reaction.

You should take **RHO-PIROXICAM** (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 **RHO-PIROXICAM** (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.

If you take **RHO-PIROXICAM** (piroxicam) once a day and if you miss a dose of this medicine and remember within 8 hours of the missed dose, take it right away. If you take **RHO-PIROXICAM** (piroxicam) twice a day and if you miss a dose and remember within 2 hours of the missed dose take it right away. Then go back to your regular dosing schedule. If you have any questions about this, check with your doctor or pharmacist.

Do not take ASA (acetylsalicylic acid), ASA-containing compounds or other drugs to relieve symptoms of arthritis while taking **RHO-PIROXICAM** (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.

Along with its beneficial effect, **RHO-PIROXICAM** (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, hives or swelling, itching;
- indigestion, nausea, vomiting, stomach pain or diarrhea;
- yellow discolouration of the skin or eyes, with or without fatigue;

- any change 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 **RHO-PIROXICAM** (piroxicam) or other related medicines of the NSAID group such as acetylsalicylic acid, diclofenac, diflunisal, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, mefenamic acid, sulindac, tiaprofenic acid or tolmetin;
- have a history of stomach upset, ulcers, or liver or kidney diseases;
- are pregnant or intend to become pregnant while taking this medication;
- are breast feeding;
- are taking any other medication (either prescription or non-prescription);
- 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;
- 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 require more information on this drug, consult your doctor or pharmacist.

PHARMACEUTICAL INFORMATION

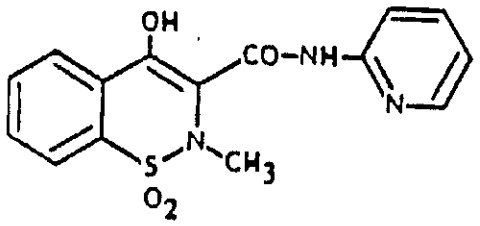
CHEMISTRY: **RHO-PIROXICAM** (piroxicam) is a member of a chemical class of nonsteroidal anti-inflammatory agents known as N-heterocyclic carboxamides of 1,2-benzothiazine-1,1-dioxide.

TRADE NAMES: **RHO-PIROXICAM** Capsules

PROPER NAME: piroxicam

CHEMICAL NAME: N-(2-pyridyl)-4-hydroxy-2-methyl-2H1,2-benzothiazine-3-carboxamide 1,1-dioxide.

STRUCTURAL FORMULA:



MOLECULAR FORMULA: $C_{15}H_{13}N_3O_4S$

MOLECULAR WEIGHT: 331.35

DESCRIPTION: Piroxicam is a white, crystalline, hygroscopic solid which melts in the range 196 to 200°C. It is poorly soluble in water, dilute acid and most organic solvents. It is slightly soluble in alcohols and in aqueous alkaline solution. Piroxicam is an amphoteric compound. It exhibits 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.

COMPOSITION:

RHO-PIROXICAM Capsules contain 10 or 20 mg of piroxicam and the following non-medicinal ingredients: lactose, corn starch, magnesium stearate/sodium lauryl sulfate and in capsule shells: gelatin, silicon dioxide, sodium lauryl sulfate, FD & C Red #3, FD & C Blue #1 and titanium dioxide.

PHARMACOLOGY

Animal

The anti-inflammatory activity of piroxicam, given orally, has been demonstrated in rats, guinea pigs and dogs. At 4.0 mg/kg dose given to rats produced 50% inhibition of carageenan-induced foot edema. Piroxicam at doses of 0.3-3.3 mg/kg also caused inhibition of adjuvant-induced arthritis in rats. At doses of 10 and 18 mg/kg, an inhibition of cotton string-induced granuloma formation in rats was observed. At 0.3 mg/kg dose of piroxicam given to guinea pigs produced 50% inhibition of the erythema induced by

ultraviolet light. Intravenous administration of piroxicam (5 mg/kg) to dogs inhibited urate-induced inflammation of knee joints.

The analgesic activity of piroxicam, at an oral dose of 1.85 mg/kg, was demonstrated in mice using the phenylquinone-induced writhing test. Piroxicam at 1.0, 3.2 and 10.0 mg/kg orally was active in the Randall-Sellito test in which painful pressure is applied to the inflamed foot pad of the rat. It was inactive in hot-plate and tail-flick tests at oral doses up to 100 mg/kg.

The antipyretic activity of piroxicam at 10 mg/kg orally was demonstrated in the hyperpyrexia induced in rats by intramuscular infections of E. coli lipopolysaccharide.

Piroxicam inhibits prostaglandin synthetase, thereby reducing the biosynthesis of prostaglandins. The drug also inhibits collagen-induced platelet aggregation. The anti-inflammatory activity of piroxicam does not depend upon adrenal stimulation. Its activity was demonstrated in adrenalectomized rats. Piroxicam has no significant cardiovascular or central nervous system activity.

Human (clinical):

See ACTIONS AND CLINICAL PHARMACOLOGY Section.

TOXICOLOGY

Acute Toxicity:

Species	Sex	Oral LD_{50} mg/kg (95% C.I.)	I.P. LD_{50} mg/kg (95% C.I.)
Mice	M	360 (321-404)	360 (305-425)
	F	approx. 360	
Rat	M	270 (231-316)	220 (197-241)

Toxic effects observed in mice and rats included ataxia, depression, laboured respiration, prostration, weight gain inhibition and weight loss. Necropsy of these animals revealed marked visceral adhesions and erosions of the stomach and intestines.

In the dog, repeated emesis, chronic anorexia, and diarrhea occurred at dosage levels of 5, 25, 50, 400 and 700 mg/kg; fecal occult blood was observed 24 hours after dosing. A weight loss of about 15% and bloody diarrhea occurred with the 50, 400 and 700 mg/kg doses. Necropsy of the dogs receiving 5 mg/kg revealed mucosal erosions and hemorrhage. These lesions, together with ulcerations of the pyloric antrum and/or sphincter, were also observed at the higher dose levels.

Subacute and Chronic Toxicity:

Piroxicam administered orally to beagles dogs at a dose of 1.0 mg/kg/day for 373 consecutive days caused signs of gastrointestinal and renal toxicity. These included emesis, diarrhea, duodenal and gastric ulceration or erosion, fecal occult blood, anemia, proteinuria, hematuria, renal papillary necrosis and one case of pyelonephritis. Other effects considered to be related to the primary pathology were integumental signs, leukocytosis and decreased serum calcium levels.

A one year study in the rhesus monkey at daily oral doses of 2.5, 5.0 and 10.0 mg/kg revealed epithelial casts within the collecting tubules of the kidneys in 67% of high dose females. There was no evidence of gastrointestinal toxicity at any dose. 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.

In an 18 month rat study, daily oral doses of 0.3, 1.0 and 3.0 mg/kg gave dose- and duration-related renal papillary necrosis, elevation of BUN and necrotizing gastrointestinal lesions. At the highest dose, gastrointestinal

lesions and renal papillary necrosis were present in more females than males. Dose-related anemia in males also occurred.

An 18 month mouse study was conducted at daily oral doses of 2, 4 and 8 mg/kg. There was increased mortality at 8 mg/kg. Dose-related renal papillary necrosis with secondary chronic diffuse interstitial nephritis, elevated BUN and necrotizing gastrointestinal lesions were observed.

Reproduction and Teratology Studies

Consistent with its inhibitory effect on prostaglandin biosynthesis, piroxicam prolongs the gestational period of the rat. The effects are dependent on dose and time.

When piroxicam was administered in oral doses of 2, 5 and 10 mg/kg daily to pregnant rats from day 15 post-coitum onwards, a dose-dependent increase in mortality and prolongation of gestation and parturition occurred. Parturition was completely inhibited by piroxicam at 10 mg/kg administered for 8 days. The dystocia, together with the gastrointestinal toxicity of the drug, caused weakness and death of dams and offspring. When treatment was stopped after 5 days of drug administration, deaths and prolonged labour still occurred.

When pregnant rats received 10 mg/kg/day of piroxicam orally from day 1 post-coitum to day 16, 17, 18, 19 or 20 post-coitum, all groups displayed gestational prolongation and the delay increased with length of treatment. Prolongation of parturition and increased mortality of the offspring occurred. There was dose-related suppression of lactation.

Piroxicam was administered in oral doses of 2, 5 and 10 mg/kg/day to male and female rats for 81 and 14 days respectively, before mating. Dosing in females was continued to day 6 post-coitum. Neither sex exhibited a modification of sexual behaviour or diminished fertility. Fetal development was normal. Viability and growth of pups were comparable to controls, and no drug-induced malformation or lesion was seen.

Oral administration of piroxicam to pregnant rats and rabbits, during the critical period of organogenesis, induced no embryotoxic or teratogenic effect at doses of 2, 5 and 10 mg/kg/day.

Oral administration of piroxicam to female rats on days 1-12 of the lactation period inhibited postnatal body weight gain in pups owing to suppression of lactation in dams. This effect was explored at doses of 2, 5 and 10 mg/kg/day and was dose-related.

Mutagenicity:

Piroxicam demonstrated no mutagenic activity in any of the test systems.

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, but higher incidence at 1 mg/kg, of non-neoplastic lesions than in the 18-month rat study. 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.

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