gastrointestinal in nature. Peptic ulcers, perforation or GI bleeding, sometimes fatal, particularly in the elderly, may occur Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease have been reported following administration. Less frequently, gastritis has been observed. Pancreatitis has been reported very rarely.

Hypersensitivity reactions: Hypersensitivity reactions have been reported following treatment with NSAIDs. These may consist of (a) non-specific allergic reactions and anaphylaxis (b) respiratory tract reactivity comprising asthma, aggravated asthma, bronchospasm or dyspnoea, or (c) assorted skin disorders, including rashes of various types, pruritus, urticaria, purpura, angiodema and, more rarely exfoliative and bullous dermatoses (including epidermal necrolysis and erythema multiforme). Vasculitis and serum sickness have been rarely reported.

Cardiac: Oedema, hypertension, and cardiac failure, have been reported in association with NSAID treatment. Possibility of precipitating congestive cardiac failure in elderly patients.
Clinical trial and epidemiological data suggest that use of some NSAIDs (particularly at high doses and in long term treatment) may be associated with an increased risk of arterial thrombotic events (for example, myocardial infarction or stroke)

Other adverse reactions reported less commonly include:
Neurological and special senses: Optic neuritis, dizziness, headache, vertigo. Rarely drowsiness, malaise, fatigue tiredness. In isolated cases disturbances of sensation as anxiety, convulsions, confusion, depression, hallucinations, disorientation, disturbance of vision (blurred vision, diplopia), impaired hearing, insomnia, irritability, memory disturbance, nightmares, paraesthesia, psychotic reactions, tinnitus, tremor, reports of aseptic meningitis (especially in patients with existing autoimmune disorders, such as systemic lupus erythematosus, mixed connective tissue disease), with symptoms such as stiff neck, headache, nausea, vomiting, fever or disorientation .Taste alteration disorders.

Dermal hypersensitivity: Rash and pruritus. Onycholysis and alopecia have been rarely reported. Photosensitivity reactions occur infrequently. Bullous reactions including Stevens Johnson Syndrome and Toxic Epidermal Necrolysis (very rare). Photosensitivity.

Renal function: Reversible elevations of blood urea nitrogen (BUN) and creatinine have been reported (see other special warnings and precautions). Nephrotoxicity in various forms, including interstitial nephritis, nephritic syndrome and renal failure.

Haematological: Decreases in haemoglobin and haematocrit, unassociated with obvious gastrointestinal bleeding, have occurred. Anaemia; thrombocytopenia and non-thrombocytopenic purpura (Henoch-Schoenlein); neutropenia, agranulocytosis, leucopenia and eosinophilia have been reported. Cases of aplastic anaemia, haemolytic anaemia and epitaxis have been rarely reported.

Liver function: Changes in various liver function parameters have been observed. As with most other NSAIDs, some patients may develop increased serum transaminase during treatment with piroxicam. Severe hepatic reactions, including jaundice and cases of fatal hepatitis have been reported. Although such reactions are rare, if abnormal liver function tests persist or worsen, if clinical signs or symptoms consistent with liver disease develop, or if systemic manifestations occur (*eg* eosinophilia, rash), piroxicam should be discontinued.

Other: The following have been rarely reported: Palpitations and dyspnoea, anecdotal cases of positive antinuclear antibosy test (ANA),, anecdotal cases of hearing impairment, metabolic abnormalities such as hypoglycaemia, weight increase or decrease.
Swollen eyes, blurred vision, and eye irritations have been reported. Routine ophthalmoscopy and slit-lamp examination have revealed no evidence of ocular changes. Malaise and tinnitus may occur.

OVERDOSE:
a) Symptoms
Symptoms include headache, nausea, vomiting, epigastric pain, gastrointestinal bleeding, rarely diarrhoea, disorientation, excitation, coma, drowsiness, dizziness, tinnitus, fainting, occasionally convulsions. In cases of significant poisoning acute renal failure and liver damage are possible.

b) Therapeutic measure
Patients should be treated symptomatically as required. Within one hour of ingestion of a potentially toxic amount, activated charcoal should be considered. Alternatively, in adults, gastric lavage should be considered within one hour of ingestion of a potentially life-threatening overdose. Good urine output should be ensured.

Renal and liver function should be closely monitored.

Patients should be observed for at least four hours after ingestion of potentially toxic amounts.

Frequent or prolonged convulsions should be treated with intravenous diazepam.

Other measures may be indicated by the patient's clinical condition

PRESENTATION:
Blister Pack of 10's

STORAGE:
STORE BELOW 30°C. PROTECT FROM LIGHT.
KEEP OUT OF REACH OF CHILDREN.

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For the use of a Registered Medical practitioner or a Hospital or a Laboratory only.

PIRICAM
PIROXICAM CAPSULES USP

COMPOSITION:
PIRICAM 10
Piroxicam Capsules USP 10mg
Each Hard Gelatin Capsule Contains:
Piroxicam USP 10mg
Approved colours used in capsule shell.

PIRICAM 20
Piroxicam Capsules USP 20mg
Each Hard Gelatin Capsule Contains:
Piroxicam USP 20mg
Approved colours used in capsule shell.

DESCRIPTION:
Piroxicam is a member of the oxicam group of nonsteroidal anti-inflammatory drugs (NSAIDs). The chemical name for piroxicam is 4-hydroxyl-2-methyl-N-2-pyridinyl-2H-1,2,-benzothiazine-3-carboxamide 1,1-dioxide. The molecular weight of piroxicam is 331.35. Its molecular formula is $C_{15}H_{13}N_3O_4S$.

CLINICAL PHARMACOLOGY:
Pharmacodynamic properties
Piroxicam is a non-steroidal anti-inflammatory agent with analgesic and antipyretic activity.

Piroxicam inhibits prostaglandin (thromboxane) synthesis in the platelets, rendering them less sticky. Like other NSAIDs, it acts as a uterotropic agent by inhibiting the synthesis of prostaglandins in the uterus which are normally increased in amount in the hours before parturition.

Piroxicam also helps to promote salt and water retention by interfering with the prostaglandin- induced inhibition of both chloride re-absorption and the action of ADH. Prostaglandins, particularly E1 and E2, are synthesized by the gastric mucosa and seem to promote integrity of that mucosa by stimulating the secretion of cytoprotective mucus. Piroxicam, by inhibiting the synthesis of these prostaglandins may lead to gastric erosions and ulceration.

Pharmacokinetic Properties:
Piroxicam is absorbed from the GI tract. Absorption is not influenced by either food or antacids. Peak plasma concentrations are reached 3-5 hours after an oral dose. Piroxicam plasma concentrations do not appear to be significantly influenced by concomitant aspirin, iron or antacids. In man it penetrates into the synovial fluid of patients with rheumatoid arthritis, osteoarthritis and re-active synovitis, where mean concentrations are approximately 40% of those in the plasma; it is also demonstable in synovial tissues. It is metabolised in the liver by hydroxylation and conjugation with glucuronic acid and excreted predominantly in the urine and smaller amounts in the faeces. Less than 5% of a dose is excreted unchanged. Piroxicam is extensively bound to plasma proteins (about 99%) and has a long plasma half-life of about 50 hours. Pharmacokinetics do not appear to be age related, and renal function has only a limited influence on the elimination of piroxicam, but plasma concentrations are increased in patients with severe liver dysfunction.

THERAPEUTIC INDICATIONS:
Piroxicam is a non-steroidal anti-inflammatory agent with analgesic and antipyretic activity.
Piroxicam is indicated for the symptomatic relief of rheumatoid arthritis, osteoarthritis or ankylosing spondylitis.
Due to its safety profile, piroxicam is not a first line option should an NSAID be indicated. The decision to prescribe piroxicam should be based on an assessment of the individual patient's overall risks .

RECOMMENDED DOSE AND METHOD OF ADMINISTRATION:
The prescription of piroxicam should be initiated by physicians with experience in the diagnostic evaluation and treatment of patients with inflammatory or degenerative rheumatic diseases.
The maximum recommended daily dose is 20mg.
Undesirable effects may be minimised by using the minimum effective dose for the shortest duration necessary to control symptoms. The benefit and tolerability of treatment should be reviewed within 14 days. If continued treatment is considered necessary, this should be accompanied by frequent review.
Given that piroxicam has been shown to be associated with an increased risk of gastrointestinal complications, the possible need for combination therapy with gastroprotective agents (e.g. misoprostol or proton pump inhibitors) should be carefully considered, in particular for elderly patients.

Adults: Initially 20mg given as a single daily dose. The majority of patients may be maintained on 20mg a day, a relatively small group of patients may be maintained on 10mg daily.

Children: Not recommended for children under 12 years of age.

Elderly: There are no specific modifications required in the elderly, except where hepatic, renal or cardiac function is impaired, in which case dosage should be individually assessed.
The elderly are at increased risk of the serious consequences of adverse reactions. If an NSAID is considered necessary, the lowest effective dose should be used and for the shortest possible duration. The patient should be monitored regularly for GI bleeding during NSAID therapy.

Method of Administration
For oral administration. To be taken preferably with or after food.

CONTRAINDICATIONS:
Patients with active peptic ulcer, inflammatory gastrointestinal disorder or gastrointestinal bleeding.
History of gastro-intestinal ulceration, bleeding or perforation.
Patient history of gastrointestinal disorders that predispose to bleeding disorders

280 mm

140 mm

such as ulcerative colitis, Crohn's disease, gastrointestinal cancers or diverticulitis.

Concomitant use with other NSAIDs, including COX-2 selective NSAIDs and aspirin at analgesic doses.

Concomitant use with anticoagulants.

History of previous serious allergic drug reaction of any type, especially cutaneous reactions such as erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis.

Piroxicam should not therefore be administered to patients in whom aspirin and other NSAIDs induce the symptoms of angioneurotic oedema, asthma, rhinitis, nasal polyps or urticaria.

Patients with severe heart failure.

Hypersensitivity to the active substance, previous skin reaction (regardless of severity) to piroxicam, other NSAIDs and other medications.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE:

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms. The clinical benefit and tolerability should be re-evaluated periodically and treatment should be immediately discontinued at the first appearance of cutaneous reactions or relevant gastrointestinal events.

Cardiovascular and cerebrovascular effects

Appropriate monitoring and advice are required for patients with a history of hypertension and/or mild to moderate congestive heart failure as fluid retention and oedema have been reported in association with NSAID therapy.

Clinical trial and epidemiological data suggest that use of some NSAIDs (particularly at high doses and in long term treatment) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke). There are insufficient data to exclude such a risk for piroxicam.

Patients with uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with piroxicam after careful consideration. Similar consideration should be made before initiating longer-term treatment of patients with risk factors for cardiovascular disease (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking).

Cardiovascular, Renal and Hepatic Impairment

The administration of an NSAID may cause a dose dependent reduction in prostaglandin formation and precipitate renal failure. Patients at greatest risk of this reaction are those with impaired renal function, cardiac impairment, liver dysfunction, those taking diuretics and the elderly. Renal function should be monitored in these patients .

In rare cases, NSAIDs may cause interstitial nephritis, glomerulonephritis, papillary necrosis and the nephrotic syndrome.

Due to the renal excretion of piroxicam, patients with severely impaired renal function should be closely monitored.

Elderly

The elderly have an increased frequency of adverse reactions to NSAIDs, especially gastrointestinal bleeding and perforation which may be fatal.

Respiratory disorders

Caution is required if administered to patients suffering from or with a previous history of bronchial asthma since NSAIDs have been reported to precipitate bronchospasm in such patients.

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

Gastrointestinal bleeding, ulceration and perforation

NSAIDs, including piroxicam, can cause serious gastrointestinal events including bleeding, ulceration, and perforation of the stomach, small intestine or large intestine, which can be fatal. These serious adverse events can occur at any time, with or without warning symptoms, in patients treated with NSAIDs.

NSAID exposures of both short and long duration have an increased risk of serious GI event. Evidence from observational studies suggests that piroxicam may be associated with a high risk of serious gastrointestinal toxicity, relative to other NSAIDs.

Patients with significant risk factors for serious GI events should be treated with piroxicam only after careful consideration.

The possible need for combination therapy with gastro-protective agents (e.g. misoprostol or proton pump inhibitors) should be carefully considered and also for patients requiring concomitant low dose aspirin, or other drugs likely to increase gastrointestinal risk.

Serious GI Complications

Identification of at-risk subjects: The risk for developing serious GI complications increases with age. Age over 70 years is associated with high risk of complications. The administration to patients older than 80 years should be avoided.

The risk of GI bleeding, ulceration or perforation is higher with increasing NSAID doses, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation and in the elderly. These patients should commence treatment on the lowest dose available.

When GI bleeding or ulceration occurs in patients receiving piroxicam the treatment should be withdrawn.

NSAIDs should be given with care to patients with a history of gastrointestinal disease (ulcerative colitis, Crohn's disease) as these conditions may be exacerbated.

Patients taking concomitant oral corticosteroids, selective serotonin reuptake inhibitors (SSRIs) or anti-platelet agents such as low-dose aspirin are at increased risk of serious GI complications.

Patients and physicians should remain alerted for signs and symptoms of GI ulceration and/or bleeding during piroxicam treatment. Patients should be asked to report any new or unusual abdominal symptom during treatment. If a gastrointestinal complication is suspected during treatment, piroxicam should be discontinued immediately and additional clinical evaluation and treatment should be considered.

SLE and mixed connective tissue disease

In patients with systemic lupus erythematosus (SLE) and mixed connective tissue disorders there may be an increased risk of aseptic meningitis.

Dermatological

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported very rarely in association with the use of NSAIDs . Evidence from observational studies suggests that piroxicam may be associated with a higher risk of serious skin reactions than other NSAIDs. Patients appear to be at a highest risk of these reactions early in the course of therapy, the onset of the reaction 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.

Impaired female fertilty

The use of piroxicam may impair female fertility and is not recommended in women attempting to conceive. In women who have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of Piroxicam should be considered.

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION:

Other analgesics including cyclooxygenase-2 selective inhibitors: Avoid concomitant use of two or more NSAIDs (including aspirin) as this may increase the risk of adverse effects. As with other NSAIDs, the use of piroxicam together with aspirin or concomitant use with other NSAIDs, including other piroxicam formulations, must be avoided, since data are inadequate to show that such combinations produce greater improvement than that achieved with piroxicam alone; moreover, the potential for adverse reactions is enhanced . Human studies have shown that concomitant use of piroxicam and aspirin reduces the plasma piroxicam concentration to about 80% of the usual value.

Anti-hypertensives: Reduced anti-hypertensive effect.

Diuretics: Reduced diuretic effect. Diuretics can increase the risk of nephrotoxicity of NSAIDs.

Cardiac glycosides: NSAIDs may exacerbate cardiac failure, reduce GFR and increase plasma glycoside levels.

Lithium: Decreased elimination of lithium

Methotrexate: Decreased elimination of methotrexate.

Ciclosporin: Increased risk of nephrotoxicity.

Mifepristone: NSAIDs should not be used for 8-12 days after mifepristone administration as NSAIDs can reduce the effect of mifepristone.

Corticosteroids: Increased risk of gastrointestinal ulceration or bleeding.

Anti-coagulants: NSAIDs, including piroxicam, may enhance the effects of anticoagulants, such as warfarin. Therefore, the use of piroxicam with concomitant anticoagulant such as warfarin should be avoided.

Quinolone antibiotics: Animal data indicate that NSAIDs can increase the risk of convulsions associated with quinolone antibiotics. Patients taking NSAIDs and quinolones may have an increased risk of developing convulsions.

Anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs): Increased risk of gastrointestinal bleeding.

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

Zidovudine: Increased risk of haematological toxicity when NSAIDs are given with zidovudine. There is evidence of an increased risk of haemarthroses and haematoma in HIV(+) haemophiliacs receiving concurrent treatment with zidovudine and ibuprofen.

Cimetidine: Results of two separate studies indicate a slight but significant increase in absorption of piroxicam following cimetidine administration but no significant changes in elimination rate constants or half-life. The small increase in absorption is unlikely to be clinically significant. Piroxicam is highly protein-bound and therefore may be expected to displace other protein-bound drugs; hence, patients receiving them should be closely monitored for change in dosage requirements.

FERTILITY, PREGNANCY AND LACTATION:

Pregnancy:

Congenital abnormalities have been reported in association with NSAID administration in man; however, these are low in frequency and do not appear to follow any discernible pattern. 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. In view of the known effects of NSAIDs on the foetal cardiovascular system (risk of closure of the ductus arteriosus), use in the last trimester of pregnancy is contraindicated. The onset of labour may be delayed and the duration increased with an increased bleeding tendency in both mother and child. NSAIDs should not be used during the first two trimesters of pregnancy or labour unless the potential benefit to the patient outweighs the potential risk to the foetus.

Lactation:

In limited studies so far available, NSAIDs can appear in breast milk in very low concentrations. A study indicated that piroxicam appears in breast milk at about 1-3% of the maternal plasma concentrations. No accumulation of piroxicam occurred in milk relative to that in plasma during treatment for up to 52 days. NSAIDs should, if possible, be avoided when breastfeeding.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Undesirable effects such as dizziness, drowsiness, fatigue and visual disturbances are possible after taking NSAIDs. If affected, patients should not drive or operate machinery.

UNDESIRABLE EFFECTS:

Gastrointestinal: The most commonly-observed adverse events are

280 mm

140 mm