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PIRAM-D

Piroxicam

Presentation

Tablet (dispersible) 10 mg: white, flat bevel edged round tablet, 10 mm diameter, imprinted PX/10 on one side and G on the other side.

Tablet (dispersible) 20 mg: white, capsule shaped tablet, 17 mm x 6 mm, imprinted PX/20 on one side and G on the other side.

Uses

Actions

PIRAM-D is a non-steroidal anti-inflammatory drug (NSAID), which also possesses analgesic and antipyretic properties. In laboratory animals oedema, erythema, tissue proliferation, fever and pain can all be inhibited by the administration of piroxicam.

It exerts its effects regardless of the aetiology of the inflammation.

While its mode of action is not fully understood, independent studies *in vitro* 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 migration and monocytes to the area of inflammation; inhibition of lysosomal enzyme release from stimulated leucocytes; inhibition of super-oxide anion generation by the neutrophil; reduction both of systemic and synovial fluid rheumatoid factor concentration 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 of cartilage metabolism.

Pharmacokinetics

PIRAM-D is well absorbed following oral administration. When taken with food there is a slight delay in the rate but not the extent of absorption. The plasma half-life of piroxicam is approximately 50 hours in man and the mean half-life is apparently not age related. However, the range of half-life values is large and the half-life may be particularly long in some subjects. 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 first is achieved at between one and four weeks after commencement.

Piroxicam plasma concentrations are proportional for 10 and 20 mg doses and generally peak within 3 to 5 hours after medication.

A single 20 mg dose generally produces peak piroxicam plasma levels of 1.5-2 µg/ml while maximum piroxicam plasma concentrations, after repeated daily ingestion of 20 mg piroxicam, usually stabilise at 3-8 µg/ml. Most patients approximate steady-state plasma levels within 7 to 12 days.

Piroxicam is extensively metabolised and less than 5% of the daily dose is excreted unchanged in urine and faeces.

One important metabolic pathway is hydroxylation of the pyridyl ring of the piroxicam side chain, followed by conjugation with glucuronic acid and urinary elimination.

Piroxicam is 99% bound to plasma protein. The apparent volume of distribution of piroxicam is about 0.14 L/kg body-weight.

Indications

Piroxicam is indicated for symptomatic relief of osteoarthritis (arthrosis, degenerative joint disease), rheumatoid arthritis, juvenile rheumatoid arthritis or ankylosing spondylitis.

Due to its safety profile, piroxicam is not a first line option should a NSAID be indicated. The decision to prescribe piroxicam should be based on an assessment of the individual patient's overall risks.

Dosage and 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 20 mg.

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 gastro-protective agents (e.g. misoprostol or proton pump inhibitors) should be carefully considered, in particular for elderly patients.

PIRAM-D tablets can be swallowed whole with a fluid, or may be dispersed in a minimum of 50 ml of water and then swallowed.

Adults:

The recommended starting dose is 20 mg given as a single daily dose. The majority of patients will be satisfactorily maintained on 20 mg daily. A relatively small group of patients may need as little as 10 mg daily. Administration of doses exceeding 20 mg daily (or more than several days duration) carries an increased risk of gastro-intestinal side effects.

Children:

Juvenile Rheumatoid Arthritis: As little data are available in very young children, it is recommended that only children aged six years and older are treated with PIRAM-D dispersible tablets. Dosage recommendations and indications for use in children other than in juvenile chronic arthritis have not been established.

The recommended dosages for children with juvenile rheumatoid arthritis are based on bodyweight as follows:

Weight (kg)	Dose (mg)
<15	5

16 to 25	10
26 to 45	15
>46	20

PIRAM-D should be taken once daily. The dispersible tablet may be used to obtain the exact dose required.

Use in the elderly:

Elderly, frail or debilitated patients may tolerate side effects less well and such patients should be carefully supervised. As with other NSAIDs, caution should be used in the treatment of elderly patients who are more likely to be suffering from impaired renal, hepatic or cardiac function.

Contraindications

- History of gastro-intestinal ulceration, bleeding or perforation.
- Patient history of gastrointestinal disorders that predispose to bleeding disorders such as ulcerative colitis, Crohn's disease, gastrointestinal cancers or diverticulitis.
- Patients with active peptic ulcer, inflammatory gastrointestinal disorder or gastrointestinal bleeding.
- Concomitant use with other NSAIDs, including COX-2 selective NSAIDs and acetyl-salicylic acid 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.
- Hypersensitivity to the active substance, previous skin reaction (regardless of severity) to piroxicam, other NSAIDs and other medications.
- Severe heart failure

Warnings and Precautions

Undesirable effects may be minimised by using the minimum 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.

Gastrointestinal (GI) Effects, Risk of GI Ulceration, Bleeding, 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.

Caution is advised in patients with risk factors for gastrointestinal events who may be at greater risk of developing serious gastrointestinal events, e.g. the elderly, those with a history of serious gastrointestinal events, smoking and alcoholism. When gastrointestinal bleeding or ulceration occurs in patients receiving NSAIDs, the drug should be withdrawn immediately. Doctors should warn patients about the signs and symptoms of serious gastrointestinal toxicity. Patients with significant risk factors for serious GI events should be treated with piroxicam only after careful consideration.

The concurrent use of aspirin and NSAIDs also increases the risk of serious gastrointestinal adverse events.

The possible need for combination therapy with gastro-protective agents (e.g. misoprostol or proton pump inhibitors) should be carefully considered.

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. Patients taking concomitant oral corticosteroids, selective serotonin reuptake inhibitors (SSRIs) or anti-platelet agents such as low-dose acetylsalicylic acid are at increased risk of serious GI complications. As with other NSAIDs, the use of piroxicam in combination with protective agents (e.g. misoprostol or proton pump inhibitors) must be considered for these at risk patients.

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.

Skin Reactions

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 non-oxicam NSAIDs. Patients appear to be at 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. Patients should be advised of the signs and symptoms of serious skin reactions and to consult their doctor at the first appearance of a skin rash or any other sign of hypersensitivity. Piroxicam should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Cardiovascular Thrombotic Events

Observational studies have indicated that non-selective NSAIDs may be associated with an increased risk of serious cardiovascular events, including myocardial infarction and stroke, which may increase with dose or duration of use. Patients with cardiovascular disease or cardiovascular risk factors may also be at greater risk. To minimise the potential risk of an adverse cardiovascular event in patients taking a NSAID, especially in those with cardiovascular risk factors, the lowest effective dose should be used for the shortest possible duration (see Dosage and Administration).

There is no consistent evidence that the concurrent use of aspirin mitigates the possible increased risk of serious cardiovascular thrombotic events associated with NSAID use.

Hypertension

NSAIDs may lead to the onset of new hypertension or worsening of pre-existing hypertension, and patients taking anti-hypertensives with NSAIDs may have an impaired anti-hypertensive response. Caution is advised when prescribing NSAIDs to patients with hypertension. Blood pressure should be monitored closely during initiation of NSAID treatment and at regular intervals thereafter.

NSAIDs may cause sodium, potassium 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.

Heart failure

Fluid retention and oedema have been observed in some patients taking NSAIDs; therefore caution is advised in patients with fluid retention or heart failure.

Impaired Renal Function

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 a NSAID may precipitate overt renal decompensation, which is typically followed by recovery to pretreatment 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.

Patients on long-term therapy should have blood chemistry and renal function checked periodically. Treatment should be immediately withdrawn if any impairment becomes evident.

Impaired Hepatic Function

NSAIDs should be administered to patients with impaired liver function only in cases of necessity.

Bleeding time

Bleeding has been reported when piroxicam as well as other NSAIDs have been administered to patients on coumarin type anticoagulants e.g. warfarin. Patients should be monitored closely if PIRAM-D and oral anticoagulants are administered together. PIRAM-D like other NSAIDs, decreases platelet aggregation and prolongs bleeding time. This effect, and the long half-life of piroxicam should be kept in mind when bleeding occurs. Similar considerations apply in the selection of blood donors particularly for platelet transfusion.

Asthma

Bronchospasm has been associated with NSAIDs including piroxicam and these agents should be used with particular caution in asthmatics.

Visual complaints

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

Pregnancy and lactation

Although no teratogenic effects were seen in animal testing, the safety of piroxicam use during pregnancy or during lactation has not yet been established.

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 closure of the ductus arteriosus in infants.

A study indicates that piroxicam appears in the breast milk at about 1% to 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. PIRAM-D is not recommended for use in nursing mothers as clinical safety has not been established.

Effects on ability to drive and use machines

None known.

Adverse Effects

Gastrointestinal

Gastrointestinal symptoms are the most commonly encountered side effects but in most instances do not interfere with the course of therapy. These adverse reactions include stomatitis, anorexia, epigastric distress, gastritis, nausea, vomiting, constipation, abdominal discomfort, flatulence, diarrhoea, abdominal pain and indigestion, rare cases of pancreatitis have been reported. Peptic ulceration, perforation and gastrointestinal bleeding (including haematemesis and melaena) in rare cases fatal, have been reported with piroxicam (see Warnings and Precautions).

Evidence from observational studies suggests that piroxicam may be associated with a high risk of serious gastrointestinal toxicity, relative to other NSAIDs. Administration of doses exceeding 20 mg daily (or more than several days duration) carries an increased risk of gastro-intestinal side effects, but they may also occur with lower doses.

Oedema, hypertension and cardiac failure

Oedema, hypertension and cardiac failure have been reported in association with NSAID treatment. The possibility of precipitating congestive heart failure in elderly patients or those with compromised cardiac function should therefore be borne in mind.

CNS

CNS effects, such as dizziness, headache, somnolence, insomnia, depression, nervousness, hallucinations, mood alterations, dream abnormalities, mental confusion, paraesthesia and vertigo have been reported rarely.

Dermal hypersensitivity

Dermal hypersensitivity reactions, usually in the form of skin rash and pruritus have been reported. Onycholysis and alopecia have been rarely reported. Photosensitivity reactions have infrequently been associated with therapy. As with other NSAIDs, toxic epidermal necrolysis (Lyell's disease) and Stevens-Johnson syndrome may develop in rare cases. Vesiculo bullous reactions have been reported rarely.

Hypersensitivity reactions

Hypersensitivity reactions such as anaphylaxis, bronchospasm, urticaria/angioneurotic oedema, vasculitis, and serum sickness have been reported rarely.

Renal function

Interstitial nephritis, nephrotic syndrome, renal failure and renal papillary necrosis have been reported rarely. Reversible elevations of BUN and creatinine have been reported (see Warnings and Precautions).

Haematological

Decreases in haemoglobin and haematocrit, unassociated with obvious gastrointestinal bleeding, have occurred. Anaemia, thrombocytopenia and non-thrombocytopenic purpura (Henoch-Schonlein), leukopenia and eosinophilia have been reported. Cases of aplastic anaemia, haemolytic anaemia and epistaxis have rarely been reported.

Liver function

Changes in various liver function parameters have been observed. As with most other NSAIDs, some patients may develop increased serum transaminase levels during treatment with piroxicam. Severe hepatic reactions, including jaundice and cases of fatal hepatitis have been reported with piroxicam. 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.), PIRAM-D should be discontinued.

Other

The following have been reported rarely, palpitations and dyspnoea, anecdotal cases of positive ANA, anecdotal cases of hearing abnormalities, metabolic abnormalities such as hypoglycaemia, hyperglycaemia, 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. 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).

Interactions

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

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 (see Contraindications).

Anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs): increased risk of gastrointestinal bleeding (see Warnings and Precautions).

Aspirin and other Non-Steroidal Anti-Inflammatory Drugs: As with other NSAIDs, the use of piroxicam together with acetyl-salicylic acid 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 (see Warnings and Precautions). Human studies have shown that concomitant use of piroxicam and acetyl-salicylic acid reduces the plasma piroxicam concentration to about 80% of the usual value.

Piroxicam, like other non-steroidal anti-inflammatory drugs decreases platelet aggregation and prolongs bleeding time. This effect should be kept in mind when bleeding times are determined.

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.

Corticosteroids: increased risk of gastrointestinal ulceration or bleeding (see Warnings and Precautions).

Digoxin, Digitoxin: Concurrent therapy with piroxicam and digoxin, or piroxicam and digitoxin, did not affect the plasma levels of either compound.

Diuretics: NSAIDs may cause sodium, potassium 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 the worsening of those conditions.

Highly protein-bound compounds: Piroxicam is highly protein bound and therefore might be expected to displace other protein-bound compounds. The physician should closely monitor patients for change in dosage requirements when administering PIRAM-D to patients on highly protein-bound compounds.

Lithium: NSAIDs, including piroxicam, have been reported to increase steady-state plasma lithium levels. It is recommended that these levels are monitored when initiating, adjusting and discontinuing PIRAM-D.

PIRAM-D, like other NSAIDs, may interact with the following medicines/classes of therapeutic agents:

Antihypertensives – antagonism of the hypotensive effect

Methotrexate – reduced excretion of methotrexate, possibly leading to acute toxicity

Cyclosporin – possible increased risk of nephrotoxicity

Quinolone antibiotics – possible increased risk of convulsions

Mifepristone – NSAIDs could interfere with mifepristone-mediated termination of pregnancy.

Overdosage

In the event of overdosage with PIRAM-D, supportive and symptomatic therapy is indicated. Studies indicate that administration of activated charcoal may result in reduced absorption and re-absorption of piroxicam, thus reducing the total amount of active compound available. Although there are no studies to date, haemodialysis is probably not useful in enhancing elimination of piroxicam since the compound is highly protein bound.

Pharmaceutical Precautions

Store below 30°C.

Medicine Classification

Prescription Medicine.

Package Quantities

10 mg - Bottles of 50 tablets

20 mg - Bottles of 100 tablets

Further Information

Nil.

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Date of Preparation

2 February 2009