

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Piroxicam 20mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 20mg of Piroxicam.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Appearance: Hard gelatin, maroon coloured capsule printed “CX46” both on body and cap in white.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Piroxicam is a non-steroidal anti-inflammatory agent.

Piroxicam is indicated for symptomatic relief of osteoarthritis, rheumatoid arthritis or ankylosing spondylitis.

Due to its safety profile (see sections 4.2, 4.3 and 4.4), 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 (see sections 4.3 and 4.4).

4.2 Posology and Method of Administration

For oral administration

To be taken preferably with or after food

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

Rheumatoid arthritis osteoarthritis, ankylosing spondylitis: The recommended starting dose is 20mg given as a single daily dose. The majority of patients will be maintained on 20mg daily. A relatively small group of patients may be maintained on 10mg daily. Some patients may require up to 30mg daily given in single or divided doses. Long-term administration of doses 30mg or higher carries an increased risk of gastro-intestinal side effects.

Elderly: 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.

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.

Use in children: Dosage recommendations and indications for use in children have not been established.

4.3 Contra-Indications

- 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 or any of the excipients, previous skin reaction (regardless of severity) to Piroxicam, other NSAIDs and other medications.
- NSAIDs are contraindicated in patients who have previously shown hypersensitivity reactions (e.g. asthma, rhinitis, angioedema or urticaria) in response to ibuprofen, aspirin or other non-steroidal anti-inflammatory drugs.

- Severe heart failure, hepatic failure and renal failure (see section 4.4)
- During the last trimester of pregnancy (see section 4.6)

4.4. Special Warnings and Precautions for Use

Undesirable effects may be minimized by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.2, and GI and cardiovascular risks below).

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.

The use of piroxicam with concomitant NSAIDs including cyclooxygenase-2- selective inhibitors should be avoided (see section 4,5).

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.

Patients with significant risk factors for serious GI events should be treated with Piroxicam only after careful consideration (see section 4.3 and below).

The possible need for combination therapy with gastro-protective agents (e.g. misoprostol or proton pump inhibitors) should be carefully considered (see section 4.2).

Serious GI complications

Identification of at-risk subjects

The risk for developing serious GI complications increased with age. Age over 70 years is associated with high risk of complications. The administration to patients older than 80 years old 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 (see below and section 4.5). As with other NSAIDs, the use of Piroxicam in combination with protective agents (e.g. misoprostal 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.

Patients who are known or suspected to be poor CYP2C9 metabolizers based on previous history/experience with other CYP2C9 substrates should be administered piroxicam with caution as they may have abnormally high plasma levels due to reduced metabolic clearance (see section 5.2).

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 NSAIDs (see section 4.8). 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 higher risk of these reactions early in the course of therapy, the onset of the reaction occurring in the majority of these 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.

Other effects

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

Eye disorders:

Because of reports of adverse eye findings with non-steroidal anti-inflammatory drugs it is recommended that patients who develop visual complaints during treatment with piroxicam have ophthalmic evaluation.

Protein bound drugs

Piroxicam is highly protein bound and therefore might be expected to displace other protein bound drugs. The physician should closely monitor patients for changes in dosage requirements when administering piroxicam to patients on highly protein bound drugs.

Lithium

Non-steroidal anti-inflammatory drugs, 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 piroxicam.

Elderly:

The elderly have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal (see section 4.2). As with other NSAIDs caution should be used in treatment of elderly patients who are more likely to be suffering from impaired renal, hepatic or cardiac function and are therefore at increased risk of serious adverse reactions from NSAIDs.

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.

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 (see also section 4.3).

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 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 event (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking).

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 (see section 4.8).

Impaired female fertility

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 fertility, withdrawal of piroxicam should be considered.

Lactose:

Contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5. Interactions with other Medicaments and other forms of Interaction

As with other NSAIDs, the use of Piroxicam together with acetylsalicylic 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 section 4.4). Human studies have shown that concomitant use of Piroxicam and acetylsalicylic acid reduces the plasma Piroxicam concentration to about 80% of the usual value.

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 (see section 4.4)

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. Human studies have shown that concurrent therapy with piroxicam and digoxin, or piroxicam and digitoxin did not affect plasma levels of either drug.

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 (see section 4.4).

Anti-coagulants: NSAIDs, including Piroxicam, may enhance the effects of anti-coagulants, such as warfarin. Therefore, the use of Piroxicam with concomitant anticoagulants such as warfarin and other coumarins should be avoided (see section 4.3).

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.

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 (see section 4.4)

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.

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

Antacids: Studies in man have shown that concomitant administration of antacids had no effect on piroxicam plasma levels.

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.

4.6. Pregnancy and Lactation

Pregnancy:

Although no teratogenic effects were seen in animal testing, the safety of Piroxicam 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 non-steroidal anti-inflammatory drugs, has been associated with an increased incidence of dystocia and delayed parturition in pregnant animals when drug administration was continued in 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 (see section 4.3).

Inhibition of prostaglandin synthesis might adversely affect pregnancy. Data from epidemiological studies suggest an increased risk of spontaneous

abortion after use of prostaglandin synthesis inhibitors in early pregnancy. In animals, administration of prostaglandin synthesis inhibitors has been shown to result in increased pre- and post-implantation loss. 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. NSAIDs should, if possible, be avoided when breastfeeding. A preliminary study indicates that piroxicam is found in maternal milk in a concentration of approximately 1% of that reached in plasma.

See section 4.4 Special warnings and precautions for use, regarding female fertility.

4.7 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.

4.8. Undesirable Effects

Gastro-intestinal: The most commonly-observed adverse events are gastrointestinal in nature. Peptic ulcers, perforation or GI bleeding, sometimes fatal, particularly in the elderly, may occur (see section 4.4). Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease (see section 4.4) have been reported following administration. Less frequently gastritis has been observed. Pancreatitis has been reported very rarely.

Long term administration of doses of 30mg or higher carries an increased risk of gastro-intestinal side effects.

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

Cardiovascular and cerebrovascular:

Oedema, hypertension and cardiac failure have been reported in association with

NSAID
treatment.

Clinical trial and epidemiological data suggests 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) (see section 4.4).

Palpitations have been reported rarely.

Other adverse effects reported less commonly include:

Blood and lymphatic system disorders: Thrombocytopenia, neutropenia, leucopenia, eosinophilia, agranulocytosis, aplastic anaemia and haemolytic anaemia. Anaemia or decreases in haemoglobin and haematocrit, not associated with obvious gastrointestinal bleeding, have been observed.

Metabolism and nutrition disorders: Anorexia, hypoglycaemia, hyperglycaemia

Nervous system and psychiatric disorders: Headache, paraesthesia, dizziness, drowsiness, somnolence, insomnia, abnormal dreams, depression, mood alteration, confusion, hallucinations, nervousness.

There have been reports of aseptic meningitis (especially in patients with existing auto-immune disorders, such as systemic lupus erythematosus, mixed connective tissue disease), with symptoms such as stiff neck, headache, nausea, vomiting, fever or disorientation (see section 4.4).

Eye disorders: Visual disturbances (Routine ophthalmoscopy and slit-lamp examination have revealed no evidence of ocular changes), optic neuritis, eye irritation, eye swelling

Ear and labyrinth disorders Vertigo, tinnitus, hearing impairment

Respiratory, thoracic and mediastinal disorders: Epistaxis (see also Immune system disorders)

Skin and subcutaneous tissue disorders: Bullous reactions including Stevens Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome). Photosensitivity, Henoch Schonlein purpura, alopecia, onycholysis (see also Immune system disorders)

Hepatic: Changes in different liver function parameters have been observed. As with most other non-steroidal anti-inflammatory drugs, some patients may develop increased serum transaminase levels during treatment with piroxicam. Jaundice and hepatitis may occur, and cases of fatal hepatic failure have been reported. 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), piroxicam should be discontinued.

Renal: Nephrotoxicity in various forms, including interstitial nephritis, nephrotic syndrome, renal failure and renal papillary necrosis.

General disorders: Malaise, fatigue, weight increase, weight decrease, positive anti-nuclear antibody

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard

4.9 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Piroxicam has analgesic, anti-inflammatory and antipyretic properties. It is used in rheumatic disorders such as ankylosing spondylitis, osteoarthritis and rheumatoid arthritis.

5.2. Pharmacokinetic Properties

Piroxicam is well absorbed from the gastro-intestinal tract. It is metabolised in the liver by hydroxylation and conjugation with glucuronic acid and excreted predominantly in the urine with smaller amounts in the faeces. Less than 5% of the dose is excreted unchanged. Piroxicam is extensively bound to plasma proteins (about 99%) and has a long plasma half-life of approximately 50 hours, which allows a dosage, for the majority of patients, of 20mg to be taken once daily. This will provide continuous relief of pain and inflammation over the 24 hour period.

Patients who are known or suspected to be poor CYP2C9 metabolizers based on previous history/experience with other CYP2C9 substrates should be administered piroxicam with caution as they may have abnormally high plasma levels due to reduced metabolic clearance (see section 4.4).

5.3 Preclinical safety data

There are no pre-clinical data of any relevance additional to that already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate, Maize Starch, Sodium Lauryl Sulphate, Crospovidone (Kollidon CL), Magnesium Stearate, amaranth (E123), Titanium Dioxide (E171), and Gelatin and Opacode white containing titanium dioxide, shellac, soya lecithin and Antifoam DC 1510.

6.2 Incompatibilities

None known.

6.3 Shelf life

Blister packs - 4 years

Polypropylene tubes and Tracer Packs – 3 years

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

Polypropylene tubes with low density polyethylene caps.

Blister packs consisting of clear PVC and hard temper aluminium foil contained in a carton.

Tracer Packs: Child resistant containers consisting of polypropylene tubes with high density polyethylene caps.

Pack sizes: 28, 30, 56, 60, 100, 250 and 500 capsules.

6.6 Special precautions for disposal

Not applicable.

7. MARKETING AUTHORISATION HOLDER

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WD18 9SS
Trading as: Co-pharma

8 MARKETING AUTHORISATION NUMBER(S)

PL 13606/0153

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

02/10/2008

10 DATE OF REVISION OF THE TEXT

27/04/2017