PROFESSIONAL INFORMATION

SCHEDULING STATUS

S3

1 NAME OF THE MEDICINE

PIROFEN 20 Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains: Piroxicam 20 mg.

Excipient(s) with known effect:

CONTAINS TARTRAZINE

Contains sugar: Each capsule contains lactose (189,90 mg) and mannitol (40 mg)

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsules.

PIROFEN 20 capsules are light blue/dark blue, size '2', locked hard gelatin capsules containing off-white to light-tan or light-yellow powder. Shells are opaque.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

PIROFEN 20 is indicated for a variety of conditions requiring anti-inflammatory and/or analgesic activity, such as rheumatoid arthritis, osteo-arthritis (arthrosis, degenerative joint disease), ankylosing spondylitis, acute musculoskeletal disorder and acute gout.

4.2 Posology and method of administration

Posology

Rheumatoid arthritis, osteo-arthritis (arthrosis, degenerative joint disease), ankylosing spondylitis

The usual daily dose for the relief of signs and symptoms of rheumatoid arthritis or osteoarthritis is 20 mg given in single or divided doses. Since steady state concentrations in plasma are not reached for seven to ten days, maximal therapeutic responses should not be expected for two weeks. Long-term administration of doses higher than 30 mg carries an increased risk of gastrointestinal side-effects.

Acute musculoskeletal disorders

Therapy should be initiated with 40 mg daily for the first two days given in single or divided doses. For the remainder of the seven to fourteen days treatment period, the dose should be reduced to 20 mg daily.

Acute gout

Therapy should be initiated by a single oral dose of 40 mg followed on the next 4 to 6 days by 40 mg given in a single or divided dosage. PIROFEN 20 is not indicated for the long-term management of gout.

Use the lowest effective dose for the shortest possible duration of treatment.

Method of administration

PIROFEN 20 is for oral administration.

4.3 Contraindications

Hypersensitivity to piroxicam or to any of the excipients of PIROFEN 20 (see section 6.1).

PIROFEN 20 should not be used in:

- Patients who have previously shown sensitivity to piroxicam.
- Patients who have hepatic dysfunction.
- Patients with a 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 acetylsalicylic acid at analgesic doses.
- Concomitant use with anticoagulants.
- History of previous serious allergic medicine reaction of any type, especially cutaneous reactions such as erythema multiforme, Stevens-Johsnon syndrome, toxic epidermal necrolysis.
- Previous skin reaction (regardless of severity) to piroxicam, other NSAIDs and other medications.
- Patients in whom aspirin and other non-steroidal anti-inflammatory medicines induce the symptoms of asthma, rhinitis or urticaria.
- Severe heart failure.
- During the last trimester of pregnancy.
- Pregnancy and lactation: The use of PIROFEN 20 around 20 weeks gestation or later in pregnancy may cause a rare but serious foetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. (see section 4.4 and 4.6).

Safety in pregnancy, lactation and children under 12 years of age has not been established.

4.4 Special warnings and precautions for use

Undesirable effects may be minimised by using the minimum effective dose for the shortest duration necessary to control symptoms (see section 4.2, and GI and cardiovascular (CV) 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.

Gastrointestinal (GI) Effects, Risk of GI Ulceration, Bleeding, and Perforation

NSAIDs, including PIROFEN 20, can cause serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach, small intestine or large intestine, which can be fatal.

NSAID exposures of both short and long duration have an increased risk of serious GI events (see section 4.2). Administration of doses of greater than 20 mg per day carries an increased risk of GI side effects. Evidence from observational studies reported suggests that piroxicam may be associated with a high risk of serious gastrointestinal toxicity, relative to other NSAIDs. These serious adverse events can occur at any time, with or without warning symptoms, in patients treated with NSAIDs.

Patients with significant risk factors for serious GI events should be treated with PIROFEN 20 only after careful consideration (see sections 4.2, 4.3 and below).

The possible need for combination therapy with gastro-protective medicines (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 increases with age. Age over 70 years is associated with high risk of complications. The administration to patients over 80 years should be avoided.

Patients taking concomitant oral corticosteroids, selective serotonin reuptake inhibitors (SSRIs) or anti-platelet medicines such as low-dose acetylsalicylic acid as well as those ingesting excessive amounts of alcohol are at increased risk of serious GI complications (see below and section 4.5). As with other NSAIDs, the use of PIROFEN 20 in combination

with protective medicines (e.g. misoprostol or proton pump inhibitors) must be considered for these at-risk patients.

Patients and doctors should remain alerted for signs and symptoms of GI ulceration and/or bleeding during PIROFEN 20 treatment. Patients should be asked to report any new or unusual abdominal symptom during treatment. If a gastrointestinal complication is suspected during treatment, PIROFEN 20 should be discontinued immediately and additional clinical evaluation and treatment should be considered.

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.

Patients with uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with PIROFEN 20 after careful consideration. Similar consideration should be made before initiating longer-term treatment of patients with risk factors for cardiovascular (CV) events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking).

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. The relative increase of this risk appears to be similar in those with or without known CV disease or CV risk factors. However, patients with known CV disease or CV risk factors may be at greater risk in terms of absolute incidence, due to their increased rate at baseline.

PIROFEN 20 should be used with caution in patients with a history of bronchial asthma (see also section 4.3).

Poor Metabolisers of CYP2C9 Substrates

Patients who are known or suspected to be poor CYP2C9 metabolisers based on previous history/experience with other CYP2C9 substrates should be administered PIROFEN 20

with caution as they may have abnormally high plasma levels due to reduced metabolic clearance (see section 5.2).

Skin reactions

Life-threatening cutaneous reactions (Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)) have been reported with the use of piroxicam.

Patients should be advised of the signs and symptoms and monitored closely for skin reactions. The highest risk for occurrence of SJS or TEN is within the first weeks of treatment.

If symptoms or signs of SJS or TEN (e.g. progressive skin rash often with blisters or mucosal lesions) are present, PIROFEN 20 treatment should be discontinued. The best results in managing SJS and TEN come from early diagnosis and immediate discontinuation of any suspected medicine. Early withdrawal is associated with a better prognosis.

If the patient has developed SJS or TEN with the use of PIROFEN 20, PIROFEN 20 must not be re-started in this patient at any time.

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 (see section 4.8). Evidence from observational studies reported suggests that piroxicam may be associated with a higher risk of serious skin reaction than other non-oxicam NSAIDs.

Cases of fixed drug eruption (FDE) have been reported with piroxicam. PIROFEN 20 should not be reintroduced in patients with history of piroxicam-related FDE. Potential cross reactivity might occur with other oxicams. PIROFEN 20 should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Cardiovascular, Renal and Hepatic Impairment

PIROFEN 20 should be used with caution in patients with renal, hepatic and cardiac impairment. In rare cases, non-steroidal anti-inflammatory medicines may cause interstitial nephritis, glomerulitis, papillary necrosis and the nephrotic syndrome. Such medicines inhibit the synthesis of the 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 non-steroidal anti-inflammatory medicine may precipitate overt renal decompensation, which is typically followed by recovery to pre-treatment state upon discontinuation of non-steroidal anti-inflammatory therapy. Patients at greatest risk of such a reaction are with congestive heart failure, liver cirrhosis, nephrotic syndrome and overt renal disease; such patients should be carefully monitored whilst receiving NSAID therapy.

Eye disorders

Because of reports of adverse eye findings with non-steroidal anti-inflammatory medicines, it is recommended that patients who develop visual complaints during treatment with PIROFEN 20 have ophthalmic evaluation.

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.

Impaired female fertility

The use of PIROFEN 20 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 PIROFEN 20 should be considered.

Neonatal renal impairment and Oligohydramnios:

The use of PIROFEN 20 around 20 weeks gestation or later in pregnancy may cause fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. Complications of prolonged oligohydramnios include limb contractures and delayed lung maturation, which may require invasive procedures such as exchange transfusion or dialysis. If NSAID treatment is determined necessary, limit use to the lowest effective dose and shortest duration possible.

Additionally, it should be avoided at 30 weeks and later in pregnancy because of the additional risk of premature closure of the foetal ductus arteriosus. Consider ultrasound monitoring of amniotic fluid if NSAID treatment extends beyond 48 hours. Discontinue the NSAID if oligohydramnios occurs (see Section 4.3. 4.4 and 4.6).

Drug Reaction with Eosinophillia and Systemic Symptoms (DRESS) has been reported in patients taking NSAIDs such as PIROFEN 20. Some of these events have been fatal or life-threatening. DRESS typically, although not exclusively, presents with fever, rash, lymphadenopathy, and/or facial swelling. Other clinical manifestations may include hepatitis, nephritis, haematological abnormalities, myocarditis, or myositis. Sometimes symptoms of DRESS may resemble an acute viral infection. Eosinophilia is often present. Because this disorder is variable in its presentation, other organ systems not noted here may be involved.

It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, discontinue PIROFEN 20 and evaluate the patient immediately.

Lactose

PIROFEN 20 contains lactose. Patients with rare hereditary problems of galactose

intolerance, total lactase deficiency, or glucose-galactose malabsorption should not take PIROFEN 20.

4.5 Interaction with other medicines and other forms of interaction

Antacids

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

Anti-coagulants

NSAIDs, including PIROFEN 20, may enhance the effects of anticoagulants, such as warfarin. Therefore, the use of PIROFEN 20 with concomitant anticoagulant such as warfarin should be avoided (see section 4.3).

Anti-platelet medicines and selective serotonin reuptake inhibitors (SSRIs) Increased risk of gastrointestinal bleeding (see section 4.4).

Aspirin and other Non-Steroidal Anti-Inflammatory Drugs

PIROFEN 20, like other nonsteroidal anti-inflammatory medicines decreases platelet aggregation and prolongs bleeding time. This effect should be kept in mind when bleeding times are determined. As with other NSAIDs, the use of PIROFEN 20 together with acetylsalicylic acid or concomitant use with other NSAIDs, including other piroxicam formulations, must be avoided, since data are inadequate to show that combinations produce greater improvement than that achieved with PIROFEN 20 alone; moreover, the potential for adverse reactions is enhanced (see section 4.4). Human studies reported have shown that concomitant use of piroxicam and acetylsalicylic acid reduces the plasma piroxicam concentration to about 80 % of the usual value.

Cardiac glycosides

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

Ciclosporin, Tacrolimus

Possible increased risk of nephrotoxicity when NSAIDs are given with ciclosporin or tacrolimus.

Cimetidine

Results of two separate studies reported 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 section 4.4).

Digoxin, Digitoxin

Concurrent therapy with PIROFEN 20 and digoxin, or PIROFEN 20 and digitoxin, did not affect the plasma levels of either medicine.

Anti-hypertensives including diuretics, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II antagonists (AIIA) and beta-blockers

NSAIDs can reduce the efficacy of diuretics and other anti-hypertensive medicines including ACE inhibitors, AIIA and beta-blockers. In patients with impaired renal function (e.g. dehydrated patients or elderly patients with the renal function compromised), the co-administration of an ACE inhibitor or an AIIA and/or diuretics with a cyclo-oxygenase inhibitor can increase the deterioration of the renal function, including the possibility of acute renal failure, which is usually reversible.

The occurrence of these interactions should be considered in patients taking PIROFEN 20 with an ACE inhibitor or an AIIA and/or diuretics Therefore, the concomitant administration

of these medicines should be done with caution, especially in elderly patients. Patients should be adequately hydrated and the need to monitor the renal function should be assessed in the beginning of the concomitant treatment and periodically thereafter.

Highly protein-bound medicines

Piroxicam is highly protein-bound and therefore might be expected to displace other protein-bound medicines. The doctor should closely monitor patients for change when administering PIROFEN 20 to patients on highly protein-bound medicines.

Lithium

Non-steroidal anti-inflammatory drugs, including PIROFEN 20, have been reported to increase steady state plasma lithium levels. It is recommended that these levels are monitored when initiating, adjusting and discontinuing PIROFEN 20.

PIROFEN 20, like other non-steroidal anti-inflammatory drugs, may interact with the following medicines/classes of therapeutic medicines:

Antihypertensives - antagonism of the hypotensive effect

Quinolone antibiotics - possible increased risk of convulsions

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

Methotrexate - Reduced excretion of methotrexate, possibly leading to acute toxicity. When methotrexate is administered concurrently with NSAIDs, including PIROFEN 20, NSAIDs may decrease elimination of methotrexate resulting in increased plasma levels of methotrexate. Caution is advised, especially in patients receiving high doses of methotrexate.

Care should be exercised with the use of PIROFEN 20 in patients with renal dysfunction. Blood-urea-nitrogen elevation has been observed in some patients. The rise in blood-urea-nitrogen is not associated with elevations in serum creatinine.

PIROFEN 20 decreases platelet aggregation and prolongs bleeding time. In view of the products inherent potential to cause oedema, heart failure may be precipitated in some compromised patients.

PIROFEN 20 should not be used in patients on coumarin-type anticoagulants. Changes in different liver function parameters have been observed. Some patients may develop increased serum transaminase levels during treatment with PIROFEN 20.
It should be assumed that PIROFEN 20 will precipitate bronchoconstriction in those patients who are sensitive to aspirin. PIROFEN 20 increases plasma lithium levels.

4.6 Fertility, pregnancy and lactation

Pregnancy

Although no teratogenic effects were reported in animal testing, the safety of piroxicam during pregnancy or during lactation has not yet been established.
PIROFEN 20 inhibits prostaglandin synthesis and release through a reversible inhibition of the cyclo-oxygenase enzyme. This effect, as with other non-steroidal anti-inflammatory drugs (NSAIDs) has been associated with an increased incidence of dystocia and delayed parturition in pregnant animals when medicine 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 reported 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.

Pregnant women should not use PIROFEN 20 at 20 weeks or later unless specifically advised to do so by a health care professional because it may cause foetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. Additionally, it should be avoided at 30 weeks and later in pregnancy because of the additional risk of premature closure of the foetal ductus arteriosus (see Section 4.3, 4.4 and 4.6).

Breastfeeding

A reported study indicates 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. Piroxicam is not recommended for use in nursing mothers as clinical safety has not been established.

Fertility

Based on the mechanism of action, the use of NSAIDs, including PIROFEN 20, may delay or prevent rupture of ovarian follicles, which has been associated with reversible infertility in some women. In women who have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of NSAIDs, including PIROFEN 20, should be considered.

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

a. Summary of the safety profile

Adverse reactions are ranked under headings of frequency, the most frequent first, using the following convention: frequent, less frequent and frequency unknown.

b. Tabulated summary of adverse reactions

MedDRA system organ class	**Frequency**	**Adverse reactions**
Blood and lymphatic system disorders	Frequent	Anaemia, eosinophilia, leukopenia, thrombocytopenia
	Frequency unknown	Aplastic anaemia, haemolytic anaemia
Immune system disorders	Frequency unknown	Anaphylaxis, serum sickness
Metabolism and nutrition disorders	Frequent	Anorexia, hyperglycaemia
	Less frequent	Hypoglycaemia
	Frequency unknown	Fluid retention
Psychiatric disorders	Frequency unknown	Depression, dream abnormalities, hallucinations, insomnia, mental confusion, mood alterations, nervousness
Nervous system disorders	Frequent	Dizziness, headache, somnolence, vertigo
	Frequency unknown	Paraesthesia
Eye disorders	Less frequent	Blurred vision
	Frequency unknown	Eye irritations, swollen eyes
Ear and labyrinth disorders	Frequent	Tinnitus
	Frequency unknown	Hearing impairment

MedDRA system organ class	**Frequency**	**Adverse reactions**
Cardiac disorders	Less frequent	Palpitations
	Frequency unknown	Cardiac failure, arterial thrombotic events
Vascular disorders	Frequency unknown	Vasculitis, hypertension
Respiratory, thoracic and mediastinal disorders	Frequency unknown	Bronchospasm, dyspnoea, epistaxis
Gastrointestinal disorders	Frequent	Abdominal discomfort, abdominal pain, constipation, diarrhoea, epigastric distress, flatulence, nausea, vomiting, indigestion
	Less frequent	Stomatitis
	Frequency unknown	Gastritis, gastrointestinal bleeding (including hematemesis and melena), pancreatitis, perforation, ulceration
Hepato-biliary disorders	Frequency unknown	Fatal hepatitis, jaundice
Skin and subcutaneous tissue disorders	Frequent	Pruritis, skin rash
	Less frequent	Severe cutaneous adverse reactions (SCARs): Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) (see section 4.4)
	Frequency	Fixed drug eruptions (see section 4.4),

MedDRA system organ class	**Frequency**	**Adverse reactions**
	unknown	alopecia, angioedema, exfoliative dermatitis, non-thrombocytopenic purpura (Henoch-Schoenlein), onycholysis, photoallergic reactions, urticaria, vesiculo bullous reaction, Drug Reaction with Eosinophillia and Systemic Symptoms (DRESS) (see section 4.4), erythema multiforme
Renal and urinary disorders	Less frequent	Interstitial nephritis, nephrotic syndrome, renal failure, renal papillary necrosis
	Frequency unknown	Glomerulonephritis
Reproductive system and breast disorders	Frequency unknown	Decreased female fertility
General disorders and administration site conditions	Frequent	Oedema (mainly of the ankle)
	Frequency unknown	Malaise
Investigations	Frequent	Increased serum transaminase levels, weight increase
	Frequency unknown	Positive ANA, weight decrease, decrease in haemoglobin and haematocrit unassociated with obvious gastrointestinal bleeding

c. Description of selected adverse reactions

Gastrointestinal

These are the most commonly encountered side-effects but in most instances do not interfere with the course of therapy.

Objective evaluations of gastric mucosa appearances and intestinal blood loss show that 20 mg/day of piroxicam administered either in single or divided doses is significantly less irritating to the gastrointestinal tract than aspirin.

Some epidemiological studies reported have suggested that piroxicam is associated with higher risk of gastrointestinal adverse reactions compared with some NSAIDs, but this has not been confirmed in all reported studies. Administration of doses exceeding 20 mg daily (of more than several days duration) carries an increased risk of gastrointestinal side effects, but they may also occur with lower doses (see section 4.2).

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. 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) (see section 4.4).

Liver function

Changes in various liver function parameters have been observed. Although such reactions are rare, if abnormal liver function tests persist or worsen, if clinical symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g. eosinophilia, rash etc.), piroxicam should be discontinued.

Other

Routine ophthalmoscopy and slit-lamp examination have revealed no evidence of

ocular changes.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are requested to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

In the event of overdosage with Piroxicam, supportive and symptomatic therapy is indicated.

Studies reported indicate that administration of activated charcoal may result in reduced re-absorption of piroxicam, thus reducing the total amount of active medicine available.

Although there are no studies reported to date, haemodialysis is probably not useful in enhancing elimination of piroxicam since the medicine is highly protein-bound.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 3.1 Antirheumatics (anti-inflammatory agents).

Pharmacotherapeutic group: non-steroidal anti-inflammatory agent,

ATC code: M01AC01

Piroxicam is a non-steroidal anti-inflammatory medicine which also possesses analgesic and antipyretic properties.

Oedema, erythema, tissue proliferation, fever and pain can all be inhibited in laboratory animals by the administration of piroxicam. It is effective regardless of the aetiology of the inflammation. While its mode of action is not fully understood, independent studies reported

in vitro as well as *in vivo* 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 and monocyte migration to the area of inflammation.

Inhibition of lyosomal enzyme release from stimulated leucocytes.

Reduction of both systemic and synovial fluid rheumatoid factor production 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 on cartilage metabolism.

5.2 Pharmacokinetic properties

Absorption

Piroxicam is well absorbed following oral or rectal administration. With food there is a slight delay in the rate but not the extent of absorption following administration. The plasma half-life is approximately 50 hours in man and 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 is first achieved.

Distribution

Medicine plasma concentrations are proportional for 10 and 20 mg doses and generally peak within 3 to 5 hours after medicine. A single 20 mg dose generally produces peak piroxicam plasma levels of 1,5 to 2 µg/ml while maximum plasma concentrations, after repeated daily ingestion of 20 mg piroxicam, usually stabilize at 3 to 8 µg /ml. Most patients approximate steady state plasma levels within 7 to 12 days.

Treatment with a loading dose regimen of 40 mg daily for the first 2 days followed by 20 mg

daily thereafter allows a high percentage (approximately 76 %) of steady state levels to be achieved immediately following the second dose. Steady state levels, area under the curves and elimination half-life are similar to that following a 20 mg daily dose regimen.

A multiple dose comparative study of the bioavailability of the injectable forms with the oral capsule has shown that after intramuscular administration of piroxicam, plasma levels are significantly higher than those obtained after ingestion of capsules during the 45 minutes following administration the first day, during 30 minutes the second day and 15 minutes the seventh day. Bioequivalence exists between the two dosage forms.

A multiple dose comparative study reported the pharmacokinetics and the bioavailability of Piroxicam FDDF with the oral capsule has shown that after once daily administration for 14 days, the mean plasma piroxicam concentration time profiles for capsules and Piroxicam FDDF were nearly superimposable. There were no significant differences between the mean steady state C_{max} values, C_{min} values, T½, or T_{max} values. This study concluded that Piroxicam FDDF (Fast Dissolving Dosage Form) is bioequivalent to the capsule after once daily dosing. Single dose studies have demonstrated bioequivalence as well when the tablet is taken with or without water.

Biotransformation

Piroxicam is extensively metabolised and less than 5 % of the daily dose is excreted unchanged in urine and faeces. Piroxicam metabolism is predominantly mediated via cytochrome P450 CYP2C9 in the liver. One important metabolic pathway is hydroxylation of the pyridyl ring of the piroxicam side-chain, followed by conjugation with glucuronic acid and urinary elimination.

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).

Pharmacogenetics

CYP2C9 activity is reduced in individuals with genetic polymorphisms, such as the CYP2C9*2 and CYP2C9*3 polymorphisms. Limited data from two published reports showed that subjects with heterozygous CYP2C9*1/*2 (n = 9), heterozygous CYP2C9*1/*3 (n = 9), and homozygous CYP2C9*3/*3 (n = 1) genotypes showed 1,7-, 1,7-, and 5,3 – fold higher piroxicam systemic levels, respectively, than the subjects with CYP2C9*1/*1 (n = 17, normal metabolizer genotype) following administration of an oral single dose. The mean elimination half-life values of piroxicam for subjects withCYP2C9*1/*3 (n = 9) and CYP2C9*3/*3 (n = 1) genotypes were 1,7- and 8,8 - fold higher than subjects with CYP2C9*1/*1 (n = 17). It is estimated that the frequency of the homozygous*3/*3 genotype is 0 % to 5,7 % in various ethnic groups.

5.3 Preclinical safety data

Not applicable.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content

Lactose

Mannitol

Polysorbate 80

Colloidal silicon dioxide

Magnesium stearate

Capsule shell

Brilliant blue

Tartrazine

Carmoisine

Erythrosine

Titanium dioxide

Gelatin

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store in a dry place at or below 25 °C. Protect from light.

6.5 Nature and contents of container

PIROFEN 20 will be packed in Alu-PVC blister packs.

5 Blisters of 20 capsules per carton (i.e. 100 capsules)

6.6 Special precautions for disposal and other handling

Not applicable.

7 HOLDER OF CERTIFICATE OF REGISTRATION

PHARMA-Q (PTY) LTD

50 Commando Road, Industria West,

2093, Johannesburg

South Africa

8 REGISTRATION NUMBER

31/3.1/0289

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

09 July 1999

10 DATE OF REVISION OF THE TEXT

To be confirmed