PROFESSIONAL INFORMATION

SCHEDULING STATUS: **S3**

1. NAME OF MEDICINE

PIXICAM® 20 (dispersible tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each dispersible tablet contains piroxicam 20 mg.

Contains sugar (lactose monohydrate 169 mg)

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Round, biconvex with a score notch, uniform white to light yellow tablet 9mm x 4mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

PIXICAM 20 is used in musculoskeletal and joint disorders such as ankylosing spondylitis, osteoarthritis and rheumatoid arthritis. In addition, PIXICAM 20 may be used in acute musculoskeletal conditions and acute gout.

Due to its safety profile (see 4.2 Posology and method of administration, 4.3 Contraindications and 4.4 Special warnings and precautions for use), PIXICAM 20 is not a first line option should an NSAID be indicated. The decision to prescribe PIXICAM 20 should be based on an assessment of the individual patient's overall risks (see 4.3 Contraindications and 4.4 Special warnings and precautions for use).

4.2 Posology and method of administration

The prescription of PIXICAM 20 should be initiated by physicians with experience in the diagnostic evaluation and treatment of patients with inflammatory or degenerative rheumatic diseases.

The recommended starting daily dose is 20 mg.

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see 4.4 Special warnings and precautions for use). 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 PIXICAM 20 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.

Ankylosing spondylitis, osteoarthritis and rheumatoid arthritis:

The usual dose is 20 mg daily, although doses of 10 -30 mg daily have been used. Long term administration of 30 mg or more daily, has been associated with an increase in gastro-intestinal side effects. Because of the long half-life, steady-state concentrations are not reached for 7-12 days but will occur sooner if a loading dose is given.

Acute musculo-skeletal conditions:

40 mg daily for 2 days (in single or divided doses), followed by 20 mg daily for 1-2 weeks.

Acute gout:

40 mg daily (in single or divided doses), for 4-6 days. PIXICAM 20 (piroxicam) is not indicated for long-term management of gout.

Method of administration

For oral administration

The tablets may be swallowed whole with adequate water or may be dispersed in a small quantity of water, in a glass and the solution then swallowed.

4.3 Contraindications

- Hypersensitivity to piroxicam, other oxicam compounds or to any of the excipients (see Section 6.1 List of excipients)
- Haemopoietic disorders.
- Patients in whom acetylic acid or other non-steroidal anti-inflammatory medicines induce the symptoms of asthma, rhinitis, angioedema or urticarial.History of gastrointestinal 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 coumarin-type anticoagulants
- History of previous serious allergic drug reaction of any type, especially cutaneous reactions such as erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis
- Previous skin reaction (regardless to severity) to piroxicam, other NSAIDs and other medications
- Cerebrovascular or other active haemorrhages
- General haemorrhagic diathesis
- Moderate or severe heart failure
- Severe renal or hepatic insufficiency
- Treatment of perioperative pain following bypass surgery (CABG)
- During the last trimester of pregnancy
- Children and adolescents under the age of 15 years

4.4 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 (see 4.2 Posology and method of administration 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.

Elderly patients:

The elderly has an increased frequency of adverse reactions to NSAIDs, especially gastrointestinal bleeding and perforation (PUBs) which may be fatal (see 4,2 Posology and method of administration).

Gastrointestinal (GI) bleeding, ulceration and perforation:

NSAIDs, including PIXICAM® 20, 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.

Epidemiological evidence suggests that PIXICAM 20 may be associated with a high risk of serious gastrointestinal toxicity, relative to other NSAIDs (see4.1 Therapeutic Indications and 4.2 Contraindications)

Patients with significant risk factors for serious GI events should be treated with PIXICAM 20 only after careful consideration (see 4.2 Contraindications)

The possible need for combination therapy with gastro-protective agents (e.g. misoprostol or proton pump inhibitors) should be carefully considered (see 4,2 Posology and method of administration).

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 (see below and section 4.5). As with other NSAIDs, the use of PIXICAM 20 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 PIXICAM 20 treatment. Patients should be asked to report any new or unusual abdominal symptom during treatment. If a gastrointestinal complication is suspected during treatment, PIXICAM 20 should be discontinued immediately, and additional clinical evaluation and treatment should be considered.

Cardiovascular and cerebrovascular effects

Appropriate monitoring and advice are required for patients with a history of hypertension and/or mild congestive heart failure as fluid retention and oedema have been reported in association with NSAID therapy. PIXICAM 20 is contraindicated in patients with moderate to severe heart failure (see Section 4.3 Contraindications).

Clinical trial and epidemiological data suggest that use of some NSAIDs (particularly at high doses and 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 PIXICAM 20.

Patients with uncontrolled hypertension, mild congestive heart failure, established ischaemic heart disease, and/or cerebrovascular disease should only be treated with PIXICAM 20 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).

Skin reactions

Life-threatening cutaneous reactions, Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported with the use of PIXICAM 20.

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, PIXICAM 20 treatment should be discontinued.

The best results in managing SJS and TEN come from early diagnosis and immediate discontinuation of any suspect medicine. Early withdrawal is associated with a better prognosis.

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

There have been reports of fixed drug eruption (FDE) with PIXICAM 20. Do not reintroduce PIXICAM 20 in patients with a history of piroxicam-related FDE. There is potential for cross reactivity with other oxicams. Piroxicam should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Inducible porphyria

PIXICAM 20 should be used only after strict assessment of the benefit-risk ratio in inducible porphyria.

Renal effects

In rare cases, NSAIDs may cause interstitial nephritis, glomerulonephritis, papillary necrosis and the nephrotic syndrome. Such agents 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 non-steroidal anti-inflammatory medicinal product may precipitate overt renal insufficiency, 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 those with chronic cardiac insufficiency, liver cirrhosis, nephrotic syndrome or overt renal disease, and patients after recent major surgery. Therefore, such patients should be carefully monitored whilst receiving nonsteroidal anti-inflammatory therapy.

Hepatic effects

PIXICAM 20 may induce hepatitis and jaundice with fatal outcome. Though rarely, treatment should be discontinued, if abnormal liver values persist or deteriorate, if clinical symptoms suggesting hepatopathy or systemic symptoms (e.g. eosinophilia, exanthema) occur.

Eyes

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

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 PIXICAM 20 with caution as they may have abnormally high plasma levels due to reduced metabolic clearance.

General

Patients suffering from hay fever, nasal polyps or chronic obstructive respiratory diseases as well as patients with hypersensitivity to other non-steroidal antiphlogistics/analgesics may use PIXICAM 20 only while heeding certain precautionary measures and under direct medical monitoring, as they are at higher risk of allergic reactions. These can manifest themselves as asthmatic attacks (so-called analgesic asthma), Quincke's oedema or urticaria.

Special caution is also required in patients with allergic reactions to other substances, as they are also at elevated risk of experiencing hypersensitivity reactions when using PIXICAM 20.

Like other NSAIDs PIXICAM 20 can inhibit thrombocyte aggregation and prolong bleeding time. This has to be considered if evaluating bleeding time.

Longer-term administration of PIXICAM 20 requires regular monitoring of the blood picture (haemoglobin, haematocrit), blood coagulation, as well as hepatic and renal function.

Further notes

During longer-term high-dosed, improper use of analgesics, headache may occur which must not be treated with elevated doses of the medicinal product.

Quite in general, habitual intake of analgesics, particularly in combination with several analgesic agents may lead to permanent renal damage with the risk of renal failure (analgesic nephropathy).

Laboratory tests

It is recommended when administering PIXICAM 20 in patients with hepatic or renal disease in history to check the hepatic or renal function periodically. Regular monitoring of these functions during treatment is particularly indicated in elderly patients who often exhibit progressive reduction of these functions with age.

Lactose intolerance

PIXICAM 20 contains lactose. Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not take PIXICAM 20

4.5 Interactions with other medicines and other forms of interaction

Aspirin and other NSAIDS

As with other NSAIDs, the use of PIXICAM 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 such combinations produce greater improvement than that achieved with PIXICAM 20 alone; moreover, the potential for adverse reactions is enhanced (see 4.4 Special warnings and precautions for use). Human studies have shown that concomitant use of PIXICAM 20 and acetylsalicylic acid reduces the plasma PIXICAM 20 concentration to about 80% of the usual value.

Corticosteroids

Concomitant administration of PIXICAM 20 and glucocorticoids increases the risk of gastrointestinal ulceration or bleeding (see 4.4 Special warnings and precautions for use and 4.8 Undesirable effects).

Probenecid

Concurrent intake of probenecid may result in a delay of excretion of PIXICAM 20.

Cimetidine

Concurrent intake of cimetidine may result in a delay of excretion of PIXICAM 20 and thus in an enhancement in its adverse reactions.

Phenytoin, lithium

Co-administration of PIXICAM 20 and phenytoin or lithium may increase the serum level of these medicinal products.

If PIXICAM 20 and lithium preparations are administered concurrently, monitoring of lithium concentrations in blood is necessary and dose adaption recommended if PIXICAM 20 treatment is initiated, adapted or discontinued.

Potassium-sparing diuretics, potassium-containing medicinal products

Co-administration of PIXICAM 20 and potassium-sparing diuretics as well as potassium-containing medicinal products may lead to an increased potassium level in serum.

Diuretics, antihypertensives

PIXICAM 20 can attenuate the effect of diuretics and antihypertensives and renal damage may occur.(sufficient fluid intake necessary, blood pressure should be monitored).
Patients should be adequately hydrated, and the need to monitor the renal function should be assessed at the beginning of the concomitant treatment and periodically thereafter.

Methotrexate

Administration of PIXICAM 20 prior to or following administration of methotrexate may lead to increased methotrexate serum concentration due to reduced excretion of methotrexate and subsequently to increased adverse reactions (combination should be avoided).

Anticoagulants

NSAIDs, including PIXICAM 20 may enhance the effects of anticoagulants, such as warfarin. Therefore, the use of PIXICAM 20 with concomitant anticoagulants such as warfarin is contraindicated. (see 4.3 Contraindications).

Anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs)

Increased risk of gastrointestinal bleeding (see 4.4 Special warnings and precautions for use).

Ciclosporin and tacrolimus

Co-administration of PIXICAM 20 and ciclosporin may increase the risk of gastrointestinal, renal or hepatic damage (combination should be avoided and the PIXICAM 20 dose reduced, respectively. Renal and hepatic function should be monitored.

There is a possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus.

Highly protein bound medicinal products.

PIXICAM 20 is highly protein-bound and might displace other protein-bound medicinal products thereby increasing their (adverse) effects.

Cardiac glycosides

NSAIDs are reported to increase the blood concentration of these medicinal products. However, this was not observed in a study with PIXICAM 20.

Cholestyramine

Cholestyramine may increase PIXICAM 20 elimination.

Oral antidiabetics

Concomitant administration may lead to fluctuations of blood glucose levels. Therefore, blood glucose levels should be monitored intensively.

Quinolone antibiotics

When PIXICAM 20 is given in combination with quinolone antibiotics, there is a possible increased risk of convulsions.

Mifepristone

NSAIDs, including PIXICAM 20, may interfere with mifepristone-mediated termination of pregnancy.

4.6 Fertility, pregnancy and lactation.

Fertility:

Based on the mechanism of action of NSAIDs, the use of PIXICAM 20 may delay or prevent rupture of ovarian follicles, which has been associated with reversible infertility in some women. Consider withdrawal of NSAIDs, including PIXICAM 20, in women who have difficulties conceiving or who are undergoing investigation of infertility (see Section 4.4 Special warnings and precautions for use).

Pregnancy:

Safety during pregnancy and lactation has not yet been established. Use of PIXICAM 20 is contraindicated in the last trimester of pregnancy (see Section 4.3 Contraindications). Regular use of non-steroidal anti-inflammatory drugs such as PIXICAM 20 during the third trimester of pregnancy, may result in premature closure of the foetal ductus arteriosus in utero, and possibly, in persistent pulmonary hypertension of the new-born. The onset of labour may be delayed, and its duration increased.

Lactation:

Piroxicam is distributed into breast milk. Since clinical safety has not been established, PIXICAM 20 is not recommended for use in nursing mothers.

4.7 Effects on the ability to drive or use machinery.

The effects of PIXICAM 20 on the ability to drive and use machines have not been investigated.
If central nervous side effects such as fatigue, dizziness, drowsiness, and vertigo occur during administration of PIXICAM 20 at higher dose, the ability to drive and/or to use machines can be impaired in the individual case. This applies to a higher extent in combination with alcohol. If affected, patients should not drive or operate machinery.

4.8 Undesirable effects

The evaluation of undesirable effects is based on the following information on frequency:

Frequent: (≥ 1/10), (≥ 1/100 up to < 1/10)

Less frequent: (≥ 1/1 000 up to < 1/100), (≥ 1/10 000 up to < 1/1 000), (< 1/10 000)

Not known: cannot be estimated from the available data

Blood and lymphatic system disorders:

Frequent: Anaemia, eosinophilia, leucopenia, thrombocytopenia

Not known: Aplastic anaemia, haemolytic anaemia

Immune System disorders:

Not known: Anaphylaxis, serum sickness

Metabolism and nutrition disorders:

Frequent: Anorexia, hyperglycaemia

Less frequent: Hypoglycaemia

Not known: Fluid retention

Psychiatric disorders:

Not known: Depression, dream abnormalities, hallucinations, insomnia, mental confusion, mood alterations, nervousness

Nervous system disorders:

Frequent: Dizziness, headache, somnolence, vertigo

Not known: Paraesthesia

Eye disorders:

Less frequent: Blurred vision

Not known: Eye irritations, swollen eyes

Ear and labyrinth disorders:

Frequent: Tinnitus

Not known: Hearing impairment

Cardiac disorders:

Less frequent: Palpitations.

Not known: Cardiac failure**

Vascular disorders:

Not known: Vasculitis, hypertension**, arterial thrombotic events**

Respiratory, thoracic and mediastinal disorders:

Not known: Bronchospasm, dyspnoea, epistaxis

Gastrointestinal disorders*:

Frequent: Abdominal discomfort, abdominal pain, constipation, diarrhoea, epigastric distress, flatulence, nausea, vomiting, indigestion

Less frequent: Stomatitis

Not known: Gastritis, gastrointestinal bleeding (including melaena and haematemesis), pancreatitis, perforation, ulceration, exacerbation of colitis and Crohn's disease, ulcerative stomatitis

Hepatobiliary disorders:

Not known: Fatal hepatitis*** or 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 Special warnings and precautions for use

Not known: Alopecia, angioedema, dermatitis exfoliative, erythema multiforme, non-thrombocytopenic purpura (Henoch-Schoenlein), onycholysis, photoallergic reactions, urticaria, vesiculo bullous reactions, fixed drug eruption (see Section 4.4 Special warnings and precautions for use)

Renal and urinary disorders:

Not known: Nephrotic syndrome, glomerulonephritis, interstitial nephritis****, renal failure.

Reproductive system and breast disorders:

Not known: Female fertility decreased

General disorders and administration site conditions:

Frequent: Oedema (mainly of the ankle)**

Not known: Malaise

Investigations:

Frequent: Reversible elevations of BUN, increased serum transaminase levels***, weight increase

Less frequent: Reversible elevations of creatinine

Not known: Positive ANA, weight increase, decreases in haemoglobin and haematocrit unassociated with obvious gastrointestinal bleeding

*The most commonly observed adverse events are gastrointestinal in nature.

**Oedema, hypertension and cardiac failure have been reported in association with NSAID treatment. 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 4.4 Special warnings and precautions for use).

***Changes of several liver function parameters have been observed. As with most other non-steroidal anti-inflammatory medicinal products in some patients increased serum transaminase levels during treatment with PIXICAM 20 may occur (see 4.4 Special warnings and precautions for use).

****In rare cases, NSAIDs may cause acute interstitial nephritis. Such agents 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, such as in severe congestive heart failure, dehydration, nephrotic syndrome, cirrhosis of the liver, or pre-existing renal disease.

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 asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

Symptoms of overdose

The main symptoms are gastrointestinal disturbances, such as nausea, vomiting, abdominal pain, dizziness, headache, confusion, tinnitus, hyperventilation including respiratory alkalosis.

Furthermore, sedation, hyperpyrexia, respiratory and metabolic acidosis, toxic circulatory failure, renal impairment (haematuria, proteinuria, acute renal failure) as well as hepatic impairment (hypoprothrombinaemia); cerebral and pulmonary oedema, enhanced convulsibility and coma. In children, hypoglycaemia is possible.

Therapeutic measures in overdose

No specific antidote exists. Intensive medical supervision may be necessary. The long half-life of PIXICAM 20 is to be considered.

Based on animal tests, administration of antacids and activated charcoal is assumed to possibly accelerate the excretion of PIXICAM 20.

Studies indicate that administration of activated charcoal may result in reduced absorption and reabsorption of PIXICAM 20, thus reducing the total amount of active drug available.

According to current data, haemodialysis is not suited – on account of the high protein binding of PIXICAM 20 – to eliminate PIXICAM 20 from the blood.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological class

A 3.1 Antirheumatics (anti-inflammatory agents).

ATC Classification

M01AC01 - oxicams

Anti-inflammatory and antirheumatic products, nonsteroids

Piroxicam has analgesic, anti-inflammatory and anti-pyretic properties.

5.2 Pharmacokinetic properties:

Piroxicam is well absorbed from the gastro-intestinal tract: peak plasma concentrations are reached 3 to 5 hours after an oral dose. It is metabolised in the liver by hydroxylation and conjugation with glucuronic acid and is excreted predominantly in the urine with smaller amounts in the faeces. Enterohepatic recycling occurs. 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

colloidal silica anhydrous, crospovidone, lactose monohydrate, magnesium stearate, microcrystalline cellulose, sodium docecyl sulphate

6.2 Incompatibilities

Not applicable

6.3 Shelf Life

36 months when stored at or below 25 °C. Protect from light.

6.4 Special precautions for storage

This medicine does not require any special storage conditions.

6.5 Nature and contents of container

PIXICAM 20 is available in packs of 30 and 100 dispersible tablets.

Supplied in white HDPE securitainers or polypropylene foil blisters.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

Kiara Health (Pty) Ltd

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Spartan

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South Africa

8. REGISTRATION NUMBER

29/3.1/0752

9. DATE OF FIRST AUTHORISATION

09 April 1997

10 DATE OF REVISION OF THE TEXT

08 May 2023

Additional countries registration details:

Country	*Product name*	*Scheduling status (or Category of distribution)*	*Registration number*
Namibia	PIXICAM 20	NS2	04/3.1/1348
Botswana	PIXICAM 20	S2	BOT1703203
Mauritius	PIXICAM 20		R2930/02/14
Zambia	PIXICAM 20		039/045

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