Piroxicam Capsules 20mg (TELVIDENE)

1. Name of the medicinal product

Piroxicam 20mg Capsules

2. Qualitative and quantitative composition

Each capsule contains 20mg of piroxicam

Excipient(s) with known effect: Lactose monohydrate

For a full list of excipients, see section 6.1.

3. Pharmaceutical form

Capsule, hard

Appearance: Maroon cap and body, size "3" hard gelatin capsule shells printed "CX46" on body and cap in white and filled with white powder. Approximately 16 mm in length.

4. Clinical particulars

a. 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).

b. Posology and method of administration

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

The maximum recommended daily dose is 20mg.

Undesirable effects may be minimised by using the minimum effective dose for the shortest duration necessary to control symptoms. The benefit and tolerability of treatment should be reviewed within 14 days. If continued treatment is considered necessary, this should be accompanied by frequent review.

Given that Piroxicam has been shown to be associated with an increased risk of gastrointestinal complications, the possible need for combination therapy with gastro-protective agents (e.g. misoprostol 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.

Method of administration

Oral.

To be taken preferably with or after food.

c. 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 acetylsalicylic 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, nasal polyps, angioedema or urticaria) in response to ibuprofen, aspirin or other non-steroidal anti- inflammatory drugs.

• During the last trimester of pregnancy (see section 4.6)

• Patients with severe heart failure.

d. 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.

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. NSAID exposures of both short and long duration have an increased risk of serious GI event. Administration of doses of greater than 20 mg per day carries an increased risk of GI side effects. Evidence from observational studies 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 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 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 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.

Poor Metabolisers of CYP2C9 Substrates

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

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, piroxicam treatment should be discontinued. The best results in managing SJS and TEN come from early diagnosis and immediate discontinuation of any suspect drug. Early withdrawal is associated with a better prognosis.

If the patient has developed SJS or TEN with the use of piroxicam, piroxicam 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 suggests that piroxicam may be associated with a higher risk of serious skin reaction 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. Piroxicam should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Cases of fixed drug eruption (FDE) have been reported with piroxicam.

Piroxicam should not be reintroduced in patients with history of piroxicam-related FDE. Potential cross reactivity might occur with other oxicams.

Cardiovascular, Renal and Hepatic Impairment

Piroxicam should be used with caution in patients with renal, hepatic and cardiac impairment. In rare cases, non-steroidal anti-inflammatory drugs may cause interstitial nephritis, glomerulitis, papillary necrosis and the nephrotic syndrome. Such agents 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 drug 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 drugs it is recommended that patients who develop visual complaints during treatment with piroxicam 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.

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 infraction 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.

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).

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.

Piroxicam Capsules contain lactose:

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

Piroxicam capsules contains sodium:

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

e. Interaction with other medicinal products and other forms of interaction

Anti-hypertensives: Reduced anti-hypertensive effect

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

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

Lithium: Decreased elimination of 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.

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

Ciclosporin, Tacrolimus: possible increased risk of nephrotoxicity when NSAIDs are given with ciclosporin or tacrolimus.

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

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).

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

Aspirin and other Non-Steroidal Anti-Inflammatory Drugs:

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.

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 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.

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 drugs 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 piroxicam with an ACE inhibitor or an AIIA and/or diuretics Therefore, the concomitant administration of these drugs 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.

Quinolone antibiotics: possible increased risk of convulsions.

Highly 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: 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.

f. Fertility, pregnancy and lactation

Fertility: Based on the mechanism of action, the use of NSAIDs, including piroxicam, 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 piroxicam, should be considered.

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 CV 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. From the 20th week of pregnancy onward, piroxicam use may cause oligohydramnios resulting from foetal renal dysfunction. This may occur shortly after treatment initiation and is usually reversible upon discontinuation. In addition, there have been reports of ductus arteriosus constriction following treatment in the second trimester, most of which resolved after treatment cessation. Therefore, during the first and second trimester of pregnancy, piroxicam should not be given unless clearly necessary. If piroxicam is used by a woman attempting to conceive, or during the first and second trimester of pregnancy, the dose should be kept as low and duration of treatment as short as possible. Antenatal monitoring for oligohydramnios and ductus arteriosus constriction should be considered after exposure to piroxicam for several days from gestational week 20 onward. Piroxicam should be discontinued if oligohydramnios or ductus arteriosus constriction are found.

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the foetus to:

- cardiopulmonary toxicity (with premature constriction/closure of the ductus arteriosus and pulmonary hypertension);

- renal dysfunction (see above);

the mother and the neonate, at the end of pregnancy, to:

- possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses;

- inhibition of uterine contractions resulting in delayed or prolonged labour.

Consequently, piroxicam is contraindicated during the third trimester of pregnancy (see sections 4.3 and 5.3).

Lactation: 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. Piroxicam is not recommended for use in nursing mothers as clinical safety has not been established.

g. 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.

h. Undesirable effects

System Organ Class	Very Common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1000 to <1/100	Rare ≥1/10 000 to <1 000	Very Rare <1/10000	Not Known (cannot be estimated from

						available data)
Blood and lymphatic system disorders		Anaemia Eosinophilia Leucopenia Thrombocytopenia				Aplastic anaemia Haemolytic anaemia
Immune system disorders						Anaphylaxis Serum sickness
Metabolism and nutrition disorders		Anorexia Hyperglycaemia	Hypoglycaemia			Fluid retention
Psychiatric disorders						Depression Dream abnormalities Hallucinations Insomnia Mental confusion Mood alterations Nervousness
Nervous system disorders		Dizziness Headache Somnolence Vertigo				Paresthesia
Eye disorders			Blurred vision			Eye irritations Swollen eyes
Ear and labyrinth disorders		Tinnitus				Hearing impairment
Cardiac disorders			Palpitations			Cardiac failure Arterial thrombotic events
Vascular disorders						Vasculitis Hypertension
Respiratory, thoracic and mediastinal disorders						Bronchospasm Dyspnoea Epistaxis
Gastrointestinal disorders		Abdominal discomfort Abdominal pain Constipation Diarrhoea Epigastric distress Flatulence Nausea Vomiting	Stomatitis			Gastritis Gastrointestinal bleeding (including hematemesis and melena) Pancreatitis Perforation Ulceration

		Indigestion				
Hepatobiliary disorders						Fatal hepatitis Jaundice
Renal and urinary disorders				Interstitial nephritis Nephrotic syndrome Renal failure Renal papillary necrosis		Glomerulonephritis
Skin and subcutaneous tissue disorders		Pruritis Skin rash			Severe cutaneous adverse reactions (SCARs): Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) (see section 4.4)	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)
Reproductive system and breast disorders						Female fertility decreased
General disorders and administration site conditions		Oedema (mainly of the ankle)				Malaise
Investigations		Increased serum transaminase levels Weight increase				Positive ANA Weight decrease Decreases in hemoglobin and hematocrit unassociated with obvious gastro-intestinal bleeding

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 20mg/day of piroxicam administered either in single or divided doses is significantly less irritating to the gastrointestinal tract than aspirin.

Some epidemiological studies 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 studies. Administration of doses exceeding

20mg 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 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 or search for MHRA Yellow Card in the Google Play or Apple App Store.

i. Overdose

i. 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.

ii. 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

a. Pharmacodynamic properties

Pharmacotherapeutic group: non-steroidal anti-inflammatory agent ATC code: M01A C01

Piroxicam is a non-steroidal anti-inflammatory agent 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 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 lysosomal 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.

b. Pharmacokinetic properties

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 20mg/day for periods of 1 year produces similar blood levels to those seen once steady state is first achieved.

Drug plasma concentrations are proportional for 10 and 20mg doses and generally peak within 3 to 5 hours after medication. A single 20mg dose generally produces peak piroxicam plasma levels of 1.5 to 2 mcg/ml while maximum plasma concentrations, after repeated daily ingestion of 20mg piroxicam, usually stabilise at 3 to 8 mcg/ml. Most patients approximate steady state plasma levels within 7 to 12 days.

Treatment with a loading dose regimen of 40mg daily for the first 2 days followed by 20mg 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 20mg 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 of 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 Cmax values, C_{min} values, T½, or T_{max} values. This study concluded that piroxicam 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.

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 CYP 2C9 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 with CYP2C9*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.

c. Preclinical safety data

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

6. Pharmaceutical particulars

a. List of excipients

Lactose monohydrate, Maize Starch, Sodium Lauryl Sulphate, Crospovidone NF (Kollidon CL), Magnesium Stearate, indigotine (E132). Titanium Dioxide (E171), Erythrosin (E127), black iron oxide (E172) and Gelatin and Opacode white containing titanium dioxide (E171), shellac, soya lecithin and Antifoam DC 1510.

b. Incompatibilities

None known.

c. Shelf life

Blister packs - 4 years

Polypropylene tubes and Tracer Packs – 3 years

d. Special precautions for storage

Do not store above 30°C

e. 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

f. Special precautions for disposal and other handling

Not applicable

7. Marketing authorisation holder

Strides Pharma UK Ltd,

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WD18 9SS,

United Kingdom

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

22/09/2023

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