SUMMARY OF PRODUCT CHARACTERISTICS

1. **Product Name**: BELCAM CAPSULES (Prioxicam Capsules BP 20 mg)

2.Composition:

Each hard Gelatin Capsule contains:

Piroxicam BP 20 mg

Excipients Q.S.

Approved colour used in hard gelatin capsule shells.

3. Pharmaceutical form

Red & white colour size 2 hard gelatin capsule of printing "BELCAM"

4. CLINICAL PARTICULARS:

4.1 Therapeutic Indications

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

Due to its safety profile, 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

4.2 Dosage and administration:

Posology

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 need for possible combination therapy with gastroprotective agents (e.g. misoprostol or proton pump inhibitors) should be carefully considered, in particular for elderly patients.

Elderly

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

Method of Administration

For oral administration. To be taken preferably with or after food.

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms.

4.3 Contraindications:

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

• 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.

• Previous skin reaction (regardless of severity) to piroxicam, other NSAIDs and other medications.

• Patients in whom aspirin and other non-steroidal anti-inflammatory drugs induce the symptoms of asthma, nasal polyps, angioedema or urticaria.

• Severe heart failure.

• During the last trimester of pregnancy

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 (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 piroxicam, can cause serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach, small intestine or large intestine, which can be fatal

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 agents such as low-dose acetylsalicylic acid as well as those ingesting excessive amounts of alcohol are at increased risk of serious GI complications. As with other NSAIDs, the use of piroxicam in combination with protective agents (e.g. misoprostol or proton pump inhibitors) must be considered for these at-risk patients.

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.

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.

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 infertility, withdrawal of Piroxicam should be considered.

Lactose

Piroxicam Capsules contain lactose.

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

Sodium

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

4.5 Interaction with other Medicinal products and other forms of Interaction

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

Anti-coagulants: NSAIDs, including piroxicam, may enhance the effects of anticoagulants, such as warfarin. Therefore, the use of piroxicam with concomitant anticoagulant such as warfarin should be avoided.

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

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. Human studies 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 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 piroxicam and digoxin, or piroxicam and digitoxin, did not affect the plasma levels of either drug.

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.

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 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.

Piroxicam, like other non-steroidal anti-inflammatory drugs, may interact with the following drugs / classes of therapeutic agents:

Antihypertensives -antagonism of the hypotensive effect

Quinolone antibiotics - possible increased risk of convulsions

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

4.6 Fertility, 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 (NSAIDs) 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.

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.

Breast-feeding

A 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 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.

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

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 Thrombo-cytopenia				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				Paraesthesia
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						Bronchospasm Dyspnoea Epistaxis

mediastinal disorders						
Gastrointestinal disorders		Abdominal discomfort Abdominal pain Constipation Diarrhoea Epigastric distress Flatulence Nausea Vomiting Indigestion	Stomatitis			Gastritis Gastrointestinal bleeding (including hematemesis and melena) Pancreatitis Perforation Ulceration
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, DRESS syndrome, Fixed drug eruption
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 haemoglobin and haematocrit 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.

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).

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

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

Distribution:

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 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 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.

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.

5.3 Preclinical safety data

Not Applicable

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS:

Lactose

Magnesium stearate

Maize starch

Polysorbate

The capsule shell contains:

Gelatin

Erythrosine (E127)

Titanium Dioxide (E171)

Red Iron Oxide (E172)

Propylene glycol

6.2 Incompatibilities

None known.

6.3 Shelf Life

36 Months

6.4 Special Precautions for Storage

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

6.5 Nature and Contents of Container

1 x 10 Capsules

6.6 Special Precautions for Disposal and Other Handling

No special requirements

7. MARKETING AUTHORISATION HOLDER

None