1.3.1 Summary of product characteristics

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

1.1 (Invented) Name of the Medicinal Product

Piroxicam Capsules

1.2 Strength

20 mg

1.3 Pharmaceutical Form

Capsule

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule Contains:

Piroxicam…….20mg

Magnesium Stearate……1.168mg

Sodium dodecyl sulfate……1.156mg

Starch……95.6mg

Sr. No.	Ingredients	Overages (%)	Quantity Per Batch (kg)
1	Lincomycin Hydrochloride	N/A	20
2	Magnesium Stearate	N/A	1.168
3	Sodium dodecyl sulfate	N/A	1.156
4	Starch	N/A	95.6

3.PHARMACEUTICAL FORM

Capsule,

4.CLINICAL PARTICULARS

4.1Therapeutic indications

Piroxicam is indicated:

- For relief of the signs and symptoms of osteoarthritis.
- For relief of the signs and symptoms of rheumatoid arthritis.

4.2 Dosage and method of administration

Carefully consider the potential benefits and risks of piroxicam and other treatment options before deciding to use piroxicam. Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals.

After observing the response to initial therapy with piroxicam, the dose and frequency should be adjusted to suit an individual patient's needs.

For the relief of rheumatoid arthritis and osteoarthritis, the dosage is 20 mg given orally once per day. If desired, the daily dose may be divided. Because of the long half-life of piroxicam, steady-state blood levels are not reached for 7 to 12 days. Therefore, although the therapeutic effects of piroxicam are evident early in treatment, there is a progressive increase in response over several weeks and the effect of therapy should not be assessed for two weeks.

4.3 Side Effects & Drug Interactions

SIDE EFFECTS

The following adverse reactions have been identified during post approval use of piroxicam. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Body As a Whole: Fever, infection, sepsis, anaphylactic reactions, appetite changes, death, flu-like syndrome, pain (colic), serum sickness

Cardiovascular System: Congestive heart failure, hypertension, tachycardia, syncope, arrhythmia, exacerbation of angina, hypotension, myocardial infarction, vasculitis

Digestive System: Dyspepsia, elevated liver enzymes, gross bleeding/perforation, heartburn, ulcers (gastric/duodenal), dry mouth, esophagitis, gastritis, glossitis, hematemesis, hepatitis, jaundice, melena, rectal bleeding, eructation, liver failure, pancreatitis

Hemic and Lymphatic System: Anemia, increased bleeding time, ecchymosis, eosinophilia, epistaxis, leukopenia, purpura, petechial rash, thrombocytopenia, agranulocytosis, hemolytic anemia, aplastic anemia, lymphadenopathy, pancytopenia

Hypersensitivity: Positive ANA

Metabolic and Nutritional: Weight changes, Fluid retention, hyperglycemia, hypoglycemia

Nervous System: Anxiety, asthenia, confusion, depression, dream abnormalities, insomnia, malaise, nervousness, paresthesia, somnolence, tremors, akathisia, convulsions, coma, hallucinations, meningitis, mood alterations

Respiratory System: Asthma, dyspnea, respiratory depression, pneumonia

Skin and Appendages: Alopecia, bruising, desquamation, erythema, photosensitivity, sweat, angioedema, toxic epidermal necrosis, erythema multiforme, exfoliative dermatitis, onycholysis, Stevens Johnson Syndrome, urticaria, vesiculobullous reaction

Special Senses: Conjunctivitis, hearing impairment, swollen eyes

Urogenital System: Abnormal renal function, cystitis, dysuria, hematuria, hyperkalemia, interstitial nephritis, nephrotic syndrome, oliguria/polyuria, proteinuria, renal failure, glomerulonephritis

Reproductive System and Breast Disorders: Female fertility decreased

DRUG INTERACTIONS

See Table 1 for clinically significant drug interactions with piroxicam.

Drugs That Interfere with Hemostasis	
Clinical Impact:	• Piroxicam and anticoagulants such as warfarin have a synergistic effect on bleeding. The concomitant use of piroxicam and anticoagulants have an increased risk of serious bleeding compared to the use of either drug alone. • Serotonin release by platelets plays an important role in hemostasis. Case-control and cohort epidemiological studies showed that concomitant use of drugs that interfere with serotonin reuptake and an NSAID may potentiate the risk of bleeding more than an NSAID alone.
Intervention:	Monitor patients with concomitant use of piroxicam with anticoagulants (e.g., warfarin), antiplatelet drugs (e.g., aspirin), SSRIs, and SNRIs for signs of bleeding
Aspirin	
Clinical Impact:	Controlled clinical studies showed that the concomitant use of NSAIDs and analgesic doses of aspirin does not produce any greater therapeutic effect than the use of NSAIDs alone. In a clinical study, the concomitant use of an NSAID and aspirin was associated with a significantly increased incidence of GI adverse reactions as compared to use of the NSAID alone.
Intervention:	Concomitant use of piroxicam and analgesic doses of aspirin is not generally recommended because of the increased risk of bleeding Piroxicam is not a substitute for low dose aspirin for cardiovascular protection.
ACE Inhibitors, Angiotensin Receptor Blockers, and Beta-Blockers	
Clinical Impact:	• NSAIDs may diminish the antihypertensive effect of ACE inhibitors, ARBs, or beta-blockers (including propranolol). • In patients who are elderly, volume-depleted (including those on diuretic therapy), or have renal impairment, coadministration of an NSAID with ACE inhibitors or ARBs may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible.
Intervention:	• During concomitant use of piroxicam and ACE inhibitors, ARBs, or beta-blockers, monitor blood pressure to ensure that the desired blood pressure is obtained. • During concomitant use of piroxicam and ACE inhibitors or ARBs in patients who are elderly, volume-depleted, or have impaired renal function, monitor for signs of worsening renal function • When these drugs are administered concomitantly, patients should be adequately hydrated. Assess renal function at the beginning of the concomitant treatment and periodically thereafter.
Diuretics	
Clinical	Clinical studies, as well as postmarketing observations, showed that NSAIDs reduced

Impact:	the natriuretic effect of loop diuretics (e.g., furosemide) and thiazide diuretics in some patients. This effect has been attributed to the NSAID inhibition of renal prostaglandin synthesis.
Intervention:	During concomitant use of piroxicam with diuretics, observe patients for signs of worsening renal function, in addition to assuring diuretic efficacy including antihypertensive effects
Digoxin	
Clinical Impact:	The concomitant use of piroxicam with digoxin has been reported to increase the serum concentration and prolong the half-life of digoxin.
Intervention:	During concomitant use of piroxicam and digoxin, monitor serum digoxin levels.
Lithium	
Clinical Impact:	NSAIDs have produced elevations in plasma lithium levels and reductions in renal lithium clearance. The mean minimum lithium concentration increased 15%, and the renal clearance decreased by approximately 20%. This effect has been attributed to NSAID inhibition of renal prostaglandin synthesis.
Intervention:	During concomitant use of piroxicam and lithium, monitor patients for signs of lithium toxicity.
Methotrexate	
Clinical Impact:	Concomitant use of NSAIDs and methotrexate may increase the risk for methotrexate toxicity (e.g., neutropenia, thrombocytopenia, renal dysfunction).
Intervention:	During concomitant use of piroxicam and methotrexate, monitor patients for methotrexate toxicity.
Cyclosporine	
Clinical Impact:	Concomitant use of piroxicam and cyclosporine may increase cyclosporine's nephrotoxicity.
Intervention:	During concomitant use of piroxicam and cyclosporine, monitor patients for signs of worsening renal function.
NSAIDs and Salicylates	
Clinical	Concomitant use of piroxicam with other NSAIDs or salicylates (e.g., diflunisal,

Impact:	salsalate) increases the risk of GI toxicity, with little or no increase in efficacy
Intervention:	The concomitant use of piroxicam with other NSAIDs or salicylates is not recommended.
Pemetrexed	
Clinical Impact:	Concomitant use of piroxicam and pemetrexed may increase the risk of pemetrexed-associated myelosuppression, renal, and GI toxicity (see the pemetrexed prescribing information).
Intervention:	During concomitant use of piroxicam and pemetrexed, in patients with renal impairment whose creatinine clearance ranges from 45 to 79 mL/min, monitor for myelosuppression, renal and GI toxicity. NSAIDs with short elimination half-lives (e.g., diclofenac, indomethacin) should be avoided for a period of two days before, the day of, and two days following administration of pemetrexed. In the absence of data regarding potential interaction between pemetrexed and NSAIDs with longer half-lives (e.g., meloxicam, nabumetone), patients taking these NSAIDs should interrupt dosing for at least five days before, the day of, and two days following pemetrexed administration.
Highly Protein Bound Drugs	
Clinical Impact:	Piroxicam is highly protein bound and, therefore, might be expected to displace other protein bound drugs.
Intervention:	Physicians should closely monitor patients for a change in dosage requirements when administering piroxicam to patients on other highly protein bound drugs.
Corticosteroids	
Clinical Impact:	Concomitant use of corticosteroids with piroxicam may increase the risk of GI ulceration or bleeding.
Intervention:	Monitor patients with concomitant use of piroxicam with corticosteroids for signs of bleeding

Table 1: Clinically Significant Drug Interactions with Piroxicam

4.4 Warning

Cardiovascular Thrombotic Events

Clinical trials of several cyclooxygenase-2 (COX-2) selective and nonselective NSAIDs of up to three years duration have shown an increased risk of serious cardiovascular (CV) thrombotic events, including myocardial infarction (MI), and stroke, which can be fatal. Based on available data, it is unclear that the risk for CV thrombotic events is similar for all NSAIDs. The relative increase in serious CV thrombotic events over baseline conferred by NSAID use appears to be similar in those with and without known CV disease or risk factors for CV disease. However, patients with known CV disease or risk factors had a higher absolute incidence of excess serious CV thrombotic events, due to their increased baseline rate. Some observational studies found that this increased risk of serious CV thrombotic events began as early as the first weeks of treatment. The increase in CV thrombotic risk has been observed most consistently at higher doses.

To minimize the potential risk for an adverse CV event in NSAID-treated patients, use the lowest effective dose for the shortest duration possible. Physicians and patients should remain alert for the development of such events, throughout the entire treatment course, even in the absence of previous CV symptoms. Patients should be informed about the symptoms of serious CV events and the steps to take if they occur.

There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious CV thrombotic events associated with NSAID use. The concurrent use of aspirin and an NSAID, such as piroxicam, increases the risk of serious gastrointestinal (GI) events *[see Warnings and Precautions (5.2)]*.

Status Post Coronary Artery Bypass Graft (CABG) Surgery

Two large, controlled clinical trials of a COX-2 selective NSAID for the treatment of pain in the first 10 to 14 days following CABG surgery found an increased incidence of myocardial infarction and stroke. NSAIDs are contraindicated in the setting of CABG *[see Contraindications (4)]*.

Post-MI Patients

Observational studies conducted in the Danish National Registry have demonstrated that patients treated with NSAIDs in the post-MI period were at increased risk of reinfarction, CV-related death, and all-cause mortality beginning in the first week of treatment. In this same cohort, the incidence of death in the first year post-MI was 20 per 100 person years in NSAID-treated patients compared to 12 per 100 person years in non-NSAID exposed patients. Although the absolute rate of death declined somewhat after the first year post-MI, the increased relative risk of death in NSAID users persisted over at least the next four years of follow-up.

Avoid the use of piroxicam in patients with a recent MI unless the benefits are expected to outweigh the risk of recurrent CV thrombotic events. If piroxicam is used in patients with a recent MI, monitor patients for signs of cardiac ischemia.

Gastrointestinal Bleeding, Ulceration, and Perforation

NSAIDs, including piroxicam, cause serious gastrointestinal (GI) adverse events including inflammation, bleeding, ulceration, and perforation of the esophagus, 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. Only one in

five patients who develop a serious upper GI adverse event on NSAID therapy is symptomatic. Upper GI ulcers, gross bleeding, or perforation caused by NSAIDs occurred in approximately 1% of patients treated for 3 to 6 months, and in about 2% to 4% of patients treated for one year. However, even short-term NSAID therapy is not without risk.

Risk Factors for GI Bleeding, Ulceration, and Perforation

Patients with a prior history of peptic ulcer disease and/or GI bleeding who used NSAIDs had a greater than 10-fold increased risk for developing a GI bleed compared to patients without these risk factors. Other factors that increase the risk of GI bleeding in patients treated with NSAIDs include longer duration of NSAID therapy; concomitant use of oral corticosteroids, antiplatelet drugs (such as aspirin), anticoagulants, or selective serotonin reuptake inhibitors (SSRIs); smoking; use of alcohol; older age; and poor general health status. Most postmarketing reports of fatal GI events occurred in elderly or debilitated patients. Additionally, patients with advanced liver disease and/or coagulopathy are at increased risk for GI bleeding.

Strategies to Minimize the GI Risks in NSAID-treated patients:

- Use the lowest effective dosage for the shortest possible duration.
- Avoid administration of more than one NSAID at a time.
- Avoid use in patients at higher risk unless benefits are expected to outweigh the increased risk of bleeding. For such patients, as well as those with active GI bleeding, consider alternate therapies other than NSAIDs.
- Remain alert for signs and symptoms of GI ulceration and bleeding during NSAID therapy.
- If a serious GI adverse event is suspected, promptly initiate evaluation and treatment, and discontinue piroxicam until a serious GI adverse event is ruled out.
- In the setting of concomitant use of low-dose aspirin for cardiac prophylaxis, monitor patients more closely for evidence of GI bleeding

Hepatotoxicity

Elevations of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) (three or more times the upper limit of normal [ULN]) have been reported in approximately 1% of NSAID-treated patients in clinical trials. In addition, rare, sometimes fatal, cases of severe hepatic injury, including fulminant hepatitis, liver necrosis, and hepatic failure have been reported.

Elevations of ALT or AST (less than three times ULN) may occur in up to 15% of patients treated with NSAIDs including piroxicam.

Inform patients of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, diarrhea, pruritus, jaundice, right upper quadrant tenderness, and "flu-like" symptoms). If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash), discontinue piroxicam immediately, and perform a clinical evaluation of the patient.

Hypertension

NSAIDs, including piroxicam, can lead to new onset of hypertension or worsening of preexisting hypertension, either of which may contribute to the increased incidence of CV events. Patients taking angiotensin converting enzyme (ACE) inhibitors, thiazide diuretics, or loop diuretics may have impaired response to these therapies when taking NSAIDs
Monitor blood pressure (BP) during the initiation of NSAID treatment and throughout the course of therapy.

Heart Failure and Edema

The Coxib and traditional NSAID Trialists' Collaboration meta-analysis of randomized controlled trials demonstrated an approximately two-fold increase in hospitalizations for heart failure in COX-2 selective-treated patients and nonselective NSAID-treated patients compared to placebo-treated patients. In a Danish National Registry study of patients with heart failure, NSAID use increased the risk of MI, hospitalization for heart failure, and death.

Additionally, fluid retention and edema have been observed in some patients treated with NSAIDs. Use of piroxicam may blunt the CV effects of several therapeutic agents used to treat these medical conditions (e.g., diuretics, ACE inhibitors, or angiotensin receptor blockers [ARBs]) .
Avoid the use of piroxicam in patients with severe heart failure unless the benefits are expected to outweigh the risk of worsening heart failure. If piroxicam is used in patients with severe heart failure, monitor patients for signs of worsening heart failure.

Renal Toxicity and Hyperkalemia

Renal Toxicity

Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury.

Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of an NSAID may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, dehydration, hypovolemia, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors or ARBs, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state.

No information is available from controlled clinical studies regarding the use of piroxicam in patients with advanced renal disease. The renal effects of piroxicam may hasten the progression of renal dysfunction in patients with preexisting renal disease.

Correct volume status in dehydrated or hypovolemic patients prior to initiating piroxicam. Monitor renal function in patients with renal or hepatic impairment, heart failure, dehydration, or hypovolemia during use of piroxicam . Avoid the use of piroxicam in patients with advanced renal disease unless the benefits are expected to outweigh the

risk of worsening renal function. If piroxicam is used in patients with advanced renal disease, monitor patients for signs of worsening renal function.

Hyperkalemia

Increases in serum potassium concentration, including hyperkalemia, have been reported with use of NSAIDs, even in some patients without renal impairment. In patients with normal renal function, these effects have been attributed to a hyporeninemic-hypoaldosteronism state.

Anaphylactic Reactions

Piroxicam has been associated with anaphylactic reactions in patients with and without known hypersensitivity to piroxicam and in patients with aspirin-sensitive asthma.
Seek emergency help if an anaphylactic reaction occurs.

Exacerbation of Asthma Related to Aspirin Sensitivity

A subpopulation of patients with asthma may have aspirin-sensitive asthma which may include chronic rhinosinusitis complicated by nasal polyps; severe, potentially fatal bronchospasm; and/or intolerance to aspirin and other NSAIDs. Because cross-reactivity between aspirin and other NSAIDs has been reported in such aspirin-sensitive patients, piroxicam is contraindicated in patients with this form of aspirin sensitivity. When piroxicam is used in patients with preexisting asthma (without known aspirin sensitivity), monitor patients for changes in the signs and symptoms of asthma.

Serious Skin Reactions

NSAIDs, including piroxicam, can cause serious skin adverse reactions such as exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. These serious events may occur without warning. Inform patients about the signs and symptoms of serious skin reactions, and to discontinue the use of piroxicam at the first appearance of skin rash or any other sign of hypersensitivity. Piroxicam is contraindicated in patients with previous serious skin reactions to NSAIDs .

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) has been reported in patients taking NSAIDs such as piroxicam. 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, hematological 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 piroxicam and evaluate the patient immediately.

Fetal Toxicity

Premature Closure of Fetal Ductus Arteriosus

Avoid use of NSAIDs, including piroxicam, in pregnant women at about 30 weeks

gestation and later. NSAIDs, including piroxicam, increase the risk of premature closure of the fetal ductus arteriosus at approximately this gestational age.

Oligohydramnios/Neonatal Renal Impairment

Use of NSAIDs, including piroxicam, at about 20 weeks gestation or later in pregnancy may cause fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation.

Oligohydramnios is often, but not always, reversible with treatment discontinuation. Complications of prolonged oligohydramnios may, for example, include limb contractures and delayed lung maturation. In some postmarketing cases of impaired neonatal renal function, invasive procedures such as exchange transfusion or dialysis were required.

If NSAID treatment is necessary between about 20 weeks and 30 weeks gestation, limit piroxicam use to the lowest effective dose and shortest duration possible. Consider ultrasound monitoring of amniotic fluid if piroxicam treatment extends beyond 48 hours. Discontinue piroxicam if oligohydramnios occurs and follow up according to clinical practice .

Hematologic Toxicity

Anemia has occurred in NSAID-treated patients. This may be due to occult or gross blood loss, fluid retention, or an incompletely described effect on erythropoiesis. If a patient treated with piroxicam has any signs or symptoms of anemia, monitor hemoglobin or hematocrit.

NSAIDs, including piroxicam, may increase the risk of bleeding events. Co-morbid conditions such as coagulation disorders, concomitant use of warfarin, other anticoagulants, antiplatelet drugs (e.g., aspirin), SSRIs, and serotonin norepinephrine reuptake inhibitors (SNRIs) may increase this risk. Monitor these patients for signs of bleeding .

Masking of Inflammation and Fever

The pharmacological activity of piroxicam in reducing inflammation, and possibly fever, may diminish the utility of diagnostic signs in detecting infections.

Laboratory Monitoring

Because serious GI bleeding, hepatotoxicity, and renal injury can occur without warning symptoms or signs, consider monitoring patients on long-term NSAID treatment with a complete blood count (CBC) and a chemistry profile periodically .

Ophthalmologic Effects

Because of reports of adverse eye findings with nonsteroidal anti-inflammatory agents, it is recommended that patients who develop visual complaints during treatment with piroxicam have ophthalmic evaluations.

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4.5 Overdosage & Contraindications

OVERDOSE

Symptoms following acute NSAID overdoses have been typically limited to lethargy, drowsiness, nausea, vomiting, and epigastric pain, which are generally reversible with supportive care. Gastrointestinal bleeding has occurred. Hypertension, acute renal failure, respiratory depression, and coma have occurred, but were rare .
Manage patients with symptomatic and supportive care following an NSAID overdose. There are no specific antidotes. Consider emesis and/or activated charcoal (60 grams to 100 grams in adults, 1 gram to 2 grams per kg of body weight in pediatric patients) and/or osmotic cathartic in symptomatic patients seen within four hours of ingestion or in patients with a large overdosage (5 to 10 times the recommended dosage).

The long plasma half-life of piroxicam should be considered when treating an overdose with piroxicam. Forced diuresis, alkalinization of urine, hemodialysis, or hemoperfusion may not be useful due to high protein binding.

CONTRAINDICATIONS

Piroxicam is contraindicated in the following patients:

- Known hypersensitivity (e.g., anaphylactic reactions and serious skin reactions) to piroxicam or any components of the drug product
- History of asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs. Severe, sometimes fatal, anaphylactic reactions to NSAIDs have been reported in such patients
- In the setting of CABG surgery

4.6 Clinical Pharmacology

Mechanism of Action

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

The mechanism of action of piroxicam, like that of other NSAIDs, is not completely understood but involves inhibition of cyclooxygenase (COX-1 and COX-2).

Piroxicam is a potent inhibitor of prostaglandin (PG) synthesis in vitro. Piroxicam concentrations reached during therapy have produced in vivo effects. Prostaglandins sensitize afferent nerves and potentiate the action of bradykinin in inducing pain in animal models. Prostaglandins are mediators of inflammation. Because piroxicam is an inhibitor of prostaglandin synthesis, its mode of action may be due to a decrease of prostaglandins in peripheral tissues.

Pharmacokinetics

General pharmacokinetic characteristics

The pharmacokinetics of piroxicam have been characterized in healthy subjects, special populations and patients. The pharmacokinetics of piroxicam are linear. Proportional increase in exposure is observed with increasing doses. The prolonged half-life (50 hours) results in the maintenance of relatively stable plasma concentrations throughout the day on once daily doses and

significant accumulation upon multiple dosing. Most patients approximate steady state plasma levels within 7 to 12 days. Higher levels, which approximate steady state at two to three weeks, have been observed in patients in whom longer plasma half-lives of piroxicam occurred.

Absorption

Piroxicam is well absorbed following oral administration. Drug plasma concentrations are proportional for 10 mg and 20 mg doses and generally peak within three to five hours after administration. A single 20 mg dose generally produces peak piroxicam plasma levels of 1.5 mcg/mL to 2 mcg/mL, while maximum drug plasma concentrations, after repeated daily administration of 20 mg piroxicam, usually stabilize at 3 mcg/mL to 8 mcg/mL.

With food there is a slight delay in the rate but not the extent of absorption following oral administration. The concomitant administration of antacids (aluminum hydroxide or aluminum hydroxide with magnesium hydroxide) have been shown to have no effect on the plasma levels of orally administered piroxicam.

Distribution

The apparent volume of distribution of piroxicam is approximately 0.14 L/kg. Ninety nine percent of plasma piroxicam is bound to plasma proteins. Piroxicam is excreted into human milk. The presence in breast milk has been determined during initial and long term conditions (52 days). Piroxicam appeared in breast milk at approximately 1% to 3% of the maternal concentration. No accumulation of piroxicam occurred in milk relative to that in plasma during treatment.

Elimination

Metabolism

Metabolism of piroxicam occurs by hydroxylation at the 5 position of the pyridyl side chain and conjugation of this product; by cyclodehydration; and by a sequence of reactions involving hydrolysis of the amide linkage, decarboxylation, ring contraction, and N-demethylation. In vitro studies indicate cytochrome P4502C9 (CYP2C9) as the main enzyme involved in the formation to the 5′-hydroxy-piroxicam, the major metabolite. The biotransformation products of piroxicam metabolism are reported to not have any anti-inflammatory activity.

Higher systemic exposure of piroxicam has been noted in subjects with CYP2C9 polymorphisms compared to normal metabolizer type subjects.

Excretion

Piroxicam and its biotransformation products are excreted in urine and feces, with about twice as much appearing in the urine as in the feces. Approximately 5% of a piroxicam dose is excreted unchanged. The plasma half-life (t½) for piroxicam is approximately 50 hours.

Specific Populations

Pediatric

Piroxicam has not been investigated in pediatric patients.

Race

Pharmacokinetic differences due to race have not been identified.

Hepatic Impairment

The effects of hepatic disease on piroxicam pharmacokinetics have not been established. However, a substantial portion of piroxicam elimination occurs by hepatic metabolism. Consequently,

patients with hepatic disease may require reduced doses of piroxicam as compared to patients with normal hepatic function.

Renal Impairment

Piroxicam pharmacokinetics have been investigated in patients with renal insufficiency. Studies indicate patients with mild to moderate renal impairment may not require dosing adjustments. However, the pharmacokinetic properties of piroxicam in patients with severe renal insufficiency or those receiving hemodialysis are not known.

Drug Interaction Studies

Antacids

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

Aspirin

When piroxicam was administered with aspirin, its protein binding was reduced, although the clearance of free piroxicam was not altered. Plasma levels of piroxicam were decreased to approximately 80% of their normal values when piroxicam was administered (20 mg/day) in conjunction with aspirin (3900 mg/day). The clinical significance of this interaction is not known.

Pharmacogenomics

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 a single oral 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 1% in the population at large; however, frequencies as high as 5.7% have been reported in certain ethnic groups.

Poor Metabolizers of CYP2C9 Substrates: In patients who are known or suspected to be poor CYP2C9 metabolizers based on genotype or previous history/experience with other CYP2C9 substrates (such as warfarin and phenytoin) consider dose reduction as they may have abnormally high plasma levels due to reduced metabolic clearance.

4.7 Nonclinical Toxicology

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Long-term animal studies have not been conducted to characterize the carcinogenic potential of piroxicam.

Mutagenesis

Piroxicam was not mutagenic in an Ames bacterial reverse mutation assay, or in a dominant lethal mutation assay in mice, and was not clastogenic in an in vivo chromosome aberration assay in mice.

Impairment of Fertility

Reproductive studies in which rats were administered piroxicam at doses of 2, 5, or 10 mg/kg/day (up to 5 times the MRHD of 20 mg based on mg/m^2 body surface area [BSA]) revealed no impairment of male or female fertility.

6. PHARMACEUTICAL PARTICULARS

List of Excipients

Magnesium Stearate

sodium dodecyl sulfate

Starch

6.1 Incompatibilities

None

6.2 Shelf life

36 months

6.3 Special precautions for storage

Store at a temperature not exceeding 30 ℃ in a dry place, protected from light.

6.4 Nature and contents of container

The content of this product is white crystalline powder.

The product is taken into the Alu / PVC blister foil for medicine, then put into the box. Boxes will be then sealed and labeled, successively be packed in the carton with 1 leaflet, packed in transport shipper, and finally the shipper will seal and strap.

6.5 Special precautions for disposal

No special requirements

7. REGISTRANT

MARKETING AUTHORISATION HOLDER

Liaoning Huarui Union Pharmaceutical Co., Ltd.

MANUFACTURING SITE ADDRESS

Yuanqu Road, No.1 Tongyuanpu Economic Development Zone, Dandong City, Liaoning Province

8.DATE OF REVISION OF THE TEXT

11/2021