PIROXICAM- piroxicam capsule
DIRECT RX

PIROXICAM

WARNING: RISK OF SERIOUS CARDIOVASCULAR AND GASTROINTESTINAL EVENTS

Cardiovascular Thrombotic Events

Nonsteroidal anti-inflammatory drugs (NSAIDs) cause an increased risk of serious cardiovascular thrombotic events, including myocardial infarction and stroke, which can be fatal. This risk may occur early in treatment and may increase with duration of use. [see WARNINGS AND PRECAUTIONS (5.1)] .
Piroxicam Capsules USP is contraindicated in the setting of coronary artery bypass graft (CABG) surgery [see CONTRAINDICATIONS (4) and WARNINGS AND PRECAUTIONS (5.1)].

Gastrointestinal Bleeding, Ulceration, and Perforation

NSAIDs cause an increased risk of serious gastrointestinal (GI) adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients and patients with a prior history of peptic ulcer disease and/or GI bleeding are at greater risk for serious GI events [see WARNINGS AND PRECAUTIONS (5.2)] .

Piroxicam Capsules USP is indicated:

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

Carefully consider the potential benefits and risks of Piroxicam Capsules USP and other treatment options before deciding to use Piroxicam Capsules USP. Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals [see WARNINGS AND PRECAUTIONS (5)].

After observing the response to initial therapy with Piroxicam Capsules USP, 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 Capsules USP, steady-state blood levels are not reached for 7–12 days. Therefore, although the therapeutic effects of Piroxicam Capsules USP 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.

Piroxicam Capsules USP:

10 mg are maroon cap and blue body imprinted with '10' on cap and 'FPL' on body in white ink

20 mg are maroon cap and body imprinted with '20' on cap and 'FPL' on body in white ink

Piroxicam Capsules USP 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 [see WARNINGS AND PRECAUTIONS (5.7 , 5.9)]
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 [see WARNINGS AND PRECAUTIONS (5.7 , 5.8)]
In the setting of coronary artery bypass graft (CABG) surgery [see WARNINGS AND

PRECAUTIONS (5.1)]

5.1 Cardiovascular Thrombotic Events

Clinical trials of several 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 10–14 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 Capsules USP in patients with a recent MI unless the benefits are expected to outweigh the risk of recurrent CV thrombotic events. If Piroxicam Capsules USP is used in patients with a recent MI, monitor patients for signs of cardiac ischemia.

5.2 Gastrointestinal Bleeding, Ulceration, and Perforation

NSAIDs, including Piroxicam Capsules USP, 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 3–6 months, and in about 2%-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, 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 Capsules USP 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 [see DRUG INTERACTIONS (7)].

5.3 Hepatotoxicity

Elevations of ALT or 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, etc.), discontinue Piroxicam Capsules USP immediately, and perform a clinical evaluation of the patient.

5.4 Hypertension

NSAIDs, including Piroxicam Capsules USP, 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 [see DRUG INTERACTIONS (7)].

Monitor blood pressure (BP) during the initiation of NSAID treatment and throughout the course of therapy.

5.5 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]) [see DRUG INTERACTIONS (7)].

Avoid the use of Piroxicam Capsules USP in patients with severe heart failure unless the benefits are expected to outweigh the risk of worsening heart failure. If Piroxicam Capsules USP is used in patients with severe heart failure, monitor patients for signs of worsening heart failure.

5.6 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 Capsules USP in patients with advanced renal disease. The renal effects of Piroxicam Capsules USP 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 Capsules USP. Monitor renal function in patients with renal or hepatic impairment, heart failure, dehydration, or hypovolemia during use of Piroxicam Capsules USP [see DRUG INTERACTIONS (7)]. Avoid the use of Piroxicam Capsules USP in patients with advanced renal disease unless the benefits are expected to outweigh the risk of worsening renal function. If Piroxicam Capsules USP 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.

5.7 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 [see CONTRAINDICATIONS (4) and WARNINGS AND PRECAUTIONS (5.8)].

Seek emergency help if an anaphylactic reaction occurs.

5.8 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 Capsules USP is contraindicated in patients with this form of aspirin sensitivity [see CONTRAINDICATIONS (4)]. When Piroxicam Capsules USP is used in patients with preexisting asthma (without known aspirin sensitivity), monitor patients for changes in the signs and symptoms of asthma.

5.9 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 Capsules USP at the first appearance of skin rash or any other sign of hypersensitivity. Piroxicam Capsules USP is contraindicated in patients with previous serious skin reactions to NSAIDs [see CONTRAINDICATIONS (4)].

5.10 Premature Closure of Fetal Ductus Arteriosus

Piroxicam may cause premature closure of the fetal ductus arteriosus. Avoid use of NSAIDs, including Piroxicam Capsules USP, in pregnant women starting at 30 weeks of gestation (third trimester) [see USE IN SPECIFIC POPULATIONS (8.1)].

5.11 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 Capsules USP has any signs or symptoms of anemia, monitor hemoglobin or hematocrit.

NSAIDs, including Piroxicam Capsules USP, may increase the risk of bleeding events. Co-morbid conditions such as coagulation disorders, concomitant use of warfarin, other anticoagulants, antiplatelet agents (e.g., aspirin), serotonin reuptake inhibitors (SSRIs), and serotonin norepinephrine reuptake inhibitors (SNRIs) may increase this risk. Monitor these patients for signs of bleeding [see DRUG INTERACTIONS (7)].

5.12 Masking of Inflammation and Fever

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

5.13 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 CBC and a chemistry profile periodically [see WARNINGS AND PRECAUTIONS (5.2, 5.3, 5.6)].

5.14 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 Capsules USP have ophthalmic evaluations.

The following adverse reactions are discussed in greater detail in other sections of the labeling:

Cardiovascular Thrombotic Events [see WARNINGS AND PRECAUTIONS (5.1)]
GI Bleeding, Ulceration and Perforation [see WARNINGS AND PRECAUTIONS (5.2)]
Hepatotoxicity [see WARNINGS AND PRECAUTIONS (5.3)]
Hypertension [see WARNINGS AND PRECAUTIONS (5.4)]
Heart Failure and Edema [see WARNINGS AND PRECAUTIONS (5.5)]
Renal Toxicity and Hyperkalemia [see WARNINGS AND PRECAUTIONS (5.6)]
Anaphylactic Reactions [see WARNINGS AND PRECAUTIONS (5.7)]
Serious Skin Reactions [see WARNINGS AND PRECAUTIONS (5.9)]
Hematologic Toxicity [see WARNINGS AND PRECAUTIONS (5.11)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In patients taking Piroxicam Capsules USP or other NSAIDs, the most frequently reported adverse experiences occurring in approximately 1–10% of patients are:

Cardiovascular System: Edema

Digestive System: Anorexia, abdominal pain, constipation, diarrhea, flatulence, nausea, vomiting

Nervous System: Dizziness, headache, vertigo

Skin and Appendages: Pruritus, rash

Special Senses: Tinnitus

Additional adverse experiences reported occasionally include:

Cardiovascular System: Palpitations

Digestive System: Stomatitis

Nervous System: Drowsiness

Special Senses: Blurred vision

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of Piroxicam Capsules USP. 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

See Table 1 for clinically significant drug interactions with piroxicam.

Table 1: 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 Capsules USP with anticoagulants (e.g., warfarin), antiplatelet agents (e.g., aspirin), selective serotonin reuptake inhibitors (SSRIs), and serotonin norepinephrine reuptake inhibitors (SNRIs) for signs of bleeding [see WARNINGS AND PRECAUTIONS (5.11)].

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 [see WARNINGS AND PRECAUTIONS (5.2)].

Intervention:
Concomitant use of Piroxicam Capsules USP and analgesic doses of aspirin is not generally recommended because of the increased risk of bleeding [see WARNINGS AND PRECAUTIONS (5.11)]. Piroxicam Capsules USP 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 angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), or beta-blockers (including propranolol).

In patients who are elderly, volume-depleted (including those on diuretic therapy), or have renal impairment, co-administration 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 Capsules USP and ACE-inhibitors, ARBs, or beta-blockers, monitor blood pressure to ensure that the desired blood pressure is obtained. During concomitant use of Piroxicam Capsules USP and ACE-inhibitors or ARBs in patients who are elderly, volume-depleted, or have impaired renal function, monitor for signs of worsening renal function [see WARNINGS AND PRECAUTIONS (5.6)]. 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 Impact:
Clinical studies, as well as post-marketing observations, showed that NSAIDs reduced 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 Capsules USP with diuretics, observe patients for signs of worsening renal function, in addition to assuring diuretic efficacy including antihypertensive effects [see WARNINGS AND PRECAUTIONS (5.6)].

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 Capsules USP 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 Capsules USP 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 Capsules USP and methotrexate, monitor patients for methotrexate toxicity.

Cyclosporine

Clinical Impact:

Concomitant use of Piroxicam Capsules USP and cyclosporine may increase cyclosporine's nephrotoxicity.

Intervention:

During concomitant use of Piroxicam Capsules USP and cyclosporine, monitor patients for signs of worsening renal function.

NSAIDs and Salicylates

Clinical Impact:

Concomitant use of piroxicam with other NSAIDs or salicylates (e.g., diflunisal, salsalate) increases the risk of GI toxicity, with little or no increase in efficacy [see WARNINGS AND PRECAUTIONS (5.2)].

Intervention:

The concomitant use of piroxicam with other NSAIDs or salicylates is not recommended.

Pemetrexed

Clinical Impact:

Concomitant use of Piroxicam Capsules USP 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 Capsules USP 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 Capsules USP 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 Capsules USP to patients on other highly protein bound drugs.

Corticosteroids

Clinical Impact:

Concomitant use of corticosteroids with Piroxicam Capsules USP may increase the risk of GI ulceration or bleeding.

Intervention:

Monitor patients with concomitant use of Piroxicam Capsules USP with corticosteroids for signs of bleeding [see WARNINGS AND PRECAUTIONS (5.2)].

8.1 Pregnancy

Pregnancy Category C prior to 30 weeks gestation; Category D starting at 30 weeks gestation.

Risk Summary

Use of NSAIDs, including Piroxicam Capsules USP, during the third trimester of pregnancy increases the risk of premature closure of the fetal ductus arteriosus. Avoid use of NSAIDs, including Piroxicam Capsules USP, in pregnant women starting at 30 weeks of gestation (third trimester).

There are no adequate and well-controlled studies of Piroxicam Capsules USP in pregnant women.

Data from observational studies regarding potential embryofetal risks of NSAID use in women in the first or second trimesters of pregnancy are inconclusive. In the general U.S. population, all clinically recognized pregnancies, regardless of drug exposure, have a background rate of 2-4% for major malformations, and 15-20% for pregnancy loss. In animal reproduction studies in rats and rabbits, there was no evidence of teratogenicity at exposures up to 5 and 10 times the MRHD, respectively. In rat studies with piroxicam, fetotoxicity (postimplantation loss) was observed at exposures 2 times the MRHD, and delayed parturition and an increased incidence of stillbirth were noted at doses equivalent to the MRHD of piroxicam. Based on animal data, prostaglandins have been shown to have an important role in endometrial vascular permeability, blastocyst implantation, and decidualization. In animal studies, administration of prostaglandin synthesis inhibitors such as piroxicam, resulted in increased pre- and post-implantation loss.

Clinical Considerations

Labor or Delivery

There are no studies on the effects of Piroxicam Capsules USP during labor or delivery. In animal studies, NSAIDS, including piroxicam inhibit prostaglandin synthesis, cause delayed parturition, and increase the incidence of stillbirth.

Data

Animal data

Pregnant rats administered piroxicam at 2, 5, or 10 mg/kg/day during the period of organogenesis (Gestation Days 6 to 15) demonstrated increased post-implantation losses with 5 and 10 mg/kg/day of piroxicam (equivalent to 2 and 5 times the maximum recommended human dose [MRHD], of 20 mg respectively, based on a mg/m2 body surface area [BSA]). There were no drug-related developmental abnormalities noted in offspring. Gastrointestinal tract toxicity was increased in pregnant rats in the last trimester of pregnancy compared to non-pregnant rats or rats in earlier trimesters of pregnancy. Pregnant rabbits administered piroxicam at 2, 5, or 10 mg/kg/day during the period of organogenesis (Gestation Days 7 to 18) demonstrated no drug-related developmental abnormalities in offspring (up to 10 times the MRHD based on a mg/m2

BSA).

In a pre- and post-natal development study in which pregnant rats were administered piroxicam at 2, 5, or 10 mg/kg/day on Gestation Day 15 through delivery and weaning of offspring, reduced weight gain and death were observed in dams at 10 mg/kg/day (5 times the MRHD based on a mg/m2 BSA) starting on Gestation Day 20. Treated dams revealed peritonitis, adhesions, gastric bleeding, hemorrhagic enteritis and dead fetuses in utero. Parturition was delayed and there was an increased incidence of stillbirth in all piroxicam-treated groups (at doses equivalent to the MRHD). Postnatal development could not be reliably assessed due to the absence of maternal care secondary to severe maternal toxicity.

8.2 Lactation

Risk Summary

Limited data from 2 published reports that included a total of 6 breastfeeding women and 2 infants showed piroxicam is excreted in human milk at approximately 1% to 3% of the maternal concentration.

No accumulation of piroxicam occurred in milk relative to that in maternal plasma during treatment. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Piroxicam Capsules USP and any potential adverse effects on the breastfed infant from the Piroxicam Capsules USP or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

Infertility

Females

Based on the mechanism of action, the use of prostaglandin-mediated NSAIDs, including Piroxicam Capsules USP, may delay or prevent rupture of ovarian follicles, which has been associated with reversible infertility in some women. Published animal studies have shown that administration of prostaglandin synthesis inhibitors has the potential to disrupt prostaglandin-mediated follicular rupture required for ovulation. Small studies in women treated with NSAIDs have also shown a reversible delay in ovulation. Consider withdrawal of NSAIDs, including Piroxicam Capsules USP, in women who have difficulties conceiving or who are undergoing investigation of infertility.

8.4 Pediatric Use

Piroxicam Capsules USP has not been investigated in pediatric patients. The safety and effectiveness of Piroxicam Capsules USP have not been established.

8.5 Geriatric Use

Elderly patients, compared to younger patients, are at greater risk for NSAID-associated serious cardiovascular, gastrointestinal, and/or renal adverse reactions. If the anticipated benefit for the elderly patient outweighs these potential risks, start dosing at the low end of the dosing range, and monitor patients for adverse effects [see WARNINGS AND PRECAUTIONS (5.1, 5.2, 5.3, 5.6, 5.13)].

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 [see WARNINGS AND PRECAUTIONS (5.1, 5.2, 5.4, 5.6)].

Manage patients with symptomatic and supportive care following an NSAID overdose. There are no specific antidotes. Consider emesis and/or activated charcoal (60–100 grams in adults, 1–2 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.

For additional information about overdosage treatment contact a poison control center (1-800-222-1222).

Piroxicam Capsules USP is a nonsteroidal anti-inflammatory drug, available as maroon and blue # 10 mg capsules and maroon # 20 mg capsules for oral administration. The chemical name is 4-hydroxyl-2-methyl-N-2 pyridinyl-2H-1,2,-benzothiazine-3-carboxamide 1,1-dioxide. The molecular weight is 331.35. Its molecular formula is C15H13N3O4S, and it has the following chemical structure.

[piroxicam-nivagen-figure-01]

Piroxicam occurs as a white crystalline solid, sparingly soluble in water, dilute acid, and most organic solvents. It is slightly soluble in alcohol and in aqueous solutions. It exhibits a weakly acidic 4-hydroxy proton (pKa 5.1) and a weakly basic pyridyl nitrogen (pKa 1.8).

The inactive ingredients in Piroxicam Capsules USP include: colloidal anhydrous silica, corn starch, FD&C Blue # 1, FD&C Red #40, FD&C Yellow #6, lactose monohydrate, magnesium stearate, sodium lauryl sulfate.

12.1 Mechanism of Action

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

The mechanism of action of Piroxicam Capsules USP, 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.

12.3 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 7–12 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 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 to 2 mcg/mL, while maximum drug plasma concentrations, after repeated daily administration of 20 mg piroxicam, usually stabilize at 3–8 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 [see CLINICAL PHARMACOLOGY (12.5)]. 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 [see CLINICAL PHARMACOLOGY (12.5)].

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 Capsules USP 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 Capsules USP was not altered. Plasma levels of piroxicam were decreased to approximately 80% of their normal values when Piroxicam Capsules USP was administered (20 mg/day) in conjunction with aspirin (3900 mg/day). The clinical significance of this interaction is not known [see DRUG INTERACTIONS (7)].

12.5 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.

13.1 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 maximum recommended human dose [MRHD] of 20 mg based on mg/m2 body surface area [BSA]) revealed no impairment of male or female fertility.

In controlled clinical trials, the effectiveness of Piroxicam Capsules USP has been established for both acute exacerbations and long term management of rheumatoid arthritis and osteoarthritis.

The therapeutic effects of Piroxicam Capsules USP are evident early in the treatment of both diseases with a progressive increase in response over several (8–12) weeks. Efficacy is seen in terms of pain relief and, when present, subsidence of inflammation.

Doses of 20 mg/day Piroxicam Capsules USP display a therapeutic effect comparable to therapeutic doses of aspirin, with a lower incidence of minor gastrointestinal effects and tinnitus.

Piroxicam Capsules USP has been administered concomitantly with fixed doses of gold and corticosteroids. The existence of a "steroid sparing" effect has not been adequately studied to date.

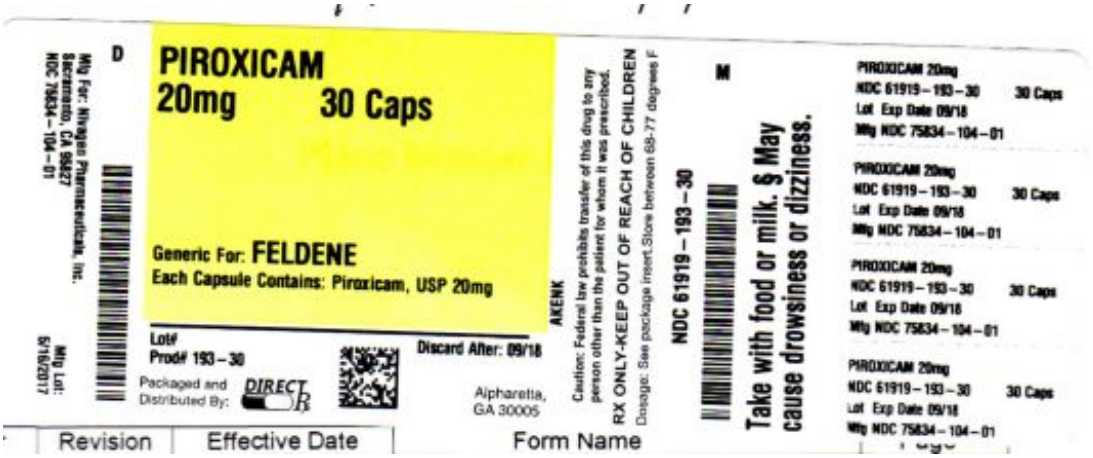
Piroxicam Capsules USP, 10 mg are maroon cap and blue body imprinted with '10' on cap and 'FPL' on body in white ink, supplied as:

Piroxicam Capsules USP, 20 mg are maroon cap and body imprinted with '20' on cap and 'FPL' on body in white ink, supplied as:

Storage

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

Dispense in tight, light-resistant containers.



PIROXICAM

piroxicam capsule

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:61919-193(NDC:75834-104)
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
PIROXICAM (UNII: 13T4O6VMAM) (PIROXICAM - UNII:13T4O6VMAM)	PIROXICAM	20 mg

Inactive Ingredients	
Ingredient Name	**Strength**
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
FD&C RED NO. 40 (UNII: WZB9127XOA)	
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
SODIUM LAURYL SULFATE (UNII: 368GB5141J)	
STARCH, CORN (UNII: O8232NY3SJ)	
FD&C BLUE NO. 1 (UNII: H3R47K3TBD)	
FD&C YELLOW NO. 6 (UNII: H77VEI93A8)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	

Product Characteristics			
Color	red	**Score**	no score
Shape	CAPSULE	**Size**	18mm
Flavor		**Imprint Code**	20;FPL
Contains			

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:61919-193-30	30 in 1 BOTTLE; Type 0: Not a Combination Product	07/18/2017	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA207938	07/18/2017	

Labeler - DIRECT RX (079254320)

Registrant - DIRECT RX (079254320)

Establishment

Name	Address	ID/FEI	Business Operations
DIRECT RX		079254320	repack(61919-193)