

PRODUCT MONOGRAPH

^{Pr}**APO-PIROXICAM**

Piroxicam, USP

10 mg and 20 mg Capsules

Apotex Standard

Nonsteroidal Anti-inflammatory Drug (NSAID)

**APOTEX INC.
150 Signet Drive
Weston, Ontario
M9L 1T9**

**DATE OF REVISION:
June 23, 2010**

Control Number: 137970

Table of Contents

PART I: HEALTH PROFESSIONAL INFORMATION..... 3

SUMMARY PRODUCT INFORMATION 3

INDICATIONS AND CLINICAL USE 3

CONTRAINDICATIONS 4

WARNINGS AND PRECAUTIONS 5

ADVERSE REACTIONS 15

DRUG INTERACTIONS 19

DOSAGE AND ADMINISTRATION 23

OVERDOSAGE..... 24

ACTION AND CLINICAL PHARMACOLOGY..... 24

STORAGE AND STABILITY 26

DOSAGE FORMS, COMPOSITION AND PACKAGING 26

PART II: SCIENTIFIC INFORMATION 27

PHARMACEUTICAL INFORMATION 27

CLINICAL TRIALS 27

DETAILED PHARMACOLOGY 29

TOXICOLOGY 29

REFERENCES..... 32

PART III: CONSUMER INFORMATION..... 34

Pr **APO-PIROXICAM**
Piroxicam, USP

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Capsules 10 mg and 20 mg	Lactose and Gelatin <i>For a complete listing see Dosage Forms, Composition and Packaging section.</i>

INDICATIONS AND CLINICAL USE

APO-PIROXICAM (piroxicam) is indicated for the symptomatic treatment of:

- rheumatoid arthritis,
- osteoarthritis (degenerative joint disease), and
- ankylosing spondylitis.

Throughout this document, the term NSAIDs refers to both non-selective NSAIDs and selective COX-2 inhibitor NSAIDs, unless otherwise indicated.

For patients with an increased risk of developing CV and/or GI adverse events, other management strategies that do NOT include the use of NSAIDs should be considered first. (See Contraindications and Warnings and Precautions)

Use of APO-PIROXICAM should be limited to the lowest effective dose for the shortest possible duration of treatment in order to minimize the potential risk for cardiovascular or gastrointestinal adverse events. (See Contraindications and Warnings and Precautions)

APO-PIROXICAM, as a NSAID, does NOT treat clinical disease or prevent its progression.

APO-PIROXICAM, as a NSAID, only relieves symptoms and decreases inflammation for as long as the patient continues to take it.

Geriatrics (> 65 years of age): Evidence from clinical studies and post-market experience suggests that use in the geriatric population is associated with differences in safety (See **Warnings and Precautions**).

Pediatrics (< 16 years of age): Safety and efficacy have not been established in the pediatric population.

CONTRAINDICATIONS

APO-PIROXICAM is contraindicated in:

- the peri-operative setting of coronary artery bypass graft surgery (CABG). Although APO-PIROXICAM has NOT been studied in this patient population, a selective COX-2 inhibitor NSAID studied in such a setting has led to an increased incidence of cardiovascular/thromboembolic events, deep surgical infections and sternal wound complications.
- the third trimester of pregnancy, because of risk of premature closure of the ductus arteriosus and prolonged parturition
- women who are breastfeeding, because of the potential for serious adverse reactions in nursing infants
- severe uncontrolled heart failure
- known hypersensitivity to Piroxicam or to any of the components/excipients of APO-PIROXICAM.
- history of asthma, urticaria, or allergic-type reactions after taking acetylsalicylic acid (ASA) or other NSAIDs (i.e. complete or partial syndrome of ASA-intolerance - rhinosinusitis, urticaria/ angioedema, nasal polyps, asthma). Fatal anaphylactoid reactions have occurred in such individuals. Individuals with the above medical problems are at risk of a severe reaction even if they have taken NSAIDs in the past without any adverse reaction. The potential for cross-reactivity between different NSAIDs must be kept in mind (see **Warnings and Precautions – Hypersensitivity Reactions – Anaphylactoid Reactions**).
- active gastric / duodenal /peptic ulcer or active inflammatory disease of the gastrointestinal system, active GI bleeding or patients with a recent or recurrent history of these conditions
- cerebrovascular bleeding or other bleeding disorders
- inflammatory bowel disease
- severe liver impairment or active liver disease
- severe renal impairment (creatinine clearance <30 mL/min or 0.5 mL/sec) or deteriorating renal disease (individuals with lesser degrees of renal impairment are at risk

of deterioration of their renal function when prescribed NSAIDs and must be monitored) (see **Warnings and Precautions - Renal**)

- known hyperkalemia (see **Warnings and Precautions - Renal - Fluid and Electrolyte Balance**)
- children and adolescents less than 16 years of age

WARNINGS AND PRECAUTIONS

Risk of Cardiovascular (CV) Adverse Events: Ischemic Heart Disease, Cerebrovascular Disease, Congestive Heart Failure (NYHA II-IV) (See Warnings and Precautions - Cardiovascular).

APO-PIROXICAM is a non-steroidal anti-inflammatory drug (NSAID). Use of some NSAIDs is associated with an increased incidence of cardiovascular adverse events (such as myocardial infarction, stroke or thrombotic events) which can be fatal. The risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk.

Caution should be exercised in prescribing APO-PIROXICAM to any patient with ischemic heart disease (including but NOT limited to acute myocardial infarction, history of myocardial infarction and/or angina), cerebrovascular disease (including but NOT limited to stroke, cerebrovascular accident, transient ischemic attacks and/or amaurosis fugax) and/or congestive heart failure (NYHA II-IV).

Use of APO-PIROXICAM, can promote sodium retention in a dose-dependent manner, through a renal mechanism, which can result in increased blood pressure and/or exacerbation of congestive heart failure. (see also Warnings and Precautions - *Renal – Fluid and Electrolyte Balance*)

Randomized clinical trials with APO-PIROXICAM have not been designed to detect differences in cardiovascular events in a chronic setting. Therefore, caution should be exercised when prescribing APO-PIROXICAM.

Risk of Gastrointestinal (GI) Adverse Events (see Warnings and Precautions – *Gastrointestinal*)

Use of APO-PIROXICAM, is associated with an increased incidence of gastrointestinal adverse events (such as peptic/duodenal ulceration, perforation, obstruction and gastrointestinal bleeding).

General

Frail or debilitated patients may tolerate side effects less well and therefore special care should be taken in treating this population. **To minimize the potential risk for an adverse event, the lowest effective dose should be used for the shortest possible duration.** 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. For high risk patients, alternate therapies that do not involve NSAIDs should be considered.

APO-PIROXICAM is NOT recommended for use with other NSAIDs, with the exception of low-dose ASA for cardiovascular prophylaxis, because of the absence of any evidence demonstrating synergistic benefits and the potential for additive adverse reactions. (See **Drug Interactions - Drug/Drug Interactions - Acetylsalicylic acid (ASA) or other NSAIDs**).

Carcinogenesis and Mutagenesis

See Toxicology Section.

Cardiovascular

APO-PIROXICAM is a non-steroidal anti-inflammatory drug (NSAID). Use of some NSAIDs is associated with an increased incidence of cardiovascular adverse events (such as myocardial infarction, stroke or thrombotic events) which can be fatal. The risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk.

Caution should be exercised in prescribing APO-PIROXICAM to patients with risk factors for cardiovascular disease, cerebrovascular disease or renal disease, such as any of the following (NOT an exhaustive list)

- **Hypertension**
- **Dyslipidemia / Hyperlipidemia**
- **Diabetes Mellitus**
- **Congestive Heart Failure (NYHA I)**
- **Coronary Artery Disease (Atherosclerosis)**
- **Peripheral Arterial Disease**
- **Smoking**
- **Creatinine Clearance < 60 mL/min or 1 mL/sec**

Use of NSAIDs, such as APO-PIROXICAM, can lead to new hypertension or can worsen preexisting hypertension, either of which may increase the risk of cardiovascular events as described above. Thus blood pressure should be monitored regularly. Consideration should be given to discontinuing APO-PIROXICAM should hypertension either develop or worsen with its use.

Use of NSAIDs, such as APO-PIROXICAM, can induce fluid retention and edema, and may exacerbate congestive heart failure, through a renally-mediated mechanism. (See **Warnings and Precautions - Renal - Fluid and Electrolyte Balance**).

For patients with a high risk of developing an adverse CV event, other management strategies that do NOT include the use of NSAIDs should be considered first. **To minimize the potential risk for an adverse CV event, the lowest effective dose should be used for the shortest possible duration.**

Endocrine and Metabolism:

Corticosteroids:

APO-PIROXICAM (piroxicam) is NOT a substitute for corticosteroids. It does NOT treat corticosteroid insufficiency. Abrupt discontinuation of corticosteroids may lead to exacerbation of corticosteroid-responsive illness. Patients on prolonged corticosteroid therapy should have their therapy tapered slowly if a decision is made to discontinue corticosteroids. (see **Drug Interactions - Drug-Drug Interactions - Glucocorticoids**)

Gastrointestinal (GI)

Serious GI toxicity (sometimes fatal), such as peptic / duodenal ulceration, inflammation, perforation, obstruction and gastrointestinal bleeding can occur at any time, with or without warning symptoms, in patients treated with NSAIDs, including APO-PIROXICAM. Minor upper GI problems, such as dyspepsia, commonly occur at any time. Health care providers should remain alert for ulceration and bleeding in patients treated with APO-PIROXICAM, even in the absence of previous GI tract symptoms. Most spontaneous reports of fatal GI events are in elderly or debilitated patients and therefore special care should be taken in treating this population. **To minimize the potential risk for an adverse GI event, the lowest effective dose should be used for the shortest possible duration.** For high risk patients, alternate therapies that do not involve NSAIDs should be considered. (see **Warnings and Precautions - Special Populations - Geriatrics**)

Evidence from epidemiological studies suggests that APO-PIROXICAM (piroxicam) is associated with a high risk of gastrointestinal toxicity relative to some other NSAIDs.

Patients should be informed about the signs and/or symptoms of serious GI toxicity and instructed to discontinue using APO-PIROXICAM and seek emergency medical attention if they experience any such symptoms. The utility of periodic laboratory monitoring has NOT been demonstrated, nor has it been adequately assessed. Most patients who develop a serious upper GI adverse event on NSAID therapy have no symptoms. Upper GI ulcers, gross bleeding or perforation, caused by NSAIDs, appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year. These trends continue, thus increasing the likelihood of developing a serious GI event at some time during the course of therapy. Even short-term therapy has its risks.

Caution should be taken if prescribing APO-PIROXICAM to patients with a prior history of peptic / duodenal ulcer disease or gastrointestinal bleeding as these individuals have a greater than 10-fold higher risk for developing a GI bleed when taking a NSAID than patients with neither of these risk factors. Other risk factors for GI ulceration and bleeding include the following: *Helicobacter pylori* infection, increased age, prolonged use of NSAID therapy, excess alcohol intake, smoking, poor general health status or concomitant therapy with any of the following:

- Anti-coagulants (e.g. warfarin)
- Anti-platelet agents (e.g. ASA, clopidogrel)
- Oral corticosteroids (e.g. prednisone)
- Selective Serotonin Reuptake Inhibitors (SSRIs) (e.g. citalopram, fluoxetine, paroxetine, sertraline)

Gastrointestinal side effects are dose-related and doses of piroxicam greater than 20 mg daily should not be used. The minimum maintenance dose needed to control symptoms is recommended.

Genitourinary

Some NSAIDs are associated with persistent urinary symptoms (bladder pain, dysuria, urinary frequency), hematuria or cystitis. The onset of these symptoms may occur at any time after the initiation of therapy with an NSAID. Should urinary symptoms occur, in the absence of an alternate explanation, treatment with APO-PIROXICAM should be stopped to ascertain if symptoms disappear. This should be done before urological investigations or treatments are carried out.

Hematologic

NSAIDs inhibiting prostaglandin biosynthesis interfere with platelet function to varying degrees; patients who may be adversely affected by such an action, such as those on anti-coagulants or suffering from haemophilia or platelet disorders should be carefully observed when APO-PIROXICAM is administered.

Anti-coagulants:

Piroxicam is highly protein-bound, and therefore, might be expected to displace other protein-bound drugs. The physician should closely monitor dosage requirements of coumarin anticoagulants and other drugs that are highly protein-bound when these are administered concomitantly with piroxicam.

Numerous studies have shown that the concomitant use of NSAIDs and anti-coagulants increases the risk of bleeding. Concurrent therapy of APO-PIROXICAM with warfarin requires close monitoring of the international normalized ratio (INR). Even with therapeutic INR monitoring, increased bleeding may occur.

Anti-platelet Effects

NSAIDs inhibit platelet aggregation and have been shown to prolong bleeding time in some patients. Unlike acetylsalicylic acid (ASA), their effect on platelet function is quantitatively less, or of shorter duration, and is reversible.

APO-PIROXICAM and other NSAIDs have no proven efficacy as anti-platelet agents and should NOT be used as a substitute for ASA or other anti-platelet agents for prophylaxis of cardiovascular thromboembolic diseases. Anti-platelet therapies (e.g. ASA) should NOT be discontinued. There is some evidence that use of NSAIDs with ASA can markedly attenuate the cardioprotective effects of ASA. (see **Drug Interactions - Drug-Drug Interactions - Acetylsalicylic Acid (ASA) or other NSAIDs**)

Concomitant administration of APO-PIROXICAM with low dose ASA increases the risk of GI ulceration and associated complications.

Blood dyscrasias:

Blood dyscrasias (such as neutropenia, leukopenia, thrombocytopenia, aplastic anemia and agranulocytosis) associated with the use of NSAIDs are rare, but could occur with severe consequences.

Anemia is sometimes seen in patients receiving NSAIDs, including APO-PIROXICAM. This may be due to fluid retention, GI blood loss, or an incompletely described effect upon erythropoiesis. In clinical trials with piroxicam hematologic adverse reactions occurred very commonly (15%) (See **Adverse Reactions – Clinical Trial Adverse Drug Reactions –Hematologic**). At the recommended dose of 20 mg/day of piroxicam, reductions in hemoglobin and hematocrit values are observed in about 4% of the patients treated with piroxicam alone or concomitantly with ASA. These observations occurred in the absence of fecal blood loss due to gastrointestinal irritation. Therefore, hematocrit and hemoglobin values should be determined periodically.

Hepatic / Biliary/Pancreatic

As with other NSAIDs borderline elevations of one or more liver enzyme tests (AST, ALT, alkaline phosphatase) may occur in up to 15% of patients. These abnormalities may progress, may remain essentially unchanged, or may be transient with continued therapy. Elevations of ALT and AST 3 times the upper limit of normal, occurred in controlled clinical trials in less than 1% of patients. Hepatitis and jaundice occurred in less than 1% of patients.

A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of a more severe hepatic reaction while on therapy with this drug. Severe hepatic reactions including jaundice and cases of fatal hepatitis, liver necrosis and hepatic failure, some of them with fatal outcomes, have been reported with piroxicam.

Although such reactions are rare, if abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop (e.g. jaundice), or if systemic manifestations occur (e.g. eosinophilia, associated with rash, etc.), this drug should be discontinued.

If there is a need to prescribe this drug in the presence of impaired liver function, it must be done under strict observation.

Hypersensitivity Reactions:

Anaphylactoid Reactions:

As with NSAIDs in general, anaphylactoid reactions have occurred in patients without known prior exposure to APO-PIROXICAM. In post-marketing experience, rare cases of anaphylactic/ anaphylactoid reactions and angioedema have been reported in patients receiving APO-PIROXICAM. APO-PIROXICAM should NOT be given to patients with the ASA-triad. This symptom complex typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking ASA or other NSAIDs (see **Contraindications**).

ASA-Intolerance:

APO-PIROXICAM should NOT be given to patients with complete or partial syndrome of ASA-intolerance (rhinosinusitis, urticaria/angioedema, nasal polyps, asthma) in whom asthma, anaphylaxis, urticaria/angioedema, rhinitis or other allergic manifestations are precipitated by ASA or other NSAIDs. Fatal anaphylactoid reactions have occurred in such individuals. As well, individuals with the above medical problems are at risk of a severe reaction even if they have taken NSAIDs in the past without any adverse reaction (see **Contraindications**).

Cross-sensitivity:

Patients sensitive to one NSAID may be sensitive to any of the other NSAIDs as well.

Serious skin reactions:

(See **Warnings and Precautions - Skin**)

Evidence from epidemiological studies suggests that piroxicam is associated with a high risk of serious skin reactions compared to other non-oxicam NSAIDs.

Immune

(See **Warnings and Precautions - Infection- Aseptic Meningitis**)

Infection:

APO-PIROXICAM, in common with other NSAIDs, may mask signs and symptoms of an underlying infectious disease.

Aseptic Meningitis:

Rarely, with some NSAIDs including APO-PIROXICAM, the symptoms of aseptic meningitis (stiff neck, severe headaches, nausea and vomiting, fever or clouding of consciousness) have been observed. Patients with autoimmune disorders (systemic lupus erythematosus, mixed connective tissue diseases, etc.) seem to be pre-disposed.

Therefore, in such patients, the health care provider must be vigilant to the development of this complication.

Neurologic

Some patients may experience drowsiness, dizziness, blurred vision, vertigo, tinnitus, hearing loss, insomnia or depression with the use of NSAIDs, such as APO-PIROXICAM. If patients experience such adverse reaction(s), they should exercise caution in carrying out activities that require alertness.

Ophthalmologic

Blurred and/or diminished vision has been reported with the use of piroxicam and other NSAIDs. If such symptoms develop this drug should be discontinued and an ophthalmologic examination performed. Ophthalmologic examination should be carried out at periodic intervals in any patient receiving APO-PIROXICAM for an extended period of time.

Peri-Operative Considerations

(See Contraindications – Coronary Artery Bypass Graft Surgery)

Psychiatric:

(See Warnings and Precautions – Neurologic)

Renal

Long-term administration of piroxicam to animals has resulted in renal papillary necrosis and other abnormal renal pathology. In humans, there have been reports of acute interstitial nephritis with hematuria, proteinuria, and occasionally nephrotic syndrome.

Acute renal failure and hyperkalemia as well as reversible elevations of BUN and serum creatinine have been reported with piroxicam.

Renal insufficiency due to NSAID use is seen in patients with pre-renal conditions leading to reduction in renal blood flow or blood volume. Under these circumstances, renal prostaglandins

help maintain renal perfusion and glomerular filtration rate (GFR). In these patients, administration of a NSAID may cause a reduction in prostaglandin synthesis leading to impaired renal function. Patients at greatest risk of this reaction are those with pre-existing renal insufficiency (GFR < 60 mL/min or 1 mL/s), dehydrated patients, patients on salt restricted diets, those with congestive heart failure, cirrhosis, liver dysfunction, taking angiotensin-converting enzyme inhibitors, angiotensin-II receptor blockers, cyclosporin, diuretics, and those who are elderly. Serious or lifethreatening renal failure has been reported in patients with normal or impaired renal function after short term therapy with NSAIDs. Even patients at risk who demonstrate the ability to tolerate a NSAID under stable conditions may decompensate during periods of added stress (e.g. dehydration due to gastroenteritis). Discontinuation of NSAIDs is usually followed by recovery to the pretreatment state.

Caution should be used when initiating treatment with APO-PIROXICAM in patients with considerable dehydration. Such patients should be rehydrated prior to initiation of therapy. Caution is also recommended in patients with pre-existing kidney disease. Because of the extensive renal excretion of APO-Piroxicam and its biotransformation products (less than 5% of the daily dose excreted unchanged), lower doses of APO-PIROXICAM should be anticipated in patients with impaired renal function and they should be carefully monitored.

Kidney function should be monitored periodically.

Advanced Renal Disease:

(See **Contraindications**)

Fluid and Electrolyte Balance:

Use of NSAIDs, including APO-PIROXICAM, can promote sodium retention in a dose-dependent manner, which can lead to fluid retention and edema, and consequences of increased blood pressure and exacerbation of congestive heart failure. Thus, caution should be exercised in prescribing APO-PIROXICAM in patients with a history of congestive heart failure, compromised cardiac function, hypertension, increased age or other conditions predisposing to fluid retention (See **Warnings and Precautions - Cardiovascular**).

Use of NSAIDs, including APO-PIROXICAM, can increase the risk of hyperkalemia, especially in patients with diabetes mellitus, renal failure, increased age, or those receiving concomitant therapy with adrenergic blockers, angiotensin-converting enzyme inhibitors, angiotensin-II receptor antagonists, cyclosporin, or some diuretics.

Electrolytes should be monitored periodically (see **Contraindications**).

Respiratory

ASA-induced asthma is an uncommon but very important indication of ASA and NSAID sensitivity. It occurs more frequently in patients with asthma who have nasal polyps.

Sexual Function / Reproduction:

The use of APO-PIROXICAM, as with any drug known to inhibit cyclooxygenase/prostaglandin synthesis, may impair fertility and is not recommended in women attempting to conceive. Therefore, in women who have difficulties conceiving, or who are undergoing investigation of infertility, withdrawal of APO-PIROXICAM should be considered.

Skin

In rare cases, serious skin reactions such as Stevens-Johnson syndrome, toxic epidermal necrolysis, exfoliative dermatitis and erythema multiforme have been associated with the use of some NSAIDs, including APO-PIROXICAM. Because the rate of these reactions is low, they have usually been noted during post-marketing surveillance in patients taking other medications also associated with the potential development of these serious skin reactions. Thus, causality is not clear. These reactions are potentially life threatening but may be reversible if the causative agent is discontinued and appropriate treatment instituted. Patients should be advised that if they experience a skin rash they should discontinue their NSAID and contact their physician for assessment and advice, including which additional therapies to discontinue.

Evidence from epidemiological studies suggests that piroxicam is associated with a higher risk of serious skin reactions compared to other non-oxicam NSAIDs.

Photosensitivity has been occasionally associated with the use of piroxicam.

A combination of dermatological and/or allergic signs and symptoms suggestive of serum sickness has occasionally occurred in conjunction with the use of APO-PIROXICAM. These include arthralgias, pruritus, fever, fatigue, and rash including vesiculo bullous reactions and exfoliative dermatitis.

Special Populations

Pregnant Women:

APO-PIROXICAM is CONTRAINDICATED for use during the third trimester of pregnancy because of risk of premature closure of the ductus arteriosus and the potential to prolong parturition (see Toxicology).

The use of APO-PIROXICAM during the first and second trimester of pregnancy is not recommended as its safety in this condition has not been established. Based on animal data caution should be exercised in prescribing APO-PIROXICAM during the first and second trimesters of pregnancy (see Toxicology).

Inhibition of prostaglandin synthesis may adversely affect pregnancy and/or the embryofoetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation after use of a prostaglandin synthesis inhibitor in early pregnancy.

In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation loss and embryo-foetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period.

Nursing Women:

(See **Contraindications**)

Pediatrics:

(See **Contraindications**)

Geriatrics (> 65 years of age):

Patients older than 65 years (referred to in this document as older or elderly) and frail or debilitated patients are more susceptible to a variety of adverse reactions from NSAIDs. The incidence of these adverse reactions increases with dose and duration of treatment. In addition, these patients are less tolerant to ulceration and bleeding. Most reports of fatal GI events are in this population, especially those with cardiovascular disease. Older patients are also at risk of lower esophageal ulceration and bleeding.

For such patients, consideration should be given to a starting dose lower than the one usually recommended, with individual adjustment when necessary and under close supervision.

Monitoring and Laboratory Tests

Cardiovascular: Blood Pressure should be monitored regularly during treatment with APO-PIROXICAM (See **Warnings and Precautions - Cardiovascular**).

Hematologic: Patients should have their hemoglobin or hematocrit checked periodically. Concurrent therapy of APO-PIROXICAM with warfarin requires close monitoring of the international normalized ratio (INR) (See **Warnings and Precautions - Haematology**).

Hepatic: Liver function tests should be monitored periodically (See **Warnings and Precautions - Hepatic/Biliary/Pancreatic**).

Ophthalmologic: Ophthalmic examination should be performed at periodic intervals. (See **Warnings and Precautions - Ophthalmologic**).

Renal: Patients with pre-existing renal insufficiency (GFR > 60 mL/min or 1 mL/s), dehydrated patients, patients on salt restricted diets, those with congestive heart failure, cirrhosis, liver dysfunction, taking angiotensin-converting enzyme inhibitors, angiotensin-II receptor blocker, cyclosporin, diuretics, and the elderly should have their renal function monitored (e.g. urine output, serum creatinine, creatinine clearance and serum urea) during therapy with APO-PIROXICAM (See **Warnings and Precautions - Renal**).

Serum electrolytes should be monitored periodically, especially in those patients who are at risk (**Warnings and Precautions – Renal – Fluid and Electrolyte Balance**).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The most common adverse reactions encountered with NSAIDs are gastrointestinal, of which peptic ulcer, with or without bleeding is the most severe. Fatalities have occurred, particularly in the elderly. Evidence from epidemiological studies suggests that piroxicam is associated with a high risk of gastrointestinal toxicity relative to some other NSAIDs (**Warnings and Precautions - Gastrointestinal**).

Serious skin reactions have been associated with NSAID use. Evidence from epidemiological studies suggests that piroxicam is associated with higher risk of serious skin reactions compared to other non-oxicam NSAIDs (**Warnings and Precautions - Skin**).

Use of some NSAIDs is associated with an increased incidence of cardiovascular adverse events (**Warnings and Precautions -Cardiovascular**).

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

In approximately 2300 patients receiving a daily dose of 20 mg or less of piroxicam in clinical trials, the most frequent side effects observed have been gastrointestinal (approximately 20% of the patients). Of the patients experiencing gastrointestinal side effects, approximately 5% discontinued therapy with an overall incidence of peptic ulceration of about 1% and gastrointestinal bleeding of approximately 0.1%. Very Common ($\geq 10\%$) and Common ($>1\%$ and $\leq 10\%$) adverse drug reactions are summarized in Tables 1 and 2, respectively.

Table 1. Very Common ($\geq 10\%$) Clinical Trial Adverse Drug Reactions

Body System	Frequency (N≈2300) (%)
Gastrointestinal	17.4
epigastric distress	6.4
nausea	4.1
constipation	2.4
abdominal discomfort	2.2

flatulence	2.1
diarrhea	1.8
abdominal pain	1.5
indigestion	1.3
anorexia	1.2
peptic ulceration	About 1
stomatitis	< 1
vomiting	< 1
hematemesis	< 1
melena	< 1
perforation	< 1
dry mouth	< 1
pancreatitis	< 1
Hematologic 15.0	15.0
decrease in hemoglobin	4.6
decrease in hematocrit	4.2
thrombocytopenia	2.4
eosinophilia	1.8
leukocytosis	1.7
basophilia	1.7
leukopenia	1.4
petechial rash	< 1
ecchymosis	< 1
bone marrow depression	< 1
including aplastic anemia and epistaxis	< 1

Table 2. Common ($\geq 1\%$ and $\leq 10\%$) Clinical Trial Adverse Drug Reactions

Adverse Reactions	Frequency (N\approx2300) (%)
Central Nervous System	5
headache	1.8
malaise	1.0
dizziness	< 1
drowsiness/sedation (somnolence)	< 1
vertigo	< 1
depression	< 1
hallucinations	< 1
insomnia	< 1
nervousness	< 1
paresthesia	< 1
personality change	< 1

dream abnormalities	< 1
mental confusion	< 1
Dermatologic (2.0%)	2.0
rash	2.0
pruritus	< 1
erythema	< 1
bruising	< 1
desquamation	< 1
exfoliative dermatitis	< 1
erythema multiforme	< 1
toxic epidermal necrolysis	< 1
vesiculo bullous reaction	< 1
onycholysis	< 1
Stevens-Johnson syndrome	< 1
photoallergic skin reactions	< 1
Renal	1
(See Warnings and Precautions)	
oedema	1.6
dysuria	< 1
hematuria	< 1
proteinuria	< 1
interstitial nephritis	< 1
renal failure	< 1
hyperkalemia	< 1
glomerulitis	< 1
nephrotic syndrome	< 1

Special Populations: Patients older than 65 years and frail or debilitated patients are more susceptible to a variety of adverse reactions from NSAIDs. The incidence of these adverse reactions increases with dose and duration of treatment. In addition, these patients are less tolerant to ulceration and bleeding. Most reports of fatal GI events are in this population. Older patients are also at risk of lower esophageal injury, including ulceration and bleeding.

Less Common Clinical Trial Adverse Drug Reactions (<1%)

Allergic (<1%): anaphylaxis, bronchospasm, urticaria/ angioedema, vasculitis, serum sickness (see **Warning and Precautions**), each in less than 1% of patients.

Cardiovascular (<1%): hypertension, palpitations, worsening of congestive heart failure (see **Warning and Precautions, Cardiovascular**), exacerbation of angina, each in less than 1% of patients.

Special senses: Eyes, ears, nose and throat reactions (<1%): tinnitus (about 1%); blurred vision, eye irritation/swelling, each in less than 1% of patients.

Hepatic (<1%): jaundice, hepatitis (See **Warnings and Precautions, Hepatic/Biliary/Pancreatic**), each in less than 1% of patients.

Respiratory (<1%): dyspnea

Metabolic (<1%): hypoglycemia, hyperglycemia, weight increase/decrease, each in less than 1% of patients

Miscellaneous (<1%): sweating, pain (colic), fever, flu-like syndrome (see **Warning and Precautions, Skin, Infection / Aseptic Meningitis**), weakness, each in less than 1% of patients

Other: Isolated reports have included delayed wound healing, thrombophlebitis, pemphigus, alopecia, mastodynia, reduction or loss of libido, impotence, urinary frequency, oliguria, menorrhagia, amnesia, anxiety, tremor, hearing impairment, deafness, thirst, chills, increased appetite, akathisia, tachycardia, flushing, tooth discolouration, glossitis, chest pain, anemia, hemolytic anemia and positive antinuclear factor (ANA); a causal relationship has not been established for these rarely reported events.

Abnormal Hematologic and Clinical Chemistry Findings

Hematologic (15.0%): See **Table 1, Very common (≥10%) Clinical Trial Adverse Drug Reactions**. See **Warnings and Precautions, Hematologic**.

Laboratory Parameters: Changes in laboratory parameters observed during APO-PIROXICAM therapy have included an elevation of BUN, creatinine (See **Warnings and Precautions, Renal**), uric acid and liver enzymes LDH, AST, ALT and alkaline phosphatase.

Post-Market Adverse Drug Reactions

Evidence from epidemiological studies suggests that piroxicam is associated with high risk of gastro-intestinal toxicity relative to some other NSAIDs.

Evidence from epidemiological studies suggests that piroxicam is associated with higher risk of serious skin reaction compared to other non-oxicam NSAIDs.

In patients taking piroxicam the most frequently reported adverse experiences occurring commonly (in 1-10% of patients) are:

Cardiovascular System	Oedema
Digestive System	Anorexia, abdominal pain, constipation, diarrhoea, dyspepsia, elevated liver enzymes, flatulence, gross bleeding/perforation, heartburn, nausea, ulcers, (gastric/duodenal), vomiting
Hemic and Lymphatic System	Anaemia, increased bleeding time
Nervous System	Dizziness, headache

Skin and Appendages	Pruritus, rash
Special Senses	Tinnitus
Urogenital System	Abnormal renal function

Adverse experiences reported in 0.1% -1% of patients include:

Body as a Whole	Fever, infection, sepsis
Cardiovascular System	Congestive heart failure, hypertension, tachycardia, syncope
Digestive System	Dry mouth, esophagitis, gastritis, glossitis, hematemesis, hepatitis, jaundice, melena, rectal bleeding, stomatitis
Hemic and Lymphatic System	Ecchymosis, eosinophilia, epistaxis, leukopenia, purpura, petechial rash, thrombocytopenia
Metabolic and Nutritional	Weight changes
Nervous System	Anxiety, asthenia, confusion, depression, dream abnormalities, drowsiness, insomnia, malaise, nervousness, paresthesia, somnolence, tremors, vertigo
Respiratory System	Asthma, dyspnoea
Skin and Appendages	Alopecia, bruising, desquamation, erythema, photosensitivity, sweat
Special Senses	Blurred vision
Urogenital System	Cystitis, dysuria, hematuria, hyperkalemia, interstitial nephritis, nephritic syndrome, oliguria/polyuria, proteinuria, renal failure

Other adverse reactions, which occur rarely (0.01% -<0.1%) are:

Body as a Whole	Anaphylactic reactions, appetite change, death, flu-like syndrome, pain (colic), serum sickness
Cardiovascular System	Arrhythmia, exacerbation of angina, hypotension, myocardial infarction, palpitations, vasculitis
Digestive System	Eructation, liver failure, pancreatitis
Hemic and Lymphatic System	Agranulocytosis, haemolytic anemia, aplastic anemia, lymphadenopathy, pancytopenia
Metabolic and Nutritional	Hyperglycemia, hypoglycemia
Nervous System	Akathisia, convulsions, coma, hallucinations, meningitis, mood alterations
Respiratory System	Respiratory depression, pneumonia
Skin and Appendages	Angioedema, toxic epidermal necrosis, erythema multiforme, exfoliative dermatitis, onycholysis, Stevens-Johnson syndrome, urticaria, vesiculobullous reaction
Special Senses	Conjunctivitis, hearing impairment, swollen eyes

DRUG INTERACTIONS

Highly Protein Bound Drugs:

APO-PIROXICAM is highly protein bound, and therefore might be expected to displace other proteinbound drugs. The physician should closely monitor dosage requirement of coumarin anticoagulants and other drugs that are highly protein-bound when these are administered concomitantly with APO-PIROXICAM.

Acetylsalicylic acid (ASA) or other NSAIDs:

The use of APO-PIROXICAM in addition to any other NSAID including over the counter one (such as ASA and ibuprofen) for analgesic and /or anti-inflammatory effects is NOT recommended because of the absence of any evidence demonstrating synergistic benefits and the potential for additive side reactions.

The exception is the use of low dose ASA for cardiovascular protection, when another NSAID is being used for its analgesic/anti-inflammatory effect, keeping in mind that combination NSAID therapy is associated with additive adverse reactions, and that NSAIDs may interfere with the antiplatelet effects of low dose ASA, possibly by competing with ASA for access to the active site of cyclooxygenase-I.

Anticoagulants:

(See **Warnings and Precautions -Hematologic – Anti-coagulants**)

Numerous studies have shown that the concomitant use of NSAIDs and anticoagulants increases the risk of GI adverse events such as ulceration and bleeding. Because prostaglandins play an important role in hemostasis, and NSAIDs affect platelet function, concurrent therapy of APO-PIROXICAM with warfarin requires close monitoring to be certain that no change in anticoagulant dosage is necessary. APO-PIROXICAM is highly protein-bound, and therefore, might be expected to displace other protein-bound drugs. The physician should closely monitor dosage requirements of coumarin anticoagulants and other drugs that are highly protein-bound when these are administered concomitantly with APO-PIROXICAM.

Anti-hypertensives:

NSAIDs may diminish the antihypertensive effect of Angiotensin Converting Enzyme (ACE) inhibitors.

Combinations of ACE inhibitors, angiotensin-II antagonists, or diuretics and NSAIDs might have an increased risk for acute renal failure and hyperkalemia. Blood pressure and renal function (including electrolytes) should be monitored more closely in this situation, as occasionally there can be a substantial increase in blood pressure.

Concomitant administration of APO-PIROXICAM with propranolol can reduce the hypotensive effect. Patients should be monitored for altered antihypertensive or antianginal response to betablockers when APO-PIROXICAM is initiated or discontinued.

Anti-Platelet Agents (including ASA):

There is an increased risk of bleeding, via inhibition of platelet function, when antiplatelet agents are combined with NSAIDs, such as APO-PIROXICAM (see **Warnings and Precautions – Hematologic - Anti-platelet Effects**).

Cholestyramine:

In healthy subjects co-administration of cholestyramine to piroxicam results in enhanced elimination of piroxicam (i.e. reduction in half-life by 40% and increase in clearance by 52%). Although the magnitude of these changes in piroxicam disposition appears sufficient to inhibit its therapeutic effects, studies in patients are needed to confirm this. It is suggested that the doses of APO-PIROXICAM and cholestyramine be separated as much as possible, and that the patients be monitored for inadequate response to piroxicam therapy. If an inadequate anti-inflammatory response appears to be related to the concomitant use of cholestyramine, consideration should be given to the use of alternative hypolipidemic therapy.

Cimetidine:

Results of two separate studies indicate a slight increase in absorption of piroxicam following cimetidine administration but no significant changes in elimination parameters. Cimetidine increases the area under the curve (AUC 0-120 hrs) and C_{max} of piroxicam by approximately 13 to 15%. Elimination rate constants and half-life show no significant differences. The clinical significance of this small but significant increase in absorption is yet unknown.

Cyclosporin:

Inhibition of renal prostaglandin activity by NSAIDs may increase the plasma concentration of cyclosporin and/or the risk of cyclosporin induced nephrotoxicity. Patient should be carefully monitored during concurrent use.

Diuretics:

Clinical studies as well as post-marketing observations have shown that NSAIDs can reduce the effect of diuretics. During concomitant therapy with NSAIDs, the patient should be closely observed for signs and symptoms of renal failure (**Warnings and Precautions - Renal**) as well as to assess diuretic efficacy.

Glucocorticoids:

Some studies have shown that the concomitant use of NSAIDs and oral glucocorticoids increases the risk of GI adverse events such as ulceration and bleeding. This is especially the case in older (>65 years of age) individuals.

Lithium:

Piroxicam has been reported to increase steady state plasma lithium concentrations. It is recommended that these concentrations are monitored when initiating, adjusting and discontinuing APO-PIROXICAM treatment.

Methotrexate:

Although up to date there have been no reports of an interaction with APO-PIROXICAM, isolated cases indicate that the concomitant use of some NSAIDs in patients receiving methotrexate may be associated with severe or sometimes fatal methotrexate toxicity.

Until more information is available on this interaction, caution should be used if APO-PIROXICAM is administered concomitantly with methotrexate, particularly in patients with preexisting renal impairment, who may be more susceptible.

Selective Serotonin Reuptake Inhibitors (SSRIs):

Concomitant administration of NSAIDs and SSRIs may increase the risk of gastrointestinal ulceration and bleeding (see **Warnings and Precautions - Gastrointestinal**).

Tacrolimus:

Inhibition of renal prostaglandin activity by NSAIDs may increase the plasma concentration of tacrolimus and/or the risk of tacrolimus induced nephrotoxicity. Patient should be carefully monitored during concurrent use.

Oral Contraceptives:

No drug interaction information is available for APO-PIROXICAM co-administered with oral contraceptives.

Oral Hypoglycemics:

An interaction has been noted with some NSAIDs, however no interaction data are available for the co-administration of these agents with APO-PIROXICAM.

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

Drug-Lifestyle Interactions

Concurrent use of alcohol with APO-PIROXICAM may increase the risk of gastrointestinal side effects, including ulceration and haemorrhage.

Smoking has been associated with an increased risk of gastrointestinal side effects, including ulceration and bleeding.

Patients experiencing visual disturbances, dizziness, vertigo, somnolence or other central nervous system disturbances while taking APO-PIROXICAM should exercise caution in carrying out activities that require alertness and should refrain from driving or using machines.

DOSAGE AND ADMINISTRATION

Dosing Considerations:

Frail or debilitated patients may tolerate side effects less well and therefore special care should be taken in treating this population. **To minimize the potential risk for an adverse event the lowest effective dose should be used for the shortest possible duration.** 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. Consideration should be given to a starting dose that is lower than usual and to an increase of the dose only if symptoms remain uncontrolled. Such patients must be carefully supervised. For high risk patients, alternate therapies that do not involve NSAIDs should be considered.

Hepatic Insufficiency: A substantial portion of piroxicam elimination occurs by hepatic metabolism. Consequently, patients with hepatic disease may require reduced doses of APO-PIROXICAM. APO-PIROXICAM is contraindicated in severe liver impairment or active liver disease.

Renal Insufficiency: Because of the extensive renal excretion of APO-PIROXICAM and its biotransformation products (less than 5% of the daily dose excreted unchanged), lower doses of APO-PIROXICAM should be anticipated in patients with impaired renal function and they should be carefully monitored. APO-PIROXICAM is contraindicated in severe renal impairment and in deteriorating renal disease (See **Contraindications**).

Recommended Dose and Dose Adjustment

Use of APO-PIROXICAM should be limited to the lowest effective dose for the shortest possible duration of treatment (See Contraindications and Warnings and Precautions)

The recommended starting dose is a single daily dose of 20 mg, or 10 mg b.i.d.

In rheumatoid arthritis and ankylosing spondylitis most patients will be maintained on 20 mg daily. Some patients may be maintained on 10 mg daily.

In osteoarthritis the usual maintenance dose is 10-20 mg daily.

APO-PIROXICAM should not be given in doses greater than 20 mg daily.

APO-PIROXICAM capsules should be taken immediately after a meal or with food or milk. If stomach upset (indigestion, nausea, vomiting, stomach pain or diarrhea) occurs and continues, a doctor should be consulted.

Hepatic Insufficiency: (See Dosing Considerations).

Renal Insufficiency: (See Dosing Considerations).

Geriatrics (>65 years of age), Frail or Debilitated: (See Dosing Considerations).

Pediatrics (<16 years of age): (See Contraindications).

Missed Dose

If a dose of APO-PIROXICAM is taken once a day and a dose of this medicine is missed, a dose of APO-PIROXICAM should be taken right away if remembered by the patient within 8 hours of the missed dose. If APO-PIROXICAM is taken twice a day and a dose is missed, which the patient remembers within 2 hours of the missed dose then the dose should be taken right away and the patient should go back to the regular dosing schedule.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Cases of overdose, up to 1800 mg piroxicam, have been reported. Recovery was complete without sequelae. In the event of overdose with APO-PIROXICAM (piroxicam) supportive and symptomatic therapy is indicated. Studies indicate that administration of activated charcoal may result in reduced absorption and reabsorption of piroxicam thus reducing the total amount of active drug available.

Piroxicam is highly protein bound, therefore dialysis of this drug is not feasible as a course of action due to an overdose.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

APO-PIROXICAM inhibits the activity of prostaglandin synthetase. The resulting decrease in prostaglandin biosynthesis may partially explain its anti-inflammatory action. APO-PIROXICAM does not act by pituitary-adrenal stimulation.

In rheumatoid arthritis the efficacy of piroxicam 20 mg daily has been found to be similar to 4.2 g daily of ASA.

Pharmacodynamics

APO-PIROXICAM is a non-steroidal anti-inflammatory agent with analgesic and antipyretic properties. Its mechanism of action is incompletely known. (See **Action and Clinical Pharmacology, Mechanism of Action**)

Pharmacokinetics

Absorption: Piroxicam is well-absorbed following oral or rectal administration. After a single oral dose of 20 mg, peak plasma levels of piroxicam are achieved in about 4 hours. When the drug is administered daily, plasma concentrations increase for seven to twelve days during which a steady state is reached. Concentrations attained are not exceeded following further constant daily drug intake. The plasma half-life is approximately 50 hours in man. The extent and rate of absorption are not influenced by administration with food or antacids.

Metabolism: Piroxicam is extensively metabolized and less than 5% of the daily dose is excreted unchanged in urine and feces. The main metabolic pathway is hydroxylation of the pyridyl ring, followed by conjugation with glucuronic acid and urinary elimination. Approximately 5% of the dose is metabolized to and excreted as saccharin.

Excretion: Approximately 5% of the dose is metabolized to and excreted as saccharin.

Over a four day period of observation, twenty healthy men, taking piroxicam 20 mg daily in single or divided doses, showed significantly less mean daily fecal blood loss than did ten healthy male controls taking 3.9 g of ASA daily.

Special Populations and Conditions

Gender / Geriatrics: The effects of age and sex on the pharmacokinetics of piroxicam have been examined in three single-dose, three multiple dose, and five therapeutic drug monitoring studies. Although not consistent across all studies, some indicated a tendency towards a modest decrease in total body clearances and an increase in elimination half-life and steady-state plasma

concentrations in the elderly, particularly elderly females. Irrespective of age, some patients had plasma concentration levels that are substantially greater than the mean.

Hepatic Insufficiency: A substantial portion of piroxicam elimination occurs by hepatic metabolism. Consequently, patients with hepatic disease may require reduced doses of APO-PIROXICAM. APO-PIROXICAM is contraindicated in severe liver impairment or active liver disease.

Renal Insufficiency: Because of the extensive renal excretion of APO-PIROXICAM and its biotransformation products, lower doses of APO-PIROXICAM should be anticipated in patients with impaired renal function and they should be carefully monitored. APO-PIROXICAM is contraindicated in severe renal impairment and in deteriorating renal disease.

STORAGE AND STABILITY

Store between 15°C and 30°C.

DOSAGE FORMS, COMPOSITION AND PACKAGING

APO-PIROXICAM (piroxicam) hard gelatin capsules, 10 mg each, are opaque No. 2 maroon and blue printed APO 10.

APO-PIROXICAM (piroxicam) hard gelatin capsules, 20 mg each, are opaque No. 2 maroon printed APO 20.

Each capsule contains 10 or 20 mg of piroxicam, USP. Available in bottles of 100 and 500 capsules.

In addition to the active ingredient, piroxicam, each capsule also contains the non-medicinal ingredients, D&C Red #28, FD&C Blue #1, FD&C Red #40, gelatin, lactose, microcrystalline cellulose, sodium lauryl sulfate, sorbitan monolaurate, starch, stearic acid, talc and titanium dioxide.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

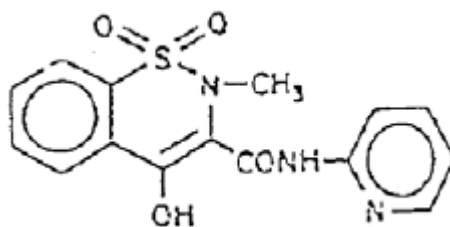
Drug Substance

Proper Name: Piroxicam, USP

Chemical Name: 4-hydroxy-2-methyl-N-2-pyridyl-2H-1,2-benzothiazine-3-carboxamide 1,1-dioxide

Molecular formula and molecular weight: $C_{15}H_{13}N_3O_4S$ 331.35

Structural Formula:



Physicochemical properties:

Piroxicam is a white crystalline, hygroscopic solid which melts in the range 196 to 200°C. It is poorly soluble in water, dilute acids, and most organic solvents. It is slightly soluble in alcohols and aqueous alkaline solutions.

CLINICAL TRIALS

Comparative Bioavailability Studies

A comparative bioavailability studies were performed using normal human volunteers. The rate and extent of absorption after a single 20 mg dose of Feldene 10 mg, APO-PIROXICAM 10 mg, Feldene 20 mg and APO-PIROXICAM 20 mg was measured and compared. The results from measured data are summarized as follows:

Summary Table of the Comparative Bioavailability Data				
Piroxicam				
(A single 20 mg dose: 2 x 10 mg Capsules)				
From measured data				
Geometric Mean				
Arithmetic Mean (CV%)				
Parameter	Apo-Piroxicam	Feldene® [†]	% Ratio of Geometric Means	90% Confidence Interval
AUC _T (mcg.h/mL)	111 113.66 (22.0)	111 112.96 (18.5)	100.0	96.2 – 104.0
AUC _I (mcg.h/mL)	143 145.20 (33.1)	139 138.20 (25.8)	103.5	97.2 – 110.2
C _{max} (mcg/mL)	2.05 2.08 (16.9)	2.11 2.13 (13.5)	97.4	93.7 – 101.1
T _{max} [§] (h)	2.7 (46.5)	1.8 (95.9)		
T _½ [§] (h)	55.1 (25.3)	50.8 (25.7)		

[†] Feldene® is manufactured by Pfizer Canada Inc., and was purchased in Canada.

[§] Expressed as the arithmetic mean (CV %) only.

Summary Table of the Comparative Bioavailability Data				
Piroxicam				
(A single 20 mg dose: 1 x 20 mg Capsule)				
From measured data				
Geometric Mean				
Arithmetic Mean (CV%)				
Parameter	Apo-Piroxicam	Feldene® [†]	% Ratio of Geometric Means	90% Confidence Interval
AUC _T (mcg.h/mL)	112 113.84 (19.2)	118 119.42 (18.3)	95.1	91.7 – 98.7
AUC _I (mcg.h/mL)	142 140.80 (27.8)	150 149.80 (32.6)	94.3	87.8 – 101.2
C _{max} (mcg/mL)	2.10 2.13 (16.5)	2.17 2.17 (8.5)	97.0	91.9 – 102.4
T _{max} [§] (h)	2.4 (38.6)	2.6 (50.6)		
T _½ [§] (h)	52.1 (22.5)	52.3 (30.9)		

[†] Feldene® is manufactured by Pfizer Canada Inc., and was purchased in Canada.

[§] Expressed as the arithmetic mean (CV %) only.

DETAILED PHARMACOLOGY

Animal Studies

The anti-inflammatory activity of piroxicam, given orally, has been demonstrated in rats, guinea pigs and dogs. A 4.0 mg/kg dose given to rats produced 50% inhibition of carrageenan-induced foot edema. Piroxicam at doses of 0.3 to 3.3 mg/kg also caused inhibition of adjuvant-induced arthritis in rats. At doses of 10 and 18 mg/kg, an inhibition of cotton string-induced granuloma formation in rats was observed. A 0.3 mg/kg dose of piroxicam given to guinea pigs produced 50% inhibition of the erythema induced by ultraviolet light. Intravenous administration of piroxicam (5 mg/kg) to dogs inhibited urate-induced inflammation of knee joints.

The analgesic activity of piroxicam, at an oral dose of 1.85 mg/kg, was demonstrated in mice using the phenylquinone-induced writhing test. Piroxicam at 1.0, 3.2 and 10 mg/kg orally was active in the Randall-Sellito test in which painful pressure is applied to the inflamed foot pad of the rat. It was inactive in hot-plate and tail-flick tests at oral doses up to 100 mg/kg. The antipyretic activity of piroxicam at 10 mg/kg orally was demonstrated in the hyperpyrexia induced in rats by intramuscular injections of *E. coli* lipopolysaccharide.

Piroxicam inhibits prostaglandin synthetase, thereby reducing the biosynthesis of prostaglandins. The drug also inhibits collagen-induced platelet aggregation. The anti-inflammatory activity of piroxicam does not depend upon adrenal stimulation. Its activity was demonstrated in adrenalectomized rats. Piroxicam has no significant cardiovascular or central nervous system activity

Human Studies: See Actions and Clinical Pharmacology section.

TOXICOLOGY

Acute Toxicity:

Species	Sex	LD50 (95% Confidence Limits) mg/kg	
		Oral	I.P
Mice	M	360 (321-404)	360 (305-425)
	F	approx. 360	
Rat	M	270 (231-316)	220 (197-241)

Toxic effects observed in mice and rats included ataxia, depression, laboured respiration, prostration, weight gain inhibition and weight loss. Necropsy of these animals revealed marked visceral adhesions and erosions of the stomach and intestines.

In the dog, repeated emesis, chronic anorexia, and diarrhea occurred at dosage levels of 5, 25, 50, 400 and 700 mg/kg; fecal occult blood was observed 24 hours after dosing. A weight loss of about 15% and bloody diarrhea occurred with the 50, 400 and 700 mg/kg doses. Necropsy of the dogs receiving 5 mg/kg revealed mucosal erosions and hemorrhage. These lesions, together with ulcerations of the pyloric antrum and/or sphincter, were also observed at the higher dose level.

Subacute and Chronic Toxicity: Piroxicam administered orally to beagle dogs at a dose of 1.0 mg/kg/day for 373 consecutive days caused signs of gastrointestinal and renal toxicity. These included emesis, diarrhea, duodenal and gastric ulceration or erosion, fecal occult blood, anemia, proteinuria, hematuria, renal papillary necrosis and one case of pyelonephritis. Other effects considered to be related to the primary pathology were integumental signs, leukocytosis and decreased serum calcium levels.

A one year study in the rhesus monkey at daily oral doses of 2.5, 5.0 and 10.0 mg/kg revealed epithelial casts within the collecting tubules of the kidneys in 67% of high dose females. There was no evidence of gastrointestinal toxicity at any dose. Another study in rhesus monkeys was conducted over 90 days at the same dose levels. Occasional erosions of the gastrointestinal mucosa were observed only in the animals receiving the highest dose. However, one female monkey, receiving 2.5 mg/kg/day, did develop an acute gastric ulcer.

In an 18-month rat study, daily oral doses of 0.3, 1.0 and 3.0 mg/kg gave dose- and duration-related renal papillary necrosis, elevation of BUN and necrotizing gastrointestinal lesions. At the highest dose, gastrointestinal lesions and renal papillary necrosis were present in more females than males. Dose-related anemia in males also occurred.

An 18-month mouse study was conducted at daily oral doses of 2, 4 and 8 mg/kg. There was increased mortality at 8 mg/kg. Dose-related renal papillary necrosis with secondary chronic diffuse interstitial nephritis, elevated BUN and necrotizing gastrointestinal lesions were observed.

Reproduction and Teratology Studies: Consistent with its inhibitory effect on prostaglandin biosynthesis, piroxicam prolongs the gestational period of the rat. The effects are dependent on dose and time.

When piroxicam was administered in oral doses of 2, 5 and 10 mg/kg daily to pregnant rats from day 15 post-coitum onwards, a dose-dependent increase in mortality and prolongation of gestation and parturition occurred. Parturition was completely inhibited by piroxicam at 10 mg/kg administered for 8 days. The dystocia, together with the gastrointestinal toxicity of the drug, caused weakness and death of dams and offspring. When treatment was stopped after 5 days of drug administration, deaths and prolonged labour still occurred.

When pregnant rats received 10 mg/kg/day of piroxicam orally from day 1 post-coitum to day 16, 17, 18, 19 or 20 post-coitum, all groups displayed gestational prolongation and the delay increased with length of treatment. Prolongation of parturition and increased mortality of the offspring occurred. There was dose-related suppression of lactation.

Piroxicam was administered in oral doses of 2, 5 and 10 mg/kg/day to male and female rats for 81 and 14 days respectively, before mating. Dosing in females was continued to day 6 postcoitum. Neither sex exhibited a modification of sexual behaviour or diminished fertility. Fetal development was normal. Viability and growth of pups were comparable to controls, and no drug-induced malformation or lesion was seen.

Oral administration of piroxicam to pregnant rats and rabbits, during the critical period of organogenesis, induced no embryotoxic or teratogenic effect at doses of 2, 5 and 10 mg/kg/day.

Oral administration of piroxicam to female rats on days 1-12 of the lactation period inhibited postnatal body weight gain in pups owing to suppression of lactation in dams. This effect was explored at doses of 2, 5 and 10 mg/kg/day and was dose-related.

Mutagenicity: Piroxicam demonstrated no mutagenic activity in any of the test systems.

Carcinogenicity: In a 24-month rat study, piroxicam administered in the diet to provide doses of 0.3 and 1.0 mg/kg, induced the same spectrum, but higher incidence at 1 mg/kg, of non-neoplastic lesions than in the 18-month rat study. The principal drug-induced pathologic changes consisted of renal papillary necrosis, suppurative pyelonephritis and pyloric ulceration. Except for suppurative pyelonephritis, females were more often affected than males.