PRODUCT MONOGRAPH

Pr GEN-PIROXICAM

(Piroxicam, USP)

10 and 20 mg Capsules

Nonsteroidal Anti-inflammatory Drug (NSAID)

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Non-medicinal Ingredients
Oral	Capsules 10 mg and 20 mg	Lactose and Gelatin *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

Gen-Piroxicam (piroxicam) is indicated for the symptomatic treatment of

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

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 Gen-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)

Gen-Piroxicam, as a NSAID, does NOT treat clinical disease or prevent its progression.

Gen-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 postmarket 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

Gen-Piroxicam is contraindicated in:

- The peri-operative setting of coronary artery bypass graft surgery (CABG). Although Gen-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 or suspected hypersensitivity to Gen-Piroxicam or to any of the components or excipients.
- History of asthma, urticaria, or allergic-type reactions after taking 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, active GI bleeding.
- 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 0.5mL/sec) or detoriating renal disease (individual with lesser degrees of renal imparement are at risk of detoriation of their renal function when prescribed NSAIDs and must be monitored) (See **Warnings and Precautions – *Renal)***

- Gen-Piroxicam is not recommended for use with other NSAIDs because of the absence of any evidence demonstrating synergistic benefits and the potential for additive side effects.
- Known hyperkalemia (See **Warnings and Precautions - *Renal - Fluid and Electrolyte Balance***)
- Children and adolescents less than 16 years of age

WARNINGS AND PRECAUTIONS

Serious 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*)

- Gen-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 Gen-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 NSAIDs, such as Gen-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 Warnings and Precautions – *Renal – Fluid and Electrolyte Balance*)

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

- Risk of Gastrointestinal (GI) Adverse Events (See Warnings and Precautions - *Gastrointestinal*)

- Use of Gen-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.

Gen-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**)

Cardiovascular
Gen-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 Gen-Piroxicam to patients with risk factor 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 Gen-Piroxicam can lead to new hypertension or can worsen pre-existing 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 Gen-Piroxicam should hypertension either develop or worsen with its use.

Use of NSAIDs, such as Gen-Piroxicam can induce fluid retention and oedema, 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

Gen-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

Serious GI toxicity (sometimes fatal), such as peptic/duodenal ulceration, inflammation, perforation, obstruction and gastrointestinal bleeding, can occur at any time, with or without symptoms in patients treated with (NSAIDs) including Gen-Piroxicam. Minor upper GI problems, such as dyspepsia, commonly occur at any time, usually developing early in therapy. Health care providers should remain alert for ulceration and bleeding in patients treated with Gen-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 Gen-Piroxicam is associated with a high risk of gastro-intestinal 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 Gen-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 addressed. 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 Gen-Piroxicam to patients with prior history of peptic/duodenal ulcer disease, diverticulosis, or gastrointestinal bleeding, as these individuals have greater than 10-fold higher risk of 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 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)

Genitourinary

Some NSAIDs are known to cause 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. Some cases have become severe on continued treatment. Should urinary symptoms occur in the absence of an alternate explanation, treatment with Gen-Piroxicam must be stopped immediately, to obtain recovery. This should be done before any 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 Gen-Piroxicam is administered.

Anti-coagulants: Numerous studies have shown that the concomitant use of NSAIDs and anti-coagulants increases the risk of bleeding. Concurrent therapy of Gen-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.

Gen-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 Interacions – Acetylsalicylic Acid (ASA) or other NSAIDs***)

Concomitant administration of Gen-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 Gen-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 were observed in about 4% of the patients treated 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 (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 (See **Adverse Reactions – *Less Common Clinical Trial Adverse Drug Reactions and Abnormal Hematologic and Clinical Chemistry Findings***).

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 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 outcome have been reported with NSAIDs.

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 manifestation 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 Gen-Piroxicam. In post-marketing experience, rare cases of anaphylactic/ anaphylactoid reactions and angioedema have been reported in patients receiving Gen-Piroxicam. Gen-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: Gen-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:
Evidence from epidemiological studies suggests that piroxicam is associated with higher risk of serious skin reaction compared to other non-oxicam NSAIDs (See **Warnings and Precautions – *Skin***)

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

Infection
Gen-Piroxicam in common with other NSAIDs, may mask the usual signs of an underlying infectious disease.

Aseptic Meningitis
Rarely, with some NSAIDs including Gen-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 disease, etc.) seem to be pre-disposed. Therefore, in such patients, the physician 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 Gen-Piroxicam. If patients experience such adverse events, they should exercise caution in carrying out activities that require alertness.

Ophthalmologic
Blurred and/or diminished vision has been reported with the use of Gen-Piroxicam and other NSAIDs. If such symptoms develop this drug should be discontinued and an ophthalmologic examination performed; ophthalmic examination should be performed at periodic intervals in any patient receiving this drug 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 NSAIDs to animals has resulted in renal papillary necrosis and other abnormal renal pathology. In humans, there have been reports of acute interstitial nephritis, hematuria, low grade proteinuria, and occasionally nephrotic syndrome.

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 life-threatening 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 pre-treatment state. (See **Warnings and Precautions – Monitoring and Laboratory Tests – *Renal*).**

Caution should be used when initiating treatment with NSAIDs, such as Gen-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 Gen-Piroxicam and its biotransformation products (less than 5% of the daily dose excreted unchanged), lower doses of Gen-Piroxicam should be anticipated in patients with impaired renal function and they should be carefully monitored. Kidney functions should be monitored periodically.

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

Advanced Renal Disease:
(See **Contraindications)**

Fluid and Electrolyte Balance

Fluid retention and oedema have been observed in patients treated with Gen-Piroxicam. Use of NSAIDs such as Gen-Piroxicam, can promote sodium retention in a dose-dependent manner, which can lead to fluid retention and oedema and consequences of increased blood pressure and exacerbation of congestive heart failure. Thus, caution should be exercised in prescribing Gen-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***).

With nonsteroidal anti-inflammatory treatment there is a potential risk of hyperkalemia, particularly in patients with conditions such as diabetes mellitus or renal failure; elderly patient; or in patients 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**). Hyperkalemia has been reported with Gen-Piroxicam.

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 Gen-Piroxicam, as with any drug known to inhibit cyclo-oxygenase/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 Gen-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 Gen-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 Gen-Piroxicam. These include arthralgias, pruritus, fever, fatigue, and rash including vesiculo bullous reactions and exfoliative dermatitis.

Special Populations

Pregnant Women: Gen-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 Gen-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 Gen-Piroxicam during the first and second trimesters of pregnancy (See Toxicology).

Inhibition of prostaglandin synthesis may adversely affect pregnancy and/or the embryo-foetal 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 (< 16 years of age): (See **Contraindications)**

Geriatrics (> 65 years of age): Patients older than 65 years (referred to in this documents 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. Older patients are also at risk of lower esophageal injury, including 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 Gen_Piroxicam (See **Warnings and Precautions** - ***Cardiovascular***).

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

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

Opthalmologic: Opthalmic 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 inhibitor s, angiotensin-II receptor blocker, cyclosporin, diuretics, and the elderly should have their renal function monitored (e.g. urine output, serum creatinine, creatinine clearence and serum urea) during therapy with Gen-Piroxicam (See **Warnings and Precautions** - ***Renal***).

Serum electrolytres 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 gastro-intestinal, 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 Gen-Piroxicamis associated with a high risk of gastro-intestinal 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 drug 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%.

Table 1. Very Common (≥10%) Clinical Trial Adverse Drug Reactions

Adverse Reaction	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**
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 including aplastic anemia and epistaxis	< 1

Table 2. Common (≥1% and ≤10%) Clinical Trial Adverse Drug Reactions

Adverse Reaction	Frequency (N≈2300) (%)
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 (See **Warnings and Precautions**)	**1**
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 **Warnings and Precautions**), each in less than 1% of patients.

Cardiovascular (<1%): hypertension, palpitations, worsening of congestive heart failure (See **Warnings 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 **Warnings 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 Gen-Piroxicam therapy have included an elevation of BUN, creatinine (See **Warnings and Precautions, Renal**), uric acid and liver enzymes LDH, SGOT, SGPT and alkaline phosphatase.

Post-Market Adverse Drug Reactions

Evidence from epidemiological studies suggests that Gen-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

Drug-Drug Interactions

Highly Protein Bound Drugs:
Gen-Piroxicam is highly protein bound, and therefore might be expected to displace other protein-bound 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 Gen-Piroxicam.

Acetylsalicylic acid (ASA) and other NSAIDs:
The use of Gen-Piroxicam in addition to any other NSAID, including those over the counter ones (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 adverse 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.

Some NSAIDs (e.g. ibuprofen) may interfere with the anti-platelet effects of low dose ASA, possibly by competing with ASA for access to the active site of cyclooxygenase-1.

Plasma concentrations of Gen-Piroxicam are reduced to approximately 80% of their normal concentrations when Gen-Piroxicam is administered in conjunction with acetylsalicylic acid (3900 mg/day).

Anti-coagulants:
(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 Gen-Piroxicam with warfarin requires close monitoring to be certain that no change in anticoagulant dosage is necessary.
Gen-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 Gen-Piroxicam.

Anti-hypertensives:
NSAIDs may diminish the anti-hypertensive effect of Angiotensin Converting Enzyme (ACE) inhibitors.
Combinations of ACE inhibitors, angiotensin-II antagonists, or diuretics with 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 Gen-Piroxicam with propranolol can reduce the hypotensive effect. Patients should be monitored for altered antihypertensive or antianginal response to beta-blockers when Gen-Piroxicam is initiated or discontinued.

Anti-platelet Agents (including ASA):
There is an increased risk of bleeding, via inhibition of platelet function, when anti-platelet agents are combined with NSAIDs, such as Gen-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 appear sufficient to inhibit its therapeutic effects, studies in patients are needed to confirm this. It is suggested that the doses of Gen-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 Cmax 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 observation have shown that NSAIDs can reduce the effect of diruetics. 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:
Numerous studies have shown that the concomitant use of NSAIDs and oral glucocorticoids increases the risk of GI side effects such as ulceration and bleeding. This is especially the case in older (>65 years of age) individuals.

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

Methotrexate:
Although up to date there have been no reports of an interaction with Gen-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 when Gen-Piroxicam is administered concomitantly with methotrexate, particularly in patients with pre-existing 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 Gen-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-administeration of these agents with Gen-Piroxicam.

Drug-Food Interactions
Interactions with food have not been established.

Drug-Herb Interactions
Interactions with herbs have not been established.

Drug-Laboratory Interactions
Interactions with laboratory tests have not been established.

Drug-Lifestyle Interactions
Concurrent use of alcohol with Gen-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 Gen-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 suffereng from impared renal, hepaticor 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 Gen-Piroxicam. Gen-Piroxicam is contraindicated in severe liver imparement or active liver disease.

Renal Insufficiency: Because of the extensive renal excretion of Gen-Piroxicam and its biotransformation products (less than 5% of the daily dose excreted unchanged), lower doses of Gen-Piroxicam should be antiocipated in patients with impared renal function and they should be carefully monitored. Gen-Piroxicam is contraindicated in severe relal imparement and in detoriating renal disease (See **Contraindications**)

Recommended Dose and Dosage Adjustment

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

Gen-Piroxicam should not be given in doses greater than 20 mg daily.

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 maintainence dose is 10-20 mg daily.

Gen-Piroxicam should be taken immidiately after a meal or with food or milk. The patient should remain standing or sitting upright for about 15-30 minutes after taking this medicine. This helps to prevent irritation that may lead to trouble swallowing. The patient should be advised to consult their doctor if stomach upset (indigestion, nausea, vomiting, stomach pain or diarrhea) occurs and continues.

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 Gen-Piroxicam is taken once a day and a dose of this medicine is missed, a dose of Gen-Piroxicam should be taken right away if remembered by the patient within 8 hours of the missed dose. If Gen-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

Cases of overdose, up to 1800 mg Gen-Piroxicam, have been reported. Recovery was complete without sequelae. In the event of overdosage with Gen-Piroxicam supportive and symptomatic therapy is indicated. Preliminary studies indicate that administration of activated charcoal may result in reduced absorption and reabsorption of Gen-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 overdosage.

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

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Gen-Piroxicam inhibits the activity of prostaglandin synthetase. The resulting decrease in prostaglandin biosynthesis may partially explain its anti-inflammatory action. Gen-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 that of ASA 4.2 g daily.

Pharmacodynamics

Gen-Piroxicam is a non-steroidal anti-inflammatory agent with analgesic properties. Its mechanism of action is incompletely known. (See **Action And Clinical Pharmacology, *Mechanism of Action*)**

Pharmacokinetics

Absorption: Piroxicam is well absorbed following oral 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.

Distribution: Ninety-nine percent of plasma piroxicam is bound to plasma proteins. The presence of Piroxicam in breast milk has been determined during initial and long term dosing conditions (52 days). Piroxicam appeared in breast milk at about 1% to 3% of the maternal plasma concentration. No accumulation of Gen-Piroxicam occurred in milk relative to that in plasma during treatment.

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.

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.

Excretion: Piroxicam and its biotransformation products are excreated in urine and feces, with about twice as much appearing in the urine as in the feces. Approximately 5% of a piroxicam dose is excreted unchanged. The plasma half-life ($T_{1/2}$) for piroxicam is approximately 50 hours.

Special Population and Conditions:

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, perticularly 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 Gen-Piroxicam. Gen-Piroxicam is contraindicated in severe liver impairment or active liver disease.

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

STORAGE AND STABILITY

Store between 15 and 30°C. Protect from moisture.

SPECIAL HANDLING INSTRUCTIONS

Not applicable.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Gen-Piroxicam (piroxicam) 10 mg are hard gelatin capsules with deep powder blue opaque bodies imprinted with “026” and maroon opaque caps imprinted with “G” in black.

Gen-Piroxicam (piroxicam) 20 mg are hard gelatin capsules with maroon opaque bodies imprinted with “027” and maroon opaque caps imprinted with “G” in black.

Gen-Piroxicam Capsules contain 10 or 20 mg of piroxicam, USP. In addition, they contain cornstarch, D&C Red #28, FD&C Blue #1, FD&C Red #40, gelatin, lactose, magnesium stearate, sodium lauryl sulphate and titanium dioxide.

Gen-Piroxicam capsules are available in bottles of 100’s and 500’s.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

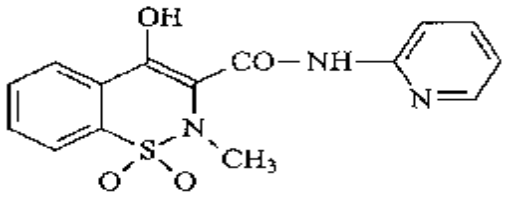
Drug Substance

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 mass: $C_{15}H_{13}N_30_45$; 331 .35

Structural formula:



Physicochemical properties: Gen-Piroxicam is an off-white to light tan or light yellow, odorless powder. Forms a monohydrate that is yellow. It is very slightly soluble in water, in dilute acids, and in most organic solvents, slightly soluble in alcohol and in aqueous alkaline solutions.

CLINICAL TRIALS

Randomized clinical trials with piroxicam have NOT been designed to detect differences in cardiovascular adverse events in a chronic setting.

Comparative Bioavailability Studies

A comparative, two-way, single-dose bioavailability study was performed on Gen-Piroxicam Capsules 20 mg and FELDENE (piroxicam) 20 mg Capsules. The pharmacokinetic data calculated for the Gen-Piroxicam and FELDENE are presented below.

Table 3. Pharmacokinetic Data calculated for Gen-Piroxicam and FELDENE

Geometric mean Arithmetic mean (C.V.)			
Parameter	Test	Reference	Ratio of means %
AUC_t (mcg.h/mL)	125 134 (35.8)	125 131 (31.7)	100
AUC_i (mcg.h/mL)	143 155 (42.3)	140 149 (35.9)	102
C_{max} (mcg/mL)	2.32 2.34 (11.7)	2.24 2.26 (15.8)	104
T_{max}* (h)	2.23 (1.69)	2.60 (1.30)	
$T_{½}$* (h)	53.2 (20.4)	54.7 (18.1)	

* For T_{max} and $T_{1/2}$ arithmetic mean (standard deviation) are presented.

DETAILED PHARMACOLOGY

Animal Pharmacology: 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 footpad 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 (clinical): See Actions and Clinical Pharmacology section.

TOXICOLOGY

<u>Acute Toxicity</u>

		LD_{50} (95% Confidence Limits) mg/kg	
Species	**Sex**	**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 levels.

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 labor 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, post-coitum. 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 bodyweight 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.

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PART III: CONSUMER INFORMATION

GEN-PIROXICAM
(Piroxicam Capsules, USP)

Read this information each time you refill your prescription in case new case information has been added.

This leaflet is a summary designed specifically for you to read. It will NOT tell you everything about Gen-Piroxicam. See your health care provider and pharmacist regularly and ask them questions about your health and any medications you take.

ABOUT THIS MEDICATION

Your health care provider has prescribed Gen-Piroxicam for you for symptomatic relief of one or more of the following medical conditions:

- rheumatoid arthritis;
- osteoarthritis (degenerative joint disease);
- ankylosing spondylitis

What it does:
Gen-Piroxicam (piroxicam), as a nonsteroidal anti-inflammatory drug (NSAID), can reduce the chemicals produced by your body, which cause pain and swelling.

Gen-Piroxicam, as a nonsteroidal anti-inflammatory drug (NSAID), does NOT cure your illness or prevent it from getting worse. Gen-Piroxicam can only relieve pain and reduce swelling as long as you continue to take it.

When it should not be used:
DO NOT TAKE Gen-Piroxicam if you have any of the following medical conditions:

- **Heart bypass surgery (planning to have or recently had)**
- **Severe uncontrolled heart failure**
- **Bleeding in the brain or other bleeding disorder**
- **Current pregnancy (after 28 weeks of pregnancy)**
- **Currently breastfeeding (or planning to breastfeed)**
- **Allergy to ASA (Acetylsalicylic Acid) or other NSAIDs (Nonsteroidal Anti-Inflammatory Drugs)**
- **Ulcer (active)**
- **Bleeding from the stomach or gut (active)**
- **Inflammatory bowel disease (Crohn's Disease or Ulcerative Colitis)**
- **Liver disease (active or severe)**
- **Kidney disease (severe or worsening)**
- **High potassium in the blood**
- **Allergy to piroxicam or any other component of Gen-Piroxicam capsules.**

Patients who took a drug in the same class as Gen-Piroxicam after a type of heart surgery (coronary artery bypass grafting (CABG)) were more likely to have heart attacks, strokes, blood clots in the leg(s) or lung(s), and infections or other complications than those who did NOT take that drug.

Gen-Piroxicam should NOT be used in patients under 16 years of age since the safety and effectiveness have NOT been established.

What the medicinal ingredient is:
Piroxicam

What the important nonmedicinal ingredients are:
Gen-Piroxicam Capsules contain 10 or 20 mg of Gen-Piroxicam, USP. In addition, they contain cornstarch, D&C Red #28, FD&C Blue #1, FD&C Red #40, gelatin, lactose, magnesium stearate, sodium lauryl sulphate and titanium dioxide.

What dosage forms it comes in:
Gen-Piroxicam is available as capsules of 10 mg and 20 mg.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

If you have, or previously had, any of the following medical conditions, see your health care provider to discuss treatment options other than Gen-Piroxicam**:**

- **Heart Attack or Angina**
- **Stroke or Mini-stroke**
- **Loss of Vision**
- **Current Pregnancy (less than 28 weeks)**
- **Congestive Heart Failure**

Before taking this medication, tell your health care provider if you have any of the following:

- High blood pressure
- High cholesterol
- Diabetes mellitus or on a low sugar diet
- Atherosclerosis
- Poor circulation to your extremities
- Smoker or ex-smoker
- Kidney disease or urine problems
- Previous ulcer or bleeding from the stomach or gut
- Previous bleeding in the brain
- Bleeding problems
- Family history of allergy to NSAIDs, such as acetylsalicylic acid (ASA), celecoxib, diclofenac, diflunisal, etodolac, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, mefenamic acid, meloxicam, nabumetone, naproxen, oxaprozin, piroxicam, rofecoxib, sulindac, tenoxicam, tiaprofenic acid, tolmetin, or valdecoxib (NOT a complete list)
- Family history of asthma, nasal polyps, long-term swelling of the sinus (chronic sinusitis) or hives

Also, before taking this medication, tell your health care provider if you are planning to get pregnant.

While taking this medication:

- tell any other doctor, dentist, pharmacist or other health care professional that you see, that you are taking this medication, especially if you are planning to have heart surgery;
- do NOT drink alcoholic beverages while taking this medication because you would be more likely to develop stomach problems;
- fertility may be decreased. The use of Gen-Piroxicam is not recommended in women trying to get pregnant. In women who have difficulty conceiving, stopping Gen-Piroxicam should be considered.

INTERACTIONS WITH THIS MEDICATION

Talk to your health care provider and pharmacist if you are taking any other medication (prescription or non-prescription) such as any of the following (NOT a complete list):

- Acetylsalicylic Acid (ASA) or other NSAIDs
  - e.g. ASA, celecoxib, diclofenac, ibuprofen, indomethacin, ketorolac, meloxicam, naproxen
- Antacids
- Antidepressants
  - Selective Serotonin Reuptake Inhibitors (SSRIs)
    - e.g. citalopram, fluoxetine, paroxetine, sertraline
- Blood pressure medications
  - ACE (angiotensin converting enzyme) inhibitors
    - e.g. enalapril, lisinopril, perindopril, ramipril
  - ARBs (angiotensin II receptor blockers)
    - e.g. candesartan, irbesartan, losartan, valsartan
- Blood thinners
  - e.g. warfarin, ASA, clopidogrel
- Cholestyramine
- Cimetidine
- Corticosteroids (including glucocorticoids)
  - e.g. prednisone
- Cyclosporin
- Diuretics
  - e.g. furosemide, hydrochlorothiazide
- Lithium
- Methotrexate
- Oral contraceptives
- Oral hypoglycemics (diabetes medications)
- Tacrolimus

Your health care provider may prescribe low dose ASA (acetylsalicylic acid) as a blood thinner to reduce your risk of having a heart attack or stroke while you are taking Gen-Piroxicam. Take only the amount of ASA prescribed by your health care provider. You are more likely to upset or damage your stomach if you take both Gen-Piroxicam and ASA than if you took Gen-Piroxicam alone.

PROPER USE OF THIS MEDICATION

Medical Condition	Starting Dose	Maximum Dose (per day)
Rheumatoid Arthritis,	20 mg once daily or 10 mg twice daily. According to therapeutic response, the dose may be reduced to 10 mg once daily.	20 mg
Ankylosing Spondylitis	20 mg once daily or 10 mg twice daily. According to therapeutic response, the dose may be reduced to 10 mg once daily.	20 mg
Osteoarthritis	20 mg once daily or 10 mg twice daily. According to therapeutic response, the dose may be reduced to 10 mg once daily.	20 mg

Take Gen-Piroxicam only as directed by your health care provider. **Do NOT take more of it, do NOT take it more often and do NOT take it for a longer period of time than your health care provider recommended. If possible, you should take the lowest dose of this medication for the shortest time period**. Taking too much Gen-Piroxicam may increase your chances of unwanted and sometimes dangerous side effects, especially if you are elderly, have other diseases or take other medications.
See your health care provider regularly to discuss whether this medicine is working for you and if it is causing you any unwanted effects.

This medication has been prescribed specifically for you. Do NOT give it to anyone else. It may harm them, even if their symptoms seem to be similar to yours.

Gen-Piroxicam is NOT recommended for use in patients under 16 years of age since safety and effectiveness have NOT been esetablished.

Gen-Piroxicam should be taken immediately after a meal or with food or milk. You should remain standing or sitting upright for about 15-30 minutes after taking this medicine

Missed Dose:
If you take Gen-Piroxicam once a day and if you miss a dose of this medicine and remember within 8 hours of the missed dose, take it right away. If you take Gen-Piroxicam twice a day and if you miss a dose and remember within 2 hours of the missed dose, take it right away. Then go back to your regular dosing schedule. If you have any question, check with your doctor or pharmacist.

Overdose:
If you have taken too much Gen-Piroxicam (more than prescribed by your doctor), contact your doctor, nearest Emergency Department, or Poison Control Centre.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Gen-Piroxicam may cause some side effects, especially when used for a long time or in large doses. When these side effects occur, you may require medical attention. Report all symptoms or side effects to your health care provider.
Gen-Piroxicam may cause you to become drowsy or tired. Be careful about driving or participating in activities that require you to be alert. If you become drowsy, dizzy or light-headed after taking Gen-Piroxicam, do NOT drive or operate machinery.
Gen-Piroxicam may cause you to become more sensitive to sunlight. Any exposure to sunlight or sunlamps may cause sunburn, skin blisters, skin rash, redness, itching or discolouration, or vision changes. If you have a reaction from the sun, check with your health care provider.

Check with your health care provider IMMEDIATELY if you develop chills, fever, muscle aches or pains, or other flu-like symptoms, especially if they occur before or together with a skin rash. These symptoms may be the first signs of a SERIOUS ALLERGIC REACTION to this medication.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom	STOP taking Gen-Piroxicam and get emergency medical attention IMMEDIATELY	Stop taking Gen-Piroxicam and talk to your physician or pharmacist
Bloody or black tarry stools	✓	
Shortness of breath, wheezing, any trouble breathing or chest tightness	✓	
Skin rash, hives, swelling or itching	✓	
Blurred vision, or any visual disturbance	✓	
Any change in the amount or colour of your urine (red or brown)	✓	
Any pain or difficulty experienced while urinating		✓
Swelling of the feet, lower legs; weight gain		✓
Vomiting or persistent indigestion, nausea, stomach pain or diarrhoea		✓
Yellow discolouration of the skin or eyes, with or without itchy skin		✓
Malaise, fatigue, loss of appetite		✓
Headaches, stiff neck		✓
Mental confusion, depression		✓
Dizziness, lightheadedness		✓
Hearing problems		✓

This is NOT a complete list of side effects. If you develop any other symptoms while taking Gen-Piroxicam, see your health care provider.

HOW TO STORE IT

Store between 15 and 30°C. Protect from moisture.

Do Not keep outdated medicine or medicine no longer needed. Any outdated or unused medicine should be returned to your pharmacist.

Keep out of reach of children.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

Report online at www.healthcanada.gc.ca/medeffect
Call toll-free at 1-866-234-2345
Complete a Canada Vigilance Reporting Form and:

- Fax toll-free to 1-866-678-6789, or
- Mail to: Canada Vigilance Program, Health Canada
  Postal Locator 0701C
  Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect

NOTE: Should you require information related to the management of the side effect, please contact your health care provider before notifying Canada Vigilance. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be requested by contacting the sponsor Genpharm ULC at:
1-888-575-1375
Email: customerservice@genpharm.ca

This leaflet was prepared by Genpharm ULC

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