PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrTEVA-PIROXICAM

Piroxicam Capsules

Capsules, 10 mg and 20 mg, For Oral Use

USP

Nonsteroidal Anti-inflammatory Drug (NSAID)

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RECENT MAJOR LABEL CHANGES

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PrTEVA-PIROXICAM

Piroxicam Capsules

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

TEVA-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 2 CONTRAINDICATIONS and 7 WARNINGS AND PRECAUTIONS)

Use of TEVA-PIROXICAM (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 2 CONTRAINDICATIONS and 7 WARNINGS AND PRECAUTIONS)

TEVA-PIROXICAM (piroxicam), as a NSAID, does NOT treat clinical disease or prevent its progression.

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

1.1 Pediatrics (< 16 years of age):

Based on the data submitted and reviewed by Health Canada, the safety and efficacy of TEVA-PIROXICAM in pediatric patients has not been established; therefore, Health Canada has not authorized an indication for pediatric use (see 2 CONTRAINDICATIONS).

1.2 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 4.2 Recommended Dose and Dosage

Adjustment and 7.1.4 Geriatrics).

2 CONTRAINDICATIONS

TEVA-PIROXICAM is contraindicated in:

- the peri-operative setting of coronary artery bypass graft surgery (CABG). Although TEVA-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 ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

- 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 7 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 7 WARNINGS AND PRECAUTIONS- Renal)

- known hyperkalemia (see Warnings and Precautions - *Renal - Fluid and Electrolyte Balance*)

- children and adolescents less than 16 years of age

3 SERIOUS WARNING AND PRECAUTIONS

Risk of Cardiovascular (CV) Adverse Events: Ischemic Heart Disease, Cerebrovascular Disease, Congestive Heart Failure (NYHA II-IV)
(See 7 WARNINGS AND PRECAUTIONS – Cardiovascular)

TEVA-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 may be at greater risk.

Caution should be exercised in prescribing TEVA-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 TEVA-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 7 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 TEVA-PIROXICAM.

Risk of Gastrointestinal (GI) Adverse Events (See 7 WARNINGS AND PRECAUTIONS - Gastrointestinal)

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

Risk in Pregnancy: Caution should be exercised in prescribing TEVA-PIROXICAM during the first and second trimesters of pregnancy. Use of NSAIDS at approximately 20 weeks of gestation or later may cause fetal renal dysfunction leading to oligohydramnios and neonatal renal impairment or failure (see 7.1.1 **Pregnant Women**). TEVA-PIROXICAM is contraindicated for use during the third trimester because of risk of premature closure of the ductus arteriosus and uterine inertia (prolonged parturition) (see **2 CONTRAINDICATIONS**).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

Use of TEVA-PIROXICAM should be limited to the lowest effective dose for the shortest possible duration of treatment. See 1 INDICATIONS.

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 2 CONTRAINDICATIONS and 7 WARNINGS AND PRECAUTIONS)

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.

4.2 Recommended Dose and Dose Adjustment

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.

The total daily dose of TEVA-PIROXICAM should not exceed 20 mg per day.

Pediatrics (< 16 years of age): Health Canada has not authorized an indication for pediatric use (See 2 CONTRAINDICATIONS).

Geriatrics (> 65 years of age): Consideration should be given to a starting dose lower than the one usually recommended, with individual adjustment when necessary and under close supervision (See 7.1.4 Geriatrics).

Renal Insufficiency: Because of the extensive renal excretion of TEVA-PIROXICAM and its biotransformation products (less than 5% of the daily dose excreted unchanged), lower doses of TEVA-PIROXICAM should be anticipated in patients with impaired renal function and they should be carefully monitored. TEVA-PIROXICAM is contraindicated in severe renal impairment and in deteriorating renal disease (See **2 CONTRAINDICATIONS**).

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

4.4 Administration

TEVA-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.

4.5 Missed Dose

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

5 OVERDOSAGE

Cases of overdose, up to 1800 mg piroxicam, have been reported. Recovery was complete without sequelae. In the event of overdosage with TEVA-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 overdosage.

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

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/ /Composition	Non-medicinal Ingredients
Oral	Capsules, 10 mg and 20 mg of piroxicam	Magnesium stearate, sodium lauryl sulphate, sodium starch glycolate and starch.

The 10 mg capsule is a maroon/blue opaque hard gelatin capsule and the 20 mg capsule is a maroon opaque hard gelatin capsule, both comprised of FD&C Blue #1, FD&C Red #3 and titanium dioxide.

TEVA-PIROXICAM 10 mg and 20 mg capsules are available in bottles of 100, 250 and 500 and also in unit dose boxes of 100.

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

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.

TEVA-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 ***9 DRUG INTERACTIONS – 9.4 Drug/Drug Interactions - Acetylsalicylic acid (ASA) or other NSAIDs***)

Carcinogenesis and Mutagenesis
(see **16 NON-CLINICAL TOXICOLOGY**)

Cardiovascular
TEVA-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 TEVA-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 TEVA-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 TEVA-PIROXICAM should hypertension either develop or worsen with its use.

Use of NSAIDs, such as TEVA-PIROXICAM, can induce fluid retention and edema, and may exacerbate congestive heart failure, through a renally-mediated mechanism. (See **7 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.

Driving and Operating Machinery

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

Endocrine and Metabolism

Corticosteroids:
TEVA-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 **9 DRUG INTERACTIONS – 9.4 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 warning symptoms, in patients treated with NSAIDs, including TEVA-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 TEVA-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 **7 WARNINGS AND PRECAUTIONS – 7.1 *Special Populations - Geriatrics***)

Evidence from epidemiological studies suggests that 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 TEVA-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 TEVA-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 TEVA-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 TEVA-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 TEVA-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.

TEVA-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 **9 DRUG INTERACTIONS - *Drug-Drug Interactions - Acetylsalicylic Acid (ASA) or other NSAIDs***)

Concomitant administration of TEVA-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 TEVA-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 8 ADVERSE REACTIONS 8.4 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 function 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.

Immune

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

Aseptic Meningitis:
Rarely, with some NSAIDs, including TEVA-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.

Also, see **Sensitivity/Resistance.**

Monitoring and Laboratory Tests

Pregnancy: If TEVA-PIROXICAM is administered in the middle (approximately 20 weeks) to the end of the second trimester, it is recommended that pregnant women on TEVA-PIROXICAM be closely monitored for amniotic fluid volume since TEVA-PIROXICAM may result in reduction of amniotic fluid volume and even oligohydramnios (see 7.1.1 Special Populations). TEVA-PIROXICAM is contraindicated for use in the third trimester of pregnancy.

Cardiovascular: Blood Pressure should be monitored regularly during treatment with TEVA-PIROXICAM (See 7 Warnings and Precautions - *Cardiovascular*).
Hematologic: Patients should have their hemoglobin or hematocrit checked periodically. Concurrent therapy of TEVA-PIROXICAM with warfarin requires close monitoring of the international normalilized ratio (INR) (See 7 Warnings and Precautions - *Haematology*).

Hepatic: Liver function tests should be monitored periodically (See 7 Warnings and Precautions – *Hepatic/Biliary/Pancreatic*).
Opthalmologic: Opthalmic examination should be performed at periodic intervals. (See 7 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 TEVA-PIROXICAM (See 7 Warnings and Precautions - *Renal*).
Serum electrolytes should be monitored periodically, especially in those patients who are at risk (7 Warnings and Precautions – *Renal – Fluid and Electrolyte Balance*).

Drug interactions: See 9 DRUG INTERACTIONS for other situations requiring monitoring.

Neurologic
Some patients may experience drowsiness, dizziness, blurred vision, vertigo, tinnitus, hearing loss, insomnia or depression with the use of NSAIDs, such as TEVA-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 TEVA-PIROXICAM should be discontinued and an ophthalmologic examination performed. Ophthalmologic examination should be carried out at periodic intervals in any patient receiving TEVA-PIROXICAM for an extended period of time.

Peri-Operative Considerations
(See 2 **CONTRAINDICATIONS** - Coronary Artery Bypass Graft Surgery)

Psychiatric
(See 7 **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, 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 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.

Caution should be used when initiating treatment with TEVA-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 TEVA-PIROXICAM and its biotransformation products (less than 5% of the daily dose excreted unchanged), lower doses of TEVA-PIROXICAM should be anticipated in patients with impaired renal function and they should be carefully monitored.

Advanced Renal Disease:
(See 2 **CONTRAINDICATIONS**)

Fluid and Electrolyte Balance:
Use of NSAIDs, including TEVA-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 TEVA-PIROXICAM in patients with a history of congestive heart failure, compromised cardiac function, hypertension, increased age or other conditions predisposing to fluid retention (See 7 **Warnings and Precautions - *Cardiovascular***).

Use of NSAIDs, including TEVA-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 2 **CONTRAINDICATIONS**).

Reproductive Health: Female and Male Potential

- **Fertility:**

The use of TEVA-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 TEVA-PIROXICAM should be considered.

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.

Sensitivity/Resistance

Anaphylactoid Reactions:

As with NSAIDs in general, anaphylactoid reactions have occurred in patients without known prior exposure to TEVA-PIROXICAM. In post-marketing experience, rare cases of anaphylactic/ anaphylactoid reactions and angioedema have been reported in patients receiving TEVA-PIROXICAM. TEVA-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 **2 CONTRAINDICATIONS**).

ASA-Intolerance:

TEVA-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 **2 CONTRAINDICATIONS**).

Cross-sensitivity:

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

Serious skin reactions:

(See **7 WARNINGS AND PRECAUTIONS - *Skin***)

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

Skin

Serious skin reactions: Use of some NSAIDs, such as TEVA-PIROXICAM, have been associated with rare post-market cases of serious, fatal or otherwise life-threatening skin reactions, including:

- drug reaction with eosinophilia and systemic symptoms (DRESS)
- Stevens-Johnson syndrome,
- toxic epidermal necrolysis,
- exfoliative dermatitis and
- erythema multiforme.

Patients appear to be at higher risk for these events early in the course of therapy, with the onset of cases usually occurring within the first month of treatment. These reactions may be reversible if the causative agent is discontinued and appropriate treatment instituted. Patients should be advised that they should discontinue their NSAID at the first appearance of a skin rash, mucosal lesions or any other sign of hypersensitivity, and contact their physician immediately for assessment and advice, including which therapies to discontinue.

DRESS typically, although not exclusively, presents with fever, rash, lymphadenopathy, and/or facial swelling. Other clinical manifestations may include hepatitis, nephritis, hematological abnormalities, myocarditis, or myositis. Sometimes symptoms of DRESS may resemble an acute viral infection, and eosinophilia is often present. Because this disorder is variable in its presentation, other organ systems not noted here may be involved. It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident.

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 piroxicam. These include arthralgias, pruritus, fever, fatigue, and rash including vesiculo bullous reactions and exfoliative dermatitis.

7.1 Special Populations

7.1.1 Pregnant Women

TEVA-PIROXICAM is contraindicated for use during the third trimester of pregnancy because of risks of premature closure of the ductus arteriosus and the potential to prolong parturition (see

16 NON-CLINICAL TOXICOLOGY). Caution is recommended in prescribing TEVA-PIROXICAM during the first and second trimesters of pregnancy, particularly from the middle to end of the second trimester of pregnancy (onset at approximately 20 weeks) due to possible fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment or failure.

Published studies and postmarketing reports describe maternal NSAID use at approximately 20 weeks gestation or later in pregnancy associated with fetal renal dysfunction leading to oligohydramnios, and in some cases, neonatal renal impairment or failure. NSAIDs were shown to cause significant reduction in fetal urine production prior to reduction of amniotic fluid volume. There have also been a limited number of case reports of maternal NSAID use and neonatal renal dysfunction and renal impairment without oligohydramnios, some of which were irreversible, even after treatment discontinuation.

These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation. Complications of prolonged oligohydramnios may for example, include limb contractures and delayed lung maturation. In some postmarketing cases of impaired neonatal renal function, invasive procedures such as exchange transfusion or dialysis were required.

If after careful consideration of the benefit-risk, NSAID treatment is considered necessary to be administered anywhere from the middle (onset at approximately 20 weeks) to the end of the second trimester of pregnancy, the use should be limited to the lowest effective dose and shortest duration possible. It is also recommended that ultrasound monitoring of amniotic fluid be considered if TEVA-PIROXICAM treatment extends beyond 48 hours and that NSAIDs treatment be discontinued if oligohydramnios occurs, followed by appropriate medical follow up.

Inhibition of prostaglandin synthesis may adversely affect pregnancy and/or embryo-fetal 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-fetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenesis period.

7.1.2 Nursing Women:
(See **2 CONTRAINDICATIONS**)

7.1.3 Pediatrics:

(See **2 CONTRAINDICATIONS)**

7.1.4 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 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.

8 ADVERSE REACTIONS

8.1 Adverse Drug Reaction Overview
The most common adverse reactions encountered with nonsteroidal anti-inflammatory drugs 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 (**7 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 (**7 WARNINGS AND PRECAUTIONS - *Skin***).

Use of some NSAIDs is associated with an increased incidence of cardiovascular adverse events (**7 WARNINGS AND PRECAUTIONS -*Cardiovascular***).

8.2 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 (≥10%) and Common (>1% and ≤ 10%) adverse drug reactions are summarized in Tables 2 and 3 respectively.

Table 2. Very Common (≥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	< 1
epistaxis	< 1

Table 3. Common (≥1% and ≤10%) Clinical Trial Adverse Drug Reactions

Adverse Reactions	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	**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.

8.3 Less Common Clinical Trial Adverse Drug Reactions

Allergic (<1%): anaphylaxis, bronchospasm, urticaria/angioedema, vasculitis, serum sickness (see **7 WARNINGS AND PRECAUTIONS**), each in less than 1% of patients.

Cardiovascular (<1%): hypertension, palpitations, worsening of congestive heart failure (see **7 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 **7 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 **7 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.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial Findings

Hematologic (15.0%): See **Table 2 Very common (≥10%) Clinical Trial Adverse Drug Reactions**. See 7 **WARNINGS AND PRECAUTIONS**, Hematologic.

Laboratory Parameters:
Changes in laboratory parameters observed during piroxicam therapy have included an elevation of BUN, creatinine (see **7 WARNINGS AND PRECAUTIONS,** Renal), uric acid and liver enzymes LDH, SGOT, SGPT and alkaline phosphatase.

8.5 Post-Market Adverse 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

9 DRUG INTERACTIONS

9.3 Drug-Behaviour Interactions

Concurrent use of alcohol with TEVA-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 TEVA-PIROXICAM should exercise caution in carrying

out activities that require alertness and should refrain from driving or using machines.

9.4 Drug-Drug Interactions

Highly Protein Bound Drugs:
TEVA-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 TEVA-PIROXICAM.

Acetylsalicylic acid (ASA) or other NSAIDs:
The use of TEVA-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 anti-platelet effects of low dose ASA, possibly by competing with ASA for access to the active site of cyclooxygenase-1.

Anti-coagulants:
(See **7 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 TEVA-PIROXICAM with warfarin requires close monitoring to be certain that no change in anticoagulant dosage is necessary. TEVA-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 TEVA-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 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 TEVA-PIROXICAM with propranolol can reduce the hypotensive effect. Patients should be monitored for altered antihypertensive or antianginal response to betablockers when TEVA-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 TEVA-PIROXICAM (see **7 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 TEVA-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 ($AUC_{0\text{-}120\ hrs}$) 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.

Digoxin:
The concomitant use of piroxicam with digoxin has been reported to increase the serum concentration and prolong the half-life of digoxin. During the concomitant use of TEVA-PIROXICAM and digoxin, monitor serum digoxin levels.

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 (**7 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 TEVA-PIROXICAM treatment.

Methotrexate:
Although up to date there have been no reports of an interaction with 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 TEVA-PIROXICAM is administered concomitantly with methotrexate, particularly in patients with pre existing renal impairment, who may be more susceptible.

Quinolone antibacterials:
There have been isolated reports of convulsions which may have been due to concomitant use of quinolones and NSAIDs. Patients should be observed for adjustment of dose if required.

Selective Serotonin Reuptake Inhibitors (SSRIs):
Concomitant administration of NSAIDs and SSRIs may increase the risk of gastrointestinal ulceration and bleeding (see **7 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. Patients should be carefully monitored during concurrent use.

Oral Contraceptives:
No drug interaction information is available for TEVA-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 TEVA-PIROXICAM**.**

Pemetrexed:
Concomitant use of TEVA-PIROXICAM and pemetrexed may increase the risk of pemetrexed-associated myelosuppression, renal, and GI toxicity. In patients with mild to moderate renal impairment monitor for myelosuppression, renal and GI toxicity. Patients taking TEVA-PIROXICAM should interrupt dosing for at least five days before, the day of, and at least two days following pemetrexed administration. If concomitant administration is necessary, patients should be monitored closely for toxicity.

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

9.6 Drug-Herb Interactions
Interactions with herbal products have not been established.

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

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action
Piroxicam inhibits the activity of prostaglandin synthetase. The resulting decrease in prostaglandin biosynthesis may partially explain its anti-inflammatory action. Piroxicam capsules do 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 acetylsalicylic acid (ASA).

10.2 Pharmacodynamics
Piroxicam is a non-steroidal anti-inflammatory agent with analgesic and antipyretic properties. Its mechanism of action is incompletely known. (See **10 CLINICAL PHARMACOLOGY**, 10.1 Mechanism of Action).

10.3 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 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.

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 TEVA-PIROXICAM. TEVA-PIROXICAM is contraindicated in severe liver impairment or active liver disease.

Renal Insufficiency: Because of the extensive renal excretion of piroxicam and its biotransformation products, lower doses of TEVA-PIROXICAM should be anticipated in patients with impaired renal function and they should be carefully monitored. TEVA-PIROXICAM is

contraindicated in severe renal impairment and in deteriorating renal disease.

11 STORAGE, STABILITY AND DISPOSAL

TEVA-PIROXICAM (piroxicam) capsules should be protected from light and stored at room temperature (15 - 30°C). The unit dose boxes should be stored at a temperature not exceeding 25°C and protected from light and high humidity.

12 SPECIAL HANDLING INSTRUCTIONS

None

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

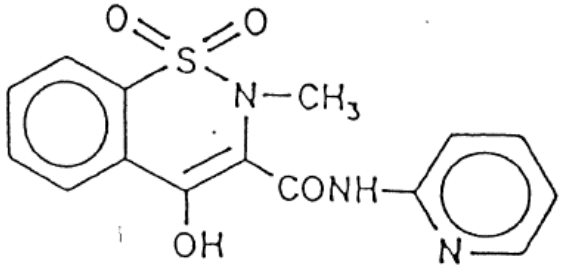
Common name: Piroxicam

Chemical name: 2H-1,2-benzothiazine-3-carboxamide, 4 hydroxy-2-methyl-N-2-pyridinyl-1,1-dioxide

Molecular formula: $C_{15}H_{13}N_3O_4S$

Molecular mass: 331.35

Structural formula:



Physicochemical properties: Piroxicam is a white, crystalline, hygroscopic solid. Melting point is 196 - 200ºC. It is poorly soluble in water, dilute acid and most organic solvents and slightly soluble in alcohols and aqueous alkaline solution.

Piroxicam belongs to the chemical class of N-heterocyclic carboxamides of 1, 2-benzothiazine-1, 1-dioxide(oxicams). An amphoteric compound, piroxicam has a weakly acidic 4-hydroxy proton (pKa 5.1) and a weakly basic pyridyl nitrogen (pKa 1.5) as determined by ultraviolet absorption spectrophotometry in methanol:water (2.5:97.5 v/v) solvent medium.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

The clinical trial data on which the indications were authorized are not available.

14.2 Comparative Bioavailability Studies

Bioavailability

A comparative two-way, single dose bioavailability study was performed on TEVA-PIROXICAM 20 mg Capsules and FELDENE 20 mg Capsules. The pharmacokinetic data (mean ± standard deviation) for the two formulations is tabulated below:

Piroxicam
(1 x 20 mg)
From measured data
Arithmetic Mean (± Standard Deviation)

Parameter	Test*	Reference†	% Ratio of Arithmetic Means
AUC_{0-144} (µg*h/mL)	135.99 ± 43.95	139.90 ± 47.28	98.8 ± 16.0
C_{MAX} (µg/mL)	2.18 ± 0.31	2.24 ± 0.39	99.50 ± 15.03
T_{MAX} (h)	1.34 ± 0.60	1.25 ± 0.55	
$T_{½}$ (h)	56.35 ± 33.21	56.11 ± 41.84	
K_{el} (1/h)	0.019 ± 0.021	0.023 ± 0.024	

* TEVA-PIROXICAM 20 mg Capsules (Novopharm Limited, Canada)

† FELDENE 20 mg Capsules (Pfizer Canada Inc., Canada), purchased in Canada

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

Acute Toxicity:

		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 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.

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.

Reproductive and Developmental Toxicology:
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 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 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.

17 SUPPORTING PRODUCT MONOGRAPHS

FELDENE (piroxicam) 10 and 20 mg Capsules and Suppositories Product Monograph. Pfizer Canada Inc. Date of Preparation: April 1, 1981, Date of Revision: August 24, 1993.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]TEVA-PIROXICAM
PIROXICAM CAPSULES USP

Read this carefully before you start taking **TEVA-PIROXICAM** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **TEVA-PIROXICAM.**

Serious Warnings and Precautions

Heart and blood vessel problems:

- TEVA-PIROXICAM can cause heart and blood vessel problems like heart attacks, stroke, blood clots, high blood pressure and heart failure. These can lead to death.
- The risk of having heart problems is higher if you take TEVA-PIROXICAM for long periods of time and/or at higher doses and/or in people who have heart disease.
- Tell your healthcare professional if you have or had heart problems, high blood pressure or diabetes.

Stomach and intestine (gastrointestinal) problems:

- TEVA-PIROXICAM can cause stomach and intestine problems like ulcers, inflammation, bleeding, holes/perforation, blockage or pain.

Pregnancy:

- **DO NOT** take TEVA-PIROXICAM if you are pregnant and in a later stage of pregnancy (28 weeks or later).
- If you are pregnant and in an earlier stage of pregnancy (less than 28 weeks) **only** take TEVA-PIROXICAM if you are told to do so by your healthcare professional. Medicines like TEVA-PIROXICAM may cause harm to you and your baby. Your healthcare professional will need to closely monitor your health and that of your baby (including your amniotic fluid levels) if they prescribe TEVA-PIROXICAM during this time.
- Tell your healthcare professional right away if you become pregnant, think you may be pregnant or want to get pregnant during your treatment with TEVA-PIROXICAM.

What is TEVA-PIROXICAM used for?
TEVA-PIROXICAM is used to treat the signs and symptoms of arthritis disorders such as:

- rheumatoid arthritis

- osteoarthritis (degenerative joint disease)
- ankylosing spondylitis

How does TEVA-PIROXICAM work?

- TEVA-PIROXICAM belongs to a group of medicines called nonsteroidal anti-inflammatory drugs (NSAIDs). It can reduce the chemicals produced by your body, which cause pain and swelling.

- TEVA-PIROXICAM only treats the symptoms and relieves pain and inflammation as long as you take it. TEVA-PIROXICAM does not cure the illness or stop it from getting worse.

What are the ingredients in TEVA-PIROXICAM?

Medicinal ingredients: piroxicam
Non-medicinal ingredients: FD&C blue#1, FD&C red #3, magnesium stearate, sodium lauryl sulphate, sodium starch glycolate, starch and titanium dioxide.

TEVA-PIROXICAM comes in the following dosage forms:

Capsules: 10 mg and 20 mg

Do not use TEVA-PIROXICAM if:

- you are planning to have or have recently had heart bypass surgery
- you have severe, uncontrolled heart failure
- you have bleeding in the brain or other bleeding disorders
- you are pregnant and in a later stage of pregnancy (28 weeks of pregnancy or later)
- you are currently breastfeeding (or are planning to breastfeed)
- you are allergic to piroxicam or any other ingredients in this medicine or part of the container
- you have a history of asthma, hives, growths in your nose, sinus swelling or symptoms of an allergic reaction after taking Acetylsalicylic Acid (ASA) or other NSAIDs
- you have active stomach or intestine ulcers
- you have active bleeding from the stomach or gut
- you have inflammatory bowel disease (Crohn's Disease or Ulcerative Colitis)
- you have liver disease (active or severe)
- you have kidney disease (severe or worsening)
- you have high potassium in the blood
- you are under 16 years of age

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take TEVA-PIROXICAM. Talk about any health conditions or problems you may have, including if you:

- have high blood pressure, high cholesterol or diabetes
- have atherosclerosis. This is when fats and cholesterol build up in your arteries.

- have or had heart attacks, chest pain, heart disease, stroke or heart failure
- have poor circulation to your extremities (like your hands and feet)
- smoke or used to smoke
- drink a lot of alcohol
- have a stomach infection
- have liver or kidney problems, urine problems or are dehydrated
- have a history of ulcer or bleeding from the stomach or gut (small or large intestine)
- have other bleeding or blood problems
- have asthma
- have immune system problems
- are taking other NSAID products including low-dose ASA or aspirin
- are on a low-salt diet
- are pregnant, planning on becoming or become pregnant while taking TEVA-PIROXICAM.

Other warnings you should know about:

- **Blood and bleeding problems:**
    - TEVA-PIROXICAM can cause blood problems, bleeding and prolonged bleeding.
    - Taking TEVA-PIROXICAM with the following drugs can increase your risk for bleeding:
        - Anticoagulants, which prevent blood clots
        - Corticosteroids, which treat inflammation
        - Selective serotonin reuptake inhibitors (SSRIs), which treat depression

- **Serious Skin Reactions:** In rare cases, serious, life-threatening allergic and skin reactions have been reported with some NSAIDs, such as TEVA-PIROXICAM. These skin problems happen most often during the first month of treatment. Tell your healthcare professional immediately if you notice any changes in your skin during or after your treatment.

  TEVA-PIROXICAM might cause you to become more sensitive to sunlight. Sunlight or sunlamps may cause sunburn, skin blisters, skin rash, redness, itching, changes in skin color, or vision changes. If you have a reaction from the sun, talk to your healthcare professional.

Check-ups and testing: You will have regular visits with your healthcare professional during treatment with TEVA-PIROXICAM to monitor your health. They will:

- Check your blood pressure.
- Check your eyes. TEVA-PIROXICAM can cause blurred or reduced vision.
- Do blood and urine tests to check your liver, kidney and blood health.

Surgery: Tell any doctor, dentist, pharmacist or healthcare professional that you see, that you are taking this medicine. This is especially important if you are planning to have heart surgery.

Driving and Using Machines: TEVA-PIROXICAM may cause eye or nervous system problems. This includes tiredness, trouble sleeping, blurred vision, spinning or dizziness (vertigo), hearing problems or depression. Be careful about driving or doing activities that require you to be alert. If you become drowsy, dizzy or light-headed after taking TEVA-PIROXICAM, do NOT drive or operate machinery.

Fertility in Women: TEVA-PIROXICAM may affect your fertility. This means that it may be difficult for you to have a child. If you have trouble having a child, you might need to stop taking TEVA-PIROXICAM. Talk to your healthcare professional if you have questions about this.

Adults (65 years or older): Side effects like gastrointestinal problems may happen more often. Your healthcare professional might have you start with a lower dose of TEVA-PIROXICAM. They will monitor your health during and after treatment.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with TEVA-PIROXICAM:

- Acetylsalicylic Acid (ASA) or other NSAIDs used to treat pain, fever and inflammation like celecoxib, diclofenac, ibuprofen naproxen
- medicines used to treat depression (antidepressants) like citalopram, fluoxetine, paroxetine, sertraline and lithium
- medicines used to treat high blood pressure like enalapril, ramipril, candesartan, irbesartan, propranolol
- medicines used as blood thinners like warfarin, ASA, clopidogrel
- medicines used to lower extra fluid levels (called diuretics) like furosemide, hydrochlorothiazide
- medicines used to treat diabetes like sulphonylurea or other hypoglycemics
- medicines used to lower the risk of organ rejection like tacrolimus and cyclosporin
- corticosteroids (including glucocorticoids) such as prednisone, used as an anti-inflammatory
- cholestyramine, used to lower cholesterol levels
- digoxin, used to treat heart disorders
- medicines used to treat different cancers, like methotrexate and pemetrexed
- medicines used to treat bacterial infections called quinolone antibacterials
- alcohol

How to take TEVA-PIROXICAM

- Take TEVA-PIROXICAM exactly as your healthcare professional has told you. They should recommend the lowest dose possible for your treatment for the shortest time needed.

- You may be told to take your TEVA-PIROXICAM once per day or twice per day.
- Swallow capsules whole after a meal with food or milk.
- **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.**
- If you have indigestion, nausea, vomiting, stomach pain or diarrhea after taking your TEVA-PIROXICAM, contact your healthcare professional.

Usual dose:
Adults 16 years and older:
Your healthcare professional will decide the best dose for you based on your condition. They will tell you how much to take and how often to take it.

Your healthcare professional may change your dose, stop your treatment for a period of time or recommend that you stop treatment completely. This may happen if:
- you have serious side effects, or
- your condition gets worse.

Overdose:

If you think you, or a person you are caring for, have taken too much TEVA-PIROXICAM, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:
Once per day treatment:
If you miss a dose of TEVA-PIROXICAM and it is:
- within 8 hours of when you should have taken your dose: take it right away.
- more than 8 hours late: skip the dose and continue with your usual schedule.

Twice per day treatment:
If you miss a dose of TEVA-PIROXICAM and it is
- within 2 hours of the missed dose: take it right away.
- more than 2 hours late: skip the missed dose and continue with your usual schedule.

What are possible side effects from using TEVA-PIROXICAM?
These are not all the possible side effects you may have when taking TEVA-PIROXICAM. If you experience any side effects not listed here, tell your healthcare professional.

TEVA-PIROXICAM may cause side effects, some of which can be serious. When these side effects occur, you may require medical attention. Report all symptoms or side effects to your health care provider.

Serious side effects and what to do about them			
Symptom / effect	**Talk with your healthcare provider or pharmacist**		**Stop taking drug and seek immediate medical help**
	Only if severe	**In all cases**	
COMMON			
Gastrointestinal (GI) problems (bleeding, blockage, holes, ulcers or inflammation in your GI tract)**:** blood in vomit, bloody or black tarry stools, dizziness, stomach pain, bloating, loss of appetite, weight loss, nausea, vomiting, diarrhea, constipation, chills or fever		X	
Hypertension (high blood pressure): fatigue, dizziness or fainting, chest pain	X		
UNCOMMON			
Anaphylaxis/hypersensitivity (severe allergic reactions): sudden wheeziness and chest pain or tightness; or swelling of eyelids, face, lips, tongue or throat, swelling or anaphylactic reaction/shock			X
Aseptic meningitis (inflammation of the protective lining of the brain that is not caused by infection): headaches, stiff neck, nausea and vomiting, fever or clouding of consciousness		X	
Blood problems (low white and/or red blood cell or platelet count): feeling tired or weak, pale skin, bruising or bleeding for longer than usual if you hurt yourself, fever, chills		X	
Congestive heart failure (heart does not pump blood as well as it should): shortness of breath, fatigue and weakness, swelling in ankles, legs and feet, cough, fluid retention, lack of appetite, nausea, rapid or irregular heartbeat, reduced ability to exercise			X
Cystitis (bladder infection): increased need to urinate, pain in the pelvis or lower back, frequent urination during the night, cloudy urine that may contain blood, burning or pain urinating		X	

Depression (sad mood that will not go away): difficult sleeping or sleeping too much, changes in appetite or weight, reduced sex drive and thoughts of death or suicide		X	
Kidney disorder/problems (including kidney failure): nausea, vomiting, fever, swelling of extremities, fatigue, thirst, dry skin, irritability, dark urine, increased or decreased urine output, blood in the urine, rash, weight gain (from retaining fluid), loss of appetite, mental status changes (drowsiness, confusion, coma)		X	
Liver problems (including hepatitis, liver failure, cholestasis): yellowing of your skin and eyes (jaundice), right upper stomach area pain or swelling, nausea or vomiting, unusual dark urine, unusual tiredness		X	
Lung problems, asthma: increased shortness of breath, wheezing, difficulty breathing, cough and chest tightness, irregular heartbeat			X
Myocardial infarction (heart attack): pressure or squeezing pain between the shoulder blades, in the chest, jaw, left arm or upper abdomen, shortness of breath, dizziness, fatigue, light-headedness, clammy skin, sweating, indigestion, anxiety, feeling faint and possible irregular heartbeat			X
Stroke (bleeding or blood clot in the brain): sudden numbness, weakness or tingling of the face, arm, or leg, particularly on one side of the body, sudden headache, blurry vision, difficulty swallowing or speaking, or lethargy, dizziness, fainting, vomiting, trouble understanding, trouble with walking and loss of balance			X
Tinnitus (hearing problems): includes ringing, buzzing, clicking or hissing in ears, loss of hearing		X	
Vertigo (a sense of severe spinning dizziness, lightheadedness)		X	
RARE			
Serious Skin Reactions: fever, severe rash,			X

swollen lymph glands, flu-like feeling, blisters and peeling skin that may start in and around the mouth, nose, eyes and genitals and spread to other areas of the body, swelling of face and/or legs, yellow skin or eyes, shortness of breath, dry cough, chest pain or discomfort, feeling thirsty, urinating less often, less urine or dark urine			

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html)for information on how to report online, by mail or by fax; or

- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
Store at room temperature (15 - 30°C). Protect from light and humidity.

Do NOT keep expired medicine or medicine you no longer need. Return all outdated or unused medicine to your pharmacist.

Keep out of the sight and reach of children.

If you want more information about TEVA-PIROXICAM:

- Talk to your healthcare professional
- Find the full Product Monograph that is prepared for healthcare professionals and includes this Patient Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website

http://www.tevacanada.com; or by calling 1-800-268-4127 ext. 3; or email druginfo@tevacanada.com.

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