PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]APO-TIAPROFENIC

Tiaprofenic Acid Tablets

Tablets, 200 mg and 300 mg, for oral use

Non-Steroidal Anti-Inflammatory Drug (NSAID)

APOTEX INC.

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Toronto, Ontario
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RECENT MAJOR LABEL CHANGES

2 CONTRAINDICATIONS	11/2023
3 SERIOUS WARNINGS AND PRECAUTIONS BOX	11/2023
7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests, *Pregnancy*	11/2023
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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

APO-TIAPROFENIC (tiaprofenic acid) is indicated for:

- The relief of signs and symptoms of rheumatoid arthritis and osteoarthritis (degenerative joint disease).

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 should be considered first. (See 2 CONTRAINDICATIONS and 7 WARNINGS AND PRECAUTIONS).

Use of APO-TIAPROFENIC 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)

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

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

1.1 Pediatrics

Pediatrics (< 18 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of tiaprofenic acid in pediatric patients has not been established; therefore, Health Canada has not authorized an indication for pediatric use. See 2 CONTRAINDICATIONS.

1.2 Geriatrics

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 7.1.4 Geriatrics.

2 CONTRAINDICATIONS

APO-TIAPROFENIC is contraindicated in:

- the peri-operative setting of coronary artery bypass graft surgery (CABG). Although tiaprofenic acid 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
- patients who are hypersensitive to this drug 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 ASA or other (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 in the past without any adverse reaction. The potential for cross-reactivity between different must be kept in mind (see 7 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 0.5 mL/sec) or deteriorating renal disease (individuals with lesser degrees of renal impairment are at risk of deterioration of their renal function when prescribed and must be monitored) (see 7 WARNINGS AND PRECAUTIONS - Renal)
- known hyperkalemia (see 7 WARNINGS AND PRECAUTIONS - Renal - Fluid and Electrolyte Balance)
- children and adolescents less than 18 years of age.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- **Risk of Cardiovascular (CV) Adverse Events: Ischemic Heart Disease, Cerebrovascular Disease, Congestive Heart Failure (NYHA II-IV):**

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

  Caution should be exercised in prescribing APO-TIAPROFENIC 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, such as APO-TIAPROFENIC 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 7 WARNINGS AND PRECAUTIONS - Renal - Fluid and Electrolyte Balance

Randomized clinical trials with tiaprofenic acid have not been designed to detect differences in cardiovascular events in a chronic setting. Therefore, caution should be exercised when prescribing APO-TIAPROFENIC. See 7 WARNINGS AND PRECAUTIONS - Cardiovascular

- **Risk of Gastrointestinal (GI) Adverse Events:**

  Use of NSAIDs, such as APO-TIAPROFENIC, is associated with an increased incidence of gastrointestinal adverse events (such as peptic/duodenal ulceration, perforation, obstruction and gastrointestinal bleeding). See 7WARNINGS AND PRECAUTIONS - Gastrointestinal

- **Risk in Pregnancy:**

  Caution should be exercised in prescribing APO-TIAPROFENIC 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). APO-TIAPROFENIC 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 APO-TIAPROFENIC should be limited to the lowest effective dose for the shortest possible duration of treatment. See 1 INDICATIONS

4.2 Recommended Dose and Dosage Adjustment

Rheumatoid Arthritis: The usual initial and maintenance dose is 600 mg daily in 3 divided doses. Some patients may do well on 300 mg twice daily. The maximum daily dose is 600 mg.

Osteoarthritis: The usual initial and maintenance dose is 600 mg daily in 2 or 3 divided doses. In rare cases patients may be maintained on 300 mg daily in divided doses. The maximum maintenance daily dose is 600 mg.

Pediatrics (< 18 years of age): Health Canada has not authorized an indication for pediatric use. See 2 CONTRAINDICATIONS

Geriatrics (>65 years of age): In the elderly, frail and debilitated, the dosage should be reduced to the lowest level providing control of symptoms, and adjusted when necessary. See 7.1.4 Geriatrics

Renal impairment: A lower dose should be considered in patients with mild and moderate renal impairment. APO-TIAPROFENIC is contraindicated in 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 2 CONTRAINDICATIONS

Hepatic impairment: A lower dose should be considered in patients with mild and moderate hepatic impairment. APO-TIAPROFENIC is contraindicated in severe liver impairment or active liver disease. See 2 CONTRAINDICATIONS

4.4 Administration

APO-TIAPROFENIC should be administered with food.

4.5 Missed Dose

If a dose is missed, the patient should take it as soon as it is recognized. If it is almost time for the next dose, skip the missed dose and continue with the next scheduled dose. The patient should be instructed not take 2 doses at the same time.

5 OVERDOSAGE

There have been no reports of overdosage with tiaprofenic acid. No specific antidote is known, therefore, the patient should be observed carefully and given symptomatic and supportive treatment.

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	Tablets; 200 mg and 300 mg	Colloidal silicon dioxide, hydroxypropyl cellulose, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol and titanium dioxide.

Description

APO-TIAPROFENIC 200 mg Tablets:

Each round, white, film-coated, biconvex tablet, bisected and engraved "APO" over "200" on

one side contains 200 mg of tiaprofenic acid.

Available in bottles of 100 and 250, unit dose packages of 100 (10x 10), 620 (nursing cards of 20 x 31) and 700 (nursing cards of 20 x 35).

APO-TIAPROFENIC 300 mg Tablets:

Each round, white, film-coated, biconvex tablet, bisected and engraved "APO" over "300" on one side contains 300 mg of tiaprofenic acid.

Available in bottles of 100 and 500, unit dose packages of 100 (10 x 10), 620 (nursing cards of 20 x 31) and 700 (nursing cards of 20 x 35).

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, 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 should be considered.

APO-TIAPROFENIC is NOT recommended for use with other, 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 9.4 Drug-Drug Interactions - Acetylsalicylic acid (ASA) or other)

Carcinogenesis and Mutagenesis

See 16 NON-CLINICAL TOXICOLOGY

Cardiovascular

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

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

- **Hypertension**

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

Use of NSAIDs, such as (APO-TIAPROFENIC), 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 (APO-TIAPROFENIC) should hypertension either develop or worsen with its use.

Use of, such as APO-TIAPROFENIC, 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 should be considered first. **To minimize the potential risk for an adverse CV event, the lowest effective dose should be used for the shortest possible duration.**

Endocrine and Metabolism

Corticosteroids: APO-TIAPROFENIC 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.

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, such as tiaprofenic acid. 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 tiaprofenic acid, 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 should be considered. (see 7.1.4 Geriatrics)

Patients should be informed about the signs and/or symptoms of serious GI toxicity and

instructed to discontinue using APO-TIAPROFENIC 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, appear to occur in approximately 1% of patients treated for 3 to 6 months, and in about 2 to 4% of patients treated for one year. These trends continue, thus increasing the likelihood of developing a serious GI event at some time during the course of therapy. Even short-term therapy has its risks.

Caution should be taken if prescribing APO-TIAPROFENIC 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)

Genitourinary

Some 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 a NSAID. Should urinary symptoms occur, in the absence of an alternate explanation, treatment with APO-TIAPROFENIC should be stopped to ascertain if symptoms disappear. This should be done before urological investigations or treatments are carried out.

Hematologic

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

Anti-coagulants: Numerous studies have shown that the concomitant use of and anti-coagulants increases the risk of bleeding. Concurrent therapy of APO-TIAPROFENIC with warfarin requires close monitoring of the international normalized ratio (INR).

Even with therapeutic INR monitoring, increased bleeding may occur.

Anti-platelet Effects: Inhibit platelet aggregation and have been shown to prolong bleeding time in some patients. Unlike acetylsalicylic acid (ASA), their effect on platelet function is

quantitatively less, or of shorter duration, and is reversible.

APO-TIAPROFENIC and other 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 with ASA can markedly attenuate the cardioprotective effects of ASA. See 9.4 Drug-Drug Interactions - Acetylsalicylic Acid (ASA) or other)

Concomitant administration of APO-TIAPROFENIC 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 non-steroidal anti-inflammatory drugs are rare, but could occur with severe consequences.

Anemia is sometimes seen in patients receiving, including APO-TIAPROFENIC. This may be due to fluid retention, GI blood loss, or an incompletely described effect upon erythropoiesis.

Patients on long-term treatment with NSAIDs>, including APO-TIAPROFENIC, should have their hemoglobin or hematocrit checked if they exhibit any signs or symptoms of anemia or blood loss.

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.

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 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 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

In common with other anti-inflammatory drugs, APO-TIAPROFENIC may mask the usual signs of infection.

Aseptic Meningitis: Rarely, with some NSAIDs, 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.

Monitoring and Laboratory Tests

Cardiovascular: Patients on long-term treatment with APO-TIAPROFENIC should have their blood pressure monitored regularly.

Hematology: Hemoglobin, hematocrit, red blood cells (RBCs), white blood cells (WBCs), and platelets should be checked in patients on long-term treatment with APO-TIAPROFENIC. Additionally, concurrent therapy with warfarin requires close monitoring of the international normalized ratio (INR).

Hepatic: Serum transaminase and bilirubin should be monitored regularly during APO-TIAPROFENIC therapy.

Ophthalmologic: Ophthalmic examination should be carried out at periodic intervals in any patient receiving this drug for an extended period of time.

Renal: Serum creatinine, creatine clearance and serum urea should be checked in patient during APO-TIAPROFENIC therapy. Electrolytes including serum potassium should be monitored periodically.

Pregnancy: If APO-TIAPROFENIC is administered in the middle (approximately 20 weeks) to the end of the second trimester, it is recommended that pregnant women on APO-TIAPROFENIC be closely monitored for amniotic fluid volume since APO-TIAPROFENIC may result in reduction of amniotic fluid volume and even oligohydramnios. See 7.1.1 Pregnant Women

APO-TIAPROFENIC is contraindicated for use in the third trimester of pregnancy.

Neurologic

Some patients may experience drowsiness, dizziness, blurred vision, vertigo, tinnitus, hearing loss, insomnia or depression with the use of NSAIDs, such as tiaprofenic acid. 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 NSAIDs. If such symptoms develop should be discontinued and an ophthalmologic examination performed. Ophthalmologic examination should be carried out at periodic intervals in any patient receiving tiaprofenic acid 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 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.

Caution should be used when initiating treatment with NSAIDs, such as tiaprofenic acid 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.

Advanced renal disease: (See 2 CONTRAINDICATIONS)

***Fluid and Electrolyte Balance*:** Use of NSAIDs, such as APO-TIAPROFENIC, can promote sodium retention in a dose-dependent manner, which can lead to fluid retention and edema, and consequences of increased blood pressure and exacerbation of congestive heart failure. Thus, caution should be exercised in prescribing APO-TIAPROFENIC 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, such as APO-TIAPROFENIC, 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 tiaprofenic acid, as with any drug known to inhibit cyclooxygenase/prostaglandin synthesis, may impair fertility and is not recommended in women attempting to conceive. Therefore, in women who have difficulties conceiving, or who are undergoing investigation of infertility, withdrawal of APO-TIAPROFENIC 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 tiaprofenic acid. In post-marketing experience, rare cases of anaphylactic/ anaphylactoid reactions and angioedema have been reported in patients receiving APO-TIAPROFENIC. Tiaprofenic acid 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: Tiaprofenic acid 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.

Skin

Serious skin reactions: Use of some NSAIDs, such as APO-TIAPROFENIC, 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.

7.1 Special Populations

7.1.1 Pregnant Women

APO-TIAPROFENIC 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 APO-TIAPROFENIC 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 APO-TIAPROFENIC 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 Breast-feeding

APO-TIAPROFENIC is contraindicated in breast-feeding women. See 2 CONTRAINDICATIONS

7.1.3 Pediatrics

Pediatrics (< 18 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of tiaprofenic acid in pediatric patients has not been established; therefore, Health Canada has not authorized an indication for pediatric use. See 2 CONTRAINDICATIONS.

7.1.4 Geriatrics

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. 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 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 on occasion, particularly in the elderly.

As with all drugs in this class, the frequency and severity of adverse events depends on several factors: the dose of the drug and duration of treatment; the age, the sex, physical condition of the patient; any concurrent medical diagnoses or individual risk factors.

8.2 Clinical Trial Adverse Reactions

The following side effects were encountered in clinical trials with tiaprofenic acid in 1,361 patients.

Table 2

	Percentage Incidence	
	Short term (up to 8 weeks)	Long term (3-36 months)
GASTROINTESTINAL (16%)		
Indigestion	3.1	13.5
Nausea	5.8	8.2
Heartburn	3.3	6.0
Epigastric pain	2.5	5.3
Vomiting	1.1	4.1
Abdominal pain	2.4	3.1
Constipation	2.9	2.7
Flatulence	1.5	2.2
Diarrhea	2.9	2.2
Less than 1%		
Enterocolitis	0.4	0.2
Melena	0.4	0.0

Rare incidents of gastric or duodenal ulceration have been reported although not seen in this series of patients.

Table 3

CENTRAL NERVOUS SYSTEM (6.2%)		
Dizziness	2.4	3.9
Drowsiness	0.4	3.1
Headache	2.9	3.4
Depression	0.8	1.9
Less than 1% (range 0.2 – 0.7%)		
Disorientation, tinnitus, insomnia, anxiety, tiredness/weakness		
CUTANEOUS (2.1%)		
Rash, erythema, pruritus	1.7	7.2
Less than 1% (range 0.2 – 0.8%)		
Dry skin, onycholysis		
CARDIOVASCULAR (1.1%)		

Hot flushes	1.0	1.4
Less than 1% (range 0.3–0.5%)		
Chest pain, angina, bruising		
RENAL (1.1%)		
Edema	1.2	1.9
Less than 1% (range 0.1–0.5%)		
Incontinence, polyuria, oliguria		
HEPATIC (Less than 1%)		
(See LABORATORY AND BIOCHEMICAL TOLERANCE)		
MISCELLANEOUS (2.2%)		
Dry mouth/tongue,	1.1	2.4
stomatitis		
Nosebleeds	0.1	1.4

Less than 1% (range 0.1 to 0.5%).

Eye itching/conjunctivitis/red eyes, minor eye ulcers, blurred vision, anorexia, weight gain, cramps, dyspnea, intermenstrual bleeding/vaginal spotting, paresthesia of fingers, sneezing, sweating.

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

Laboratory and Biochemical Tolerance

Combined decrease of hematocrit and hemoglobin: 2.8% of patients. Decrease of hemoglobin: 2.8% of patients. Increased white blood cell count 0.6%; decreased count 0.3%.

Increased gammaglutamic transferase and AST(SGOT): less than 1%. Increased alkaline phosphatase from previously normal levels: less than 1%. In patients with initially high alkaline phosphatase the levels remained high or increased.

Increase in blood urea nitrogen (BUN): 2.5% of total patients (11.8% in the elderly). Increase in BUN and creatinine: 0.4% of patients.

Hyperkalemia: 2.4% of patients.

8.5 Post-Market Adverse Reactions

Gastrointestinal: Disorders of intestinal transit, ulcer, perforation, overt or occult gastrointestinal haemorrhage resulting in anaemia.

Muco-cutaneous: Purpura, urticaria, very rarely erythema multiforme and bulbous eruptions (Stevens-Johnson syndrome or exceptionally toxic epidermal necrolysis); very rarely

photosensitivity reactions.

Hypersensitivity Reactions: Asthmatic attacks, especially in subjects allergic to aspirin and other non-steroidal anti-inflammatory agents, angio-oedema, anaphylactic shock.

Haematological: thrombocytopenia, prolongation of bleeding time.

Urinary System: Urinary symptoms (bladder pain, dysuria, and frequency), haematuria or cystitis may occur. When treatment with tiaprofenic acid has been continued for months after onset of the urinary symptoms, inflammatory changes to the urinary tract, sometimes severe, have been observed and a few patients have undergone surgical procedures. Therefore, should any urinary symptom occur, treatment with tiaprofenic acid must be discontinued immediately, Complete recovery after discontinuation is the rule (See 7 WARNINGS AND PRECAUTIONS - Renal).

Nervous System: Vertigo, tinnitus, tremor.

Renal: Sodium and water retention (see 7 WARNINGS AND PRECAUTIONS - Renal). As with other NSAIDS, isolated cases of acute interstitial nephritis have been reported with tiaprofenic acid.

Hepatic: Liver test abnormalities.

Other: Palpebral oedema, palpitations.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

Tiaprofenic acid is highly bound to serum albumin (98%). This may lead to interaction with anticoagulants, sulfonylurea, hypoglycemic agents, sulfonamides, phenytoin, lithium and certain chemotherapeutic agents such as methotrexate. Therefore, caution should be used when these drugs are used concurrently.

9.4 Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 4 - Established or Potential Drug-Drug Interactions

Proper/Common name	Source of Evidence	Effect	Clinical comment
Acetylsalicylic acid (ASA) or other NSAIDs	CT	• The concomitant use of APO-TIAPROFENIC and other NSAIDs (such as ASA and ibuprofen) does not produce any greater therapeutic effect than the use of NSAIDs alone. • The concomitant use of an NSAID and ASA (such as aspirin) was associated with a significantly increased incidence of GI adverse reactions as compared to use of the NSAID alone.	• Concomitant use of APO-TIAPROFENIC and analgesic doses of ASA or other NSAIDs is not recommended because of the increased risk of bleeding. See 7 WARNINGS AND PRECAUTIONS - Gastrointestinal
ACE Inhibitors, Angiotensin Receptor Blockers, and Beta-Blockers	T	• NSAIDs may diminish the antihypertensive effect of ACE inhibitors, ARBs, or beta-blockers (including propranolol). • In patients who are elderly, volume-depleted (including those on diuretic therapy), or have RI, co-administration of an NSAID with ACE inhibitors or ARBs may result in deterioration of renal function, including possible acute renal failure and hyperkalemia. These effects are usually reversible.	• 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. See 7 WARNINGS AND PRECAUTIONS - Cardiovascular
Albumin-Bound Drugs	T	• Tiaprofenic acid is highly bound to plasma albumin; it thus has a theoretical potential for interaction with other albumin-bound drugs such as coumarin-type anticoagulants,	• Patients should be under careful observation for adjustment of dose if required.

Proper/Common name	Source of Evidence	Effect	Clinical comment
		warfarin, sulfonamide or sulphonylureas, hydantoins, other NSAIDs, and ASA.	
Anti-coagulants	CT	• Tiaprofenic acid and anticoagulants such as warfarin have a synergistic effect on bleeding. • The concomitant use of tiaprofenic acid and anticoagulants have an increased risk of serious bleeding compared to the use of either drug alone.	• Anticoagulation/INR should be monitored and warfarin dosage adjustments. See 7 WARNINGS AND PRECAUTIONS - Hematologic
Anti-platelets Agents (including ASA)	CT	• There is an increased risk of bleeding, via inhibition of platelet function, when anti-platelet agents are combined with tiaprofenic acid.	• Monitor patients for signs of bleeding. See 7 WARNINGS AND PRECAUTIONS - Hematologic
Cyclosporin and Tacrolimus	T	• Inhibition of renal prostaglandin activity by NSAIDs may increase the nephrotoxic effect of cyclosporin or tacrolimus.	• Patients should be monitored for necessary dosage adjustment. • Monitor patients for signs of worsening renal function or hypertension.
Cholestyramine	N/A	• Concomitant administration of cholestyramine can decrease the absorption of tiaprofenic acid resulting in a reduced serum concentration and potentially a decrease in efficacy.	• Concomitant administration is not recommended.
Digoxin	C	• Concomitant use of tiaprofenic acid with digoxin may decrease the excretion rate of Digoxin which could result in a higher serum	• Monitor serum digoxin levels.

Proper/Common name	Source of Evidence	Effect	Clinical comment
		level and a risk digitalis toxicity.	
Diuretics	CT	• Clinical studies as well as post-marketing observations have shown that NSAIDs can reduce the effect of diuretics. • This effect has been attributed to the NSAID inhibition of renal prostaglandin synthesis.	• Observe patients for signs of worsening renal function, in addition to assuring diuretic efficacy including antihypertensive effects.
Glucocorticoids	CT	• The concomitant use of NSAIDs and oral glucocorticoids increases the risk of GI adverse events such as ulceration and bleeding, especially in older (>65 years of age) patients.	• Monitor patients particularly those over 65 years of age for signs of bleeding. See 7 WARNINGS AND PRECAUTIONS - Gastrointestinal
Lithium	CT	• NSAIDs have produced elevations in plasma lithium levels and reductions in renal lithium clearance. This effect has been attributed to NSAID inhibition of renal prostaglandin synthesis.	• Monitor patients for plasma lithium concentrations when stopping or starting a NSAID.
Methotrexate	N/A	• Concomitant use of NSAIDs and methotrexate may increase the risk for methotrexate toxicity (e.g., neutropenia, thrombocytopenia, renal dysfunction).	• Monitor patients for methotrexate toxicity.
Oral hypoglycemic agents		• An inhibition of metabolism of sulphonylurea drugs, prolonged half-life and increased risk of hypoglycaemia has been reported.	• Patients should be under careful observation for adjustment of dose if required.

Proper/Common name	Source of Evidence	Effect	Clinical comment
Pemetrexed	CT	• Concomitant use may decrease the excretion rate of pemetrexed which could result in a higher serum level and thus the risk of pemetrexed- associated myelosuppression, renal, and GI toxicity.	• In patients with RI, monitor for myelosuppression, renal and GI toxicity.
Probenecid	CT	• Concomitant use may decrease the excretion rate of tiaprofenic acid which could result in a higher serum level	• Patients should be observed for adjustment of dose if required.
Quinolone antibacterials	C	• 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)	C	• Serotonin release by platelets plays an important role in hemostasis. • Concomitant administration of NSAIDs and SSRIs may increase the risk of gastrointestinal ulceration and bleeding.	• Monitor patients for signs of bleeding. See 7 WARNINGS AND PRECAUTIONS - Gastrointestinal

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical; GI = Gastrointestinal; CV = Cardiovascular; INR = International normalized ratio; ASA = Acetylsalicylic acid; NSAID = Non-Steroidal Anti-Inflammatory Drug; ACE = Angiotensin converting enzyme; ARB = Angiotensin Receptor Blockers; RI = Renal impairment;

9.5 Drug-Food Interactions

Concomitant administration of food can delay the absorption of tiaprofenic acid.

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

APO-TIAPROFENIC (tiaprofenic acid), is a non-steroidal, anti-inflammatory agent with analgesic and antipyretic properties. It is a propionic acid derivative. The exact mechanism of action responsible for the anti–inflammatory, analgesic action is unknown. Tiaprofenic acid inhibits the enzyme prostaglandin synthetase which may be responsible for the reduction in inflammation and pain. The therapeutic effect of tiaprofenic acid does not result from pituitary– adrenal stimulation.

10.2 Pharmacodynamics

Tiaprofenic acid did not depress the biosynthesis of proteoglycans nor alter the differentiation of proteoglycans secreted in different experimental models with cartilage and cultures of human chondrocytes. The degradation of proteoglycan aggregates was also inhibited. These *in vitro* results suggest a positive effect of tiaprofenic acid on the joint cartilage. The clinical significance of these findings has to be further investigated.

10.3 Pharmacokinetics

Absorption

Tiaprofenic acid is rapidly absorbed at the gastric and duodenal levels after oral administration. Peak serum levels are obtained in 30 to 90 minutes. Food delays the absorption and the time to reach peak plasma concentrations by 10%. Tiaprofenic acid is approximately 98% protein bound. The plasma half–life is approximately 2 hours, following a single dose of 200 mg tiaprofenic acid.

Elimination

Tiaprofenic acid is primarily eliminated in the urine, 50% as unchanged tiaprofenic acid and two metabolites (II & Ill) accounting for less than 10%. The metabolites are inactive.

Chronic administration at a dosage of 200 mg tid demonstrated rapid elimination and absence of accumulation. Steady state was attained after one day's treatment and plasma levels approached zero within 24 hours of the last dose.

The times to reach mean peak serum levels were tested in two groups of arthritic patients treated with 200 mg tid and 300 mg bid for 7 days or more. The times were found to be 78 and 50 minutes, respectively. In synovial fluid, the mean time to peak levels was approximately 4 hours for both dosages. Following a 200 mg dose, peak serum and synovial fluid levels reached 26 mcg/mL and 5 mcg/mL respectively and 50 mcg/mL and 7.7 mcg/mL after a 300 mg dose. At 8 hours serum blood levels were lower than those of synovial fluids but by 11 hours these levels were approximately the same.

In another study, rheumatoid arthritis patients were given tiaprofenic acid 200 mg tid for 7 days. After the first dose, a fall in the synovial PGE_2 level occurred inversely to a rise in drug

level. The level of PGE_2 remained low after one week's continuous medication. These results indicate that tiaprofenic acid reaches its target organ and is retained within the joint. It also suggests that reduction in PGE_2 production is one of the ways in which tiaprofenic acid acts. The clinical significance of the relative serum and synovial fluid levels has, however, not been elucidated.

A pharmacokinetic study conducted in elderly patients receiving tiaprofenic acid 300 mg bid for 3 months showed no significant differences for all pharmacokinetic parameters (C_{max}, T_{max}, C_9, $AUC_{0\text{-}9\ h}$, $t_{½}$) measured at weeks 0, 4, 8 and 12, thus suggesting lack of accumulation.

Fecal blood loss at the therapeutic dose range was less than with usual clinical doses of ASA.

Special Populations and Conditions

Pediatrics: The pharmacokinetics of tiaprofenic acid have not been investigated in pediatric patients.

Hepatic Insufficiency: Patients with acute and chronic hepatic disease may require reduced doses of tiaprofenic acid compared to patients with normal hepatic function.

Renal Insufficiency: Tiaprofenic acid and its metabolites are eliminated primarily by the kidneys, therefore the drug should be used with great caution in patients with impaired renal function. In these cases utilization of lower doses of tiaprofenic acid should be considered and patients carefully monitored.

11 STORAGE, STABILITY AND DISPOSAL

Store at room temperature 15 to 30°C. Protect from excessive heat, light and humidity.

Keep out of reach and sight of children.

12 SPECIAL HANDLING INSTRUCTIONS

Not Applicable.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

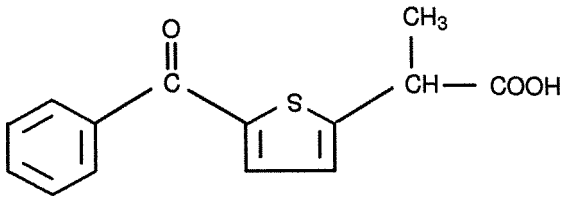
Proper name: Tiaprofenic acid

Chemical name: alpha-(5-benzoyl-2-thienyl) propionic acid or

5-benzoyl-alpha-methyl-2 thiophene acetic acid.

Molecular formula and molecular mass: $C_{14}H_{12}O_3S$ and 260.3 g/mol

Structural formula:



Physicochemical properties: Tiaprofenic acid is a white microcrystalline powder with a melting point of about 95°C. It is readily soluble in alcohol, chloroform and acetone, but is only sparingly soluble in water. The pKa is approximately 3.0.

14 CLINICAL TRIALS

The clinical trial data on which the original indication was authorized is not available.

14.2 Comparative Bioavailability Studies

A randomized, two-treatment, two-period, single dose (1 x 300 mg), crossover comparative bioavailability study of APO-TIAPROFENIC (Apotex Inc.) and SURGAM (Roussel Canada Inc.) was conducted in healthy male subjects under fasting conditions. A summary of the data from the 19 subjects that were included in the pharmacokinetic and statistical analyses is presented in the following table.

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Tiaprofenic acid (1 x 300 mg) Geometric Mean Arithmetic Mean (CV %)				
Parameter	**Test[1]**	**Reference[2]**	**Ratio of Geometric Means (%)**	**90% Confidence Interval (%)**
AUC_T (mcg•h/mL)	70.7 72.6 (23.5)	71.9 72.6 (14.1)	98.8	90.0 – 108.3
AUC_I (mcg•h/mL)	72.8 74.7 (23.2)	73.8 74.6 (14.4)	99.0	90.5 – 108.2
C_{max} (mcg/mL)	25.7 28.0 (37.0)	26.7 28.0 (27.4)	96.9	76.6 – 122.7
T_{max}[3] (h)	1.25 (0.50 – 6.00)	1.25 (0.75 – 6.00)		
$T_{½}$[4] (h)	2.23 (35.1)	2.07 (37.3)		
[1] APO-TIAPROFENIC (Tiaprofenic acid), Tablets, 300 mg (Apotex Inc.) [2] SURGAM, (Tiaprofenic acid), Tablets, 300 mg (Roussel Canada Inc.) [3] Expressed as the median (range) only [4] Expressed as the arithmetic mean (CV %) only				

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology

Comparative Non-Clinical Pharmacology and Toxicology

Acute Toxicity: LD_{50} (95% confidence limits) mg/kg.

Table 5:

Species	Sex	Route of Administration			
		Oral	Subcutaneous	Intraperitoneal	Intravenous
Mouse	Male	780 (684-889)	640 (595-688)	680 (523-884)	600 (567-633)
Mouse	Female	600 (512-702)	640 (592-691)	670 (587-764)	640 (581-704)

Species	Sex	Route of Administration			
		Oral	Subcutaneous	lntraperitoneal	Intravenous
Rat	Male	253 (195-322)	230 (170-310)	253 (204-314)	370 (235-573)
Rat	Female	190 (148-244)	240 (169-312)	220 (166-280)	350 (218-560)
Rabbit	Male	380 (287-501)	-	-	340 (279-415)

Signs of toxicity observed in mice, rats and rabbits included respiratory distress, bradypnea, cyanosis, convulsions, excitability, depression, tremors, motor incoordination, writhing, prostration, ptosis and weight loss. Necropsies showed ascites, peritonitis, hypertrophy and congestion of the mesenteric ganglia.

Long-Term Toxicity:

Tiaprofenic acid was administered orally to rats (35 animals/group/sex) at doses of 0, 10, 20 and 30 mg/kg/day, 6 days a week for 24 consecutive weeks. Signs of toxicity observed were dose and sex–related; the 10 mg/kg/day dose was well tolerated. At 20 mg/kg/day jejunoileal ulcerations with perforations and peritonitis were identified and a few cases of hepatic abscesses and pancreatitis were observed. At a dose of 30 mg/kg/day, anemia and splenic myeloid metaplasia were also observed. A higher death rate from anemia in females was evident.

In a six month study conducted in 32 beagle dogs (4 animals/group/sex) at daily oral doses of 0, 10, 20 and 40 mg/kg. Four animals treated with 10 and 20 mg/kg showed a slight to moderate erosion of the gastric mucosa. At 4 weeks, at a dose of 20 mg/kg, a transient reduction in red blood cell count in females was observed. The following toxic signs in animals receiving 40 mg/kg were observed. Weight loss, anemia, reticulocytosis, transient leucocytosis, reactive polycythaemia, fecal occult blood, jejunum and gastric ulceration, increased megakaryocyte and erythrocyte count and splenic myeloid metaplasia. These effects had been observed after 2 to 1/2 months.

In another study conducted in baboons (3 animals/group/sex), tiaprofenic acid was orally administered at 0, 10, 30 and 90 mg/kg/day for 6 months. No histological changes occurred in the gastrointestinal tract in the 0, 10 and 30 mg/kg/day groups. At 90 mg/kg/day there was: increased BUN, diarrhea, fecal occult blood, vomiting, weight loss, anemia, leucocytosis, decreased LAP, transient increased SGPT, gastric and ileum lesions. Slight degeneration of the renal tissue and hyalin areas in cortical tubuli were also observed. One female was sacrificed after 8 weeks of treatment due to a general deteriorating condition of unknown cause.

In a one year study, baboons (5 animals/group/sex) were given tiaprofenic acid orally at doses

of 0, 10, 25, 50 and 75 mg/kg/day. At the highest dose of 75 mg/kg/day there were microscopic changes in the gastrointestinal tract, especially in the stomach, indicating minor erosions of the mucosa. Similar lesions, confined to the intestines, were noted, in 3 animals at 50 mg/kg/day and 2 female baboons at 25 mg/kg/day. There was no evidence of such lesions in animals killed after a recovery period of 16 weeks.

Carcinogenicity

No evidence of carcinogenicity of tiaprofenic acid was found in mice (60 male and 60 female/group) and in rats (50 male and 50 female/main group; 35 male and 35 female/supplementary group) at oral doses of 0 (control), 10, 20 and 30 mg/kg/day for 80 weeks and 104 weeks, respectively.

Mutagenicity

No evidence of mutagenicity of tiaprofenic acid was observed in the diffusion method, the Ames Test in bacterial strains, or in the mouse using the micronucleus test.

Reproductive and Developmental Toxicology

Mice (24 animals/group) were treated with doses of 0, 25, 50 and 100 mg/kg/day from days 0 to 17 of pregnancy. No treatment–related effects on pregnancy were observed except for a small increase in the rate of fetal loss at the 100 mg/kg dose.

Rats (24 animals/group) were administered tiaprofenic acid at 0, 5, 10 and 25 mg/kg/day from days 0 to 20 of gestation. At the 10 mg/kg and 25 mg/kg, a slight increase in fetal loss was observed.

Rabbits (20 animals/group) received doses of 0, 25, 50 and 75 mg/kg/day from days 0 to 27 of pregnancy. At the 75 mg/kg/day dose, the number of implantation sites were reduced. The rate of fetal loss was also increased at this dose.

Rats (20 males and 24 females per group) were given daily oral doses of 0, 5, 10 and 20 mg/kg, prior to pairing and during the mating period. Mated females were treated throughout gestation (21 days) except for the last 3 days before parturition. A second group was treated during the lactation period (21 days). There was no effect observed on the fertility and the reproductive performance of rats at all doses; however, at the 20 mg/kg/day, the pre and post implantation losses were slightly increased. There was no effect or influence on development and reproduction of the two subsequent generations (F_1 and F_2 off–spring).

In another study in rats (24 animals/group), tiaprofenic acid was administered orally at daily doses of 0, 8, 16 and 24 mg/kg, from day 15 of gestation until day 21 post partum. At doses of 16 and 24 mg/kg, 9 females in each group showed a delayed or lengthened parturition. Means of the length of gestation were 22.42 ± .16 and 22.73 ± 0.18 days on 16 and 24 mg/kg, respectively, versus 21.62 ± 0.16 for the control group. Another group of pregnant rats (12 animals) received 16 mg/kg orally from day 0 to 18 of gestation and from parturition until day 21 post partum. There were no adverse effects observed during gestation, parturition or lactation on mothers or pups.

17 SUPPORTING PRODUCT MONOGRAPHS

1 TEVA–TIAPROFENIC ACID Tablets, 200 mg and 300 mg, submission control: 261587, Product Monograph, Teva Canada Limited (AUG 15, 2022)

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]APO-TIAPROFENIC

Tiaprofenic Acid Tablets

Read this carefully before you start taking **APO-TIAPROFENIC** 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 **APO-TIAPROFENIC**.

Serious Warnings and Precautions

Heart and blood vessel problems:

- APO-TIAPROFENIC 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 APO-TIAPROFENIC 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:

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

Talk to your healthcare professional about any medical conditions you have and drugs you are taking.

Pregnancy:

- **DO NOT** take APO-TIAPROFENIC 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 APO-TIAPROFENIC if you are told to do so by your healthcare professional.
- Medicines like APO-TIAPROFENIC 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 APO-TIAPROFENIC 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 APO-TIAPROFENIC.

What is APO-TIAPROFENIC used for?

APO-TIAPROFENIC is used to relieve signs and symptoms of:

- Arthritis disorders such as:
  - Osteoarthritis
  - Rheumatoid arthritis

How does APO-TIAPROFENIC work?

- APO-TIAPROFENIC belongs to a group of medicines called non-steroidal anti-inflammatory drugs (NSAIDs). It can reduce the chemicals produced by your body which cause pain and swelling.
- APO-TIAPROFENIC only treats the symptoms and relieves pain and inflammation as long as you take it. APO-TIAPROFENIC does not cure the illness or stop it from getting worse.

What are the ingredients in APO-TIAPROFENIC?

Medicinal ingredients: Tiaprofenic acid

Non-medicinal ingredients: Colloidal silicon dioxide, hydroxypropyl cellulose, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol and titanium dioxide.

APO-TIAPROFENIC comes in the following dosage forms:

Tablets, 200 mg and 300 mg

Do not use APO-TIAPROFENIC if:

- have heart bypass surgery (planning to have or recently had).
- have severe, uncontrolled heart failure.
- are bleeding in the brain or other bleeding disorders.
- are pregnant and in a later stage of pregnancy (28 weeks or later).
- are currently breastfeeding (or planning to breastfeed).
- are allergic to tiaprofenic acid or any of the other ingredients in this medicine or the container.
- 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.
- have active stomach or intestine ulcers.
- have active bleeding from the stomach or gut.
- have inflammatory bowel disease (Crohn's Disease or Ulcerative Colitis).
- have liver disease (active or severe).
- have kidney disease (severe or worsening).
- have high potassium in the blood.
- are under 18 years old.

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

- have high blood pressure, high cholesterol or diabetes
- have or had heart attacks, chest pain, heart disease, stroke or heart failure
- have poor blood flow 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 had a previous bleeding in the brain
- have a 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)
- have asthma
- are pregnant, planning on becoming or become pregnant while taking APO-TIAPROFENIC
- have immune system problems

Other warnings you should know about:

Serious Side Effects: APO-TIAPROFENIC can cause serious side effects, including:

- **Blood and bleeding problems:**
  - APO-TIAPROFENIC can cause blood problems, bleeding and prolonged bleeding.
  - Taking APO-TIAPROFENIC with the following drugs can increase the risk of bleeding:
    - anticoagulants (prevents blood clots), corticosteroids (anti-inflammatory) or antidepressants like selective serotonin reuptake inhibitors (SSRIs).

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

  APO-TIAPROFENIC might cause you to become more sensitive to sunlight. 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, talk to your healthcare professional.

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

- Check your blood pressure.
- Check your eyes. APO-TIAPROFENIC 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: APO-TIAPROFENIC 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 APO-TIAPROFENIC, do NOT drive or operate machinery.

Fertility in Women: APO-TIAPROFENIC 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 APO-TIAPROFENIC. 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 APO-TIAPROFENIC. 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 APO-TIAPROFENIC:

- 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
- Medicines used to treat high blood pressure like enalapril, ramipril, candesartan, irbesartan, propranolol
- Medicines used as blood thinners or to prevent blood clots, like warfarin, ASA, clopidogrel
- Medicines used to lower extra fluid levels (diuretics), like furosemide, hydrochlorothiazide
- Medicines used to treat diabetes, like sulphonylurea or other oral hypoglycemics
- Medicines used to treat bacterial infections (antibiotics) like quinolone or sulphonamide
- 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 seizures like phenytoin, hydantoin
- Medicines used to treat different cancers, like methotrexate and pemetrexed
- Probenecid, used to prevent gout
- Lithium, used as a mood stabilizer
- Alcohol

How to take APO-TIAPROFENIC:

- Take exactly as your healthcare professional has told you. They should recommend the lowest dose possible for your treatment for the shortest time needed.
- Take with food.
- **This medicine 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 will be taking APO-TIAPROFENIC for more than 7 days, see your healthcare professional regularly. They will check if APO-TIAPROFENIC is working for you and if it is causing any side effects.

Usual dose:

Adults:

- Your healthcare professional will decide on the best dosage for you based on your condition.
- Your healthcare professional may lower your dose, stop your treatment for a period of time or recommend that you stop treatment completely. This may happen if you:
  - experience serious side effects, or
  - your disease gets worse.

Overdose:

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

Missed Dose:

- If you miss a dose of APO-TIAPROFENIC tablets, take it as soon as you remember. Take your next dose at the usual time.
- If it is close to the time of your next dose, skip the missed dose. Take your next dose at the usual time.
- Do not take two doses at the same time to make up for a forgotten dose.

What are possible side effects from using APO-TIAPROFENIC?

These are not all the possible side effects you may have when taking APO-TIAPROFENIC. If you experience any side effects not listed here, tell your healthcare professional.

- Nausea, vomiting, diarrhea, constipation, stomach upset/abdominal pain, heartburn, indigestion, feeling gassy
- Headache, dizziness, light-headedness
- Feeling of burning/prickliness/numbing
- Confusion, hard to concentrate or think, short-term memory loss, nervousness
- Bruises
- Skin rash
- Thirst, dry mouth
- Mouth sores
- Increased sweating, hot flushes
- Problems with your period (women)

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get 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, black tarry or bloody stool, dizziness, stomach pain, bloating, loss of appetite, weight loss, nausea, vomiting, constipation or diarrhea, chills or fever		√	
Hypertension (high blood pressure): fatigue, dizziness or fainting, chest pain	√		
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			√
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		√	
Blood problems (low white and/or red blood cell or platelet count): feeling tired or		√	

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
weak, pale skin, bruising or bleeding for longer than usual if you hurt yourself, fever, chills			
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			√
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		√	
Depression (sad mood that will not go away): difficulty sleeping or sleeping too much, changes in appetite or weight, reduced sex drive and thoughts of death or suicide.		√	
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)		√	
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		√	
Lung problems, asthma: increased shortness of breath, wheezing, difficulty breathing, cough and chest tightness, irregular heartbeat			√
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			√

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
skin, sweating, indigestion, anxiety, feeling faint and possible irregular heartbeat.			
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			√
Tinnitus (hearing problems): includes ringing, buzzing, clicking or hissing in ears, loss of hearing		√	
Vertigo (a sense of severe spinning dizziness, lightheadedness)		√	
RARE			
Serious Skin Reactions: fever, severe rash, 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, hives, red or dry itchy skin, purple or red spots on skin			√

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°C to 30°C. Protect from excessive heat, light and humidity.
- Keep out of reach and sight of children.

If you want more information about APO-TIAPROFENIC:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication 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.apotex.ca/products), or by calling 1-800-667-4708.

This leaflet was prepared by Apotex Inc., Toronto, Ontario, M9L 1T9.

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