PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrTEVA-PROFEN

Ibuprofen

Tablets, 600 mg, for oral use

USP

ATC code: M01AE01

Non-Steroidal Anti-inflammatory Drug (NSAID)

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RECENT MAJOR LABEL CHANGES

2 Contraindications	01/2022
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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

TEVA-PROFEN (ibuprofen) is indicated for the following:

- The relief of the signs and symptoms of rheumatoid arthritis
- The relief of the signs and symptoms of osteoarthritis

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

Ibuprofen tablets, particularly at higher doses (2400 mg/day), is associated with an increased risk of serious cardiovascular adverse events that is comparable to COX-2 inhibitors. Ibuprofen doses of 2400 mg/day should not be given to patients, especially those with ischemic heart disease, cerebrovascular disease, congestive heart failure (NYHA II-IV), or with risk factors for cardiovascular disease. For patients with an increased risk of developing cardiovascular disease, other management strategies that do NOT include the use of NSAIDs, particularly COX-2 inhibitors, diclofenac or ibuprofen, should be considered first See 2 CONTRAINDICATIONS and 7 WARNINGS AND PRECAUTIONS.

For patients with increased risk of developing gastrointestinal adverse events, other management strategies that do not include NSAIDs should be considered first. See 2 CONTRAINDICATIONS and 7 WARNINGS AND PRECAUTIONS.

Use of TEVA-PROFEN 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-PROFEN , as a NSAID, does NOT treat clinical disease or prevent its progression.

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

1.1 Pediatrics

Pediatrics (< 12 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of TEVA-PROFEN 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 experience suggest that use in the geriatric population is associated with differences in safety or effectiveness and a brief discussion can be found in the appropriate sections See 4 DOSAGE AND ADMINISTRATION and 7.1.4 Geriatrics

2 CONTRAINDICATIONS

TEVA-PROFEN is contraindicated in:

- the peri-operative setting of coronary artery bypass graft surgery (CABG). Although TEVA-PROFEN 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 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
- 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 NSAIDs and must be monitored) See 7 WARNINGS AND PRECAUTIONS
- known hyperkalemia. See 7 WARNINGS AND PRECAUTIONS
- children and adolescents less than 12 years of age
- patients with systemic lupus erythematosus as an anaphylaxis-like reaction with fever may occur, particularly when ibuprofen has been administered previously.

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):**

  TEVA-PROFEN is a non-steroidal anti-inflammatory drug (NSAID). Ibuprofen, particularly at higher doses (2400 mg/day), is associated with an increased risk of serious cardiovascular adverse events (such as myocardial infarction, stroke or thrombotic events, which can be fatal), comparable to COX-2 inhibitors, as evidenced by meta-analyses of randomized clinical trials. Large population-based observational studies conducted in the general population also support these findings. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk. Doses of ibuprofen 2400 mg/day should not be used in patients, especially those with ischemic heart disease, cerebrovascular disease, patients with congestive heart failure (NYHA II-IV), or patients with risk factors for cardiovascular disease (e.g. hypertension, hyperlipidemia, diabetes mellitus and smoking). For patients with a high risk of developing an adverse cardiovascular event, other management strategies that do NOT include NSAIDs, particularly COX-2 inhibitors, ibuprofen or diclofenac, should be considered first. To minimize the potential for an adverse cardiovascular event, the lowest effective dose should be used for the shortest possible duration.

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

  Use of NSAIDs, such as TEVA-PROFEN, 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.

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

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

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

- **Risk in Pregnancy**

  Caution should be exercised in prescribing TEVA-PROFEN 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-PROFEN 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-PROFEN should be limited to the lowest effective dose for the shortest possible duration of treatment. See 1 INDICATIONS AND CLINICAL USE
- Individuals older than 65 years who are frail or debilitated should be given a starting dose lower than the one usually recommended, with individual adjustments when necessary.
- A lower dose should be considered in patients with renal or hepatic impairment.

4.2 Recommended Dose and Dosage Adjustment

Adults:

Rheumatoid arthritis, osteoarthritis:

Initial dose of 600 mg BID, increase to 600 mg TID if necessary. Do not exceed 1800 mg per day.

Maintenance dosage: 600 to 1200 mg daily.

Pediatrics (< 12 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. TEVA-PROFEN 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. TEVA-PROFEN is contraindicated in severe liver impairment or active liver disease. See 2 CONTRAINDICATIONS

4.4 Administration

The administration of ibuprofen with food or milk is recommended since occasional and mild heartburn, upset stomach or stomach pain may occur with its use.

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

A clear pattern of clinical features associated with accidental or intentional overdose of ibuprofen has not been established. Reported cases of overdose have often been complicated by co-ingestions or additional suicidal gestures. The range of symptoms observed has included nausea, vomiting, abdominal pain, drowsiness, nystagmus, diplopia, headache, tinnitus, impaired renal function, coma and hypotension. A review of four fatalities associated with ibuprofen overdose indicates other contributing factors co-existed so it would be difficult to identify the toxicity of ibuprofen as a specific cause of death.

Post-ingestion blood levels may be useful to confirm a diagnosis and to quantify the degree of exposure but otherwise have not been helpful in predicting clinical outcome. Generally, full recovery can be expected with appropriate symptomatic management.

The following cases of overdose have been reported. A 19-month-old child 1-1/2 hours after the ingestion of seven to ten 400 mg tablets of ibuprofen presented apnea, cyanosis and responded only to painful stimuli. After treatment with O_2, NaHCO3, infusion of dextrose and normal saline, the child was responsive and 12 hours after ingestion appeared completely recovered. Blood levels of ibuprofen reached 102.9 µg/mL, 8-1/2 hours after the accident. Two other children weighing approximately 10 kg had taken an estimated 120 mg/kg. There were no signs of acute intoxication or late sequelae. In one child the ibuprofen blood level at 90 minutes after ingestion was approximately 700 µg/mL. A nineteen-year-old male who ingested 8000 mg of ibuprofen reported dizziness and nystagmus was noted. He recovered with no reported sequelae after parenteral hydration and 3 days of bed rest.

For perspective, a single 200 mg oral dose study in 6 fasting healthy men produced a peak plasma concentration of 15.0 Fg/mL at 0.75 hr. Another study using a single oral 400 mg dose in humans produced a peak serum level of 31.9 + 8.8 Fg/mL 0.5 hour after ingestion and at 16 hours serum concentrations had dropped to 1 Fg/mL. See 16 NON-CLINICAL TOXICOLOGY

Appropriate interventions to decontaminate the gastrointestinal tract may be beneficial within the first four hours after ingestion. Routine symptomatic and supportive treatment is then recommended. Physicians should contact the Regional Poison Control Centre for additional guidance about ibuprofen overdose management.

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	Tablet 600 mg of ibuprofen	carnauba wax, colloidal silicon dioxide, FD&C yellow # 6 aluminum lake, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polydextrose, polyethylene glycol, pregelatinized starch, silicon dioxide, sodium lauryl sulfate, sodium starch glycolate and titanium dioxide.

Description

TEVA-PROFEN 600 mg: Each peach coloured, oval-shaped bi-convex film coated tablets, engraved modified N on one side and 600 on the reverse. Available in bottles of 100 and 500 tablets.

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-PROFEN 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

Carcinogenesis and Mutagenesis

See 16 NON-CLINICAL TOXICOLOGY

Cardiovascular

TEVA-PROFEN is a non-steroidal anti-inflammatory drug (NSAID). Ibuprofen, particularly at higher doses (2400 mg/day), is associated with an increased risk of serious cardiovascular adverse events (such as myocardial infarction, stroke or thrombotic events, which can be fatal), comparable to COX-2 inhibitors. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk. Risk may increase with duration of use. Doses of ibuprofen 2400 mg/day should not be used in patients, especially those with ischemic heart disease, cerebrovascular disease, patients with congestive heart failure (NYHA II-IV), or patients with risk factors for cardiovascular disease (e.g. hypertension, hyperlipidemia, diabetes mellitus and smoking). Epidemiological data suggest that there is a slight increase in cardiovascular risk at doses of ibuprofen > 1800 and ≤ 2399 mg/day. To minimize the potential risk for an adverse cardiovascular event, the lowest effective dose should be used for the shortest possible duration. For patients with a high risk of developing an adverse cardiovascular event, other management strategies that do NOT include NSAIDs, particularly COX-2 inhibitors, ibuprofen or diclofenac, should be considered first.

Caution should be exercised in prescribing TEVA-PROFEN 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-PROFEN, 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-PROFEN should hypertension either develop or worse with its use.

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

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

Endocrine and Metabolism

Corticosteroids: TEVA-PROFEN (Ibuprofen) 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 (GI)

Serious GI toxicity (sometimes fatal), such as peptic / duodenal ulceration, inflammation, perforation, obstruction and gastrointestinal bleeding, can occur at any time, with or without warning symptoms, in patients treated with NSAIDs, such as TEVA-PROFEN. 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-PROFEN, 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 7.1.4 Geriatrics

Patients should be informed about the signs and/or symptoms of serious GI toxicity and instructed to discontinue using TEVA-PROFEN 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.

Patients should be advised to seek the consultation of a physician if gastrointestinal side effects occur consistently, persist, or appear to worsen.

Caution should be taken if prescribing TEVA-PROFEN 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 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 ibuprofen 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 ibuprofen tablets is administered.

Anti-coagulants: Numerous studies have shown that the concomitant use of NSAIDs and anti-coagulants increases the risk of bleeding. Concurrent therapy of TEVA-PROFEN with warfarin requires close monitoring of the international normalized ratio (INR). Even with therapeutic INR monitoring, increased bleeding may occur. See 9 DRUG INTERACTIONS

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-PROFEN 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

Concomitant administration of TEVA-PROFEN 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 NSAIDs, including TEVA-PROFEN. This may be due to fluid retention, GI blood loss, or an incompletely described effect upon erythro poiesis. Patients on long-term treatment with NSAIDs, including TEVA-PROFEN, should have their hemoglobin or hematocrit checked if they exhibit any signs or symptoms of anemia or blood loss.

Hepatic / Biliary/Panceatic

As with other NSAIDs borderline elevations of one or more liver enzyme tests (AST, ALT, ALP) 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 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

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

***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 TEVA-PROFEN should have their blood pressure monitored regularly and an ophthalmic examination should be carried out at periodic intervals.

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

***Hepatic*:** Serum transaminase and bilirubin should be monitored regularly during TEVA-PROFEN therapy.

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

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

TEVA-PROFEN 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 TEVA-PROFEN. 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 TEVA-PROFEN should be discontinued and an ophthalmologic examination performed. Ophthalmologic examination should be carried out at periodic intervals in any patient receiving TEVA-PROFEN for an extended period of time.

Peri-Operative Considerations

See 2 CONTRAINDICATIONS

Psychiatric

Some patients may experience depression with the use of NSAIDs, such as TEVA-PROFEN.

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 with hematuria, 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 TEVA-PROFEN, 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 TEVA-PROFEN, 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-PROFEN in patients with a history of congestive heart failure, compromised cardiac function, hypertension, increased age or other conditions predisposing to fluid retention.

Use of NSAIDs, such as TEVA-PROFEN, 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-PROFEN, 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-PROFEN should be considered. See 7.1.1 Pregnant Women

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-PROFEN. In post-marketing experience, rare cases of anaphylactic / anaphylactoid reactions and angioedema have been reported in patients receiving TEVA-PROFEN. Ibuprofen TEVA-PROFEN 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-PROFEN 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 ibuprofen tablets , 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

TEVA-PROFEN is contraindicated for use during the third trimester of pregnancy because of risk of premature closure of the ductus arteriosus and the potential to prolong parturition See 2 CONTRAINDICATIONS and 16 NON-CLINICALTOXICOLOGY. Caution is recommended in prescribing TEVA-PROFEN 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-PROFEN 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 the embryofoetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation after use of a prostaglandin synthesis inhibitor in early pregnancy.

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

7.1.2 Breast-feeding

TEVA-PROFEN is contraindicated in breast-feeding women. See 2 CONTRAINDICATIONS

7.1.3 Pediatrics

Pediatrics (< 12 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of TEVA-PROFEN 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, especially those with cardiovascular disease. Older patients are also at risk of lower esophageal ulceration and bleeding.

For such patients, consideration should be given to a starting dose lower than the one usually recommended, with individual adjustment when necessary and under close supervision. See 7 WARNINGS AND PRECAUTIONS

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The most common adverse reactions encountered with non-steroidal anti-inflammatory drugs are gastrointestinal, of which peptic ulcer, with or without bleeding, is the most severe. Fatalities have occurred 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

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.
No data is available.

8.5 Post-Market Adverse Reactions

Additional reports of serious adverse events temporally associated with TEVA-PROFEN during worldwide post-marketing experience are included below. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or clearly establish a causal relationship to TEVA-PROFEN exposure.

Gastrointestinal:	nausea, epigastric pain, heartburn, diarrhea, abdominal distress, nausea and vomiting, indigestion, constipation, abdominal cramps and pain, gastrointestinal l tract fullness (bloating or flatulence), gastric or duodenal ulcer with bleeding and/or perforation, gastrointestinal hemorrhage, melena
Infections:	aseptic meningitis, meningioencephalitis
Hematologic:	leukopenia and decreases in hemoglobin and hematocrit, hemolytic anemia, thrombocytopenia, granulocytopenia, bleeding episodes (e.g. prupura, epistaxis, hematuria, menorrhagia), auto-immune hematological anemia, fatal aplastic anemia
Immune System Disorders:	anaphylaxis, lupus erythematosus syndrome, fever, serum sickness
Metabolic and Nutrition Disorders:	decreased appetite, edema, fluid retention, hypoglycemic reaction
Nervous System Disorders:	dizziness, headache, nervousness, depression, insomnia, paresthesias, hallucinations, dream abnormalities, cognitive dysfunction
Eye Disorders:	amblyopia, conjunctivitis, diplopia, optic neuritis
Ear and Labyrinth Disorders:	tinnitus
Cardiac Disorders:	congestive heart failure in patients with marginal cardiac function, elevated blood

pressure, arterial thrombotic events, arrhythmias

Skin and Subcutaneous Tissue Disorders: rash, pruritis, vesiculobullous eruptions, urticarial, erythema multiforme, alopecia, Stevens-Johnson Syndrome

Renal and Urinary Disorders: decreased creatinine clearance, polyuria, azotemia, renal papillary necrosis

Reproductive System and Breast Disorders: menstrual delays, gynecomastia

9 DRUG INTERACTIONS

9.3 Drug-Behavioural Interactions

Alcohol: There may be an increased risk of gastrointestinal side effects, including ulceration or hemorrhage, when administered concomitantly with NSAIDs.

There are no specific studies about effects on the ability to drive vehicles and to use machinery. Patients who experience visual disturbances, drowsiness or other central nervous system disturbances should refrain from these activities.

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 2 - 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 ibuprofen tablets and other NSAIDs (such as ASA and naproxen) 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 ibuprofen tablets and analgesic doses of ASA or other NSAIDs is not recommended because of the increased risk of bleeding. See 7 WARNINGS AND PRECAUTIONS

		• Some NSAIDs (e.g. ibuprofen and naproxen) 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.	
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
Albumin-Bound Drugs	T	• Ibuprofen is highly bound to plasma albumin; it thus has a theoretical potential for interaction with other albumin-bound drugs such as coumarin-type anticoagulants, warfarin, sulfonamide or sulphonylureas, hydantoins, other NSAIDs, and ASA.	• Patients should be under careful observation for adjustment of dose if required.
Antacids	N/A	• Concomitant administration of some antacids (magnesium oxide or aluminum hydroxide) and sucralfate can delay the absorption of NSAIDs.	• Concomitant administration is not recommended.
Anti-coagulants	CT	• Ibuprofen tablets and anticoagulants such as warfarin have a synergistic effect on bleeding. • The concomitant use of NSAIDs and anticoagulants have an increased risk of serious bleeding compared	• Anticoagulation/INR should be monitored and warfarin dosage adjustments. See 7 WARNINGS AND PRECAUTIONS

		to the use of either drug alone.	
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 ibuprofen tablets.	• Monitor patients for signs of bleeding. See 7 WARNINGS AND PRECAUTIONS
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.
Cholestyramine	N/A	• Concomitant administration of cholestyramine can delay the absorption of ibuprofen.	• Concomitant administration is not recommended.
Digoxin	C	• The concomitant use of NSAIDs with digoxin has been reported to increase the serum concentration and prolong the half-life of digoxin which may result in digitalis toxicity.	• Monitor serum digoxin levels.
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. • Patients with impaired renal function taking potassium-sparing diuretics who develop ibuprofen-induced renal insufficiency might be in serious danger of fatal hyperkalemia.	• Observe patients for signs of worsening renal function, in addition to assuring diuretic efficacy including antihypertensive effects. See 7 WARNINGS AND PRECAUTIONS
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
Lithium	CT	• NSAIDs have produced elevations in plasma lithium levels and reductions in	• Monitor patients for plasma lithium concentrations when stopping or starting a

		renal lithium clearance. This effect has been attributed to NSAID inhibition of renal prostaglandin synthesis.	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 hypoglycemics		• Ibuprofen may increase the hypoglycemic effects of oral sulfonylurea hypoglycemic agents.	• Patients should be under careful observation for adjustment of dose if required.
Probenecid	N/A	• Extends ibuprofen's plasma half-life significantly.	• 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. • Case-control and cohort epidemiological studies showed that concomitant use of drugs that interfere with serotonin reuptake and an NSAID may potentiate the risk of bleeding more than an NSAID alone.	• Monitor patients for signs of bleeding. See 7 WARNINGS AND PRECAUTIONS

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical; GI = Gastrointestinal; CV = Cardiovascular; INR = International normalized ratio; PD = Pharmacodynamic; 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 ibuprofen, but does not affect its extent of absorption.

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

Ibuprofen is a member of the class of agents commonly known as non-steroidal anti-inflammatory drugs (NSAID). Like all NSAIDs, ibuprofen is an analgesic, antipyretic, and anti-inflammatory medication.

It is generally accepted that the basic mechanism of pharmacological action of ibuprofen, and other NSAIDs, is the inhibition of prostaglandin synthesis.

10.2 Pharmacodynamics

Nonselective NSAIDs (such as ibuprofen) and ASA act by inhibiting systemic (peripheral and central) prostaglandin G/H synthase isoenzymes, also known as cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2). These isoenzymes are responsible for the conversion of arachidonic acid to various tissue specific prostaglandins and thromboxanes. COX-1 is constitutively expressed in all tissues and is responsible for generating prostaglandins that maintain organ function, protect the integrity of the gastric mucosa and generate platelet-derived thromboxane responsible for platelet aggregation and vasoconstriction. During the inflammatory process COX-2 is induced, generating prostaglandins that mediate pain and inflammation. COX-2 is also present constitutively in the kidneys and vascular endothelium. Reported adverse experiences with ASA and other NSAIDs can be understood on the basis of this mechanism of action.

10.3 Pharmacokinetics

Absorption: Ibuprofen is rapidly absorbed after oral administration, with peak serum or plasma levels generally appearing within 1 to 2 hours. Oral absorption is estimated to be 80% of the dose. Both the rate of absorption and peak plasma concentrations are reduced when the drug is taken with food, but bioavailability as measured by total area under the concentration-time curve is minimally altered.

Distribution: Ibuprofen, like most drugs of its class, is highly protein bound (>99% bound at 20 μg/mL). Tissue distribution of ibuprofen is also extensive in humans. Studies comparing synovial fluid levels with serum concentrations indicated that equilibration time post-ingestion occurred within approximately 3 to 5 hours.

Metabolism: It is rapidly metabolized in the liver through oxidation first and followed by glucuronic acid conjugation prior to urinary excretion.

Elimination: Ibuprofen is rapidly metabolized and eliminated in the urine. Less than 10% is excreted unchanged in the urine. The excretion of ibuprofen is virtually complete 24 hours after the last dose. It has a biphasic plasma elimination time curve with a half-life of approximately two hours.

Special Populations and Conditions

Pediatrics (< 12 years of age): Some differences in the pharmacokinetic parameters of volume of distribution and clearance have been observed between adults and children. Febrile children <11 years old have a volume of approximately 0.2 L/kg while adults have a volume of approximately 0.12 L/kg. There is no difference in the observed terminal elimination rate or half-life between children and adults, however, there is an age-or fever-related change in total clearance. Health Canada has not authorized an indication for pediatric use. See 2 CONTRAINDICATIONS

Geriatrics (> 65 years of age): Studies demonstrate no apparent clinically significant alterations in ibuprofen pharmacokinetics in the elderly.

Hepatic insufficiency: Ibuprofen pharmacokinetics have also been studied in patients with alcoholic liver disease who have been assessed to have fair to poor hepatic function. Results suggest that, despite the liver being the primary organ of metabolism of ibuprofen, its kinetic parameters are not substantially altered by this condition.

11 STORAGE, STABILITY AND DISPOSAL

Store between 15°C and 30°C.

Keep out of reach of children.

12 SPECIAL HANDLING INSTRUCTIONS

Not Applicable.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

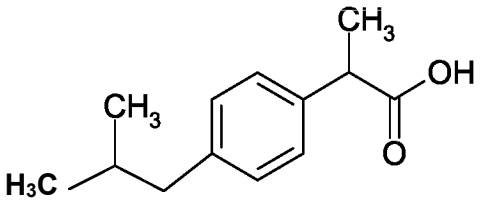
Drug Substance

Proper name: Ibuprofen

Chemical name: 2 - (4-isobutylphenyl) propionic acid

Molecular formula and molecular mass: $C_{13}H_{18}O_2$, 206.3

Structural formula:



Physicochemical properties: Ibuprofen is a white crystalline solid. It is non-hygroscopic and relatively insoluble in water. The compound is readily soluble in organic solvent and aqueous alkalis. (The sodium salt is highly soluble in water.) The apparent pK_a of ibuprofen is 5.2. Melting point is about 75 °C.

14 CLINICAL TRIALS

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

Large scale meta-analyses of randomized clinical trials show that high dose ibuprofen (≥ 2400 mg/day) is associated with an increased risk of stroke, cardiovascular death, and death from any cause when compared with placebo.

14.3 Comparative Bioavailability Studies

A single dose (1 x 600 mg), crossover, comparative bioavailability study of ibuprofen tablets (ibuprofen) 600 mg tablets and MOTRIN® (ibuprofen) 600 mg tablets (Upjohn Company of Canada) in 12 healthy male subject was conducted under fasting conditions.

Table 3

Ibuprofen (1 x 600 mg tablet) From measured data **uncorrected for potency** Geometric Mean Arithmetic Mean (CV %)

Parameter	Test*	Reference†	% Ratio of Geometric Means	Confidence Interval 90%
AUC_T (µg·h/mL)	185.3 191.50 (15.6)	189.1 192.80 (17.1)	98	92 – 104
AUC_I (µg·h/mL)	190.6 197.7 (16.8)	191.9 198.2 (17.6)	99	93 – 106
C_{max} (µg/mL)	41.6 43.78 (22.6)	51.0 53.96 (25.5)	82	66 – 101
T_{max} (h)	1.91 1.92 (35.4)	1.73 1.64 (61.0)		
$T_{½}$ ³ (h)	2.30	2.21		

* TEVA-PROFEN FCT, 600 mg tablets

†MOTRIN® 600 mg tablets, Upjohn Company of Canada (Don Mills, Ontario, Canada)

³ Expressed as the arithmetic mean only

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

Toxicity studies have been conducted using a variety of species, including: mice, rats, rabbits, guinea pigs and beagle dogs.

General Toxicology

Acute Toxicity Studies

Single-dose acute toxicity studies indicate that ibuprofen in lethal doses depresses the central nervous system of rodents and that large doses are ulcerogenic in both rodents and nonrodents. Ulcerogenesis may occur with both parenteral and oral administration indicating that the mechanism may have both a systemic as well as topical component.

Acute toxicity of ibuprofen in the rodent was studied in a number of models.

Single graded doses of ibuprofen were administered by oral intubation or by intraperitoneal or subcutaneous injection to groups of l0 male albino mice and male albino rats. Gross reactions were observed and mortalities recorded over a period of l4 days. The LD_{50} values determined by this method were 800 mg/kg orally and 320 mg/kg intraperitoneally in the mouse and l600 mg/kg orally and l300 mg/kg subcutaneously in the rat. Acute signs of poisoning were

prostration in mice, and sedation, prostration, loss of righting reflex and labored respiration in rats. Death occurred within 3 days from perforated gastric ulcers in mice and intestinal ulceration in rats, irrespective of the route of administration.

Similar LD_{50} determinations in other strains of rats and mice are summarized in the following Table 4.

Table 4 - Acute Toxicity in Rodents (LD50)

Species	Route	LD_{50} Range (mg/kg)
Albino Mice (40,37)	Oral Intraperitoneal	800-1000 320
Albino Rats (40)	Oral Subcutaneous	1600 1300
Sprague Dawley Rat (61)		1050
Long Evans Rat (62)		1000

In a comparison of several non-steroidal anti-inflammatory drugs (NSAID) including ibuprofen, male rats were sacrificed and the stomachs removed and examined for ulceration either 3 or 24 hours after oral administration of various single doses of ibuprofen. Using a standard scoring technique a mean score for each dosage group was calculated and the ulcerogenic potential was expressed as a minimum ulcerogenic dose. The minimum oral ulcerogenic dose for ibuprofen in rats was calculated to be 6-13 mg/kg.

Another group studied the production of gastrointestinal lesions in the rat comparing ulcerogenic doses of ibuprofen and other NSAIDs after oral or intravenous administration. Both male and female Long Evans rats were used in all experiments. Prior to drug administration the animals were fasted for 8 hours. After treatment they were fed a normal diet and sacrificed after l7 hours. Gastric and intestinal mucosa was examined for presence of ulcers. The ulcerogenic dose in 50% of treated animals (UD_{50}) was calculated. The UD_{50} following oral administration of ibuprofen was determined to be 70 mg/kg while for intravenous ibuprofen it was 210 mg/kg. The intestinal UD_{50} was 88 mg/kg following oral and 172 mg/kg with intravenous administrations. A calculated "severity index" of gastric lesions was higher by the oral than the IV route at all doses tested.

Studies of the ulcerogenic potential of ibuprofen are summarized in the following Table 5.

Table 5 - Single Dose Ulcerogenicity Studies in Rodents

Species	Route	UD_{50}*(mg/kg)	MUD**(mg/kg)
Long Evans Rat (62)	Oral IV	70 210	50 -
Sprague Dawley Rat (63)	Oral	-	6-13

*UD50 = ulcerogenic dose in 50% treated animals **MUD = minimum ulcerogenic dose

Acute toxicity has also been studied in dogs.Various single oral doses of ibuprofen were administered to dogs with subsequent hematologic examination and biochemical analyses of blood and urine, and examination of feces for occult blood. Gross examination of the major organs occurred after the animals were sacrificed. No ill effects were seen following doses of 20 or 50 mg/kg. Oral doses of 125 mg/kg or greater produced emesis, scouring, albuminuria, fecal blood loss and erosions in the gastric antrum and pylorus.

Multiple Dose Toxicity Studies

Multiple dose ulcerogenicity studies of ibuprofen have also been conducted.

Rats were dosed by the oral route for a specific number of consecutive days, then sacrificed for examination. The ulcerogenic effect of oral ibuprofen was graded and reported by various scoring systems such as percent of animals in which ulcers were produced by a specific dose, or the UD50.

In one typical such study, Long Evans rats were administered comparative NSAIDs orally once a day for 5 days. The gastric and small intestinal mucosa were then examined for ulceration. The UD_{50}, MUD and potency ratio of the drugs tested were calculated. The minimal ulcerogenic doses of ibuprofen were 25 mg/kg for the stomach and 50 mg/kg for the intestine.

Similar studies of multiple dose ulcerogenic potential of ibuprofen are summarized in the following Table 6.

Table 6 - Multiple Oral Dose Toxicity Studies

Species	**Daily Dose**	**Duration**	**Ulcerogenic Factor**
Albino Rat (64)	400mg/kg	30 hours	Ulcers in 100%
Albino Rat ([37])		4 days	UD_{50} = 455 mg/kg/day UD_{28} = 240 mg/kg/day
Long Evans Rat ([62])		5 days	MUD = 25 - 50 mg/kg/day
Sprague Dawley Rat ([65])	5.8-225 mg/kg	10 days	None
Albino Rat ([40])	7.5mg/kg 180mg/kg	26 weeks 26 weeks	None Ulcers in 20%
Dog ([40])	4mg/kg 8mg/kg 16mg/kg	30 days 30 days 30 days	None 100% 100%

No other organ systems were generally noted to be significantly affected by these chronic administration studies. In one 30-day study, Wistar rats receiving 157 mg/kg/day ibuprofen had serum transaminase levels approximately double of those of a control, untreated group. Lower doses of ibuprofen in the same study had no significant effect on the activity of these enzymes.

Chronic toxicity studies in dogs demonstrated no gross or clinical signs of toxicity at 4, 8 or 16 mg/kg/day for 30 days. However, in all dogs given 8 or 16 mg/kg/day, postmortem

examination revealed gastric ulcers or erosions. No lesions were observed in dogs given 4 mg/kg/day.

A more complete assessment of chronic toxicity of ibuprofen in dogs studied the effects of administration of oral doses of 0, 2, 4 or 26 mg/kg/day over 26 weeks. Periodic blood, urine and fecal sample analyses were performed. Histologic examination of selected organs and tissues was performed at the completion of the study. During the 26 week period, some reversible signs of gastrointestinal disturbance characterized by frequent vomiting, diarrhea, occasional passage of fresh blood and weight loss occurred in the 2 female dogs but not the males receiving 16 mg/kg ibuprofen. Occult blood was irregularly detected in fecal samples but urinalysis, liver function tests and other hematologic and blood biochemical values were not altered significantly. Gross examination of organs was normal except for ulcerative lesions in the gastrointestinal tract of organs of all dogs receiving 16 mg/kg/day. Dogs given 2 and 4 mg/kg/day suffered no adverse reactions or gastrointestinal damage.

Carcinogenicity

A study to evaluate the potential carcinogenic activity of ibuprofen involved administration of a minimum of 100 mg/kg/day to mice for 80 weeks and 60 mg/kg/day to rats for 2 years. The proportion of animals with tumors of all types examined did not differ from those in the control group. The studies confirm that in the rat and mouse, ibuprofen does not induce tumors of the liver or other organs. Further, despite prolonged treatment, no other drug-induced hepatic lesions were seen in either species.

Reproductive and Development Toxicology

Teratogenicity studies of ibuprofen have been conducted in rabbits and rats. Results of the experiments indicate that ibuprofen is not teratogenic when given in toxic doses to rabbits nor is there embryotoxic or teratogenic activity in pregnant rats even when administered in ulcerogenic doses.

Effects of ibuprofen on circular strips of fetal lamb ductus arterious indicate that exposure may produce contraction of the ductus. Such an effect might be anticipated because of the known prostaglandin inhibiting properties of ibuprofen.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrTEVA-PROFEN
Ibuprofen Tablets

Read this carefully before you start taking **TEVA-PROFEN** 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-PROFEN.**

Serious Warnings and Precautions

Heart and blood vessel problems:

- TEVA-PROFEN, mostly at higher doses (2400 mg/day), 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-PROFEN 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-PROFEN 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 TEVA-PROFEN 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-PROFEN if you are told to do so by your healthcare professional.
- Medicines like TEVA-PROFEN 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-PROFEN 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-PROFEN.

What is TEVA-PROFEN used for?

TEVA-PROFEN is used in adults to relieve the signs and symptoms in the following conditions:

- Rheumatoid arthritis
- Osteoarthritis

How does TEVA-PROFEN work?

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

What are the ingredients in TEVA-PROFEN?

Medicinal ingredients: ibuprofen
Non-medicinal ingredients : Carnauba wax, colloidal silicon dioxide, FD&C yellow # 6 aluminum lake, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polydextrose, polyethylene glycol, pregelatinized starch, silicon dioxide, sodium lauryl sulfate, sodium starch glycolate and titanium dioxide.

TEVA-PROFEN comes in the following dosage forms:

Tablets: 600 mg

Do not use TEVA-PROFEN if you:

- 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 allergy to ibuprofen or any of the other ingredients in this medicine or the container.
- have a history of developing 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 liver disease (active or severe)
- have kidney disease (severe or worsening)
- have high potassium in the blood.
- have systemic lupus erythematosus.
- are under 12 years old.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take TEVA-PROFEN. 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 asthma
- Have immune system problems
- Are pregnant, planning on becoming or become pregnant while taking TEVA-PROFEN.

Other warnings you should know about:

Serious Side Effects: TEVA-PROFEN can cause serious side effects, including:

- **Blood and bleeding problems:**
  -TEVA-PROFEN can cause blood problems, bleeding and prolonged bleeding.
  -Taking TEVA-PROFEN 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 TEVA-PROFEN.-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.

  TEVA-PROFEN 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 TEVA-PROFEN to monitor your health. They will:
- Check your blood pressure.
- Check your eyes. TEVA-PROFEN 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-PROFEN 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-PROFEN, do NOT drive or operate machinery.

Fertility in Women: TEVA-PROFEN 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-PROFEN. 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-PROFEN. 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-PROFEN:

- Acetylsalicylic Acid (ASA) or other NSAIDs, used to treat pain, fever and inflammation, like celecoxib, diclofenac, ibuprofen, naproxen
- Antacids, used to treat symptoms of excess stomach acid
- 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 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 bacteria 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
- Hydantoin, used to treat seizures
- Medicines used to treat different cancers, like methotrexate and pemetrexed
- Oral birth control, used to prevent pregnancy
- Probenecid, used to prevent gout
- Alcohol

How to take TEVA-PROFEN?

- Take exactly as your healthcare professional has told you. They should recommend the lowest dose possible for your treatment for the shortest time needed.
- Swallow capsules whole with food or milk. Do NOT split, chew or crush the tablets.
- **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 TEVA-PROFEN for more than 7 days, see your healthcare professional regularly. They will check if TEVA-PROFEN is working for you and if it is causing any side effects.

Usual dose:
Adults:

- Starting Dose: 600 mg (1 tablet) twice daily
  - Maintenance Dosage: 600 to 1200 mg daily (1 to 2 tablets daily)
  - Maximum Dosage: 1800 mg (3 tablets) daily
- 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 TEVA-PROFEN, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

- If you miss a dose of TEVA-PROFEN, take the dose as soon as possible. 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 TEVA-PROFEN?

These are not all the possible side effects you may have when taking TEVA-PROFEN. 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, itching
- Taste disorder, thirst, dry mouth
- Muscle pain
- Mouth sores
- Hair loss
- Increased sweating
- 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,		✓	

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**	
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 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		✓	

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**	
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 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 between 15°C and 30°C.

Do NOT keep expired medicine or medicine no longer needed. Return the medicine to your healthcare professional.

Keep out of reach and sight of children.

If you want more information about TEVA-PROFEN:

- 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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