PRODUCT MONOGRAPH

[Pr]pms-IBUPROFEN

Ibuprofen Tablets, USP

600 mg tablets

Nonsteroidal Anti-Inflammatory Drug,
Analgesic, Antipyretic Agent

Pharmascience Inc
6111 Royalmount Avenue
Montreal, Quebec
H4P 2T4

www.pharmascience.com

Submission Control No: 183725

Date of Revision:
August 21, 2015

Table of Contents

[Pr]pms-IBUPROFEN

Ibuprofen Tablets, USP
600 mg Tablets

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Non-medicinal Ingredients
oral	tablet / 600 mg	colloidal silicon dioxide, FD&C yellow # 6 aluminium lake, lactose monohydrate, povidone, pre-gelatinized starch, sodium starch glycolate, starch, stearic acid, titanium dioxide, triacetin and yellow iron oxide

INDICATIONS AND CLINICAL USE

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 nonsteroidal anti-inflammatory drugs (NSAIDs) refer to both non-selective NSAIDs and selective COX-2 inhibitor NSAIDs, unless otherwise indicated.

Ibuprofen, 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 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 CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS).

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

Use of pms-IBUPROFEN should be limited to the lowest effective dose for the shortest possible duration of treatment in order to minimize the potential risk for cardiovascular or gastrointestinal adverse events (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS).

pms-IBUPROFEN, as a NSAID, does NOT treat clinical disease or prevent its progression.

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

Geriatrics (> 65 years of age): Evidence from clinical studies and 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 **Warnings and Precautions**).

Pediatrics (< 12 years of age): pms-IBUPROFEN 600 mg tablet is not recommended for use in children less than 12 years of age.

CONTRAINDICATIONS

pms-IBUPROFEN is contraindicated in:

- the peri-operative setting of coronary artery bypass graft surgery (CABG). Although pms-IBUPROFEN has NOT been studied in this patient population, a selective COX-2 inhibitor NSAID studied in such a setting has led to an increased incidence of cardiovascular / thromboembolic events, deep surgical infections and sternal wound complications.

- the third trimester of pregnancy, because of risk of premature closure of the ductus arteriosus and prolonged parturition

- women who are breastfeeding, because of the potential for serious adverse reactions in nursing infants

- severe uncontrolled heart failure

- known hypersensitivity to ibuprofen or to any of the components / excipients

- history of asthma, urticaria, or allergic-type reactions after taking acetylsalicylic acid (ASA) or other NSAIDs (i.e. complete or partial syndrome of ASA-intolerance - rhinosinusitis, urticaria / angioedema, nasal polyps, asthma). Fatal anaphylactoid reactions have occurred in such individuals. Individuals with the above medical problems are at risk of a severe reaction even if they have taken NSAIDs in the past without any adverse reaction. The potential for cross-reactivity between different NSAIDs must be kept in mind (see **Warnings and Precautions** – ***Hypersensitivity Reactions - Anaphylactoid Reactions***).

- active gastric / duodenal / peptic ulcer, 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 **Warnings and Precautions** - ***Renal***)

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

- 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

WARNINGS AND PRECAUTIONS

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

pms-IBUPROFEN is a nonsteroidal 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. See WARNINGS AND PRECAUTIONS, Cardiovascular.

Caution should be exercised in prescribing (pms-IBUPROFEN) 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 pms-IBUPROFEN, can promote sodium retention in a dose dependent manner, through a renal mechanism, which can result in increased blood pressure and/or exacerbation of congestive heart failure (see also WARNINGS AND

PRECAUTIONS - *Renal - Fluid and Electrolyte Balance*).

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

Risk of Gastrointestinal (GI) Adverse Events (see WARNINGS AND PRECAUTIONS – *Gastrointestinal*)

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

General

Frail or debilitated patients may tolerate side effects less well and therefore special care should be taken in treating this population. **To minimize the potential risk for an adverse event, the lowest effective dose should be used for the shortest possible duration.** As with other NSAIDs, caution should be used in the treatment of elderly patients who are more likely to be suffering from impaired renal, hepatic or cardiac function. For high risk patients, alternate therapies that do not involve NSAIDs should be considered.

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

Carcinogenesis and Mutagenesis

See **Toxicology** section.

Cardiovascular

pms-IBUPROFEN is a nonsteroidal anti-inflammatory drug (NSAID). Ibuprofen, particularly at higher doses (2400 mg/day), is associated with an increased risk of serious cardiovascular related 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. The 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 pms-IBUPROFEN 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 pms-IBUPROFEN, 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 pms-IBUPROFEN should hypertension either develop or worse with its use.

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

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

Endocrine and Metabolism:

Corticosteroids:
pms-IBUPROFEN (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 **Drug Interactions - Drug-Drug Interactions - *Glucocorticoids***).

Gastrointestinal (GI)

Serious GI toxicity (sometimes fatal), such as peptic / duodenal ulceration, inflammation, perforation, obstruction and gastrointestinal bleeding, can occur at any time, with or without warning symptoms, in patients treated with NSAIDs, such as pms-IBUPROFEN. Minor upper GI problems, such as dyspepsia, commonly occur at any time. Healthcare providers should remain alert for ulceration and bleeding in patients treated with pms-IBUPROFEN, even in the absence of previous GI tract symptoms. Most spontaneous reports of fatal GI events are in elderly or debilitated patients and therefore special care should be taken in treating this population. **To minimize the potential risk for an adverse GI event, the lowest effective dose should be used for the shortest**

possible duration. For high risk patients, alternate therapies that do not involve NSAIDs should be considered (see **Warnings and Precautions - *Special Populations - Geriatrics***).
Patients should be informed about the signs and/or symptoms of serious GI toxicity and instructed to discontinue using pms-IBUPROFEN 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 pms-IBUPROFEN 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 pms-IBURPOFEN 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 pms-IBURPOFEN with warfarin requires close monitoring of the international normalized ratio (INR). Even with therapeutic INR monitoring, increased bleeding may occur.

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

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

Concomitant administration of pms-IBUPROFEN 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 nonsteroidal anti-inflammatory drugs are rare, but could occur with severe consequences.

Anemia is sometimes seen in patients receiving NSAIDs, including pms-IBUPROFEN. 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 pms-IBUPROFEN, 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.

Hypersensitivity Reactions

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

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

Cross-sensitivity:
Patients sensitive to one NSAID may be sensitive to any of the other NSAIDs as well.

Serious skin reactions:
(See **Warnings and Precautions - *Skin***)

Immune

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

Infection

pms-IBUPROFEN, 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 healthcare provider must be vigilant to the development of this complication.

Neurologic

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

Peri-Operative Considerations

(See **Containdications –** ***Coronary Artery Bypass Graft Surgery***)

Psychiatric

(See **Warnings and Precautions –** ***Neurologic***)

Renal

Long-term administration of NSAIDs to animals has resulted in renal papillary necrosis and other abnormal renal pathology. In humans, there have been reports of acute interstitial nephritis 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 pms-IBUPROFEN, 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 **Containdications**)

Fluid and Electrolyte Balance:
Use of NSAIDs, such as pms-IBUPROFEN, 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 pms-IBUPROFEN in patients with a history of congestive heart failure, compromised cardiac function, hypertension, increased age or other conditions predisposing to fluid retention (see **Warnings and Precautions - *Cardiovascular***).

Use of NSAIDs, such as pms-IBUPROFEN, 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.

Respiratory

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

Sexual Function / Reproduction

The use of pms-IBUPROFEN, 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 pms-IBUPROFEN should be considered.

Skin

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

Special Populations

Pregnant Women:
pms-IBUPROFEN is CONTRAINDICATED for use during the third trimester of pregnancy because of risk of premature closure of the ductus arteriosus and the potential to prolong parturition (see Toxicology).

Caution should be exercised in prescribing pms-IBUPROFEN during the first and second trimesters of pregnancy (see Toxicology).

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

Nursing Women:
(See **Contraindications**)

Pediatrics:
(See **Containdications**)

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

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

Monitoring and Laboratory Tests

***Hematologic*:** Patients on long-term treatment with NSAIDs, should have their hemoglobin, hematocrit, and blood cell count checked if they exhibit any signs or symptoms of anemia or blood loss.

Patients on long-term treatment with NSAIDs, should have their electrolytes such as serum potassium checked regularly if they exhibit any signs or symptoms of renal disease.

Blood pressure should be monitored regularly during therapy.

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

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

No data is available.

Post-Market Adverse Drug Reactions

The most common adverse reactions encountered with nonsteroidal anti-inflammatory drugs are gastrointestinal, of which gastric or duodenal ulcer, with or without bleeding, is the most severe. Fatalities have occurred, particularly in the elderly.

Experience reported with prescription use of ibuprofen has included the following adverse reactions. Note: Reactions listed below under Causal Relationship Unknown are those where a causal relationship could not be established; however, in these rarely reported events, the possibility of a relationship to ibuprofen also cannot be excluded.

The table below pertains to the nonprescription strengths of ibuprofen.

Adverse Effect	Common (> 1 % but < 10%)		Less Common (< 1%)
	Incidence 3-9%	**Incidence 1-3%**	
Allergic			• anaphylaxis (See Contraindications)
	Also reported but with unknown causal relationship, rarely: • fever • serum sickness • lupus erythematosus syndrome		
Cardiovascular			• congestive heart failure in patients with marginal cardiac function • elevated blood pressure • arterial thrombotic events Conditions such as congestive heart failure and hypertension may be aggravated by sodium retention and edema caused by ibuprofen in such patients.
	Also reported but with unknown causal relationship, rare cases of: • arrhythmias (sinus tachycardia, sinus bradycardia, palpitations)		
Central Nervous System	• dizziness	• headache • nervousness	• depression • insomnia
	Also reported but with unknown causal relationship: • paresthesias • hallucinations • dream abnormalities • aseptic meningitis has been reported in patients with systemic lupus erythematosus or other connective tissue disease • aseptic meningitis and meningioencephalitis, in one case accompanied by eosinophilia in the cerebrospinal fluids, has been reported in patients who took ibuprofen intermittently and did not have any connective tissue disease • cognitive dysfunction has been observed in elderly patients who took ibuprofen		

Adverse Effect	Common (> 1 % but < 10%)		Less Common (< 1%)
	Incidence 3-9%	**Incidence 1-3%**	
Dermatologic	• rash • (including maculopapular type)	• pruritis	• vesiculobullous eruptions • urticaria • erythema multiforme
	Also reported but with unknown causal relationship: • alopecia • Stevens-Johnson Syndrome		
Endocrine	Also reported but with unknown causal relationship, rare cases of: • gynecomastia • hypoglycemic reaction • menstrual delays of up to two weeks and dysfunctional uterine bleeding occurred in nine patients taking ibuprofen 400 mg three times a day for three days before menses		
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 • hepatitis • jaundice • abnormal liver function (SGOT, serum bilirubin and alkaline phosphatase)
	The generally modest elevations of serum transaminase activity that has been observed are usually without clinical sequelae but severe, potentially fatal toxic hepatitis can occur.		
Hematologic			• leukopenia and decreases in hemoglobin and hematocrit
	Also reported but with unknown causal relationship, rare cases of: • hemolytic anemia • thrombocytopenia • granulocytopenia • bleeding episodes (e.g., prupura, epistaxis, hematuria, menorrhagia) • auto-immune hematological anemia occurred in one patient taking 400 mg of ibuprofen three times a day for ten days • fatal aplastic anemia was reported in one patient who took 600 mg per day for eight months		
Metabolic		• decreased appetite • edema • fluid retention	
	Fluid retention generally responds promptly to drug discontinuation.		
Renal	Also reported but with unknown causal relationship: • decreased creatinine clearance • polyuria • azotemia Like other nonsteroidal anti-inflammatory agents, ibuprofen inhibits renal prostaglandin synthesis that may decrease renal function and cause sodium retention.		

Adverse Effect	Common (> 1 % but < 10%)		Less Common (< 1%)
	Incidence 3-9%	Incidence 1-3%	
	Renal blood flow glomerular filtration rate decreased in patients with mild impairment of renal functions who took 1200 mg/day of ibuprofen for one week. • Renal papillary necrosis has been reported. A number of factors appear to increase the risk of renal toxicity (see Warnings and Precautions).		
Special Senses		• tinnitus	• amblyopia (blurred and/or diminished vision, scotomata and/or changes in colour vision) Any patient with eye complaints during ibuprofen therapy should have an ophthalmological examination.
	Also reported but with unknown causal relationship: • conjunctivitis • diplopia • optic neuritis		

DRUG INTERACTIONS

Drug-Drug Interactions

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

The exception is the use of low dose ASA for cardiovascular protection, when another NSAID is being used for its analgesic / anti-inflammatory effect, keeping in mind that combination NSAID therapy is associated with additive adverse reactions.

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

Animal studies show that ASA given with NSAID agents, including ibuprofen, yield a net decrease in anti-inflammatory activity with lowered blood levels of the non-ASA drug. Single-dose bioavailability studies in normal volunteers have failed to show an effect of ASA on ibuprofen blood levels. Correlative clinical studies have not been done.

Antacids
Concomitant administration of antacids with NSAIDs may affect the rate, but generally not the extent of the absorption of the NSAID.

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

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

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

Anti-Platelet Agents (including ASA)
There is an increased risk of bleeding, via inhibition of platelet function, when anti-platelet agents are combined with NSAIDs, such as pms-IBUPROFEN (see **Warnings and Precautions -** ***Hematologic - Anti-platelet Effects***).

Cyclosporin
Nephrotoxicity of cyclosporin and tacrolimus may be increased because of the effect of NSAIDs on renal prostaglandins. Therefore, it should be given at doses lower than those that would be used in patients not receiving cyclosporin or tacrolimus.

Digoxin
An increase in serum digoxin level has been noted with some NSAIDS.

Diuretics
Clinical studies, as well as post-marketing observations, have shown that NSAIDs can reduce the effect of diuretics.

Ibuprofen, because of its fluid retention properties, can decrease the diuretic and anti-hypertensive effects of diuretics, and increased diuretic dosage may be needed. Patients with impaired renal function taking potassium-sparing diuretics who develop ibuprofen-induced renal insufficiency might be in serious danger of fatal hyperkalemia.

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

Lithium
Monitoring of plasma lithium concentrations is advised when stopping or starting a NSAID, as increased lithium concentrations can occur.

Methotrexate
Caution should be exercised when NSAIDs are administered less than 24 hours before or after treatment with methotrexate. Elevated blood concentrations of methotrexate may occur, increasing

toxicity.

Oral Contraceptives
No data is available.

Oral Hypoglycemics
Ibuprofen may increase the hypoglycemic effects of oral sulfonylurea hypoglycemic agents.

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

Tacrolimus
(See ***Cyclosporin***)

Other Drug Interactions

Although ibuprofen binds to a significant extent to plasma proteins, interactions with other protein-bound drugs occur uncommonly. Nevertheless, caution should be observed when other drugs also having a high affinity for protein binding sites are used concurrently. Some observations have suggested a potential for ibuprofen to interact with phenytoin. However, the mechanisms and clinical significance of these observations are presently not known.

Patients taking other prescribed medications should consult a physician before using ibuprofen to assure its compatibility with the other medications.

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

Drug-Lifestyle Interactions

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.

DOSAGE AND ADMINISTRATION

Dosing Considerations

pms-IBUPROFEN should be limited to the lowest effective dose for the shortest possible duration of treatment.

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.

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.

Recommended Dose

Rheumatoid arthritis, osteoarthritis:

Initially: 1200 mg in divided doses. Maximum: 1800 mg daily.
Maintenance dosage: 600 to 1200 mg daily.

Children: Not recommended for children under 12 years of age.

Missed Dose

If you miss a dose, take the missed dose as soon as you remember. If it is almost time for your next dose, wait until then to take your medicine and skip the missed dose. Do not take two doses at the same time.

OVERDOSAGE

Clinical Features

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 0_2, $NaHCO_3$, 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 mcg/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 mcg/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 **Detailed Pharmacology – *Human Studies – Pharmacokinetics - Absorption***).

Management of Overdose
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.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Ibuprofen is a member of the class of agents commonly known as nonsteroidal 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.

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.

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 Fg/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 through oxidation and glucuronic acid conjugation with urinary excretion of the inactive metabolites usually complete within 24 hours. Less than 10% is excreted unchanged in the urine.

Excretion: Ibuprofen has an elimination half-life of approximately two hours.

Special Populations and Conditions

Geriatrics: 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.

STORAGE AND STABILITY

Tablets

Temperature:
Store away from heat at controlled room temperature (15°C - 30°C).

Light:
Store away from direct light.

Others:
Keep in a safe place out of the reach of children.

DOSAGE FORMS, COMPOSITION AND PACKAGING

pms-IBUPROFEN 600 mg tablets are available as orange, oval shaped, film-coated tablets debossed with IBU 600 on one side and nothing on the other side. Packed in bottles of 100 and 500 tablets.

pms-IBUPROFEN contain 600 mg of ibuprofen and the following non-medicinal ingredients in alphabetical order: colloidal silicon dioxide, FD&C yellow # 6 aluminum lake, lactose monohydrate, povidone, pre-gelatinized starch, sodium starch glycolate, starch, stearic acid, titanium dioxide, triacetin and yellow iron oxide.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

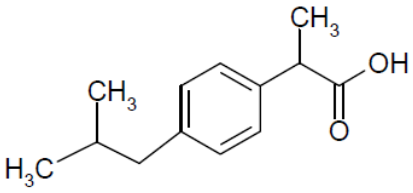
Drug Substance

a) Proper name: Ibuprofen

b) Chemical name: 2-(p-isobutylphenyl) propionic acid

c) Molecular formula and molecular mass: 206.28 g/mol

d) Structural formula:



e) Physicochemical properties: Ibuprofen is a white crystalline powder with a characteristic odor and slight taste. It is very slightly soluble in water and very soluble in alcohol and other common organic solvents. The apparent pKa of ibuprofen is 5.2. Its melting point is 75°C to 75.5°C.

CLINICAL TRIALS

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.

Comparative Bioavailability Studies

A blinded, randomized, 2-way crossover bioequivalence study of pms-Ibuprofen 400 mg tablets was performed versus the Canadian reference product, Super Strength Motrin IB® (ibuprofen) 400 mg tablets as 1 x 400 mg tablet in 25 healthy male subjects under fasting conditions.

Bioavailability data were measured and the results are summarized in the following table:

Ibuprofen (1 x 400 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 (mcg·h/mL)	111.474 113.885 (20.4)	114.351 116.568 (19.9)	97.48	94.61 – 100.45
AUC_I (mcg·h/mL)	116.819 119.569 (21.3)	119.820 122.495 (21.3)	97.50	94.47 – 100.62
C_{max} (mcg/mL)	31.662 31.996 (15.3)	37.112 37.860 (19.9)	85.31	79.49 – 91.56
T_{max}[§] (h)	1.25 (0.83 - 4.00)	0.83 (0.50 - 2.50)		
$T_{½}$[€] (h)	2.15 (12.4)	2.20 (10.9)		

[*] pms-Ibuprofen 400 mg tablets
[†] Super Strength Motrin IB® 400 mg tablets, McNeil, (Guelph, Canada)
[§] Expressed as the median (range) only
[€] Expressed as the arithmetic mean (CV %) only
[#] Based on the least square mean estimates

DETAILED PHARMACOLOGY

Animal Studies

Pharmacodynamics

While the mechanism of action of ibuprofen is not definitely known, the generally accepted mechanism is the inhibition of prostaglandin synthesis. Inhibition of prostaglandin biosynthesis prevents sensitization of tissues by prostaglandins to other inflammatory, pain and thermoregulatory mediators, hence accounting for the activity of ibuprofen and other nonsteroidal anti-inflammatory drugs against pain, inflammation and fever.

Inhibition of prostaglandin synthesis by ibuprofen has been demonstrated in several different experimental models: bull seminal vesicle microsomes, stomach, duodenum, kidney and brain of the rat[(35)], microsomal preparations from rabbit brain and kidney medulla.

The analgesic efficacy of ibuprofen has been demonstrated in several animal models: phenylbenzoquinone-induced writhing in the mouse, acetylcholine-induced writhing in the mouse, the Randall-Selitto inflammed paw model in the rat, the mouse hot plate and adjuvant-induced arthritis model in the rat.

The antipyretic activity of ibuprofen has been demonstrated in yeast-induced fever in rats.

Pharmacokinetics

Several aspects of the pharmacokinetics of ibuprofen have been studied *in vivo* in rats, rabbits, dogs

and baboons.

Studies in rats indicate that while limited absorption of ibuprofen occurs in the stomach, the principal site of absorption is the intestine. Single dose studies using C^{14}-labelled ibuprofen in rats, rabbits and dogs show rapid absorption rates.

Tissue distribution studies performed in rats after both single and repeated doses of 20 mg/kg of C^{14}-labelled ibuprofen demonstrate broad distribution with accumulation of radioactivity in the thyroid, adrenals, ovaries, fat and skin. Transplacental passage of ibuprofen was also noted with similar plasma levels measured in both the pregnant rats and fetuses.

Protein binding studies with plasma levels of 20 mcg/mL indicate the percent bound in rats 96%, dogs 99%, baboons 95% and man 99%.

Four metabolites of ibuprofen have been found in the plasma of rabbits, three in rats, none in dogs, two in baboons and two in man, with the liver suggested as the principal organ of metabolism. Excretion of metabolites was noted to varying degrees through both urine and feces indicating species variability in the bile and kidney excretion ratios.

Human Studies

Pharmacokinetics

Absorption: *In vivo* studies indicate that ibuprofen is well absorbed orally with peak plasma levels usually occurring within 1 to 2 hours. 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. Comparable serum levels and time to peak within 1-2 hours were confirmed by other investigations with 200 mg and 400 mg solid doses. A multiple dose study of administration of a 200 mg ibuprofen tablet three times a day for 2 weeks showed no evidence of accumulation of ibuprofen.

Distribution: Ibuprofen, like most drugs of its class, is highly protein bound (> 99% bound at 20 Fg/mL). Based on oral dosing data there is an age-or fever-related change in volume of distribution for ibuprofen. 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. The clinical significance of these findings is unknown. 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: Ibuprofen is extensively metabolized in humans with approximately 84% recoverable in the urine, primarily as conjugated hydroxy- and carboxy- metabolites, with only approximately l% excreted unchanged. The two major metabolites of ibuprofen in humans have been found to have no activity in the ultraviolet erythema test in guinea pigs and in the acetylcholine-induced mouse writhing test at doses of l0 mg/kg and l5 mg/kg respectively.

Elimination: Ibuprofen is rapidly metabolized and eliminated 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 2.0 hours. 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. This suggests that the observed difference in clearance is due to differences in the volume of distribution of ibuprofen, as described above. The clinical relevance of these differences in clearance is unknown, although extensive clinical experience with ibuprofen in children at the pertinent dosage range (5-10 mg/kg) indicates a wide margin of safety.

TOXICOLOGY

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

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 10 male albino mice and male albino rats. Gross reactions were observed and mortalities recorded over a period of 14 days. The LD_{50} values determined by this method were 800 mg/kg orally and 320 mg/kg intraperitoneally in the mouse and 1600 mg/kg orally and 1300 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 1.

Table l - Acute Toxicity in Rodents (LD_{50})

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 nonsteroidal 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 17 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 2.

Table 2 - 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 UD_{50}.

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 3.

Table 3 - Multiple Oral Dose Toxicity Studies

Species	Daily Dose	Duration	Ulcerogenic Factor
Albino Rat [64]	400 mg/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]	7.5 mg/kg 180 mg/kg	26 weeks 26 weeks	None Ulcers in 20%
Dog [40]	4 mg/kg 8 mg/kg 16 mg/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.

Teratogenicity and Reproduction Studies

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 produced contraction of the ductus. Such an effect might be anticipated because of the known prostaglandin inhibiting properties of ibuprofen.

REFERENCES

1. Wolfe MM, Lichtenstein DR, Singh G. Gastrointestinal toxicity of nonsteroidal antiinflammatory drugs. N Engl J Med 1999; 340: 1888-1899.

2. Garcia Rodriguez LA, Hernandez-Diaz S. The risk of upper gastrointestinal complications associated with non-steroidal anti-inflammatory drugs, glucocorticoids, acetaminophen, and combinations of these agents. Arthritis Res 2001; 3: 98-101.

3. Piper JM, Ray WA, Daugherty JR, Griffin MR. Corticosteroid use and peptic ulcer disease: role of nonsteroidal anti-inflammatory drugs. Ann Internal Med 1991; 114: 735-740.

4. Gabriel SE, Jaakkimainen L, Bombardier C. Risk for serious gastrointestinal complications related to use of nonsteroidal anti-inflammatory drugs. Ann Internal Med 1991; 115: 787-796.

5. Moller Hansen J, Hallas J, Lauritsen JM, Bytzer P. Non-steroidal anti-inflammatory drugs and ulcer complications: a risk factor analysis for clinical decision-making. Scand J Gastroenterol 1996; 31: 126-130.

6. Barry WS, Meinzinger MM, Howse CR. Ibuprofen overdose and exposure in utero: results from a postmarketing voluntary reporting system. Am J Med 1984; 77(1A):35-39.

7. Albert KS, Gernaat CM. Pharmacokinetics of ibuprofen. Amer J Med 1984; 77(1A): 40-46.

8. Kurth T, Glynn RJ, Walker AM, Chan KA, Buring JE, Hennekens CH, et al. Inhibition of clinical benefits of aspirin on first myocardial infarction by nonsteroidal antiinflammatory Drugs. Circulation. 2003; 108: 1191 – 1195.

9. Court H, Volans GN. Poisoning after overdose with non-steroidal anti-inflammatory drugs. Adverse Drug React Acute Poisoning Rev 1984; 3:1-21.

10. Adams SS, Cliffe EE, Lessel B, Nicholson JS. Some biological properties of 2-(4-isobutylphenyl)-propionic acid. J Pharm Sci 1967; 56:1686.

11. Kaiser DG, Martin RS. Electron-capture GLC determination of ibuprofen in serum. J Pharm Sci 1978; 67:627-630.

14. Insel PA. Analgesic-antipyretic and anti-inflammatory agents and drugs employed in the treatment of gout. In Molinoff PB, Ruddon RW, editors. Goodman & Gilman's The Pharmacological Basis of Therapeutics. New York: McGraw-Hill, 1996: 617-657.

15. Hillis WS. Areas of emerging interest in analgesia: Cardiovascular complications. Am J Ther 2002; 9:259-269.

16. FitzGerald GA, Patrono C. The Coxibs, selective inhibitors of cyclooxygenase-2. N Engl J Med 2001; 345: 433-442. Review

17. Konstam MA, Weir MR, Reicin A, Shapiro D, Sperling RS, Barr E, et al. Cardiovascular thrombotic events in controlled, clinical trials of refecoxib. Circulation 2001; 104:2280-2288.

18. Bombardier C, Laine L, Reicin A, Shapiro D, Burgo-Vargas R, Davis B, et al. Comparison of upper gastrointestinal toxicity of refecoxib and naproxen in patients with rheumatoid arthritis. N Engl J Med 2000; 343: 1520-1528.

19. Brooks CD, Schlagel CA, Sekhar NC, Sobota JT. Tolerance and pharmacology of ibuprofen. Curr Ther Res 1973; 15:180-190.

27. Mills RF, Adams SS, Cliffe EE, Dickinson W, Nicholson JS. The metabolism of ibuprofen. Xenobiotica 1973: 3:589-598.

28. Kober A, Sjoholm I. The binding sites of human serum albumin for some nonsteroidal antiinflammatory drugs. Mol Pharmacol 1980; 18:421-426.

29. Glass RC, Swannell AJ. Concentrations of ibuprofen in serum and synovial fluid from patients with arthritis. Br J Clin Pharmacol 1978; 6:453-454.

30. Albert KS, Gillespie WR, Wagner JG, Pau A, Lockwood GF. Effects of age on the clinical pharmacokinetics of ibuprofen. Am J Med 1984; 77(1A):47-50.

31. Juhl RP, Van Thiel DH, Dittert LW, Albert KS, Smith RB. Ibuprofen and sulindac kinetics in alcoholic liver disease. Clin Pharmacol Ther 1983; 34:104-109.

32. Cushman DW, Cheung HS. Effect of substrate concentration on inhibition of protaglandin synthetase of bull seminal vesicles by anti-inflammatory drugs and fenamic acid analogs. Biochim Biophys Acta 1976; 424:449-459.

33. Fitzpatrick FA, Wynalda MA. In Vivo suppression of prostaglandin biosynthesis by non-steroidal anti-inflammatory agents. Prostaglandins 1976; 12:1037-1051.

34. Szczeklik A, Gryglewski RJ, Czerniawska-Mysik G, Zmuda A. Aspirin induced asthma: hypersensitivity to fenoprofen and ibuprofen in relation to their inhibitory action on prostaglandin generation by different microsomal enzymic preparations. J Allergy Clin Immunol 1976; 58:10-18.

35. Aparicio L. Some aspects of the pharmacology of butibufen, a non-steroidal anti-inflammatory agent. Arch Int Pharmacodyn Ther 1977; 227:130-141.

36. Adams SS, McCullough KF, Nicholson JS. The pharmacological properties of ibuprofen, an anti-inflammatory, analgesic and antipyretic agent. Arch Int Pharmacdyn Ther 1969; 178:115-129.

37. Adams SS, Bough RG, Cliffe EE, Lessel B, Mills RFN. Absorption, distribution and toxicity of ibuprofen. Toxicol Appl Pharmacol 1969; 15:310-330.

41. Miller AC, Buckler JW, Sheldrake FE. Clinical studies of ibuprofen. Curr Med Res Opin 1975; 3:589-593

42. de Blecourt JJ. A comparative study of ibuprofen ('Brufen') and indomethacin in uncomplicated arthroses. Curr Med Res Opin 1975; 3:477-480.

43. Chahade WH, Federico WA, Josef H, Cohen M. The evaluation of the analgesic activity and anti-inflammatory activity of ibuprofen in comparison with aspirin in patients suffering from osteoarthritis of the hips, knee and/or cervical, dorsal and/or lumbar spinal column in a double blind study. Revista Brasileria de Medicina 1976; 33:347-350.

44. Tyson VC, Glynne A. A comparative study of benoxaprofen and ibuprofen in osteoarthritis in general practice. J Rheumatol (Suppl 6)1980; 7:132-138.

45. Ruoff G, Williams S, Cooper W, Procaccini RL. Aspirin-acetaminophen vs ibuprofen in a controlled multicenter double-blind study with patients experiencing pain associated with osteoarthritis. Curr Ther Res 1982; 31:821-831.

54. Muckle DS. Comparative study of ibuprofen and aspirin in soft-tissue injuries. Rheumatol Rehab 1974; 13:141-147.

55. Nasution AR. Study of the analgesic activities of ibuprofen compared with paracetamol. Proceeding of the 13th International Congress of Rheumatology, Kyoto, Japan 1973.

56. McEvoy GK, Editor. Ibuprofen. In: AHFS DI 1997. Bethesda: American Society of Health - Systems Pharmacists, 1997. p. 1499 – 1503.

57. Kaiser DG, Vangiessen GJ. GLC determination of ibuprofen [(+)-2-(p-isobutylphenyl) propionic acid] in plasma. J Pharm Sci 1974; 63:219-221.

58. Fukawa K, Kanezuka T, Ohba S, Kawano O, Hibi M, Misaki N, et al. Studies on an anti-inflammatory agent. III. Pharmacological investigations of a new non-steroidal anti-inflammatory agent: 2-oxo-3-[4-(1-oxo-2-isoindolinyl)-phenyl]-butanamide (GP 650). Arzneimittelforschung 1982; 32:225-230.

59. Cioli V, Putzolu S, Rossi V, Corradino C. A toxicological and pharmacological study of ibuprofen guaiacol ester (AF 2259) in the rat. Toxicol Appl Pharmacol 1980; 54:332-339.

60. Atkinson DC, Leach EC. Anti-inflammatory and related properties of 2-(2,4-diochlorphenoxy) phenylacetic acid (fenclofenac). Agent Actions 1976; 6:657-666.

61. Parmar NS, Ghosh MN. Gastric anti-ulcer activity of (+)-cyanidanol-3, a histidine decarboxylase inhibitor. Eur J Pharmacol 1981; 69:25-32.

62. Paroli E, Nencini P, Anania MC. Correlations of DNA, RNA and protein levels in duodenal mucosa with antiinflammatory potency and disposition to gut damage of non-steroidal agents. Comparative behaviour of glucametacine, indomethacin, phenylbutazone and ibuprofen.

Arzneimittelforschung 1978; 28:819-824.

63. Dudkiewicz J. Ibuprofen-induced gastrointestinal changes. Acta Physiol Pol (Poland) 1981: 32:693-701.

64. Adams SS, Bough RG, Cliffe EE, Dickinson W, Lessel B, McCullough KF, et al.. Some aspects of the pharmacology, metabolism and toxicology of ibuprofen. Rheumatol Phys Med 1970; 10 (Suppl 10):9-26.

65. Coceani F, White E, Bodach E, Olley PM. Age-dependent changes in the response of the lamb ductus arteriosus to oxygen and ibuprofen. Can J Physiol Pharmacol 1979; 57:825-831.

66. Proceedings of Joint Meeting, Arthritis Drugs Advisory Committee and Nonprescription Drugs Advisory Committee. Centre for Drug Evaluation and Research. Department of Health and Human Services, Rockville, Maryland. March 28, 1995.

67. Product Monograph: MOTRIN® (Ibuprofen Tablets) by McNeil Consumer Healthcare. Date of Revision: June 14, 2005, Control No.: 096753.

PART III: CONSUMER INFORMATION

[Pr]pms-IBUPROFEN
Ibuprofen Tablets

This leaflet is part III of a three-part "Product Monograph" published when pms-IBUPROFEN was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about pms-IBUPROFEN. Contact your doctor or pharmacist if you have any questions about the drug.

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

See your healthcare provider and pharmacist regularly and ask them questions about your health and any medications you take.

ABOUT THIS MEDICATION

What the medication is used for:
Your healthcare provider has prescribed pms-IBUPROFEN for you for one or more of the following medical conditions:
pms-IBUPROFEN is indicated for the relief of the signs and symptoms of rheumatoid arthritis and osteoarthritis.

High doses (2400 mg/day) of ibuprofen may increase the risk of serious heart and blood vessel side effects. Patients with an increased risk of heart and blood vessel disease should talk to their healthcare provider about other treatment options first.

What it does:
pms-IBUPROFEN is a nonsteroidal anti-inflammatory drug (NSAID) which can reduce the production of substances, called prostaglandins, which are involved in the development of pain and inflammation, pms-IBUPROFEN does not cure your illness or prevent it from getting worse, it can only relieve the pain and reduce swelling as long as you continue to take it.

When it should not be used:
***DO NOT TAKE* pms-IBUPROFEN if you have any of the following medical conditions:**
- **Heart bypass surgery (planning to have or recently had)**
- **Severe, uncontrolled heart failure**
- **Bleeding in the brain or other bleeding disorders**
- **Current pregnancy (after 28 weeks of pregnancy)**
- **Currently breastfeeding (or planning to breastfeed)**
- **Allergy to ASA (Acetylsalicylic Acid) or other NSAIDs (Nonsteroidal Anti-Inflammatory Drugs)**
- **Ulcer (active)**
- **Bleeding from the stomach or gut (active)**
- **Inflammatory bowel disease (Crohn's Disease or Ulcerative Colitis)**
- **Liver disease (active or severe)**
- **Kidney disease (severe or worsening)**
- **High potassium in the blood**

pms-IBUPROFEN should not be used if you:
- are allergic to any ingredient in the formulation (see non-medicinal ingredients below). Allergic reactions may appear as hives, difficulty breathing, rash, swelling of the face or throat or sudden collapse.
- have had asthma, hives or any allergic-type reactions after taking ASA or other NSAIDs (complete or partial syndrome of ASA intolerance).
- have systemic lupus erythematosus.

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

pms-IBUPROFEN should NOT be used in patients under 12 years of age since the safety and effectiveness have NOT been established.

What the medicinal ingredient is:
ibuprofen

What the non-medicinal ingredients are:
Colloidal silicon dioxide, FD&C yellow # 6 aluminum lake, lactose, povidone, pregelatinized starch, sodium starch glycolate, starch, stearic acid, titanium dioxide, triacetin and yellow iron oxide

What dosage forms it comes in:
Tablets: 600 mg

WARNINGS AND PRECAUTIONS

If you have, or previously had, any of the following medical conditions, see your healthcare provider to discuss treatment options other than pms-IBUPROFEN:
- **Heart Attack or Angina (chest pain)**
- **Stroke or Mini-stroke**
- **Loss of Vision**
- **Current Pregnancy (less than 28 weeks)**
- **Congestive Heart Failure**
- **Gastrointestinal conditions such as ulcers, stomach bleeding, blockages**
- **Kidney problems leading to high blood pressure**

Ibuprofen, mostly at higher doses (2400 mg/day) can increase the risk of serious heart and blood vessel side effects. This risk may be higher with longer periods of use. Patients with risk factors for (high blood pressure, high cholesterol, diabetes, smokers), or who have, heart or blood vessel disease should talk to their healthcare provider about other treatment options.

Before taking pms-IBUPROFEN, tell your healthcare provider if you have any of the following:
- High blood pressure
- High cholesterol
- Diabetes mellitus or on a low sugar diet

- Atherosclerosis (hardening of the arteries)
- Poor circulation to your extremities
- Blood-clotting disorder (e.g., hemophilia, sickle cell anemia, etc.)
- Hyperkalemia (high levels of potassium in your blood)
- Kidney disease or urine problems (bladder pain, any change in the amount and colour of urine)
- Liver disease, alcoholism, systemic lupus erythematous, or any other serious disease or condition.
- Previous ulcer or bleeding from the stomach or gut
- Previous bleeding in the brain
- Bleeding problems (dark urine, easy bruising, bloody or black tarry stools)
- Heart disease
- Family history of asthma, nasal polyps, long-term swelling of the sinus (chronic sinusitis) or hives
- 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)
- You are taking an anticoagulant (blood thinning medication), oral corticosteroid (used to treat joint pain and swelling) or any other drug
- You are taking low dose ASA
- You are dehydrated (severe fluid loss)
- You are smoker or ex-smoker
- You are over 65 years of age
- You are on a special diet (e.g., low sodium)

They may recommend an alternative analgesic such as acetaminophen.

Before taking pms-IBUPROFEN, tell your healthcare provider if you are planning to get pregnant.

While taking pms-IBUPROFEN:
- Tell any other doctor, dentist, pharmacist or other healthcare professional that you see, that you are taking pms-IBUPROFEN, especially if you are planning to have heart surgery;
- Do NOT drink alcoholic beverages while taking pms-IBUPROFEN because you are more likely to develop stomach problems;
- Fertility may be decreased. The use of pms-IBUPROFEN is not recommended in women trying to get pregnant. In women who have difficulty conceiving, stopping pms-IBUPROFEN should be considered.

INTERACTIONS WITH THIS MEDICATION

Talk to your healthcare provider and pharmacist if you are taking any other medication (prescription or non-prescription) such as any of the following (NOT a complete list):
- Acetylsalicylic Acid (ASA) or other NSAIDs
  - e.g., ASA, celecoxib, diclofenac, ibuprofen, indomethacin, ketorolac, meloxicam, naproxen
- Antacids
- Antidepressants
  - Selective Serotonin Reuptake Inhibitors (SSRIs)
    - e.g., citalopram, fluoxetine, paroxetine, sertraline
- Blood pressure medications
  - ACE (angiotensin converting enzyme) inhibitors
    - e.g., enalapril, lisinopril, perindopril, ramipril
  - ARBs (angiotensin II receptor blockers)
    - e.g., candesartan, irbesartan, losartan, valsartan
- Blood thinners
  - e.g., warfarin, ASA, clopidogrel
- Corticosteroids (including glucocorticoids)
  - • e.g., prednisone
- Cyclosporin
- Digoxin
- Diuretics
  - e.g., furosemide, hydrochlorothiazide
- Lithium
- Methotrexate
- Oral contraceptives
- Oral hypoglycemics (diabetes medications)
- Tacrolimus
- Phenytoin

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

PROPER USE OF THIS MEDICATION

Usual adult dose:
- Starting dose: 600 mg twice daily
- Maintenance dosage: 600 to 1200 mg daily (1 to 2 tablets daily)
- Maximum dosage: 1800 mg daily

Take pms-IBUPROFEN only as directed by your healthcare provider. **Do NOT take more of it, do NOT take it more often and do NOT take it for a longer period of time than your healthcare provider recommended. You should take the lowest dose of pms-IBUPROFEN for the shortest time period.** Taking too much pms-IBUPROFEN may increase your chances of unwanted and sometimes dangerous side effects, especially if you are elderly, have other diseases or take other medications.

If you will be using pms-IBUPROFEN for more than 7 days, see your healthcare provider regularly to discuss whether this medicine is working for you and if it is causing you any unwanted effects.

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

pms-IBUPROFEN is NOT recommended for use in patients under 12 years of age since safety and effectiveness have NOT been established.

pms-IBUPROFEN must be taken with food.

Overdose:

If you think you have taken too much pms-IBUPROFEN, contact your healthcare provider, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
If you missed a dose, just resume your usual schedule the following day. Do not take an extra dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

pms-IBUPROFEN may cause some side effects, especially when used for a long time or in large doses. When these side effects occur, you may require medical attention. Report all symptoms or side effects to your healthcare provider.

pms-IBUPROFEN may cause you to become drowsy or tired. Be careful about driving or participating in activities that require you to be alert. If you become drowsy, dizzy or light-headed after taking pms-IBUPROFEN, do NOT drive or operate machinery.

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

Side effects may include:

- Rash, itching
- Trouble sleeping (insomnia)
- Nausea, vomiting, stomach pain and/or cramps, heartburn, diarrhea, indigestion, constipation, bloating, gas

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

Symptom / effect	Talk with your healthcare provider or pharmacist		Stop taking drug and seek immediate medical help
	Only if severe	In all cases	
Bloody or black tarry stools			✓
Allergic reactions with symptoms such as shortness of breath, wheezing, any trouble breathing, chest tightness, skin rash, hives, swelling or itching			✓
Blurred vision, or any vision problems			✓
Bleeding problems with symptoms such as any change in the amount or colour of urine (red or brown)			
Any pain or difficulty experienced while urinating		✓	
Swelling of the feet, lower legs; weight gain		✓	
Liver problems with symptoms such as yellow of the skin or eyes, persistent indigestion, vomiting, stomach pain, nausea		✓	
Generally feeling unwell, fatigue, loss of appetite		✓	
Headaches, stiff neck		✓	
Mental confusion, depression		✓	
Dizziness, lightheadedness		✓	
Hearing problems		✓	

This is not a complete list of side effects. For any unexpected effects while taking pms-IBUPROFEN contact your healthcare provider or pharmacist.

HOW TO STORE IT

Store away from heat and direct light at room temperature (15°C - 30°C).

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

Keep out of reach and sight of children.

REPORTING SUSPECTED SIDE EFFECTS

Reporting Side Effects
You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.
3 ways to report:

- Online at MedEffect (http://www.hc-sc.gc.ca/dhp-mps/medeff/index-eng.php);
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 0701E
    Ottawa, ON
    K1A 0K9

  Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect (http://www.hc-sc.gc.ca/dhp-mps/medeff/index-eng.php).

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.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found by contacting the sponsor, Pharmascience Inc., at: 1-888-550-6060.

This leaflet was prepared by Pharmascience Inc.
www.pharmascience.com

Last revised: August 21, 2015