PRODUCT MONOGRAPH

APO-IBUPROFEN 200 mg
Ibuprofen Tablets USP, 200 mg

APO-IBUPROFEN CAPLET
Ibuprofen Tablets USP, 200 mg

APO-IBUPROFEN 300 mg
Ibuprofen Tablets USP, 300 mg

APO-IBUPROFEN 400 mg
Ibuprofen Tablets USP, 400 mg

APO-IBUPROFEN CAPLET
Ibuprofen Tablets USP, 400 mg

Non-Steroidal Anti-inflammatory Drug
Analgesic, Antipyretic Agent

APOTEX INC.
150 Signet Drive
Toronto, Ontario
M9L 1T9
Control #: 220304

DATE OF REVISION:
July 3, 2019

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Nonmedicinal Ingredients
Oral	Tablet and caplet / 200 mg	Tablets: carnauba wax, colloidal silicon dioxide, croscarmellose sodium, D&C yellow #10 and FD&C yellow #6, hydroxypropyl cellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, titanium dioxide Caplets: Carnauba wax, colloidal silicon dioxide, croscarmellose sodium, ferric oxide red, hydroxypropyl cellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, titanium dioxide.
Oral	Tablet / 300 mg	Colloidal silicon dioxide, croscarmellose sodium, hydroxypropyl cellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, titanium dioxide.
Oral	Tablet and caplet /400 mg	Tablet: colloidal silicon dioxide, croscarmellose sodium, FD&C yellow #6, hydroxypropyl cellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, titanium dioxide. Caplets: carnauba wax, colloidal silicon dioxide, croscarmellose sodium, ferric oxide red,

		hydroxypropyl cellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, titanium dioxide.

INDICATIONS AND CLINICAL USE

APO-IBUPROFEN (ibuprofen) is indicated for fast and effective relief of:

- headache pain (including mild to moderate migraine and tension headache)
- menstrual pain
- toothache (dental pain)
- pain from inflammation associated with conditions including:
    - arthritis
    - physical or athletic overexertion, (e.g. sprains or strains)
- minor aches and pains in muscles, bones and joints
- backache
- the aches and pain due to the common cold and flu
- reduction of fever

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 (e.g., Warnings and Precautions).

Pediatrics (<12 years of age): Not recommended for children under 12 years of age. Children's Ibuprofen formulations are available to treat children under 12 years of age.

CONTRAINDICATIONS

The following are contraindications to the use of APO-IBUPROFEN:

- Patients who are hypersensitive to ibuprofen, other non-steroidal anti-inflammatory drugs (NSAIDs), or to any ingredient in the formulation. For a complete listing of ingredients, see the Dosage Forms, Composition and Packaging section of the product monograph. The potential for cross-reactivity between different NSAIDs must be kept in mind.

- Ibuprofen should not be used in patients with the complete or partial syndrome of acetylsalicylic acid (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 nonsteroidal anti-inflammatory agents. 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 effects.

- Active gastric or duodenal ulcer, a history of recurrent ulceration, gastrointestinal bleeding, or active inflammatory disease of the gastrointestinal system.
- Significant hepatic impairment or active liver disease.
- Severely impaired or deteriorating renal function (creatinine clearance <30 ml/min).
- Ibuprofen should not be used in the presence of known hyperkalemia (also see Warnings and Precautions – Renal section).
- Children with kidney disease and/or who have suffered significant fluid loss.
- Ibuprofen is contraindicated in patients with systemic lupus erythematosus as an anaphylaxis-like reaction with fever may occur, particularly when ibuprofen has been administered previously.
- The third trimester of pregnancy, because of risk of premature closure of the ductus arteriosus and prolonged parturition.
- Do not use right before or after heart surgery (see Peri-Operative Considerations).

WARNINGS AND PRECAUTIONS

- Patients with heart disease and high blood pressure should not take this drug unless directed by a physician.
- Caution in patients with heart failure, hypertension or other conditions predisposing to fluid retention.
- Caution in patients prone to gastrointestinal tract irritation, particularly those with a history of peptic ulcer, diverticulosis or other inflammatory disease of the gastrointestinal tract such as ulcerative colitis and Crohn's disease.
- The elderly and patients with impaired renal function, heart failure, liver dysfunction, and those taking diuretics are at increased risk of renal toxicity.
- If persistent urinary symptoms (bladder pain, dysuria, urinary frequency), hematuria and cystitis occur, the drug should be stopped immediately.
- Ibuprofen use by women who are trying to conceive, during the first and second trimester of pregnancy, or if nursing.

General

Several medical conditions that can predispose patients to the adverse effects of non-steroidal anti-inflammatory drugs in general may be applicable to ibuprofen.

Patients with any serious medical condition should consult a physician before using ibuprofen as an analgesic or antipyretic (1).

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

If symptoms persist or get worse, or if new symptoms occur, patients should stop use and consult a physician.

Cardiovascular

Some patients with pre-existing hypertension may develop worsening of blood pressure control when placed on an NSAID and regular monitoring of blood pressure should be performed under such circumstances. NSAIDs may exacerbate congestive heart failure.

Patients who are taking low-dose ASA as cardio protective therapy should consult with a health professional prior to taking ibuprofen (see also Drug Interactions – Acetylsalicylic Acid).

NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke. This risk may increase with dose and duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk.

Gastrointestinal

Serious GI toxicity, such as ulceration, perforation, obstruction and gastrointestinal bleeding, sometimes severe and occasionally fatal, can occur at any time, with or without symptoms in patients treated with nonsteroidal anti-inflammatory drugs (NSAIDs) including ibuprofen. The risk may increase with dose and duration of use.

GI symptoms, such as dyspepsia, are common, usually developing early in therapy. Health providers should remain alert for ulceration and bleeding in patients treated with non-steroidal anti-inflammatory drugs, even in the absence of previous GI tract symptoms.

In patients observed in clinical trials of such agents, symptomatic upper GI ulcers, gross bleeding, or perforation occur in approximately 1% of patients treated for 3 to 6 months and in about 2 to 4% of patients treated for one year. The risk continues beyond one year. The incidence of these complications is related to dose, past history of known ulcer disease, and advanced age (see Special Populations). Studies have shown that the use of oral corticosteroids increases the risk of upper gastrointestinal complications associated with NSAIDs (2,3,4,5,6)

Ibuprofen should be given under close medical supervision to patients with a history of ulcer of the upper gastrointestinal tract or inflammatory disease of the gastrointestinal tract such as ulcerative colitis and Crohn's disease. In these cases the health provider must weigh the benefits of treatment against the possible hazards.

Health providers should inform patients about the signs and symptoms of serious GI toxicity and instruct them to contact a health provider immediately if they experience persistent dyspepsia or other symptoms or signs suggestive of gastrointestinal ulceration or bleeding.

Because serious GI tract ulceration and bleeding can occur without warning symptoms, health providers should follow chronically treated patients and watch for the signs and symptoms of ulceration and bleeding and should inform the patients of the importance of this follow-up.

If ulceration is suspected or confirmed, or if GI bleeding occurs ibuprofen should be discontinued immediately, appropriate treatment instituted and the patient monitored closely.

No studies, to date, have identified any group of patients *not* at risk of developing ulceration and bleeding. The major risk factors are a prior history of serious GI events and increasing age. Possible risk factors include *Helicobacter pylori* infection, excess alcohol intake, smoking, and concomitant oral steroids, anti-coagulants, anti-platelet agents (including ASA), other NSAIDs, or selective serotonin reuptake inhibitors (SSRIs).

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. Patients should be advised to seek the consultation of a physician if gastrointestinal side effects occur consistently, persist, or appear to worsen (1).

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 considered.

Hematologic

Ibuprofen, like other non-steroidal anti-inflammatory agents, can inhibit platelet aggregation but the effect is quantitatively less than that seen with acetylsalicylic acid. Ibuprofen has been shown to prolong bleeding time (but within the normal range) in normal subjects. Because this prolonged bleeding effect may be exaggerated in patients with underlying haemostatic defects, ibuprofen should be avoided by persons with intrinsic coagulation defects and by those on anticoagulant therapy. Concurrent therapy of ibuprofen with warfarin requires close monitoring of INR (see Drug Interactions).

Also, patients with underlying medical or pharmacologically - induced haemostatic defects could experience further prolongation of bleeding time through the inhibition of platelet aggregation induced to varying degrees by this class of drugs (1).

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.

Hepatic

As with other nonsteroidal anti-inflammatory drugs, 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 have been reported with nonsteroidal anti-inflammatory drugs.

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

Patients sensitive to any one of the nonsteroidal anti-inflammatory drugs may be sensitive to any of the other NSAIDs also.

As with NSAIDs in general, some patients may experience urticaria and angioedema upon exposure to ibuprofen. Ibuprofen should not be given to patients with the complete or partial syndrome of ASA-intolerance (See Contraindications).

Neurologic

Some patients may experience drowsiness, dizziness, vertigo, tinnitus or hearing loss with the use of ibuprofen. If patients experience these side effects, they should exercise caution in carrying out activities that require alertness.

In occasional rare cases, 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 tissues diseases, etc.) seem to be pre-disposed. Therefore, in such patients, the health provider must be vigilant to the development of this complication.

Ophthalmologic

Blurred and/or diminished vision, scotoma, and/or changes in colour vision have been reported. If a patient develops such complaints while taking ibuprofen, the drug should be discontinued. Patients with any visual disturbances should have an ophthalmologic examination.

Peri-Operative Considerations

In general, NSAIDs should be discontinued prior to surgeries to decrease the risk of post-operative bleeding.

Renal

Long-term administration of nonsteroidal anti-inflammatory drugs 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.

A second form of renal toxicity has been seen in patients with pre-renal conditions leading to reduction in renal blood flow or blood volume, where the renal prostaglandins have a supportive role in the maintenance of renal perfusion. In these patients, administration of a non-steroidal anti-inflammatory drug may cause a dose dependent reduction in prostaglandin formation and may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function (Glomerular Filtration Rate (GFR) < 60 ml/min or 1 ml/sec), patients on salt restricted diets, those with congestive heart failure, cirrhosis, liver dysfunction, those taking diuretics, angiotensin-converting enzyme inhibitors, angiotensin-II receptor blockers, cyclosporin, ASA and the 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 an NSAID under stable conditions may decompensate during periods of added stress, for example during states of fluid restriction as can occur during gastroenteritis. Discontinuation of nonsteroidal anti-inflammatory therapy is usually followed by recovery to the pretreatment state.

NSAIDs can increase the risk of hyperkalemia. In patients on dialysis, NSAIDs should be used with caution.

Fluid retention and edema have been observed in patients treated with ibuprofen. Therefore, as with many other NSAIDs, the possibility of precipitating congestive heart failure in elderly patients or those with compromised cardiac function should be borne in mind. Ibuprofen should be used with caution in patients with heart failure, hypertension or other conditions predisposing to fluid retention. Ask patients who are on chronic therapy and at risk for fluid retention to weigh themselves at regular intervals to assist in monitoring for fluid accumulation.

With nonsteroidal anti-inflammatory treatment there is a potential risk of hyperkalemia, particularly in patients with conditions such as diabetes mellitus or renal failure; elderly patients; or in patients receiving concomitant therapy with angiotensin-II receptor antagonists, adrenergic blockers, angiotensin-converting enzyme inhibitors or some diuretics. Patients at risk should be monitored periodically during long-term therapy.

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.

Skin

Ibuprofen may cause a severe allergic reaction, especially in patients allergic to acetylsalicylic acid. Symptoms may include hives, facial swelling, asthma (wheezing), shock, skin reddening,

rash or blisters with or without pyrexia or erythema. If any of these symptoms occur, patients should stop use and seek medical help right away.

In rare cases, serious skin reactions such as Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN), exfoliative dermatitis and erythema multiforme (EM), drug reaction with eosinophilia and systemic symptoms (DRESS) and acute generalized exanthematous pustulosis (AGEP) have been associated with the use of some NSAIDs and have been reported very rarely in patients receiving ibuprofen. 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:
No evidence specifically identifies exposure to analgesic doses of ibuprofen as a cause of harm to either mother or fetus during pregnancy (1, 7). Non-steroidal anti-inflammatory drugs in general, however, are known to affect the action of prostaglandin synthetase which could alter a variety of the physiological functions of prostaglandins or platelets during delivery such as facilitating uterine contraction in the mother, premature closure of the fetal ductus arteriosus which may result in persistent pulmonary hypertension in the newborn indant, and platelet-related haemostasis. Patients should therefore be advised not to use ibuprofen during pregnancy without the advice of a physician, particularly during the last trimester (1). Caution should be exercised in prescribing ibuprofen to women who are trying to conceive, during the first and second trimesters of pregnancy, or if nursing.

Nursing Women:
Pharmacokinetic studies indicated that following oral administration of ibuprofen 400 mg the level of drug that appeared in breast milk was below detection levels of 1 mcg/mL. The amount of ibuprofen to which an infant would be exposed through this source was considered negligible (8). However, since the absolute safety of ibuprofen ingested under these circumstances has not been determined, nursing mothers should be advised to consult a physician before using ibuprofen (1).

Geriatrics (> 65 years of age):
Patients older than 65 years and frail or debilitated patients are most susceptible to a variety of adverse reactions from nonsteroidal anti-inflammatory drugs (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. Elderly patients appear to be more susceptible to the central nervous system reactions; cognitive dysfunction (forgetfulness, inability to concentrate, a feeling of separation from the surroundings) in such patients has been reported.

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.

Pediatrics:
Caregivers should ask a physician before use if they believe that the child maybe dehydrated. Not drinking fluids, excessive fluid loss due to vomiting, diarrhea and high fevers may contribute to the risk of dehydration.

ADVERSE REACTIONS

Clinical Trial & 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.

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 • Conditions such as congestive heart failure and hypertension may be aggravated by sodium retention and edema caused by ibuprofen in such patients • myocardial infarction • stroke (cerebrovascular accident)
	Also reported but with unknown causal relationship, rare cases of: • arrhythmias (sinus tachycardia, sinus bradycardia, palpitations) • hemorrhage (non-GI)		
Central Nervous System	• dizziness	• headache • nervousness • drowsiness/somnolence	• depression • insomnia

Adverse Effect	Common (>1% but <10%)		Less Common (<1%)
	Incidence 3-9%	**Incidence 1-3%**	
	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 • psychomotor hyperactivity		
Immune System Disorders	Rare: • hypersensitivity		
Dermatologic	• rash (including maculopapular type)	• pruritis	• vesiculobullous eruptions • urticaria • erythema • erythema multiforme • angioedema
	Also reported but with unknown causal relationship: • alopecia • Stevens-Johnson Syndrome • toxic epidermal necrolysis • Drug reaction with eosinophilia and systemic symptoms (DRESS) • Acute generalised exanthematous pustulosis (AGEP)		
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 (dyspepsia) • constipation • abdominal cramps and pain • gastrointestinal 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) • pancreatitis • oral discomfort (local burning, sensation, irritation)
	The generally modest elevations of serum transaminase activity that has been observed are usually without clinical sequelae but severe, potentially fatal toxic		

<table>
<tr><th rowspan="2">Adverse Effect</th><th colspan="2">Common (>1% but <10%)</th><th rowspan="2">Less Common
(<1%)</th></tr>
<tr><th>Incidence
3-9%</th><th>Incidence
1-3%</th></tr>
<tr><td></td><td colspan="3">hepatitis can occur.</td></tr>
<tr><td>Hematologic</td><td></td><td></td><td>• leukopenia and decreases in hemoglobin and hematocrit</td></tr>
<tr><td></td><td colspan="3">Also reported but with unknown causal relationship, rare cases of:
• anemia
• 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
• bone marrow toxicity
• eosinophilia</td></tr>
<tr><td>Metabolic</td><td></td><td>• decreased appetite
• edema
• fluid retention.</td><td></td></tr>
<tr><td></td><td colspan="3">Fluid retention generally responds promptly to drug discontinuation.</td></tr>
<tr><td>Renal</td><td colspan="3">Also reported but with unknown causal relationship:
• decreased creatinine clearance
• polyuria
• azotemia
• nephritis
• nephrotic syndrome
• renal failure

Like other non-steroidal anti-inflammatory agents, ibuprofen inhibits renal prostaglandin synthesis that may decrease renal function and cause sodium retention. 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)</td></tr>
<tr><td>Special Senses</td><td></td><td>• tinnitus
• asthenia</td><td>• 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</td></tr>
<tr><td></td><td colspan="3">Also reported but with unknown causal relationship:
• conjunctivitis
• diplopia
• optic neuritis</td></tr>
</table>

Adverse Effect	Common (>1% but <10%)		Less Common (<1%)
	Incidence 3-9%	Incidence 1-3%	
General			• hypothermia
Hepatobiliary			• hepatotoxicity (hepatic function abnormal, hepatitis, transaminases increased)
Respiratory			• asthma, bronchospasms

DRUG INTERACTIONS

Serious Drug Interactions

- Use with acetylsalicylic acid (ASA) or other NSAIDs, including ibuprofen, may result in possible additive adverse side effects.
- Use with acetaminophen, may increase the risk of adverse renal effect.
- Use with anticoagulants may increase the risk of GI adverse events (e.g., bleeding).
- Use with hypoglycemic agents (oral agents and insulin) may increase the risk of hypoglycaemia.
- Use with antihypertensives may interfere with circulatory control.
- Use with diuretics may reduce the diuretic effect.
- Use with methotrexate may increase the risk of methotrexate toxicity.
- Use with lithium may increase the risk of lithium toxicity.

Acetylsalicylic Acid (ASA) or other NSAIDs

The use of ibuprofen in addition to any other NSAID is not recommended because of the absence of any evidence demonstrating synergistic benefits and the potential for additive side effects.

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.

Also, some NSAIDs may interfere with the anti-platelet effects of low dose ASA (81 to 325 mg per day), possibly by competing with ASA for access to the active site of cyclooxygenase-I. The concomitant administration of ibuprofen but not acetaminophen has been shown to antagonize the irreversible platelet inhibition induced by ASA (9). Regular use of ibuprofen in patients with increased cardiovascular risk may limit the cardio protective effects of ASA (9,10). To minimize

this interaction, regular users of ibuprofen and low-dose, immediate-release ASA should take the ibuprofen at least one hour after or 11 hours before the daily low-dose ASA. The use of delayed-release (e.g. enteric coated) ASA is not recommended when using ibuprofen regularly. Healthcare professionals should advise consumers and patients regarding the appropriate concomitant use of ibuprofen and ASA.

Anti-Platelet Agents (including ASA): See Warnings and Precautions - Hematologic section.

Anticoagulants: See Warnings and Precautions -Hematologic section.

Coumarin Type Anticoagulants:

Several short-term controlled studies failed to show that ibuprofen significantly affected prothrombin time or a variety of other clotting factors when administered to individuals on coumarin-type anticoagulants. However, bleeding has been reported when ibuprofen and other NSAID agents have been administered to patients on coumarin-type anticoagulants. The use of ibuprofen in patients who are taking anticoagulants should therefore be avoided because of the possibility of enhanced GI bleeding or an additive effect due to ibuprofen's reversible antiplatelet actions.

Oral hypoglycemics

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

Anti-hypertensives

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

Combinations of ACE inhibitors, diuretics and NSAIDs might have an increased risk for acute renal failure and hyperkalemia. In longer term therapy blood pressure and kidney function should be monitored more closely, as occasionally there can be a substantial increase in blood pressure.

Diuretics

Ibuprofen, because of its fluid retention properties, can decrease the diuretic and antihypertensive 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 side effects 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 an NSAID, as increased lithium concentrations can occur.

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 digoxin, methotrexate, and 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 (1).

DOSAGE AND ADMINISTRATION

Dosing Considerations

Do not take for pain for more than 5 consecutive days or fever for more than 3 days unless directed by a physician.

If your condition deteriorates or new symptoms occur (such as the painful area becomes unusually red, swollen or tender), consult a physician.

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.
Use the lowest effective dose for the shortest duration.

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.

Recommended Dose

Mild to moderate pain or fever.

Adults: Single oral dose may be taken every 4 to 6 hours, as required, not to exceed the maximum daily dose (1200 mg) in 24 hours unless directed by a physician.

PRODUCT	STRENGTH (IBUPROFEN MG/TABLET)	SINGLE ORAL DOSE	MAXIMUM DAILY DOSE (1200 MG)
APO-IBUPROFEN 200 mg APO-IBUPROFEN CAPLET	200 mg	1 or 2 tablets or caplets	6 tablets or caplets

APO-IBUPROFEN 300 mg	300 mg	1 tablet	4 tablets
APO-IBUPROFEN 400 mg APO-IBUPROFEN CAPLET	400 mg	1 tablet	3 tablets

Children: Not recommended for children under 12 years of age. Children's Ibuprofen formulations are available to treat children under 12 years of age.

OVERDOSAGE

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

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 lethargy, central nervous system depression, seizures, metabolic acidosis, coma, rhabdomyolysis, hypothermia, fulminant hepatic failure, apnea (primarily in very young children), cardiovascular toxicity including bradycardia, tachycardia and atrial fibrillation. 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 (0, 11).

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 mcg/mL at 0.75 hr (12). Another study using a single oral 400 mg dose in humans produced a peak serum level of 31.9 + 8.8 mcg/mL 0.5 hour after ingestion, and at 16 hours serum concentrations had dropped to 1 mcg/mL (13). (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 (11). 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 non-steroidal anti-inflammatory drugs (NSAID). Like all NSAIDs, ibuprofen is an analgesic, antipyretic, and anti-inflammatory medication (14).

It is generally accepted that the basic mechanism of pharmacological action of ibuprofen, and other NSAIDs, is the inhibition of prostaglandin synthesis (15, 16).

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 (17,15). 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 (18). During the inflammatory process COX-2 is induced, generating prostaglandins that mediate pain and inflammation (19). COX-2 is also present constitutively in the kidneys and vascular endothelium (15). Reported adverse experiences with ASA and other NSAIDs can be understood on the basis of this mechanism of action.

Pharmacodynamics

Consistent with the NSAID classification, ibuprofen exhibits anti-inflammatory activity at higher dosage ranges (20). At lower adult single doses relevant to a nonprescription dosage (200 mg to 400 mg) ibuprofen relieves pain of mild to moderate intensity (21, 22, 23, 24, 25) and reduces fever (26, 27, 28). Analogous to acetylsalicylic acid, the prototype of this class, this analgesic/antipyretic activity of ibuprofen occurs at lower doses than necessary for anti-inflammatory effects, which are thought to require sustained administration of higher individual doses (16).

Clinical studies indicate a duration of clinical effect for up to 8 hours for fever and up to 6 hours for pain.

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 mcg/mL) (29, 30). 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 (31).

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 (8).

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 (32).

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 (33).

STORAGE AND STABILTIY

Store at room temperature (15°C to 30°C).

SPECIAL HANDLING INSTRUCTIONS

Not applicable.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Apo-Ibuprofen Tablets/Caplets 200 mg:

Round Yellow Tablets:

Yellow, round, biconvex film-coated tablet engraved “IBU” over “200” on one side, plain on the other.

Apo-Ibuprofen tablets are available in bottles of 50, 100 and 1000 and blisters of 10 x 10.

Apo-Ibuprofen Tablets Non-medicinal ingredients: carnauba wax, colloidal silicon dioxide,

croscarmellose sodium, D&C yellow #10 and FD&C yellow #6, hydroxypropyl cellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, titanium dioxide.

Round Red-Brown Tablets:

Reddish-brown, round, biconvex film-coated tablet engraved "IBU" over "200" on one side, plain on the other.

Capsule –Shaped Red-Brown Caplets:

Reddish-brown, capsule-shaped, biconvex film-coated tablet engraved "200" on one side and "IBU" on the other side.

Apo-Ibuprofen Tablets are available in bottles of 24, 50, 100, 200, 250 and 1000.
Apo-Ibuprofen caplets are available in bottles of 100.

Apo-Ibuprofen Tablets/Caplets Non-medicinal ingredients: carnauba wax, colloidal silicon dioxide, croscarmellose sodium, ferric oxide red, hydroxypropyl cellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, titanium dioxide.

Apo-Ibuprofen Tablets 300 mg:

White, round, biconvex film-coated tablet engraved "APO" over "300" on one side, plain on the other.

Apo-Ibuprofen Tablets are available in bottles of 65, 100 and 1000.

Apo-Ibuprofen Tablets Non-medicinal ingredients: colloidal silicon dioxide, croscarmellose sodium, hydroxypropyl cellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, titanium dioxide.

Apo-Ibuprofen Tablets 400 mg:

Orange, round, biconvex film-coated tablet engraved "IBU" over "400" on one side, plain on the other.

Apo-Ibuprofen Tablets are available in bottles of 100 and blisters of 10 x 10.

Apo-Ibuprofen Tablets Non-medicinal ingredients: colloidal silicon dioxide, croscarmellose sodium, FD&C yellow #6, hydroxypropyl cellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, titanium dioxide.

Apo-Ibuprofen Caplets 400 mg:

Reddish-brown, capsule shaped, biconvex film-coated tablet engraved "IBU 400" on one side, plain on the other.

Apo-Ibuprofen Caplets are available in bottles of 100.

Apo-Ibuprofen Caplets Non-medicinal ingredients: carnauba wax, colloidal silicon dioxide, croscarmellose sodium, ferric oxide red, hydroxypropyl cellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, titanium dioxide.

PART II: SCIENTIFIC INFORMATION

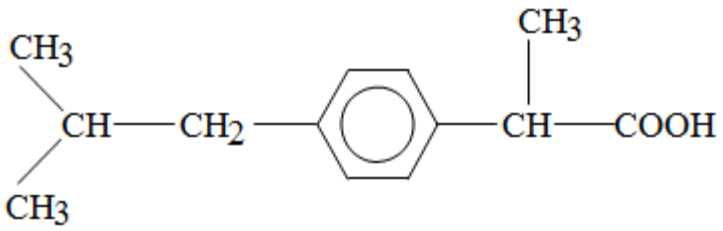
PHARMACEUTICAL INFORMATION

Drug Substance

Proper/Common Name: Ibuprofen

Chemical Names:
1) 2-(4-isobutylphenyl) propionic acid
2) a-methyl-4- (2-methylpropyl)-benzeneacetic acid

Structural Formula:



Molecular Formula: $C_{13}H_{18}O_2$

Molecular Weight: 206.28 g/mol

Description: Ibuprofen is a white crystalline solid. It is non-hygroscopic and relatively insoluble in water. The compound is readily soluble in organic solvents and aqueous alkalis. (The sodium salt is highly soluble in water).

Melting Point: ~75°C

CLINICAL TRIALS

Comparative Bioavailability Studies

A single dose, standard, 2-way crossover bioavailability study, conducted under fasting conditions, was performed on normal male volunteers. The results obtained from 12 volunteers who completed the study are summarized in the following table. The rate and extent of absorption of ibuprofen was measured and compared following a single oral dose (1 x 600 mg tablet) of Apo-Ibuprofen (ibuprofen) 600 mg tablet (Apotex Inc.) and Motrin® (ibuprofen) 600 mg tablet (Upjohn).

Ibuprofen (1 x 600 mg) From Measured Data Geometric Mean Arithmetic Mean (CV%)				
Parameter	Test*	Reference†	Ratio of Geometric Means (%)	90% Confidence Interval (%)
AUC_{12} (mcg•h/mL)	186.37 187.9 (13.3)	181.45 183.0 (13.5)	102.71	99.54 – 105.99
AUC_{inf} (mcg•h/mL)	187.89 189.6 (13.8)	182.77 184.4 (13.8)	102.80	99.59 – 106.12
C_{max} (mcg/mL)	40.99 41.6 (17.9)	53.74 54.6 (18.3)	76.26	70.55 – 82.44
T_{max}§ (h)	2.17 (33.1)	1.49 (68.6)		
T_{half}§ (h)	2.0 (8.4)	2.0 (10.4)		

* Apo–Ibuprofen (ibuprofen) 600 mg tablets (Apotex Inc.)

† Motrin® (ibuprofen) 600 mg tablets (Upjohn) were purchased in Canada.

§ Expressed as arithmetic means (CV%) only.

A randomized, 2-way crossover bioavailability study, conducted under fasting conditions, was performed on healthy male volunteers. The results obtained from 12 volunteers who completed the study are summarized in the following table. The rate and extent of absorption of ibuprofen was measured and compared following a single oral dose (1 x 300 mg tablet) of Apo-Ibuprofen (ibuprofen) 300 mg tablet (Apotex Inc.) and Motrin® (ibuprofen) 300 mg tablet (Upjohn).

Ibuprofen (1 x 300 mg) From Measured Data Geometric Mean Arithmetic Mean (CV%)				
Parameter	Test*	Reference†	Ratio of Geometric Means (%)	90% Confidence Interval (%)
AUC_{12} (mcg•h/mL)	98.87 101.6 (24.4)	95.70 97.1 (17.9)	103.32	97.35 – 109.65
AUC_{inf} (mcg•h/mL)	100.62 103.8 (26.5)	96.58 98.1 (18.9)	104.18	97.53 – 111.29
C_{max} (mcg/mL)	20.49 21.2 (28.1)	29.94 30.4 (18.6)	68.46	60.43 – 77.56
T_{max}§ (h)	2.50 (35.2)	1.38 (55.4)		
T_{half}§ (h)	2.1 (22.8)	2.1 (16.8)		
* Apo–Ibuprofen (ibuprofen) 300 mg tablets (Apotex Inc.) † Motrin® (ibuprofen) 300 mg tablets (Upjohn) were purchased in Canada. § Expressed as arithmetic means (CV%) only.				

The efficacy of ibuprofen as an analgesic and antipyretic has been demonstrated by a variety of clinical studies and pain models.

Dental Pain

In adults, the effects of a drug on post-surgical dental extraction pain serves as a standard model for relief of pain of mild to moderate intensity. Ibuprofen 200 mg and 400 mg has been clearly demonstrated to provide pain relief significantly superior to placebo. When compared to the "standard" non-prescription analgesics, ibuprofen 200 mg is found to be comparable to ASA 650 mg (21, 41).

Dysmenorrhea

Nonsteroidal anti-inflammatory drugs, which inhibit prostaglandin synthesis such as ibuprofen, are particularly suitable for management of primary dysmenorrhea. Menstrual pain is now thought to

result from abnormal uterine activity, which is secondary to increased production and release of endometrial prostaglandins at the time of menstruation.

Several adequate and well-controlled clinical trials provide substantial evidence of the safety and efficacy of ibuprofen at doses of 200 to 400 mg in relieving the pain of menstrual cramps (44, 45, 46).

A summary of trials of ibuprofen in the treatment of dysmenorrhea indicates the usual dose administered to be 400 mg. The few studies, which are available at a 200 mg dosage, indicate superiority of both ibuprofen 200 mg and 400 mg compared with ASA 650 mg (47).

Pain of Osteoarthritis

Several controlled clinical studies in adults provide substantial evidence of the safety and efficacy of ibuprofen at doses of 1200 mg or less per day in relieving the pain of osteoarthritis (48, 49, 50, 51, 52). Collectively, these studies support an indication for the temporary relief of minor pains of arthritis and, in conjunction with single dose analgesia studies, support the broader indication: for the temporary relief of minor aches and pains.

Headache

Ibuprofen has also been used satisfactorily in the management of headache. The efficacy of 200 mg of ibuprofen has been reported to be significantly superior to placebo and ASA 650 mg in the treatment of muscle contraction headaches (24). No differences in the frequency of side effects were found in the treatment groups. Similar results were reported in a study with patients referred to a Headache Clinic with frequent muscle contraction headache (53).

Soft Tissue Injury

Several studies also document the efficacy of analgesic doses of ibuprofen in the treatment of soft tissue injuries such as muscular aches or athletic injuries (54, 55).

Fever

Studies of its efficacy in the management of fever in adults and children demonstrate ibuprofen to be an effective antipyretic (26, 27, 28, 56, 57), with a duration of action of up to eight hours when administered at a dose of 7.5 mg/kg.

Controlled clinical trials comparing doses between 5 and 10 mg/kg of ibuprofen and 10 to 15 mg/kg of acetaminophen have been conducted in children 6 months to 12 years of age with fever primarily due to viral illnesses. In these studies, there were few differences between treatments in fever reduction in the first hour and maximum fever reduction occurred between 2 and 4 hours. There was some evidence that the higher dosage range of ibuprofen (10 mg/kg) resulted in a prolonged duration of effect (from six to eight hours) and that it was more effective for children with higher baseline temperatures (above 39.1°C) but the numbers of patients were not adequate to draw definitive conclusions. In children with baseline temperatures at or below 39.1°C both ibuprofen doses and acetaminophen were equally effective in their maximum effect.
One controlled clinical trial comparing a single dose of ibuprofen 7.5 mg/kg with acetaminophen

12.5 mg/kg demonstrated the superiority of ibuprofen over an eight-hour period.

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 (16).

Inhibition of prostaglandin synthesis by ibuprofen has been demonstrated in several different experimental models: bull seminal vesicle microsomes (34), stomach, duodenum, kidney and brain of the rat, (35) microsomal preparations from rabbit brain and kidney medulla (36).

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 (37, 38, 39).

The antipyretic activity of ibuprofen has been demonstrated in yeast-induced fever in rats (37, 38, 39).

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 (40).

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 (40).

Protein binding studies with plasma levels of 20 mcg/mL indicate the percent bound in rats 96%, dogs 99%, baboons 95% and man 99% (29).

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 (40, 29). 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

Pharmacodynamics

Effect of Ibuprofen on Platelet Aggregation, Bleeding and Clotting Times in Normal Volunteers: Experimental data suggest that ibuprofen may inhibit the effect of low dose ASA (81 to 325 mg per day) on platelet aggregation when they are dosed concomitantly. In one study, when a single dose of ibuprofen 400 mg was taken within 8 hours before or within 30 minutes after immediate-release ASA dosing, a decreased effect of ASA on the formation of thromboxane or platelet aggregation occurred. However, the limitations of these data and the uncertainties regarding extrapolation of *ex vivo* data to the clinical situation imply that no firm conclusions can be made for regular ibuprofen use, and no clinically relevant effect is considered to be likely for occasional ibuprofen use.

Pharmacokinetics

The pharmacokinetics of ibuprofen has also been studied in humans. Although there is little evidence of clinically significant age dependent kinetics in febrile children ages 3 months to 12 years (58), some differences in the pharmacokinetic parameters of volume of distribution and clearance have been observed between adults and children (59).

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 mcg/mL at 0.75 hr (12). Another study using a single oral 400 mg dose in humans produced a peak serum level of 31.9 + 8.8 mcg/mL 0.5 hour after ingestion, and at 16 hours serum concentrations had dropped to 1 mcg/mL (13). Comparable serum levels and time to peak within 1 to 2 hours were confirmed by other investigations with 200 mg and 400 mg solid doses (60, 31). 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 (29).

Distribution: Ibuprofen, like most drugs of its class, is highly protein bound (>99% bound at 20 mcg/mL) (29, 30). 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 (59). 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 (31).

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 (8). 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 (38).

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 (59). 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 to 10 mg/kg) indicates a wide margin of safety.

MICROBIOLOGY

Not applicable.

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 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 [40].

Similar LD_{50} determinations in other strains of rats and mice are summarized in the following Table 1.

Table 1 – Acute Toxicity in Rodent (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 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 (63). 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 to 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 (62). 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 2.

Table 2 - Single Dose Ulcerogenicity Studies in Rodents

Species	Route	UD50* (mg/kg)	MUD**(mg/kg)
Long Evans Rat [62]	Oral IV	70 210	50 -
Sprague Dawley Rat [63]	Oral	-	6-13

*UD_{50} = 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 (40). 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(62). 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 (66), 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 (40). 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 (40). 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 (67). 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 (40). 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 (68). Such an effect might be anticipated because of the known prostaglandin inhibiting properties of ibuprofen.

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PART III: CONSUMER INFORMATION

APO-IBUPROFEN 200 mg
Ibuprofen Tablets USP, 200 mg

APO-IBUPROFEN CAPLET
Ibuprofen Tablets USP, 200 mg

APO-IBUPROFEN 300 mg
Ibuprofen Tablets USP, 300 mg

APO-IBUPROFEN 400 mg
Ibuprofen Tablets USP, 400 mg

APO-IBUPROFEN CAPLET
Ibuprofen Tablets USP, 400 mg

This leaflet is part III of a three-part "Product Monograph" published when APO-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 APO-IBUPROFEN. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

Since everyone's pain is different, APO-IBUPROFEN offers 3 levels of pain relief to suit your needs. So you can choose your relief, APO-IBUPROFEN products are available in three strengths, including APO-IBUPROFEN 200 mg , APO-IBUPROFEN 300 mg and APO-IBUPROFEN 400 mg Tablets.

APO-IBUPROFEN products provide fast and effective relief of PAIN from:

- headache, including mild to moderate migraine and tension headache
- menstrual cramps
- toothache (dental pain), including dental extraction
- inflammation from arthritis, muscle strain and sprains, muscles, bones and joints, including back pain

APO-IBUPROFEN is also an effective fever reducer and will provide relief from the aches and pain due to the common cold and flu.

Clinical studies show long lasting relief for up to 8 hours for fever and up to 6 hours for pain.

What it does:

APO-IBUPROFEN ibuprofen starts to work fast and treats pain where it starts.

Ibuprofen is a member of a class of drugs called non-steroidal anti-inflammatory drugs (NSAIDs). NSAIDs work within the body by blocking the production of substances called prostaglandins, which are involved in the development of pain and inflammation.

When it should not be used:

APO-IBUPROFEN should not be used if you:

- are taking acetylsalicylic acid (ASA) or any other non-steroidal anti-inflammatory medication, including any other ibuprofen product.
- are allergic or have had a reaction to ibuprofen, acetylsalicylic acid (ASA), other non-steroidal anti-inflammatory drugs (NSAIDs) or salicylates, or 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 nasal polyps (swelling of the inside of the nose), or allergic manifestations such as asthma, anaphylaxis (sudden severe life-threatening anaphylactic reactions), urticaria/hives, rhinitis (stuffed or runny nose that may be due to allergies), skin rash or other allergic symptoms.
- have been diagnosed with severe high blood pressure or have severe coronary artery disease.
- are dehydrated (significant fluid loss) due to vomiting, diarrhea or lack of fluid intake.
- have active or recurrent stomach ulcer, gastrointestinal (GI) bleeding, or active inflammatory bowel disease (e.g. Crohn's, colitis)
- have liver or kidney disease.
- have systemic lupus erythematosus.
- are in third trimester of pregnancy.
- Right before or after heart surgery.

What the medicinal ingredient is:

Ibuprofen

What the nonmedicinal ingredients are:

APO-IBUPROFEN 200 mg is a yellow, round, biconvex film-coated tablet, engraved "IBU" over "200" on one side, plain on the other. APO-

IBUPROFEN 200 mg tablets contain: carnauba wax, colloidal silicon dioxide, croscarmellose sodium, D&C Yellow No. 10, FD&C Yellow No. 6, hydroxypropyl cellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, titanium dioxide.

APO-IBUPROFEN 200 mg is a reddish-brown, round, biconvex film-coated tablet engraved "IBU" over "200" on one side, plain on the other. APO-IBUPROFEN CAPLET is a reddish-brown, capsule-shaped, biconvex film-coated tablet engraved "200" on one side and "IBU" on the other side. APO-IBUPROFEN 200 mg tablets and caplets contain: carnauba wax, colloidal silicon dioxide, croscarmellose sodium, ferric oxide red, hydroxypropyl cellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, titanium dioxide.

APO-IBUPROFEN 300 mg is a white, round, biconvex film-coated tablet engraved "APO" over "300" on one side, plain on the other. APO-IBUPROFEN 300 mg tablets contain: colloidal silicon dioxide, croscarmellose sodium, hydroxypropyl cellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, titanium dioxide.

APO-IBUPROFEN 400 mg is an orange, round, biconvex film-coated tablet engraved "IBU" over "400" on one side, plain on the other side. APO-IBUPROFEN 400 mg tablets contain: colloidal silicon dioxide, croscarmellose sodium, FD&C Yellow No. 6, hydroxypropyl cellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, titanium dioxide.

APO-IBUPROFEN CAPLET 400 mg is a reddish-brown, capsule shaped, biconvex film-coated tablet engraved "IBU 400" on one side, plain on the other. APO-IBUPROFEN 400 mg caplets contain: carnauba wax, colloidal silicon dioxide, croscarmellose sodium, ferric oxide red, hydroxypropyl cellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, titanium dioxide.

What dosage forms it comes in:

Tablets: 200 mg, 300 mg, 400 mg
Caplets: 200 mg, 400 mg

WARNING AND PRECAUTIONS

Serious Warning and Precautions
Caution in patients prone to gastrointestinal tract irritation, including those with a history of peptic ulcer

Keep this medication out of the reach of children.

BEFORE you use APO-IBUPROFEN talk to your physician or pharmacist if you:

- have stomach ulcers, high blood pressure, asthma, heart failure or thyroid disease, kidney or liver disease, glaucoma, diabetes, alcoholism, a history of stomach bleeding, systemic lupus erythematosus, or any other serious disease or condition.
- are taking anticoagulant (blood thinning medication), oral corticosteroid or any other drug.
- are trying to conceive, in your first or second trimester of pregnancy or nursing.
- are over 65 years of age.
- are taking low-dose ASA.
- suffer from asthma or have nasal polyps (a swelling inside the nose).
- are dehydrated (severe fluid loss).
- have a blood-clotting disorder (e.g. hemophilia, sickle cell anemia, etc.).
- have a heart disease.
- have any unusual urinary symptoms (e.g. bladder problems).
- are on a special diet (e.g. low-sodium).
- suffer from hyperkalemia (high levels of potassium in your blood).

They may recommend an alternative analgesic such as acetaminophen.

Long-term continuous use may increase the risk of heart attack or stroke.

INTERACTIONS WITH THIS MEDICATION

Always tell any doctor, dentist, or pharmacist you consult that you are taking this medicine.

Drugs that may interact with APO-IBUPROFEN include: acetylsalicylic acid (ASA) or other NSAIDs, blood thinning medications (anticoagulants), blood pressure medication (anti-hypertensives), diuretics (water pills), oral steroids (glucocorticoids), lithium, diabetes medications (hypoglycemics), methotrexate, phenytoin, acetaminophen and digoxin.

Do not use this product if you are taking daily low dose ASA (81 to 325 mg) without talking to a doctor or pharmacist. Ibuprofen may interfere with the preventative benefits of ASA.

PROPER USE OF THIS MEDICATION

Usual dose:
For accurate dosing of each product strength, refer to

the dosage table and follow the instructions carefully.

PRODUCT	STRENGTH (IBUPROFEN MG/TABLET)	SINGLE ORAL DOSE	MAXIMUM DAILY DOSE (1200 MG)
APO-IBUPROFEN 200 mg; APO-IBUPROFEN CAPLET	200 mg	1 or 2 tablets	6 tablets
APO-IBUPROFEN 300 mg	300 mg	1 tablet	4 tablets
APO-IBUPROFEN 400 mg APO-IBUPROFEN CAPLET	400 mg	1 tablet	3 tablets

The single oral dose may be taken every 4 to 6 hours as needed. Do not take more than the maximum daily dose (1200 mg in 24 hours) unless advised by a doctor. Take with food or milk if mild stomach upset occurs with use. APO-IBUPROFEN should not be taken for pain for more than 5 consecutive days or for fever for more than 3 days without first talking to your doctor or dentist.

Use the lowest effective dose for the shortest duration. Do not take this product while taking ASA, other ibuprofen containing products or any other pain or fever medicine.

For effective use of this medicine, unless recommended by your doctor or dentist, DO NOT take:

- more than the recommended number of tablets or caplets in each single dose
- this product longer than the recommended period of time

Overdose:

If you think you have taken too much APO-IBUPROFEN, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed 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.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

If unusual symptoms or any of the following reactions develop during treatment, stop use and see a doctor immediately: nausea, vomiting, abdominal pain or diarrhea; heartburn, bloating or constipation; fluid retention; skin rash or itching; dizziness; any change in vision; ringing or buzzing in the ears, vomiting any blood or have tarry stools, jaundice (yellowing of the eyes or skin due to liver problems).

If you experience dizziness, blurred vision, or hearing problems while taking APO-IBUPROFEN, please use caution when carrying out activities requiring alertness.

Ibuprofen may cause a severe allergic reaction that could include wheezing, facial swelling, hives, shortness of breath, shock or a fast, irregular heartbeat. Any of these reactions could be serious. Stop using the product and get emergency medical help immediately.

This is not a complete list of side effects. For any unexpected effects while taking APO-IBUPROFEN, contact your doctor or pharmacist.

HOW TO STORE IT

Store at room temperature (15°C to 30°C).

Keep out of the reach and sight of children.

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.

MORE INFORMATION

If you want more information about APO-IBUPROFEN:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Consumer Information by visiting the Health Canada website (https://health-products.canada.ca/dpd-bdpp/index-eng.jsp). Find the Consumer Information on the manufacturer's website (http://www.apotex.ca/products), or by calling 1-800-667-4708.

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

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