PRODUCT MONOGRAPH

MOTRIN* IB
Tablets, Caplets and Gelcaps, 200mg

Extra Strength MOTRIN*IB
Tablets 300mg

Super Strength MOTRIN*IB
Tablets 400mg

Ibuprofen Tablets USP

Analgesic, Antipyretic Agent

McNeil Consumer Healthcare
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PRODUCT MONOGRAPH

NAME OF DRUG

MOTRIN*IB

Ibuprofen Tablets USP

200mg (MOTRIN*IB) tablets, caplets, gelcaps

300mg (Extra Strength MOTRIN*IB) tablets

400mg (Super Strength MOTRIN*IB) tablets

THERAPEUTIC CLASSIFICATION

Analgesic, Antipyretic Agent

CLINICAL PHARMACOLOGY

Ibuprofen is a member of the class of agents commonly known as non-steroidal anti-inflammatory drugs (NSAID). Consistent with this classification, ibuprofen exhibits anti-inflammatory activity at higher dosage ranges (Brooks *et al*.; 1973). At lower adult single doses relevant to a nonprescription dosage (200 mg to 400 mg) ibuprofen relieves pain of mild to moderate intensity (Cooper *et al*.; 1977, Gallardo & Rossi; 1980, Jain *et al*.; 1984, Vecchio *et al*.; 1983, Ihles; 1980) and reduces fever (Gaitonade *et al*.; 1973, Sheth *et al*.; 1980, Simila *et al*.; 1976). 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 (Flower *et al*.; 1985).

Ibuprofen is rapidly absorbed after oral administration, with peak serum or plasma levels generally appearing within 1-1/2 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. Ibuprofen has an elimination half-life of approximately two hours. 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 (Albert & Gernaat; 1984). Clinical studies indicate a duration of clinical effect for up to 8 hours for fever and 6+ hours for pain.

Studies demonstrate no apparent clinically significant alterations in ibuprofen pharmacokinetics in the elderly (Albert *et al*.;1984). 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 (Juhl *et al*.; 1983).

The basic mechanism of the pharmacological actions of ibuprofen, like other NSAID's, has not been precisely determined. It is generally thought to be related to the inhibition of prostaglandin synthesis (Cox I & II) (Flower *et al*.; 1985).

INDICATIONS AND CLINICAL USE

MOTRIN* IB ibuprofen is indicated for fast and effective relief of headaches, menstrual pain, toothache (dental pain), pain due to arthritis, minor aches and pains in muscles, bones and joints, such as sprains or strains, backache, the aches and pain due to the common cold and influenza and for the reduction of fever (Arthritis Advisory Committee; 1983).

CONTRAINDICATIONS

MOTRIN* IB ibuprofen should not be used in patients who have previously exhibited hypersensitivity to it or in individuals who are known to have a sensitivity (manifested as asthma, bronchospasm, hypotension, angioedema, laryngeal edema, swelling, shock or urticaria) to acetylsalicylic acid or other non-steroidal anti-inflammatory drugs (Arthritis Advisory Committee; 1983).

MOTRIN* IB ibuprofen should not be used during pregnancy (see Use in Obstetrics below). Ibuprofen levels in breastmilk are extremely low and are unlikely to affect a nursing infant, however because its safety under these

conditions has not been established consult a doctor before use in nursing mothers.

MOTRIN* IB 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. Aseptic meningitis has also been reported.

MOTRIN* IB ibuprofen should not be used in patients with acute peptic ulcer or gastrointestinal bleeding.

WARNINGS

Anaphylactoid reactions have occurred after administration of ibuprofen to patients with known acetylsalicylic acid or other NSAID sensitivity manifested as asthma, swelling, shock or hives (Arthritis Advisory Committee; 1983).

Gastrointestinal side effects to ibuprofen have been reported including dyspepsia, heartburn, nausea, vomiting, anorexia, diarrhea, constipation, stomatitis, flatulence, bloating, epigastric pain, abdominal pain. Peptic ulceration with GI bleeding or perforation has been reported and has been associated with a fatal outcome (Arthritis Advisory Committee; 1983). MOTRIN* IB ibuprofen should therefore be given only under close supervision to patients with a history of upper gastrointestinal tract disease.

PRECAUTIONS

Occasionally serious gastrointestinal side effects have been associated with the anti-inflammatory uses of ibuprofen (See Warnings). Minor gastrointestinal complaints have also been reported during the clinical use of ibuprofen at analgesic doses. The administration of MOTRIN* IB 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 (Arthritis Advisory Committee; 1983).

MOTRIN* IB 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, MOTRIN* IB ibuprofen should be avoided by persons with intrinsic coagulation defects and by those on anticoagulant therapy.

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

Advanced age, hypertension, use of diuretics, diabetes, atherosclerotic cardiovascular disease, chronic renal failure, cirrhosis and conditions which may be associated with dehydration appear to increase the risk of renal toxicity. MOTRIN* IB should therefore be used with caution when these risk factors are present.

Patients taking MOTRIN* IB should be cautioned to report to their physician signs or symptoms of GI intolerance and/or bleeding, blurred vision or other ocular symptoms, skin rash, tinnitus, dizziness, weight gain, edema or respiratory difficulties.
If MOTRIN* IB is taken in conjunction with prolonged corticosteroid therapy and it is decided to discontinue steroid therapy, the corticosteroid should be tapered slowly to avoid exacerbation of disease or adrenal insufficiency.

Particular caution should be observed in elderly patients taking MOTRIN* IB ibuprofen, as they are more likely to be taking other medications or have pre-

existing disease states which can increase the likelihood of the complications that have been associated with ibuprofen. 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.

Use in Obstetrics

No evidence specifically identifies exposure to analgesic doses of ibuprofen as a cause of harm to either mother or fetus during pregnancy (Arthritis Advisory Committee; 1983, Barry *et al*.; 1984). 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, closure of the ductus arteriosus in the fetus, and platelet-related haemostasis. Patients should therefore be advised not to use MOTRIN* IB during pregnancy without the advice of a physician, particularly during the last trimester (Arthritis Advisory Committee; 1983). Clinical information is limited on the effects of ibuprofen in pregnancy.

Use in Nursing Mothers

Pharmacokinetic studies indicated that following oral administration of ibuprofen 400 mg the level of drug which appeared in breast milk was below detection levels of 1 μg/mL. The amount of ibuprofen to which an infant would be exposed through this source was considered negligible (Albert & Gernaat; 1984). 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 MOTRIN* IB (Arthritis Advisory Committee; 1983).

Patients with Special Diseases and Conditions

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

MOTRIN* IB should be used with caution in patients with a history of cardiac failure or kidney disease because of the possibility of aggravating pre-existing states of fluid-retention or edema (Arthritis Advisory Committee; 1983). Mild impairment of renal function (decreased renal blood flow and glomerular filtration rate) can occur at maximal doses of ibuprofen. Renal papillary necrosis has been reported.

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 (Arthritis Advisory Committee; 1983).

Long term ingestion of combinations of analgesics has been associated with analgesic nephropathy. It is therefore appropriate that patients be discouraged from long-term, unsupervised consumption of analgesics, particularly in combination. Patients should therefore be directed to consult a physician if their underlying condition requires administration of MOTRIN* IB for more than 5 days. MOTRIN* IB usually should not be administered along with acetaminophen or acetylsalicylic acid (Arthritis Advisory Committee; 1983).

Patients with any serious medical condition should consult a physician before using MOTRIN* IB as an analgesic or antipyretic (Arthritis Advisory Committee; 1983).

Drug Interactions

The platelet inhibiting effects of ibuprofen, although less potent and of shorter duration than those induced by acetylsalicylic acid, warrant cautionary

supervision by a physician before co-administration of MOTRIN* IB and anti-coagulants.

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 MOTRIN* IB 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 anti-platelet actions.

Acetylsalicylic Acid

Animal studies show that ASA given with NSAID agents, including ibuprofen, yields 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.

Other Anti-Inflammatory Agents (NSAID's)

The addition of MOTRIN* IB to a pre-existent prescribed NSAID regimen in patients with a condition such as rheumatoid arthritis may result in increased risk of adverse effects.

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.

Acetaminophen

Although interactions have not been reported, concurrent use with MOTRIN* IB is not advisable.

Other Drugs

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, phenytoin and lithium salts. However, the mechanisms and clinical significance of these observations are presently not known.

Patients taking other prescribed medications should consult a physician before using MOTRIN* IB to assure its compatibility with the other medications (Arthritis Advisory Committee; 1983).

ADVERSE REACTIONS

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 adverse reactions most frequently seen with ibuprofen therapy involve the gastrointestinal system.

Adverse Effect	Incidence 3-9%	Incidence 1-3%	Incidence Less than 1%
Gastrointestinal	• nausea • epigastric pain • heartburn	• diarrhea • abdominal distress • nausea and vomiting • indigestion • 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)
	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.		
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		
Dermatologic	• rash (including maculopapular type)	• pruritis	• vesiculobullous eruptions • urticaria • erythema multiforme
	Also reported but with unknown causal relationship: • alopecia • Stevens-Johnson Syndrome		

Adverse Effect	Incidence 3-9%	Incidence 1-3%	Incidence Less than 1%
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		
Metabolic		• decreased appetite • edema • fluid retention.	
	Fluid retention generally responds promptly to drug discontinuation.		
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		

Adverse Effect	Incidence 3-9%	Incidence 1-3%	Incidence Less than 1%
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.
	Also reported but with unknown causal relationship, rare cases of: • arrhythmias (sinus tachycardia, sinus bradycardia, palpitations)		
Allergic			• anaphylaxis (See Contraindications)
	Also reported but with unknown causal relationship, rarely: • fever • serum sickness • lupus erythematosus 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		

Adverse Effect	Incidence 3-9%	Incidence 1-3%	Incidence Less than 1%
Renal	Also reported but with unknown causal relationship: • decreased creatinine clearance • polyuria • azotemia Like other non-steroidal anti-inflammatory agents, ibuprofen inhibits renal prostaglandin synthesis which 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 Precautions)		

SYMPTOMS AND TREATMENT OF OVERDOSE

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 (Barry *et al*., 1984, Court *et al*.; 1984).

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 μg/mL, 8-1/2 hours after the accident. Two other children weighing approximately 10 kg, had taken an estimated 120 mg/kg. There were no signs of acute intoxication or late sequelae. In one child the ibuprofen blood level at 90 minutes after ingestion was approximately 700

µg/mL. A nineteen year old male who ingested 8000 mg of ibuprofen reported dizziness and nystagmus was noted. He recovered with no reported sequelae after parenteral hydration and 3 days of bed rest.

For perspective, a single 200 mg oral dose study in 6 fasting healthy men produced a peak plasma concentration of 15.0 µg/mL at 0.75 hr (Adams *et al*.; 1967). Another study using a single oral 400 mg dose in humans produced a peak serum level of 31.9 $\pm$ 8.8 µg/mL 0.5 hour after ingestion, and at 16 hours serum concentrations had dropped to 1 µg/mL (Kaiser & Martin; 1978). (See Pharmacology Section)

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 (Court *et al*.; 1984). Physicians should contact the Regional Poison Control Centre for additional guidance about ibuprofen overdose management.

DOSAGE AND ADMINISTRATION

Mild to moderate pain or fever.

Adults: MOTRIN* IB 200mg: 1 to 2 tablets, caplets or gelcaps as required every 4 hours, not to exceed 1200 mg (6 tablets, caplets or gelcaps) in 24 hours unless directed by a physician.

Extra Strength MOTRIN* IB 300mg: 1 tablet as required every 4 to 6 hours, not to exceed 1200mg (4 tablets) in 24 hours unless directed by a physician.

Super Strength MOTRIN*IB 400mg: 1 tablet as required every 4 to 6 hours, not to exceed 1200mg (3 tablets) in 24 hours unless directed by a physician.

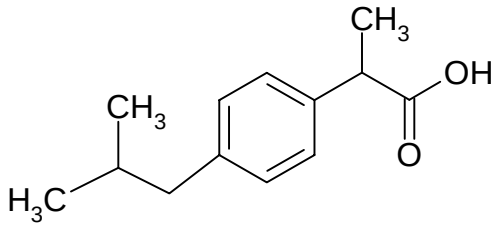
Children: It is recommended that children under 12 years of age be treated using Children's MOTRIN* formulations.

Do not take for pain for more than 5 consecutive days or fever for more than 3 days unless directed by a physician. If the painful area is red or swollen, if condition deteriorates or new symptoms occur, consult a physician.

PHARMACEUTICAL INFORMATION

Drug Substance

Ibuprofen is described chemically as 2 - (p-isobutylphenyl) propionic acid. It has a molecular weight of 206.28 and the following structural formula.



Ibuprofen is a white crystalline powder with a characteristic odour and slight taste. It is very slightly soluble in water and very soluble in alcohol and other common organic solvents. The apparent pK_a of ibuprofen is 5.2 and its melting point is 75 C to 75.5 C.

Composition

MOTRIN* IB 200mg tablets and caplets include ibuprofen 200 mg and the following non-medicinal ingredients in alphabetical order: colloidal silicon dioxide, corn starch, hypromellose, iron oxide black, polyethylene glycol, pregelatinized starch, propylene glycol, sodium cyclamate, sodium starch glycolate, stearic acid and titanium dioxide.

MOTRIN* IB 200mg gelcaps include ibuprofen 200 mg and the following non-medicinal ingredients in alphabetical order: calcium disodium EDTA, castor oil, cellulose, colloidal silicon dioxide, corn starch, FD&C yellow no. 6, gelatin, hypromellose, magnesium stearate, parabens, povidone, propylene glycol, sodium lauryl sulfate, sodium propionate, sodium starch glycolate, synthetic black iron oxide, titanium dioxide.

Extra Strength MOTRIN*IB 300mg caplets include ibuprofen 300mg and the following non-medicinal ingredients in alphabetical order: carbon black, carnauba wax, colloidal silicon dioxide, cornstarch, FD&C yellow no. 6, hypromellose, polydextrose, polyethylene glycol, pregelatinized starch, sodium cyclamate, stearic acid, and titanium dioxide.

Super Strength MOTRIN*IB 400mg caplets include ibuprofen 400mg and the following non-medicinal ingredients in alphabetical order: carbon black, colloidal silicon dioxide, cornstarch, FD&C yellow no. 6, hydroxypropyl cellulose, hypromellose, polyethylene glycol, pregelatinized starch, propylene glycol, sodium cyclamate, stearic acid and titanium dioxide.

Stability and Storage Recommendations

Tablets and Caplets: Store away from heat and direct light.
Gelcaps: Store in tightly closed container at room temperature; avoid high humidity and excessive heat (40° C, 104°F).

DOSAGE FORMS

MOTRIN* IB ibuprofen 200 mg tablets are available as white, film coated biconvex tablets, with "Motrin IB" printed in black ink, in bottles of 10, 24, 50, 100 and 150.

MOTRIN* IB ibuprofen 200 mg caplets are available as solid, white, film-coated capsule-shaped tablets, with "Motrin IB" printed in black ink, in bottles of 24 and 50.

MOTRIN* IB ibuprofen 200 mg gelcaps are available as solid, capsule-shaped tablets with white gelatin on one end and orange gelatin on the other end, with "Motrin IB" printed in grey ink, in trial sizes of 2 and in bottles of 20 and 40.

Extra Strength MOTRIN*IB ibuprofen 300mg tablets are available as solid, light orange coloured, round, biconvex, film-coated tablets, with 'MOTRIN 300mg' printed in black ink, in bottles of 20 and 65.

Super Strength MOTRIN*IB 400mg tablets are available as solid, orange coloured, round, biconvex, film-coated tablets, with 'MOTRIN 400mg' printed in black ink, in pouches of 1 and in bottles of 16 and 50.

INFORMATION FOR THE CONSUMER

The following consumer information leaflet will be provided with all MOTRIN* IB ibuprofen products:

MOTRIN* IB
Ibuprofen Tablets USP
Pain Reliever / Fever Reducer

Consumer Information Leaflet - Keep for Future Reference

Since everyone's pain is different, MOTRIN* IB offers 3 levels of pain relief to suit your needs. So you can choose your relief, MOTRIN* IB ibuprofen products are available in three strengths, including MOTRIN * IB (200 mg), Extra Strength (300 mg) and Super Strength (400 mg). MOTRIN* IB ibuprofen products provide fast and effective relief of headache pain (including mild to moderate migraine and tension headache), menstrual pain, dental pain, and pain associated with arthritis. It is also effective for relieving minor aches and pains in muscles, bones and joints such as sprains or strains, backache and pain from physical or athletic overexertion. MOTRIN* IB is an effective fever reducer and will provide relief from the aches and fever due to the common cold.

Dosage: For accurate dosing of each product strength, refer to the dosage table and follow the instructions carefully. The single dose may be repeated every 4-6 hours, not to exceed the maximum daily dose. Take with food or milk if mild stomach upset occurs with use. For effective use of this medicine, do not take more of it, do not take it more often and do not take it for a longer period of time than directed here or as ordered by your doctor or dentist. The smallest dose that will relieve your symptoms should be taken. MOTRIN* IB should not be taken for pain for more than 5 consecutive days or for fever, if not improved, for more than 3 days without first talking to your doctor or dentist.

Product	Strength (ibuprofen mg/tablet)	Single Oral Dose	Maximum Daily Dose (1200 mg)
MOTRIN* IB	200 mg	1 or 2 tablets, caplets or gelcaps	6 tablets, caplets or gelcaps
Extra Strength MOTRIN* IB	300 mg	1 tablet	4 tablets
Super Strength MOTRIN* IB	400 mg	1 tablet	3 tablets

Do not take this product if you are allergic to ibuprofen or products containing acetylsalicylic acid (ASA), other salicylates, other anti-inflammatory drugs, or if you have ASA-sensitive asthma. 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. Do not take this product while taking ASA, other ibuprofen containing products or any other pain or fever medicine. MOTRIN* IB products should not be used by children under 12 years of age, except as recommended by a doctor or dentist. For treatment of children's fever and pain, try Children's MOTRIN* products.

Precautions: Keep this medication out of the reach of children. Talk to your doctor or dentist before taking this product if you have peptic ulcers, high blood pressure, asthma, heart failure, kidney or liver disease, alcoholism, a history of stomach bleeding, any other serious disease or condition, are pregnant or nursing, or are taking any other drug. 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. Always tell any other doctor, dentist, or pharmacist you consult that you are taking this medicine.

Tablets and caplets: Store away from heat and direct light. Gelcaps: Store at room temperature; avoid high humidity and heat (40⁀C or 104⁀F).

In case of accidental overdose, even if there are no symptoms, call a doctor or Poison Control Centre at once.

If you have any questions about this information, check with your doctor, dentist or pharmacist or call our toll free number 1 888 6MOTRIN / 1 888 666-8746.

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PHARMACOLOGY

Animal Studies

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 (Adams, Bough *et al.*; 1969).

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 (Adams, Bough *et al.*; 1969).

Protein binding studies with plasma levels of 20 μg/mL indicate the percent bound in rats 96%, dogs 99%, baboons 95% and man 99% (Mills *et al.*; 1973).

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 (Adams, Bough *et al.*; 1969, Mills *et al.*; 1973). Excretion of metabolites was noted to varying degrees through both urine and feces indicating species variability in the bile and kidney excretion ratios.

Pharmacodynamics

While the mechanism of action of ibuprofen is not definitely known, it is generally believed to involve 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 (Flower *et al.*; 1985).

Inhibition of prostaglandin synthesis by ibuprofen has been demonstrated in several different experimental models: bull seminal vesicle microsomes (Cushman & Cheung; 1976), stomach, duodenum, kidney and brain of the rat, (Fitzpatrick & Wynaida; 1976) microsomal preparations from rabbit brain and kidney medulla (Szczeklik *et al.*; 1976).

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 (Aparicio; 1977, Adams, Cliffe *et al*.; 1969, Romer; 1980).

The antipyretic activity of ibuprofen has been demonstrated in yeast-induced fever in rats (Aparicio; 1977, Adams, Cliffe *et al*.; 1969, Romer; 1980).

Human Studies

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 (Kauffman *et al*.; 1989), some differences in the pharmacokinetic parameters of volume of distribution and clearance have been observed between adults and children (McEvoy; 1997).

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 µg/mL at 0.75 hr (Adams *et al*.; 1967). Another study using a single oral 400 mg dose in humans produced a peak serum level of 31.9 $\pm$ 8.8 µg/mL 0.5 hour after ingestion, and at 16 hours serum concentrations had dropped to 1 µg/mL (Kaiser & Martin; 1978). Comparable serum levels and time to peak within 1-2 hours were confirmed by other investigations with 200 mg and 400 mg solid doses (Kaiser & Vangiessen; 1974, Glass & Swannell; 1978). 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 (Mills *et al*.; 1973). As is true with most tablet and suspension formulations, Children's Motrin* suspension is absorbed somewhat faster than a tablet with a time to peak generally within one hour.

Distribution - Ibuprofen, like most drugs of its class, is highly protein bound (>99% bound at 20 µg/mL) (Mills *et al*.; 1973, Kober & Sjoholm; 1980). 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 0.12L/kg. The clinical significance of these findings is unknown (McEvoy; 1997). 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 (Glass & Swannell; 1978).

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 (Albert & Gernaat; 1984). The two major metabolities 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 (Adams, Cliffe *et al*.; 1969).

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 (McEvoy; 1997). 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.

Pharmacodynamics

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 (Cooper *et al*.; 1977, Cooper; 1984).

Sore Throat or Ear Pain (Pediatric Models)

In children 6 - 12 years, ibuprofen 10 mg/kg was found to be effective for the relief of pain using a sore throat model, both post-op sore throat (tonsillectomy) (Bertin *et al*.; 1991) and pharyngitis due to upper respiratory infection (Schachtel & Thoden; 1993).

Controlled clinical trials comparing doses of 5 and 10mg/kg ibuprofen and 12.5 mg/kg acetaminophen have been conducted in children 5 to 12 years of age with sore throat pain believed due to an infectious agent or ear pain believed due to acute otitis media. All three active treatments provided significant pain relief versus placebo within 1 to 2 hours of administration and had a duration of action of up to 6 hours. There were no statistically significant differences among the three active treatments in the degree of maximum pain relief, although the trends favored ibuprofen 10mg/kg. Ibuprofen 5mg/kg demonstrated pain relief comparable to acetaminophen 12.5mg/kg. Ibuprofen 10mg/kg demonstrated greater pain relief than acetaminophen 12.5mg/kg from 3 to 6 hours after administration. A pediatric dosage schedule has been developed for Children's Motrin* based on an ibuprofen dose of approximately 7.5 mg/kg body weight.

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 (Molla & Donald; 1974, Shapiro & Diem; 1981, Gooking *et al*.; 1983).

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 (Dawood; 1984).

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 (Miller *et al*.; 1975, deBlecourt; 1975, Chahade *et al*.; 1976, Tylson & Glynne; 1980, Ruoff *et al*.; 1982). 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 (Vecchio *et al*.; 1983). 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 (Diamond; 1983).

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 (Muckle; 1974, Naustion; 1973).

Fever
Studies of its efficacy in the management of fever in adults and children demonstrate ibuprofen to be an effective antipyretic (Gaitonde *et al*.; 1973, Sheth *et al*.; 1980, Sinila *et al*.; 1976, Walson *et al*.; 1989, Wilson *et al*.; 1991), 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 10mg/kg of ibuprofen and 10-15 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 (10mg/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 102.5F/39.1°C) but the numbers of patients were not adequate to draw definitive conclusions. In children with baseline temperatures at or below 102.5F (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.

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 (Adams, Bough *et al*.; 1969).

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 [a, b]	Oral Intraperitoneal	800-1000 320

Species	Route	LD_{50} Range (mg/kg)
Albino Rats [a]	Oral Subcutaneous	1600 1300
Sprague Dawley Rat [c]		1050
Long Evans Rat [d]		1000

[a] Adams, Bough *et al*.; 1969 [b] Aparicio; 1977
[c] Fukawa *et al*.; 1982 [d] Cioli *et al*.; 1980

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 (Atkinson & Leach; 1976). 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 (Cioli *et al*.; 1980). 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	UD_{50}*(mg/kg)	MUD**(mg/kg)
Long Evans Rat [a]	Oral IV	70 210	50 -
Sprague Dawley Rat [b]	Oral	-	6-13

* UD_{50} = ulcerogenic dose in 50% treated animals
** MUD = minimum ulcerogenic dose
[a] Cioli *et al*.; 1980 [b] Atkinson & Leach; 1976

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 (Adams, Bough *et al*.; 1969). 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 whom 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 (Cioli *et al*.; 1980). 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[a]	400mg/kg	30 hours	Ulcers in 100%
Albino Rat[b]		4 days	UD_{50} = 455 mg/kg/day UD_{28} = 240 mg/kg/day
Long Evans Rat[c]		5 days	MUD = 25 - 50 mg/kg/day
Sprague Dawley Rat[d]	5.8-225 mg/kg	10 days	None
Albino Rat[e]	7.5mg/kg 180mg/kg	26 weeks 26 weeks	None Ulcers in 20%
Dog[e]	4mg/kg 8mg/kg 16mg/kg	30 days 30 days 30 days	None 100% 100%

[a] Parmer & Ghosh; 1981
[b] Aparicio; 1977
[c] Cioli *et al*.; 1980
[d] Paroli *et al*.; 1978
[e] Adams, Bough *et al*.; 1969

No other organ systems were generally noted to be significantly affected by these chronic administration studies. In one 30 day study (Dudkeiwicz; 1970), 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 (Adams, Bough *et al*.; 1969). 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 (Adams, Bough *et al*.; 1969). 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 (Adams, Bough *et al*.; 1970). 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 (Adams, Bough *et al*.; 1969). 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 (Coceani; 1979). Such an effect might be anticipated because of the known prostaglandin inhibiting properties of ibuprofen.

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