PRODUCT MONOGRAPH

Super Strength MOTRIN® IB Liquid Gels

Ibuprofen Capsules

400 mg

Analgesic /Antipyretic

McNeil Consumer Healthcare
division of Johnson & Johnson Inc.
88 McNabb Street
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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients*
Oral	Capsule / 400 mg	None
** For a complete listing see Dosage Forms, Composition and Packaging section.*		

INDICATIONS AND CLINICAL USE

Adults over 12 years

SUPER STRENGTH MOTRIN® IB LIQUID GELS (Ibuprofen) is indicated for treatment of pain associated with migraine.

SUPER STRENGTH MOTRIN® IB LIQUID GELS is also indicated for headaches and the temporary relief of menstrual pain (dysmenorrhea), toothache (dental pain), minor aches and pains in muscles, bones and joints and for reduction of fever and for temporary relief of mild to moderate pain.

There is considerable evidence in the world literature documenting the efficacy of 200 to 400 mg doses of ibuprofen in the treatment of mild to moderate pain in a broad range of pain models.

Pediatrics

Studies conducted to date have not demonstrated pediatric-specific problems that would limit the usefulness of ibuprofen in children 6 months and older.

Ibuprofen is not recommended for use in patients under 2 months of age since safety and effectiveness have not been established.

Geriatrics

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 gastrointestinal (GI) events are in this population. Older patients are also at risk of lower oesophageal ulceration and bleeding.

For such patients, consideration should be given to a starting dose lower than the one usually recommended, with individual adjustment when necessary and under close supervision. See "Gastrointestinal (GI)-Warnings and Precautions" for further advice.

Sore Throat Pain

A double-blind, randomized study showed that ibuprofen 400 mg relieved sore throat pain significantly better than placebo and acetaminophen.[19]

Headache

A double-blind, randomized study showed that ibuprofen 400 mg relieved headache pain significantly better than acetaminophen 1000 mg and placebo.[20] Another double-blind, placebo-controlled, randomized study showed that ibuprofen 400 mg began to exert a significant analgesic effect on headache within 30 minutes after dosing.[21]

Dental Pain

A double-blind, randomized study showed that ibuprofen 400 mg relieved dental pain following removal of impacted third molars significantly better than acetaminophen and placebo.[23] Several other comparative dental studies have described similar results.[24-30]

Muscle Aches

A double-blind, randomized study showed that ibuprofen 400 mg every four hours for a total of three doses relieved muscle soreness following exercise significantly better than acetaminophen 1000 mg and placebo every four hours.[31]

Dysmenorrhea

Several studies demonstrate the significant effect of ibuprofen compared to placebo or other active analgesics on uterine pain and cramping.[32-37]

Fever

The antipyretic efficacy of ibuprofen has been demonstrated in adult.[38-40]

CONTRAINDICATIONS

The following are contraindications to the use of SUPER STRENGTH MOTRIN® IB LIQUID GELS (Ibuprofen):

1. Active peptic ulcer, a history of recurrent ulceration or active inflammatory disease of the gastrointestinal system.

2. Known or suspected hypersensitivity to the drug or other non-steroidal anti-inflammatory drugs. The potential for cross-reactivity between different NSAIDs must be kept in mind.

   SUPER STRENGTH MOTRIN® IB LIQUID GELS should not be used in patients with

the complete or partial syndrome of nasal polyps, or in whom asthma, anaphylaxis, urticaria, rhinitis or other allergic manifestations are precipitated by acetylsalicylic acid (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.

3. Significant hepatic impairment or active liver disease.

4. Severely impaired or deteriorating renal function (creatinine clearance <30 mL/min). Individuals with lesser degrees of renal impairment are at risk of deterioration of their renal function when prescribed NSAIDs and must be monitored.

5. Ibuprofen is not recommended for use with other NSAIDs because of the absence of any evidence demonstrating synergistic benefits and the potential for additive side effects.

6. Children with kidney disease and children who have suffered significant fluid loss should not be given ibuprofen.

7. Patients who are hypersensitive to the drug or to any ingredients in the formulation or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.

WARNINGS AND PRECAUTIONS

SERIOUS WARNINGS AND PRECAUTIONS

History of peptic ulcers, gastrointestinal bleeding or other diseases of the gastrointestinal tract.

General

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

Cardiovascular

Congestive heart failure in patients with marginal cardiac function, elevated blood pressure and palpitations.

Endocrine and Metabolism

Fluid retention and oedema have been observed in patients treated with ibuprofen. Therefore, as with many other nonsteroidal anti-inflammatory drugs, the possibility of precipitating congestive heart failure in elderly patients or those with compromised cardiac function should be borne in mind. SUPER STRENGTH MOTRIN® IB LIQUID GELS (Ibuprofen) should be used with caution in patients with heart failure, hypertension or other conditions predisposing to fluid retention.

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 B-adrenergic blockers, angiotensin converting enzyme inhibitors or some diuretics. Serum electrolytes should be monitored periodically during long-term therapy, especially in those patients who are at risk.

Gastrointestinal (GI)

Serious GI toxicity, such as peptic ulceration, perforation and gastrointestinal bleeding, sometimes severe and occasionally fatal, can occur at any time, with or without symptoms in patients treated with NSAIDs including ibuprofen.

Minor upper GI problems, such as dyspepsia, are common, usually developing early in therapy. Physicians 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 appear to occur in approximately 1% of patients treated for 3-6 months and in about 2-4% of patients treated for one year. The risk continues beyond one year and possibly increases. The incidence of these complications increases with increasing dose.

SUPER STRENGTH MOTRIN® IB LIQUID GELS should be given under close medical supervision to 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. In these cases the physician must weigh the benefits of treatment against the possible hazards.

Physicians should inform patients about the signs and/or symptoms of serious GI toxicity and instruct them to contact a physician 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, physicians should follow chronically treated patients by checking their haemoglobin periodically and by being vigilant 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, SUPER STRENGTH MOTRIN® IB LIQUID GELS 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. A prior history of serious GI events and other factors such as excess alcohol intake, smoking, age, female gender and concomitant oral steroid and anticoagulant use have been associated with increased risk. Studies to date show that all NSAIDs can cause GI tract adverse events. Although existing data does not clearly identify differences in risk between various NSAIDs, this may be shown in the future.

There is no definitive evidence that the concomitant administration of histamine H2-receptor antagonists and/or antacids will either prevent the occurrence of gastrointestinal side effects or allow the continuation of SUPER STRENGTH MOTRIN® IB LIQUID GELS therapy when and if these adverse reactions appear.

Genitourinary

Some NSAIDs are known to cause 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. Some cases have become severe on continued treatment. Should urinary symptoms occur, treatment with SUPER STRENGTH MOTRIN® IB LIQUID GELS must be stopped immediately to obtain recovery. This should be done before any urological investigations or treatments are carried out.

Haematologic

Drugs inhibiting prostaglandin biosynthesis do interfere with platelet function to varying degrees; therefore, patients who may be adversely affected by such an action should be carefully observed when ibuprofen is administered.

Blood dyscrasias (such as neutropenia, leukopenia, thrombocytopenia, aplastic anaemia and agranulocytosis) associated with the use of non-steroidal anti-inflammatory drugs are rare, but could occur with severe consequences.

Hepatic/ Biliary/Pancreatic

As with other nonsteroidal anti-inflammatory drugs, borderline elevations of one or more liver function tests 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 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, or if systemic manifestations occur (e.g. eosinophilia, rash, etc.), this drug should be discontinued.

During long-term therapy, liver function tests should be monitored periodically. If there is a need to prescribe this drug in the presence of impaired liver function, it must be done under strict observation.

The frequency of acute liver injury among 625,307 people who received NSAIDs in England and Wales between 1987 and 1991, was examined.[73] There were 311,716 patients who were prescribed ibuprofen. The incidence of acute liver injury among ibuprofen users was 1.6/100,000; this was the lowest incidence among the 8 NSAIDs studied and was significantly lower than the incidence among users of ketoprofen, piroxicam, fenbrufen, or sulindac. For NSAID users as a group, the only factors that had an independent effect on the occurrence of acute liver injury were the simultaneous use of hepatotoxic medication or the presence of rheumatoid arthritis. Based on these data, the short-term use of ibuprofen as an analgesic/antipyretic should not be of concern regarding the development of liver disease.

Immune

In occasional 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 tissue diseases, etc.) seem to be pre-disposed. Therefore, in such patients, the physician must be vigilant to the development of this complication.

Skin

Some people may become more sensitive to sunlight than they are normally. Brief exposure to sunlight or sunlamps may cause sunburn, blisters on the skin, skin rash, redness, itching or discoloration or vision changes.

Neurologic

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

Ophthalmologic

Blurred and/or diminished vision has been reported with the use of ibuprofen and other non-steroidal anti-inflammatory drugs. If such symptoms develop this drug should be discontinued and an ophthalmologic examination performed; ophthalmic examination should be carried out at periodic intervals in any patient receiving this drug for an extended period of time.

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 prerenal conditions leading to the 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 nonsteroidal 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, heart failure, liver dysfunction, those taking diuretics, and the elderly. Discontinuation of nonsteroidal anti-inflammatory therapy is usually followed by recovery to the pre-treatment state.

Ibuprofen and its metabolites are eliminated primarily by the kidneys; therefore the drug should be used with great caution in patients with impaired renal function. In these cases, utilisation of lower doses of SUPER STRENGTH MOTRIN® IB LIQUID GELS should be considered and patients carefully monitored.

During long-term therapy kidney function should be monitored periodically.

Sensitivity/Resistance

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

Special Populations

Pregnant Women

Reproductive studies conducted in rats and rabbits have not demonstrated evidence of developmental abnormalities. However, animal reproduction studies are not always predictive of human response. Because of the known effects of NSAIDs on the fetal cardiovascular system, use of ibuprofen during late pregnancy should be avoided. As with other drugs known to inhibit prostaglandin synthesis, an increased incidence of dystocia and delayed parturition occurred in rats. Administration of ibuprofen is not recommended during pregnancy.

Nursing Women

The high protein binding and lower pH of breast milk versus plasma tend to inhibit the excretion of ibuprofen into breast milk.[8] One study showed an ibuprofen concentration of 13 ng/mL 30 minutes after ingesting 400 mg.[18] The milk: plasma ratio was 1:126. This translates to an infant exposure of 0.0008% of the maternal dose. It is not known to what extent, if any, ibuprofen crosses the human placenta.

ADVERSE REACTIONS

Prescription Experience

The following adverse reactions have been noted in patients treated with prescription doses (≥1200 mg/day).

Note: Reactions listed below under Causal Relationship Unknown are those which occurred under circumstances where a causal relationship could not be established. However, in these rarely reported events, the possibility of a relationship to ibuprofen cannot be excluded.

Gastrointestinal

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

Incidence 3 to 9%: nausea, epigastric pain, heartburn

Incidence 1 to 3%: diarrhoea, abdominal distress, nausea and vomiting, indigestion, constipation, abdominal cramps or pain, fullness of the gastrointestinal tract (bloating or flatulence).

Incidence less than 1%: gastric or duodenal ulcer with bleeding and/or perforation, gastrointestinal haemorrhage, melena, hepatitis, jaundice, abnormal liver function (SGOT, serum bilirubin and alkaline phosphatase).

Allergic

Incidence less than 1%: anaphylaxis (see Contraindications).

Causal relationship unknown: fever, serum sickness, lupus erythematosus.

Central Nervous System

Incidence 3 to 9%: dizziness

Incidence 1 to 3%: headache, nervousness

Incidence less than 1%: depression, insomnia

Causal relationship unknown: paresthesias, hallucinations, dream abnormalities

Aseptic meningitis and meningoencephalitis, in one case accompanied by eosinophilia in the cerebrospinal fluid, have been reported in patients who took ibuprofen intermittently and did not have any connective tissue disease.

Dermatologic

Incidence 3 to 9%: rash (including maculopapular type).

Incidence 1 to 3%: pruritus

Incidence less than 1%: vesiculobullous eruptions, urticaria, erythema multiforme

Causal relationship unknown: alopecia, Stevens-Johnson syndrome.

Cardiovascular

Incidence less than 1%: congestive heart failure in patients with marginal cardiac function, elevated blood pressure.

Causal relationship unknown: arrhythmias (sinus tachycardia, sinus bradycardia, palpitations).

Special Senses

Incidence 1 to 3%: tinnitus

Incidence less than 1%: 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.

Causal relationship unknown: conjunctivitis, diplopia, optic neuritis.

Hematologic

Incidence less than 1%: leukopenia, and decreases in haemoglobin and hematocrit.

Causal relationship unknown: haemolytic anaemia, thrombocytopenia, granulocytopenia, bleeding episodes (e.g., purpura, epistaxis, hematuria, menorrhagia).

Renal

Causal relationship unknown: decreased creatinine clearance, polyuria, azotemia.

Like other non-steroidal anti-inflammatory drugs, ibuprofen inhibits renal prostaglandin synthesis, which may decrease renal function and cause sodium retention. Renal blood flow and glomerular filtration rate decreased in patients with mild impairment of renal function 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.

Hepatic

Incidence less than 1%: Hepatitis, jaundice, abnormal liver function (SGOT, serum bilirubin, and alkaline phosphatase).

Endocrine

Causal relationship unknown: gynecomastia, hypoglycaemic reaction.

Menstrual delays of up to two weeks and dysfunctional uterine bleeding occurred in nine patients taking ibuprofen, 400 mg t.i.d., for three days before menses.

Metabolic

Incidence 1 to 3%: decreased appetite, oedema, fluid retention.

Fluid retention generally responds promptly to drug discontinuation (See Warnings and Precautions).

Non-Prescription Experience: Literature (at dosages ≤ 1200 mg/day)

One researcher conducted an extensive analysis of published data concerning the relative safety of non-prescription doses of ibuprofen and acetaminophen.[87] Of a total of 96 randomized and blinded trials, there were 10 trials of seven days' duration or less where the safety of both drugs was directly compared. In three of these trials, the incidence of adverse events was higher with acetaminophen; there were no reported adverse events in six trials; and one trial reported a higher incidence with ibuprofen. In this subset of 10 studies, it was reported that gastrointestinal adverse events were found to be the most common type of event reported and were predominantly dyspepsia, nausea, or vomiting. None of the GI events appeared to warrant follow-up from which the author inferred there were no serious gastrointestinal events.

It was concluded: "Although we recognise that the above mentioned data are very selective and are based on information derived from a variety of trial designs and populations, it is nonetheless instructive for indicating a relatively low incidence of severe adverse reactions with both drugs when taken at their respective non-prescription dosages."

A double-blind, placebo-controlled study (N=1246) was conducted to prospectively evaluate the gastrointestinal tolerability, as compared to placebo, of the maximum nonprescription dose and duration (1200 mg/day for 10 consecutive days) of ibuprofen use in healthy subjects representative of a non-prescription analgesic user population.[88] Gastrointestinal adverse experiences were similar in the placebo and ibuprofen groups (67 out of 413, 16% with placebo vs. 161 out of 833, 19% with ibuprofen). There was no difference between the two groups in the proportion of discontinuing due to a gastrointestinal event. Gastrointestinal adverse experiences reported by ≥1% of subjects were: dyspepsia, abdominal pain, nausea, diarrhoea, flatulence, and constipation. Seventeen (1.4%) subjects had positive occult blood tests: their frequency was comparable between treatments. When used as directed to treat episodic pain, nonprescription ibuprofen at the maximum dose of 1200 mg/day for 10 days, is well-tolerated.

In two multitrial analyses[89,90] a meta analysis,[91] and a literature review,[87] single doses of ibuprofen had a low incidence of gastrointestinal drug reactions, comparable to that of acetaminophen and placebo. Reports from spontaneous reporting systems in the United Kingdom,[95] France and the United States,[96] where a prescription is not needed for ibuprofen at a daily dose up to 1200 mg, confirm the medication's gastrointestinal safety and acceptability. A recently-completed large-scale randomised trial[97] comparing nonprescription doses of acetylsalicylic acid, acetaminophen, and ibuprofen in 8677 adults found that the rates of significant adverse reactions were: acetylsalicylic acid 18.7%, ibuprofen 13.7%, and acetaminophen 14.5%.
Ibuprofen was not statistically different from acetaminophen. Total gastrointestinal events (including dyspepsia) and abdominal pain were less frequent with ibuprofen (4% and 2.8%, respectively) than with acetaminophen (5.3% and 3.9%) or acetylsalicylic acid (7.1% and 6.8%) [all $p < 0.035$]. It was concluded that "The overall tolerability of ibuprofen in this large-scale study was equivalent to that of paracetamol and better than that of [ASA]."

DRUG INTERACTIONS

Drug-Drug Interactions

Acetylsalicylic Acid (ASA) or other NSAIDs

The use of SUPER STRENGTH MOTRIN® IB LIQUID GELS (Ibuprofen) in addition to any other NSAID, including ASA, is not recommended because of the absence of any evidence demonstrating synergistic benefits and the potential for additive side effects. Animal studies show that acetylsalicylic acid given with NSAID agents, including ibuprofen, yields a net decrease in anti-inflammatory activity with lowered blood levels of the non-acetylsalicylic acid drug. Single-dose bioavailability studies in normal volunteers have failed to show an effect of acetylsalicylic acid on ibuprofen blood levels. Correlative clinical studies have not been conducted.

Also, some NSAIDs may interfere with the anti-platelet effects of low dose ASA 981-325 mg), 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 irreversible platelet inhibition induced by ASA. Regular use of ibuprofen in patients with increased cardiovascular risk may limit the cardioprotective effects of ASA. 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.

Acetaminophen

Although interactions have not been reported, concurrent use with SUPER STRENGTH MOTRIN® IB LIQUID GELS is not advisable: it may increase the risk of adverse renal effect.

Digoxin[74]

Ibuprofen has been shown to increase serum digoxin concentration. Increased monitoring and dosage adjustments of digitalis glycoside may be necessary during and following concurrent ibuprofen therapy.

Coumarin-type[75,76]

Numerous studies have shown that the concomitant use of NSAIDs and anticoagulants increases the risk of GI adverse events such as ulceration and bleeding. Because prostaglandins play an important role in hemostasis, and NSAIDs affect platelet function, concurrent therapy of ibuprofen with warfarin requires close monitoring to be certain that no change in anticoagulant dosage is necessary. 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. Nevertheless, the physician, should be cautious when administering SUPER STRENGTH MOTRIN® IB LIQUID GELS to patients on anticoagulants.

Hypoglycaemic Agents

Ibuprofen may increase hypoglycaemic effects of oral antidiabetic agents and insulin.

Antihypertensives

Prostaglandins are an important factor in cardiovascular homeostasis and inhibition of their synthesis by NSAIDs may interfere with circulatory control. NSAIDs may elevate blood pressure in patients receiving antihypertensive medication. Two meta analyses[77,78] have observed this relationship for NSAIDs as a class and for certain NSAIDs in particular, but ibuprofen did not significantly affect blood pressure in either meta analysis. Consistent with this lack of effect, a study by Davies et a1[79] showed that ibuprofen 1600 mg/day for 14 days did not attenuate the antihypertensive effect of two ß-adrenergic blockers. Houston et al.[80] showed no effect of three weeks' therapy with ibuprofen on the antihypertensive efficacy of verapamil, but it is not known whether this lack of interaction extends to other classes of calcium channel blockers.

When renal perfusion pressure is reduced both prostaglandins and angiotensin II are important mediators of renal autoregulation.[81] As a class, the combination of an NSAID and angiotensin converting enzyme inhibitor theoretically may have the potential to decrease renal function. One study found a clinically significant decrease in renal function in 4 of 17 patients treated with hydrochlorothioazide and fosinopril who received ibuprofen 2400 mg/day for one month.[82] In contrast, Minuz[83] found no effect on the antihypertensive effect of enalapril or on plasma renin or aldosterone following two days' treatment with ibuprofen 1200 mg/day.

The relationship of ibuprofen and antihypertensives is clearly not well defined. The benefits of concomitant medication should be analysed and compared to the potential risks before being prescribed. If ibuprofen is being recommended for **long-term** use, then periodic monitoring of blood pressure may be useful. Blood pressure monitoring is not necessary if ibuprofen is being recommended for **short-term** use as an analgesic.

Diuretics

Clinical studies, as well as random observations, have shown that ibuprofen can reduce the natriuretic effect of furosemide and thiazides in some patients. This response has been attributed to inhibition of renal prostaglandin synthesis. During concomitant therapy with ibuprofen, the patient should be observed closely for signs of renal failure as well as to assure diuretic efficacy.

Antacids[84]

A bioavailability study has shown that there was no interference with the absorption of ibuprofen when given in conjunction with an antacid containing aluminium hydroxide and magnesium hydroxide.

H-2 antagonists

In studies with human volunteers, coadministration of cimetidine or ranitidine with ibuprofen had no substantive effect on ibuprofen serum concentrations.

Methotrexate[85]

Ibuprofen as well as other NSAIDs has been reported to competitively inhibit methotrexate accumulation in rabbit kidney slices. This may indicate that ibuprofen could enhance the toxicity of methotrexate. Caution should be used when ibuprofen is administered concomitantly with methotrexate.

Lithium[86]

Ibuprofen produced an elevation of plasma lithium levels and a reduction in renal lithium clearance in a study of eleven normal volunteers. The mean minimum lithium concentration increased 15% and the renal clearance of lithium was decreased by 19% during this period of concomitant drug administration. This effect has been attributed to inhibition of renal prostaglandin synthesis by ibuprofen. Thus, when ibuprofen and lithium are administered concurrently, subjects should be observed carefully for signs of lithium toxicity.

Other Drugs

Although ibuprofen binds extensively to plasma proteins, interactions with other protein-bound drugs occur rarely. Nevertheless, caution should be observed when other drugs, also having a high affinity for protein binding sites, are used concurrently. No interactions have been reported when ibuprofen has been used in conjunction with probenecid, thyroxine, steroids, antibiotics or benzodiazepines.

Drug-Food Interactions
Interactions with food have not been established.

Drug-Herb Interactions
Interactions with herbal products have not been established.

Drug-Laboratory Interactions
Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Adults and Children over 12: Take one 400 mg capsule every four hours as needed. Do not exceed three 400 mg capsules in 24 hours, unless directed by a physician.

OVERDOSAGE

In case of suspected overdose, contact your regional Poison Control Centre.

Symptoms of Overdose [102-104]

The toxicity of ibuprofen overdose is dependent upon the amount of drug ingested and the time elapsed since ingestion; individual responses may vary, thus making it necessary to evaluate each case separately. Although uncommon, serious toxicity and death have been reported with ibuprofen overdosage. The most frequently reported symptoms of ibuprofen overdose include abdominal pain, nausea, vomiting, lethargy and drowsiness. Other CNS symptoms include headache, tinnitus, CNS depression and seizures. Metabolic acidosis, coma, acute renal failure and apnoea (primarily in very young pediatric patients) may rarely occur. Cardiovascular toxicity, including hypotension, bradycardia, tachycardia and atrial fibrillation, also have been reported.

Treatment of Overdose

In cases of acute overdose, the stomach should be emptied through induction of emesis (in alert patients only) or gastric lavage. Emesis is most effective if initiated within 30 minutes of ingestion. Orally administered activated charcoal may help in reducing the absorption of ibuprofen when given less than 2 hours following ingestion. There is some evidence that repeated administration of activated charcoal may bind the medication that has diffused from the circulation.[112] Inducing diuresis may be helpful. The treatment of acute overdose is primarily supportive. Management of hypotension, acidosis and gastrointestinal bleeding may be necessary.

In pediatric patients, the estimated amount of ibuprofen ingested per body weight may be helpful to predict the potential for development of toxicity although each case must be evaluated. Ingestion of less than 100 mg/kg is unlikely to produce toxicity. Pediatric patients ingesting 100 to 200 mg/kg may be managed with induced emesis and a minimal observation time of at least four hours. Pediatric patients ingesting 200 to 400 mg/kg of ibuprofen should have immediate gastric emptying and at least four hours observation. Pediatric patients ingesting greater than 400 mg/kg require immediate medical referral, careful observation and appropriate supportive therapy. Induced emesis is not recommended in overdoses greater than 400 mg/kg because of the risk for convulsions and the potential for aspiration of gastric contents.

In adult patients, the dose reportedly ingested does not appear to be predictive of toxicity. The need for referral and follow-up must be judged by the circumstances at the time of the overdose ingestion. Symptomatic adults should be carefully evaluated, observed and supported.

Examples of Ibuprofen Overdose

A 41-year-old man with multiple medical problems, including long-term renal insufficiency, developed near-fatal acute renal failure after ingestion of a massive dose (36 g) of ibuprofen [1]. He required dialysis for several months, at which point his renal function improved.

In children, ibuprofen overdoses less than 100 mg/kg are unlikely to produce toxicity. In adults, the dose of ibuprofen reportedly ingested does not appear to be predictive of toxicity.

With electrolyte replacement and other intensive measures, a 21-month-old child recovered within 5 days after accidental ingestion of 8 g of ibuprofen [2].A 2-year-old child who ingested approximately 8 g of ibuprofen was treated with activated charcoal, developed metabolic acidosis and acute renal insufficiency, and recovered within 72 hours [3]. A 6-year-old child became comatose after ingesting 6 g of ibuprofen [4]. He was treated with gastric lavage, charcoal, and various supportive measures and recovered within 24 hours.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of action

Ibuprofen, like all nonsteroidal anti-inflammatory drugs (NSAIDs), is an analgesic, antipyretic, and anti-inflammatory medication.[1] There is strong evidence to support the view that the main mechanism of action of ibuprofen (like other NSAIDs) is related to decreasing prostaglandin biosynthesis.[2]

Prostaglandins are naturally-occurring fatty acid derivatives that are widely distributed in the tissues. They are believed to be a common factor in the production of pain, fever, and inflammation. Prostaglandins are believed to sensitise tissues to pain- and inflammation-producing mediators such as histamine, 5-hydroxytryptamine, and kinins. The enzyme catalysing the committed step in prostaglandin biosynthesis is prostaglandin endoperoxide synthase, also know as cyclooxygenase.

There is significant evidence that the main mechanism of analgesic/antipyretic action of NSAIDs is prostaglandin biosynthesis inhibition.[3] Other pharmacologic effects such as lysosome and plasma membrane stabilisation have been observed, but the potential relevance of these effects to ibuprofen-induced analgesia and antipyresis is unclear.

A recent study confirmed that ibuprofen 400 mg provided a significantly faster onset of relief as measured by first perceptible relief, meaningful relief, per cent attaining complete relief, and superior overall analgesic efficacy compared to acetaminophen 1000 mg for relief of episodic tension-type headache.[22]

Pharmacokinetics

Absorption

Ibuprofen is rapidly and almost completely absorbed. Peak serum concentration occurs within 1-2 hours in adults.[4] Ibuprofen capsules contain solubilized ibuprofen which has peak serum concentrations within 36-42 minutes. ln febrile children ages 3 months to < 12 years, the time of peak serum concentration was 1.60 and 1.54 hours for ibuprofen 5 mg/kg and 10 mg/kg, respectively.[5] Nahata[6] found a time to peak concentration of 1 .1 and 1.2 hours for these respective doses. A similar study in febrile children by Walson[7] which used an ibuprofen suspension showed a time of peak serum concentration of 1.3 and 1.7 hours for ibuprofen 5 mg/kg and 10 mg/kg, respectively. Walson also found that mean ibuprofen plasma concentration at one hour was 21.7 ± 6.7 and 28.4 ± 15.2 μg/mL for 5 mg/kg and 10 mg/kg, respectively. Food decreases the rate but not the extent of absorption.[4]

Distribution

The volume of distribution in adults after oral administration is 0.1-0.2 L/kg.[8] In febrile children the volume of distribution is 0.18 and 0.22 L/kg for ibuprofen 5 mg/kg and 10 mg/kg, respectively.[5]

At therapeutic concentrations ibuprofen is highly bound to whole human plasma and to site II of purified albumin.[8] There is no appreciable plasma accumulation of ibuprofen or its metabolites with repeated doses.[4]

Metabolism

Ibuprofen is a racemic mixture of R-(-) ibuprofen and S-(+) ibuprofen. R-(-) ibuprofen undergoes extensive enantiomeric conversion to S-(+) ibuprofen in humans, averaging between 53% and 65%.[9] S-(+) ibuprofen is believed to be the pharmacologically more active enantiomer. Two major metabolites, 2-[4-(2-carboxypropyl)phenyl] propionic acid and 2-[4-(2-hydroxy-2-methylpropyl]propionic acid, have been identified in plasma and urine.[10] The metabolites 1-hydroxyibuprofen and 3-hydroxyibuprofen have also been found in urine in very small concentrations.[11,12] Cytochrome P450 (CYP) 2C9 has been identified as the most important catalyst for formation of all oxidative metabolites of R-(-) and S-(+) ibuprofen.[13] Approximately 80% of a dose is recovered in urine, primarily as carboxymetabolites and conjugated hydroxymetabolites.[8] Ibuprofen does not appear to induce the formation of drug metabolising enzymes in the rat.[10]

Excretion

Ibuprofen's plasma half-life in adults is 1.5-2.0 hours.[14] In febrile children the plasma half-life is 1.65 and 1.48 hours for ibuprofen 5 mg/kg and 10 mg/kg, respectively.[5] Parent drug and metabolites are primarily excreted in the urine; bile and faeces are relatively minor elimination routes. Total recovery in urine is between 70% and 90% of the administered dose within 24 hours.[8]

There is no evidence of a differential metabolism or elimination of ibuprofen in the elderly. A pharmacokinetic evaluation of ibuprofen in geriatric subjects (65 to 78 years) compared with young adult subjects (22 to 35 years) found that there was no clinically significant difference in the kinetic profiles of ibuprofen for these age groups.[15] Furthermore, there was no statistically significant difference between the two populations in the urinary excretion pattern of the drug and its major metabolites.

The pharmacokinetics of ibuprofen have also been evaluated in children, in whom the metabolism has been shown to be similar to that reported for adults. Walson reported that for ibuprofen 10 mg/kg given to children under 12 years of age, peak plasma concentration occurred at 1.5 hours and then declined with a plasma half-life of 1.8 hours.[16] Thus, ibuprofen appears to exhibit a similar pharmacokinetic profile in all age groups examined.

Special Populations and Conditions

Breast Milk and Placental Transport

Ibuprofen excretion in breast milk following ingestion of one 400 mg ibuprofen tablet every 6 hours for five doses was below the level (i.e., 1 μg/mL) of detection.[17] However, a later study using a more sensitive assay showed ibuprofen to be rapidly excreted in breast milk 30 minutes following oral ingestion of 400 mg of ibuprofen at a concentration of 13 ng/mL. A milk: plasma ratio of 1:126 was determined and the exposure of a suckling infant was calculated to be approximately 0.0008% of the maternal dose.[18] It is not known whether ibuprofen crosses the placenta.

STORAGE AND STABILITY

SUPER STRENGTH MOTRIN® IB LIQUID GELS should be stored at room temperature (15 - 30°C). Protect from heat and humidity.

SPECIAL HANDLING INSTRUCTIONS

Not applicable.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Availability of Dosage Forms:

For Adults:

SUPER STRENGTH MOTRIN® IB LIQUID GELS (Ibuprofen Capsule 400 mg): A clear, colourless to pale yellow solution in a clear oblong gelatin shell printed with the "M400" logo in black ink. SUPER STRENGTH MOTRIN® IB LIQUID GELS are available in bottles of 30 and 60.

Composition

Each capsule of SUPER STRENGTH MOTRIN® IB LIQUID GELS contains the following non-medicinal ingredients: Castor oil, gelatin, PEG-40 hydrogenated castor oil, povidone, purified water, sorbitan, sorbitol, and titanium dioxide

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name: Ibuprofen

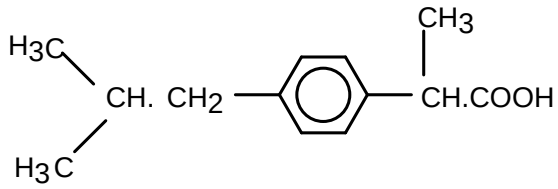
Chemical Name: (±) α-methyl-4- (2-methylpropyl) benzeneacetic acid

Other Names: (±)- p-isobutylhydratropic acid

(±) -2-(p-isobutylphenyl)propionic acid

Molecular formula and molecular weight: $C_{13}H_{18}O_2$
206.28

Structural Formula:



Physicochemical properties:

Physical characteristics:	White or almost white powder or crystals with a characteristic odour.
Solubilities:	Low solubility in water: soluble 1 in 1.5 of alcohol, 1 in 1 of chloroform, 1 in 2 of ether, and 1 in 1.5 of acetone. Ibuprofen is also soluble in an aqueous solution of alkali hydroxides and carbonates.
pKa and pH values:	pH: 4.6-6.0, in a solution of 1 in 20
Melting Point:	75- 77°C

CLINICAL TRIALS

Comparative Bioavailability Studies

A comparative bioavailability study was performed on healthy male/female volunteers under fasting conditions. The rate and extent of absorption of ibuprofen was measured and compared following a single oral dose of MOTRIN® IB LIQUID GELS (Ibuprofen capsules 200 mg) or Advil® Liqui-Gels. The results from measured data are summarized in this table.

Summary Table of the Comparative Bioavailability Data
Ibuprofen
(A single 200 mg dose: 1 x 200 mg)
From measured data
Geometric Mean
Arithmetic Mean (CV %)

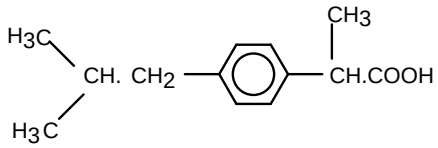
Parameter	Test MOTRIN® IB Liquid Gels	Reference Advil® Liqui-Gels® †	% Ratio of Geometric Means**	90% Confidence Interval
AUC_T (ng-hr/mL)	70625.44 71537.37 (16.30%)	69730.29 70499.77 (15.33%)	101.28	(98.96, 103.67)
AUC_I (ng-hr/mL)	72267.66 73237.90 (16.65%)	71223.30 72042.38 (15.66%)	101.47	(99.06, 103.93)
$AUC_{RefTmax}$	1.91 5.59 (120%)	4.87 5.68 (64%)	39.3	(18.6, 82.7)
C_{max} (ng/mL)	26234.00 26984.47 (23.66%)	26727.85 28117.98 (30.96%)	98.15	(90.08, 106.95)
T_{max}^* (h)	1.05 (81.45%)	0.65 (72.21%)		
$T_{½}^*$ (h)	2.16 (16.84%)	2.14 (14.29%)		

* Expressed as the arithmetic mean (CV%)
** Based on the least square means.
† Advil® Liqui-Gels® (manufactured by Whitehall-Robins Inc.-Canada) was purchased in Canada.

DETAILED PHARMACOLOGY

Structural Formula and Chemistry

Chemically, ibuprofen is described as 2-(4-isobutylphenyl) propionic acid with the following structural formula:



Ibuprofen is a white crystalline solid with a slight odour and taste. It is non-hygroscopic and has a low solubility in water. The compound is readily soluble in organic solvents and aqueous alkalis. In the dry state, it is physically and chemically stable. It has a melting point of about 75°C.

Animal

Pharmacokinetics

After single oral doses of 20 to 150 mg/kg of C^{14} labelled ibuprofen rats, the peak plasma level occurred at or before the earliest time examined (20 minutes in the 20 mg/kg group and 45 minutes in the 150 mg/kg group) and peak levels occurred with 45 minutes of dosing in nearly all tissues examined. The concentration in plasma and tissue decreased to very low levels by six hours after the 20 mg/kg dose and by 17 hours after the 150 mg/kg dose. Sixteen to 38% of the daily dose of ibuprofen was excreted in the urine.[105]

A similar dose was given to dogs for periods of up to six months with no evidence of accumulation of the drug or its metabolites.[105]

Pharmacodynamics

Inhibition of Platelet Aggregation in Animals

Like many other NSAIDs, ibuprofen inhibits platelet aggregation, as demonstrated by preventing platelet disposition in aortopulmonary arterial bypass grafts in the dog.[106] The drug's protective action against fatal pulmonary embolism in rabbits injected intravenously with arachidonic acid may also relate to platelet inhibition.[107, 108] Various prostaglandins and thromboxane A_2 (TXA_2), are important factors in normal platelet aggregation. Cyclooxygenase inhibition reduces TXA_2 production and release, thereby reducing platelet aggregation.[109] Ibuprofen may also reduce platelet membrane fluidity, which reduces aggregation,[110] but it is not known to what extent TXA_2 synthesis inhibition is involved in this effect.

Human

Pharmacokinetics

Two metabolites of ibuprofen were isolated from the urine of patients who had been treated for one month with the drug. The metabolites were identified at 2-4', (2-hydroxy-2-methylpropyl) phenylpropionic acid (metabolite A) and 2-4' (2-carboxpropyl) phenylpropionic acid (metabolite B). About 1/3 of the dose was excreted in the urine of patients as metabolite B, 1/10 as unchanged ibuprofen and 1/10 as metabolite A. The remainder of the dose could not be identified in the urine.[105]

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 (81-325 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 b made for regular ibuprofen use, and no clinically relevant effect is considered to be likely for occasional ibuprofen use.

Platelet aggregation studies using the method of Sekhar were performed. Platelet aggregation fell significantly at a dosage of 1800 mg per day of ibuprofen when given over a period of 28 days.

Ibuprofen was also found to influence ADP induced aggregation to a lesser extent than that influenced by collagen. Platelet aggregation induced by recalcification of citrated platelet-rich plasma (a thrombin induced reaction) was not influenced by ibuprofen treatment. Likewise, ibuprofen did not affect whole blood clotting time on recalcification or prothrombin time. Bleeding time performed two hours after the administration of ibuprofen showed a significant dose related increase.

MICROBIOLOGY

Not applicable.

TOXICOLOGY

Single Dose Toxicity Studies

Single dose toxicity studies have been conducted using mice, rats, and dogs.[105]

The LD_{50} values for ibuprofen, expressed as mg/kg of body weight are as follows:

Mouse:	Oral	800 mg/kg
	Intraperitoneal	320 mg/kg
Rat:	Oral	1600 mg/kg
	Subcutaneous	1300 mg/kg

Acute signs of poisoning were prostration in mice, and sedation, prostration, loss of righting reflex and laboured 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.

Following single ibuprofen doses of 125 mg/kg and above to dogs effects were observed including emesis, transient albuminuria, faecal blood loss and erosions in the gastric antrum and pylorus; no ill effects were seen with 20 or 50 mg/kg doses.

Multiple Dose Studies

The no-effect level was determined using groups of 10 male and 10 female rats which were dosed orally for 26 weeks with 180, 60, 20 or 7.5 mg/kg ibuprofen in 0.4% hydroxyethyl cellulose. The control group consisted of 20 males and 20 females which received 0.4% hydroxyethyl cellulose. Rats were weighed three times daily and blood samples were obtained in the final week of dosing. The rats were sacrificed the day after the last dose and the internal organs examined.

Rats receiving ibuprofen for 26 weeks grew normally except for males on 180 mg/kg/day, which gained significantly less weight than the controls. One male rat receiving 180 mg/kg/day died due to intestinal lesions and the death was thought to be treatment-related. Both males and females receiving 180 mg/kg/day were anaemic; leukocyte count and plasma glutamic pyruvic transaminase activities were not significantly altered. The organ to body weight ratio of males given 180 mg/kg/day was typically greater than normal. For some organs, this was because the males weighed less than the controls. Organs that were enlarged were the liver, kidney, and spleen. The same organs were also enlarged in females receiving 180 mg/kg/day, although these females were similar in body weight to the controls. In addition, the combined seminal vesicle and prostate weight was subnormal and uterine weight was increased. The thyroid gland of males receiving 180, 60, 20 mg/kg/day exhibited a slight increase in weight, which was the same for the three doses, however no such increase was observed in the females. There were no significant histological changes observed in rat tissues except for the presence of intestinal ulcers in 1 male and 3 females receiving 180 mg/kg/day.

The above experiment was adapted to establish whether the effects of ibuprofen treatment on rats were reversible when dosing ended.[105] In this instance, rats were administered 180, 60, or 20 mg/kg/day ibuprofen for 13 weeks instead of 26 weeks, whereupon half the animals in each group were sacrificed and the remaining rats were maintained, undosed, for three weeks and then sacrificed. Haematological examinations were performed after 4,8, and 12 weeks of treatment.

Results obtained from the dosing phase of this 13-week experiment reflected the results obtained previously, where rats were dosed for 26 weeks. Males receiving 180 mg/kg/day had enlarged kidneys, spleen, and testes; while those on lower doses had normal organ weights. Females on all three doses had enlarged kidneys, the extent of which was dose-dependent. Enlargement of the liver and ovaries was observed in females receiving 180 mg/kg/day, and of the spleen and ovaries on those on 60 mg/kg/day. None of the enlarged organs were histologically abnormal. Three weeks following withdrawal of treatment, the organ to body weight ratios had completely or almost completely returned to normal. Rats receiving 180 mg/kg/day were anaemic from week 4 of dosing and when examined after the final dose, were found to have intestinal lesions. These effects were not seen at the lower doses, thereby confirming the results of the first experiment. Since the highest dose of 180 mg/kg/day was only moderately toxic, an additional group of rats was dosed with 540 mg/kg/day.[105] All these rats died or were killed *in extremis* after 4 days' dosing. All had intestinal ulceration with peritonitis, and some also had slight renal tubular dilation.

The primary toxic effect of ibuprofen in rats is intestinal damage. Ibuprofen alters the organ to body weight ratio of certain organs, such as the liver, kidneys, gonads, and the secondary sex organs, although no histological abnormalities have occurred and the effect is reversible. The liver and kidney enlargement may be a reflection of work hypertrophy associated with the metabolism and excretion of the compound, whereas the significance of the effect on other organs is unknown. When administered in lethal doses, ibuprofen produces mild kidney lesions in addition to the intestinal damage.

Carcinogenicity

Thirty male and 30 female rats were given 180 mg/kg/day of ibuprofen orally for 55 weeks and 60 mg/kg/day for the next 60 weeks. The only specific pathological effect observed was intestinal ulceration. There was no evidence of tumour induction and it is concluded that ibuprofen is not carcinogenic in the rat.[111]

Teratology

Teratology Study in Rabbits

New Zealand white rabbits were given 0, 7.5, 20 and 60 mg/kg daily of ibuprofen from day 1 to day 29 of pregnancy. The mean foetal weight was unaffected; litter size was unaffected at the lower doses. Congenital malformations did occur in both treated and untreated groups with no consistent pattern except for one litter of 4 young with cylcopia. The results of this experiment indicate that ibuprofen is not teratogenic when given in toxic doses to rabbits.[105]

Teratology Study in Rats

Newly-mated female albino rats were given ibuprofen in doses of 0, 7.5, 20, 60 and 180 mg/kg/day from day 1 to day 20 of pregnancy; ibuprofen exhibited no embryotoxic or teratogenic effects even when administered at ulcerogenic doses.[105]

Penetration of Ibuprofen into the Rabbit and Rat Foetus

Rabbits and rats in late pregnancy were given single oral doses of 60 and 20 mg/kg respectively of C^{14} labelled ibuprofen. Rabbits were killed three hours after dosing and rats killed 1.5 hours after dosing when maternal and foetal blood was collected. Similar concentrations of radioactive ibuprofen were detected in both the mother and foetus indicating that the drug and its metabolites readily crossed the placental barrier into the foetal circulation.[105]

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PART III: CONSUMER INFORMATION

SUPER STRENGTH MOTRIN® IB LIQUID GELS
Ibuprofen Capsules

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

ABOUT THIS MEDICATION

What the medication is used for:
SUPER STRENGTH MOTRIN® IB LIQUID GELS is indicated for treatment of pain associated with migraine.

SUPER STRENGTH MOTRIN® IB LIQUID GELS is also indicated for headaches and the temporary relief of menstrual pain (dysmenorrhea), toothache (dental pain), minor aches and pains in muscles, bones and joints and for reduction of fever and for temporary relief of mild to moderate pain.

What it does:
SUPER STRENGTH MOTRIN® IB LIQUID GELS contains ibuprofen, which belongs to the class of drugs called non-steroidal anti-inflammatory drugs (NSAIDs), which act by decreasing the prostaglandin synthesis, which are naturally occurring substances in the body involved in the production of pain and inflammation.

When it should not be used:
Do not use this product if you:

- are taking acetylsalicylic acid (ASA) or any other non-steroidal anti-inflammatory medication, including any other ibuprofen product.
- **have been diagnosed with severe high blood pressure or have severe coronary artery disease.**
- have an active peptic ulcer (ulcer in the lining of the stomach or the first part of the small intestine), a history of recurrent ulceration (frequent ulcers) or active inflammatory disease of the gastrointestinal system.
- have a known or suspected allergy to the drug or other anti-inflammatory drugs, or to any other component of this formulation (see "What the important nonmedicinal ingredients are") Check with your doctor if you are not sure.
- are allergic to other related medicines of the NSAID group (such as ASA, diclofenac, diflunisal, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, mefenamic acid, piroxicam, sulindac, tiaprofenic acid, tolmetin, nabumetone or tenoxicam).
- have nasal polyps (small, sac-like growths of the lining of the sinuses), or in whom asthma, anaphylaxis (sudden, severe, potentially fatal, allergic reaction), urticaria /hives (red, itchy elevation of the skin surface), rhinitis (an inflammation of the inner lining of the nose) or other allergic symptoms are suddenly caused by ASA or other NSAIDs. If you have the above medical problems, you are at risk of a severe reaction even if you have taken NSAIDs in the past without any adverse effects.
- have liver disease
- have severe kidney disease. Individuals with lesser degrees of kidney disease are at risk of worsening of their renal function when prescribed NSAIDs and must be monitored.
- are also taking another NSAID.
- are a either a child with kidney disease or a child who has suffered significant fluid loss.
- are 12 years of age unless directed by a physician.
- are pregnant or nursing, unless advised otherwise by a doctor.
- have systemic lupus erythematosus.

What the medicinal ingredient is:
Ibuprofen.

What the important nonmedicinal ingredients are:
This is a complete listing of nonmedicinal ingredients: castor oil, gelatin, PEG-40 hydrogenated castor oil, povidone, purified water, sorbitan, sorbitol, and titanium dioxide.

What dosage forms it comes in:
Capsules, 400 mg

WARNINGS AND PRECAUTIONS

SERIOUS WARNINGS AND PRECAUTIONS

History of peptic ulcers, gastrointestinal bleeding or other diseases of the gastrointestinal tract.

Always Remember: Before taking this medication tell your doctor, dentist or pharmacist if you:

- have a history of stomach upset/ulcers, or liver or kidney diseases; heart failure, or if you or a family member has had asthma, nasal polyps (sac-like growth of the inner lining of the nose), chronic sinusitis or chronic hives.
- are pregnant or breastfeeding or intend to become pregnant or breastfeed while taking this medicine;
- are taking any other medication (either prescription or non-prescription) (Please see the "Interactions with this medication" section);
- have any other medical problems such as alcohol abuse, bleeding problems.
- have blood or urine disorders, high blood pressure,

diabetes, or are on any special diet, such as low sodium or low sugar.

Stomach problems may be more likely to occur if you drink alcoholic beverages. Therefore do not drink alcoholic beverages while taking this medication.

While taking this medication:

- Tell any doctor, dentist or pharmacist that you consult or see, that you are taking this medication.
- Be cautious about driving or participating in activities that require alertness if you are drowsy, dizzy or light-headed after taking this medication.
- Check with your doctor if you are not getting any relief or if any problems develop.
- Report any untoward reaction to your doctor. This is very important as it will aid in the early detection and prevention of potential complications.
- Your regular medical check-ups are essential.
- If you require more information on this drug, consult your doctor or pharmacist.

INTERACTIONS WITH THIS MEDICATION

Drugs that may interact with SUPER STRENGTH MOTRIN® IB LIQUID GELS include NSAIDs, high blood pressure medication, blood thinners, corticosteroids, methotrexate, cyclosporin, lithium, phenytoin, oral antidiabetic agents and insulin.

Drugs such as acetaminophen, digoxin and diuretics might potentially interact with SUPER STRENGTH MOTRIN® IB LIQUID GELS.

Do not take ASA, ASA- containing compounds or other drugs used to treat symptoms of arthritis while taking SUPER STRENGTH MOTRIN® IB LIQUID GELS, unless directed by a physician.

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

PROPER USE OF THIS MEDICATION

Consult your doctor if pain lasts for more than 5 consecutive days or fever more than 3 days.

Stomach upset is one of the common problems with NSAIDs. To lessen stomach upset, take this medicine immediately after a meal or with food or milk. If stomach upset (indigestion, nausea, vomiting, stomach pain or diarrhoea) occurs and continues, contact your doctor.

Usual Dose:

SUPER SRENGTH MOTRIN® IB LIQUID GELS 400 mg

Adults and children over 12: **For the pain of migraine, take 1 capsule at the first sign of symptoms, and every four hours as needed.** For all other uses, take 1 capsules every four hours as needed. Do not exceed three capsules in 24 hours, unless directed by a physician.

Overdose:

In case of overdose, contact a Poison Control Center or a doctor at once even if there are no symptoms.

Missed Dose:
If a dose is missed, resume dosing on the normal schedule without exceeding the maximum allowed for 24 hours.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Along with its needed effects, SUPER STRENGTH MOTRIN® IB LIQUID GELS like other NSAID drugs may cause some unwanted effects especially when used for a long time or in large doses. However, at the maximum daily dose of 1200 mg, there are very few side effects seen and these are primarily only gastrointestinal.

The most common side effects with this medication are indigestion, nausea, or vomiting.

The other side effects, which might be seen, are abdominal pain, diarrhoea, flatulence, and constipation.

If these symptoms persist or become bothersome, contact your doctor.

The above do not require medical attention and will usually go away on their own.

Some people may become more sensitive to sunlight than they are normally. Brief exposure to sunlight or sunlamps may cause sunburn, blisters on the skin, skin rash, redness, itching or discolouration or vision changes. If this happens, check with your doctor.

SERIOUS SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Symptom / effect	Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
	Only if severe	In all cases	
Uncommon Chills, fever, muscle aches or pains, or other flu-like symptoms shortly before or together with a skin rash		√	
Bloody or black tarry stools		√	
Hives or itching		√	
Blurred vision		√	
Swelling of feet or lower legs		√	
Hearing problems		√	
Mental confusion or depression		√	
Shortness of breath, troubled breathing, asthma, sinusitis (nasal congestion), wheezing, or tightness in the chest		√	
Vomiting blood		√	
Yellow discoloration of the skin or eyes, with or without fatigue		√	
Any changes in the amount or colour of your urine (such as dark; red or brown), any pain or difficulty experienced in urination, loss of appetite, dizziness, or light headedness		√	

In addition to checking with your doctor, if these serious side effects occur, stop taking this medication.

This is not a complete list of side effects. For any unexpected effects while taking SUPER STRENGTH MOTRIN® IB LIQUID GELS, contact your doctor or pharmacist.

HOW TO STORE IT

Store at room temperature (15-30°C). Protect from heat and humidity.

Caution: Keep out of reach of children. This package contains enough medicine to seriously harm a child.

Do not keep outdated medicine or medicine no longer needed.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 0701D
    Ottawa, ON KIA OK9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

For more information, please contact your doctor, pharmacist or other healthcare professional. This leaflet plus the full product monograph, can be obtained by request at www.motrin.ca or by contacting McNeil Consumer Healthcare at:

McNeil Consumer Healthcare
Division of Johnson & Johnson Inc.
Markham, Canada
L3R 5L2

? 1 888 6MOTRIN / 1 888 666-8746

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