

PRODUCT MONOGRAPH

IBUPROFEN CAPSULES, 400 mg (free acid and potassium salt)

Therapeutic Classification

Analgesic/Antipyretic

Manufactured by:
Banner Pharmacaps Inc.
4125 Premier Drive
High Point, North Carolina
USA 27265

Date of Preparation:
December 13 2016

Manufactured for:
Bionpharma Inc.,
600 Alexander Road, Suite 2-4B
Princeton, New Jersey
USA 08540

Control No.: 196373

Table of Contents

PART I: HEALTH PROFESSIONAL INFORMATION.....	3
SUMMARY PRODUCT INFORMATION	3
INDICATIONS AND CLINICAL USE.....	3
CONTRAINDICATIONS	4
WARNINGS AND PRECAUTIONS.....	5
ADVERSE REACTIONS.....	10
DRUG INTERACTIONS	13
DOSAGE AND ADMINISTRATION	16
OVERDOSAGE	17
ACTION AND CLINICAL PHARMACOLOGY	18
STORAGE AND STABILITY.....	20
SPECIAL HANDLING INSTRUCTIONS	20
DOSAGE FORMS, COMPOSITION AND PACKAGING	20
PART II: SCIENTIFIC INFORMATION	21
PHARMACEUTICAL INFORMATION.....	21
CLINICAL TRIALS	22
DETAILED PHARMACOLOGY	25
MICROBIOLOGY	26
TOXICOLOGY	26
REFERENCES	29
PART III: CONSUMER INFORMATION.....	37

IBUPROFEN CAPSULES, 400 mg
(free acid and potassium salt)

PART I: HEALTH PROFESSIONAL

INFORMATION SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
oral	Capsule/ 400 mg	<i>For a complete listing see Dosage Forms, Composition and Packaging section.</i>

INDICATIONS AND CLINICAL USE

Ibuprofen Capsules, 400 mg are indicated for:

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

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. In studies using ibuprofen 400 mg tablets in the dental impaction pain model, the median time to confirmed perceptible pain relief ranged from 24 to 48 minutes after dosing, and the median time to use of rescue medication, ranged from 5.7 to 10.1 hours.^{26-27, 122-129}

Geriatrics (> 65 years of age): Evidence from clinical studies and experience suggests that use in the geriatric population is associated with differences in safety or effectiveness and a brief discussion can be found in the appropriate sections (See **WARNINGS AND PRECAUTIONS**).

Pediatrics (< 12 years of age): Ibuprofen Capsules, 400 mg is not indicated for children <12 years of age.

CONTRAINDICATIONS

- Active peptic ulcer, a history of recurrent ulceration or active inflammatory disease of the gastrointestinal system.
- Known or suspected hypersensitivity to the drug or other non-steroidal anti-inflammatory drugs. Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph. The potential for cross- reactivity between different NSAIDs must be kept in mind.
- Ibuprofen Capsules, 400 mg 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 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.
- Significant hepatic impairment or active liver disease.
- 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.
- 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.
- Children with kidney disease and children who have suffered significant fluid loss due to vomiting, diarrhea or lack of fluid intake, should not be given ibuprofen.
- Ibuprofen should not be used during pregnancy or by nursing mothers.
- 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.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- Use with caution in patients with heart failure, hypertension or other conditions predisposing to fluid retention (See *WARNINGS AND PRECAUTIONS, Cardiovascular and Fluid and Electrolyte Balance; and DRUG INTERACTIONS, Antihypertensives*).
- Caution in patients prone to gastrointestinal tract irritation, including those with a history of peptic ulcer (See *WARNINGS AND PRECAUTIONS, Gastrointestinal DRUG INTERACTIONS, Coumarin-type anticoagulants*).
- Patients at greatest risk of renal toxicity are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and the elderly (See *WARNINGS AND PRECAUTIONS, Renal*).
- If urinary symptoms, hematuria and cystitis occur, the drug should be stopped immediately (See *WARNINGS AND PRECAUTIONS, Genitourinary*).
- Ibuprofen use during pregnancy/nursing should be avoided (See *WARNINGS AND PRECAUTIONS, Special Populations: Pregnant Women and Nursing Women*).

General

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

Carcinogenesis and Mutagenesis

Not applicable.

Cardiovascular

Use of ibuprofen may precipitate congestive heart failure in patients with marginal cardiac function, elevated blood pressure and palpitations.

Dependence/Tolerance

Not applicable.

Ear/Nose/Throat

Patients with complete or partial syndrome of nasal polyps should not use Ibuprofen Capsules, 400 mg (See *CONTRAINDICATIONS*).

Endocrine and Metabolism

Not applicable.

Fluid and Electrolyte Balance

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.

Ibuprofen Capsules, 400 mg 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

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.

Ibuprofen Capsules, 400 mg 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, Ibuprofen Capsules, 400 mg 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 Ibuprofen Capsules, 400 mg 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 Ibuprofen Capsules, 400 mg must be stopped immediately to obtain recovery. This should be done before any urological investigations or treatments are carried out.

Hematologic

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 liverdisease.

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.

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.

Peri-Operative Considerations

Not applicable.

Psychiatric

See *Warnings and Precautions, Neurologic*.

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, utilization of lower doses of Ibuprofen Capsules, 400 mg should be considered and patients carefully monitored. During long-term therapy kidney function should be monitored periodically

Respiratory

Not applicable.

Sensitivity/Resistance

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

Sexual Function/Reproduction

Not applicable.

Skin

Not applicable.

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.

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

Geriatrics (> 65 years of age): Patients older than 65 years and frail or debilitated patients are most susceptible to a variety of adverse reactions from nonsteroidal anti-inflammatory drugs (NSAIDs): the incidence of these adverse reactions increases with dose and duration of treatment. In addition, these patients are less tolerant to ulceration and bleeding. Most reports of fatal GI events are in this population. 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.

Monitoring and Laboratory Tests

For Monitoring and Laboratory Tests related to the use of Ibuprofen Capsules, 400 mg see

WARNINGS AND PRECAUTIONS, Fluid and Electrolyte Balance, Gastrointestinal, Hematologic, Hepatic, Renal and Special populations: Geriatrics.

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

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

Post-Market Adverse Drug 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 (See *WARNINGS AND PRECAUTIONS*).

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 recognize 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 non-prescription 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 $\geq 1\%$ 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, non-prescription ibuprofen at the maximum dose of 1200 mg/day for 10 days, is well-tolerated.

In two multi-trial 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 randomized trial⁹⁷ comparing non-prescription doses of acetylsalicylic acid, acetaminophen, and ibuprofen in 8677 adults found that the rates of significant adverse reactions were: aspirin 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 aspirin (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

Serious Drug Interactions

- With acetaminophen may increase the risk of adverse renal effect.
- With acetylsalicylic acid (ASA) or other NSAIDs, may result in possible additive side effects (See *CONTRAINDICATIONS*).
- With anticoagulants may increase the risk of GI adverse events (*e.g.*, ulceration and bleeding).
- With antihypertensives the benefit and risk must be weighed individually.
- With digoxin may increase serum digoxin concentration and the risk of digoxin toxicity.
- With diuretics may reduce the diuretic effect.
- With hypoglycaemic agents (oral agents and insulin) may increase the risk of hypoglycaemia.
- With lithium may elevate plasma lithium levels, reduce renal lithium clearance and increase the risk of lithium toxicity.
- With methotrexate may increase the risk of methotrexate toxicity.

Overview

Ibuprofen Capsules, 400 mg is not recommended for concomitant use with any other NSAIDs, including ASA. Documented or possible drug interactions with ibuprofen include acetaminophen, digoxin, anticoagulants, oral antidiabetic agents and insulin, antihypertensives, diuretics, methotrexate, lithium and other protein-bound drugs.

Drug-Drug Interactions

Acetaminophen Although interactions have not been reported, concurrent use with ibuprofen is not advisable: it may increase the risk of adverse renal effect.

Acetylsalicylic acid (ASA) or other NSAIDs

The use of ibuprofen in addition to any other NSAID, including ASA, is not recommended due to the possibility of additive side effects. Animal studies show that aspirin given with NSAIDs, including ibuprofen, yields a net decrease in anti-inflammatory activity with lowered blood levels of the non-aspirin drug. Single-dose bioavailability studies in normal volunteers have failed to show an effect of aspirin on ibuprofen blood levels. Correlative clinical studies have not been conducted.

No clinically meaningful loss of cardioprotection was observed, when patients on low dose ASA (81 mg) were administered 400 mg ibuprofen T.I.D.¹¹³

Acetylsalicylic acid (ASA) Low Dose

Ibuprofen can interfere with the anti-platelet effect of low-dose ASA (81 - 325 mg per day). Long-term daily use of ibuprofen may render ASA less effective when used for cardioprotection and stroke prevention. 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.

Antacids⁸⁴

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.

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 al⁷⁹ showed that ibuprofen 1600 mg/day for 14 days did not attenuate the antihypertensive effect of two β -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 hydrochlorothiazide and fosinopril who received ibuprofen 2400 mg/day for one month.⁸² In contrast, Minuz⁸³ 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.

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 Ibuprofen Capsules, 400 mg to patients on anticoagulants.

Digoxin⁷⁴

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.

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.

H-2 2 antagonists

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

Hypoglycaemic Agents

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

Lithium⁸⁶

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.

Methotrexate⁸⁵

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.

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, antibiotics (e.g. cyclosporine), phenytoin, corticosteroids or benzodiazepines.

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herbs have not been established.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

Drug-Lifestyle-Interactions

No lifestyle parameters are suggested for the use of Ibuprofen Capsules, 400 mg.

DOSAGE AND ADMINISTRATION

Dosing Considerations

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

The safety issues to consider when developing a dosage regimen of Ibuprofen Capsules, 400 mg for individual patients is applicable to:

- Elderly patients older than 65 years who are frail or debilitated and consideration should be given to a starting dose lower than the one usually recommended (See *WARNINGS AND PRECAUTIONS, Elderly*).

Recommended Dose and Dosage Adjustment

Ibuprofen Capsules, 400 mg:

Adults and Children over 12: Take 1 Ibuprofen Capsule, 400 mg every 6-8 hours as needed. Do not exceed 3 Ibuprofen Capsules, 400 mg in 24 hours, unless directed by a physician.

Capsules should be swallowed whole. DO NOT open, divide, crush or chew the capsules.

Missed Dose

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

Administration

See *Recommended Dose and Dosage Adjustment*.

OVERDOSAGE

Symptoms of Overdose¹⁰²⁻¹⁰⁴

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 has 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.

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

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 catalyzing the committed step in prostaglandin biosynthesis is prostaglandin endoperoxide synthase, also known 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, 400 mg contain solubilized ibuprofen which has peak serum concentrations within 36-42 minutes. In 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 Nahata⁶ found a time to peak concentration of 1.1 and 1.2 hours for these respective doses. A similar study in febrile children by Walson⁷ 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 $\mu\text{g/mL}$ 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

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., $1\mu\text{g/mL}$) 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.

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-hydroxyl-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.

STORAGE AND STABILITY

Ibuprofen Capsules, 400 mg should be stored in tightly-closed containers under room temperature (15°C-30°C) conditions. Protect from Moisture

SPECIAL HANDLING INSTRUCTIONS

Not applicable.

DOSAGE FORMS, COMPOSITION AND PACKAGING

For Adults:

Each colourless oval liquid filled soft gelatin capsule, imprinted with 400 in black ink, contains 400 mg ibuprofen as free acid and potassium salt.

Ibuprofen Capsules 400 mg are available in several package sizes between 12 and 200 capsules in HDPE bottles with child resistant lids.

Ibuprofen Capsules 400 mg *Non-medicinal ingredients*: Gelatin, iron oxide black, lecithin, medium chain triglycerides, polyethylene glycol, potassium hydroxide, propylene glycol, purified water, sorbitan, sorbitol.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

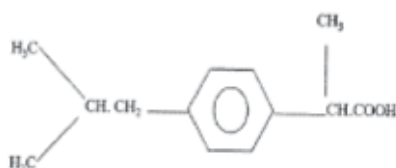
Proper name: Ibuprofen

Chemical name: α -methyl-4-(2-methylpropyl) benzene acetic acid

Other names: p-isobutylyhydratropic acid
2-(isobutylphenyl)-propionic acid

Molecular formula and molecular mass: $C_{13}H_{18}O_2$; 206.28 g/mol

Structural formula:



Physicochemical properties: White or almost white powder or crystals with a characteristic odour.

Low solubility in water (<1.0 mg/mL), 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.
pKa: 4.43

Melting Point: 75 - 77°C

CLINICAL TRIALS

Comparative Bioavailability Studies (fasting, randomized, single-dose 2-way crossover, in healthy volunteers)

A randomized, single dose, cross-over comparative bioavailability study of Ibuprofen Capsules 400 mg liquid filled soft gelatin capsules (manufactured by Banner Pharmacaps Inc.) *versus* Advil® Extra Strength Liqui- Gels® Liquid-Fast® Migraine Relief capsules (Wyeth Consumer Healthcare Inc.) in 26 healthy adult male and female volunteers was conducted under fasting conditions. See the table below for the comparative bioavailability data.

Ibuprofen (1 x 400 mg) From measured data Geometric Mean Arithmetic Mean (CV %)
--

Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval
AUC _T (µg-hr/mL)	117.26 121.56 (27.44)	116.59 120.05 (23.00)	100.58	(96.52, 104.81)
AUC _{Refmax} (µg-hr/mL)	147.17 195.46 (67.88)	136.55 157.57 (55.87)	107.78	(88.35, 131.48)
AUC _I (µg-hr/mL)	119.82 124.25 (27.82)	120.22 123.82 (23.20)	99.66	(95.66, 103.83)
C _{MAX} (µg-hr/mL)	424.37 440.17 (26.78)	387.61 408.98 (33.47)	109.48	(100.14, 119.69)
T _{MAX} § (h)	0.76 (49.55)	0.92 (55.82)		
T _{1/2} § (h)	2.16 (13.44)	2.28 (16.73)		

* Ibuprofen Capsules 400 mg liquid filled soft gelatin capsules.

† ADVIL® 400 mg Liqui-Gel Capsules, Wyeth Consumer Healthcare, purchased in Canada.

§ Expressed as the arithmetic mean (CV%) only.

Published Literature

Published studies have documented the efficacy of 200-mg and 400-mg doses of ibuprofen in treating mild to moderate pain, including sore throat pain¹¹³, headache^{114,115} and muscle aches¹¹⁶ in adults. The antipyretic efficacy of ibuprofen has been demonstrated in adults at doses of 200 and 400 mg¹¹⁷⁻¹¹⁹.

Study Results

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

Multiple published studies have demonstrated the efficacy of ibuprofen 400 mg compared to placebo, several different Cyclooxygenase 2 (COX-2) inhibitors, and other NSAIDs in the treatment of patients with moderate or severe pain following the extraction of two or more third molar teeth.^{26-27, 122-129}

The results of the trials utilized the primary end points of total pain relief at 8 hours (TOTPAR8)^{122-124, 127, 128}, Pain Intensity Difference (PID)^{26, 125}, and Sum of Pain Intensity Differences (SPID)^{27, 126-127, 129} as pain relief measures. Duration of effect was assessed using the median or mean time (hours) to use rescue medication. Global evaluation of pain relief at 8 hours was also used with subjects asked to report their level of pain relief after 8 hours.

The duration of effect was 8 hours (range from 6 to 10 hours).

In four similar randomized, single dose, placebo and active comparator controlled, parallel group studies, the analgesic efficacy of ibuprofen 400 mg was compared to placebo and various COX-2 inhibitors at different doses^{122-124, 128} when treating postoperative dental pain. The studies established that ibuprofen 400 mg had median duration of effect (in hours) of 8.9, 10.0, 10.1, and 6.1, respectively, while placebo's median duration of effect was 1.5, 1.6, 2.1 and 2.4, respectively. In all 4 studies, the pain relief measure of TOTPAR8 revealed ibuprofen 400 mg to be statistically significantly superior to placebo with $p < 0.001$. In three of the studies, the global evaluation of pain relief at 8 hours was reported and 73%, 74%, and 78% of the ibuprofen 400 mg patients reported good, very good or excellent pain relief after 8 hours compared to 19%, 7%, and 19% of placebo patients. Median time to onset of pain relief (minutes) was also proven to be statistically significantly different to placebo (>240 minutes) compared to the Ibuprofen 400 mg patients (24, 30, 30 minutes, respectively)¹²²⁻¹²⁴.

In another randomized, single dose, double blind placebo and active comparator controlled, parallel group study, the analgesic efficacy of lumiracoxib 100 (n=51) and 400 mg (n=50) was compared with ibuprofen 400 mg (n=51) and placebo (n=50). The primary endpoint was PID and the secondary measures included time to onset of analgesia and duration of effect. The results showed the PID scores for ibuprofen 400 mg were statistically superior to placebo across

all time points from 1 to 12 hours¹²⁵. Median time to onset of pain relief was 12 hours or more for placebo, 41.5 minutes for ibuprofen, which was statistically significantly different versus placebo. The duration of effect were ~2 hours placebo and ibuprofen ~8 hours (p<0.001 vs. placebo)¹²⁵.

Several other randomized, single dose, double blind placebo and active comparator controlled, parallel group studies, the analgesic efficacy of ibuprofen 400mg was compared to placebo and various NSAIDs. The studies reported that the duration of analgesic effect, as measured by the median time to use of rescue medication, was 8.5, 5.7, 6.3, 6 and 5.8 hours in patients taking 400mg ibuprofen while placebo duration of analgesic effect was 4.5, 2.8, 2.7, 1.1, 1.4 hours, respectively. The studies utilized either PID, SPID or pain relief combined with pain intensity difference (PRID) pain relief measures. The results all showed that Ibuprofen 400mg groups were statistically significantly different at 8 hours versus placebo (p<0.05).^{26-27, 126-127, 129}

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

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 A third double-blind, randomized study confirmed that ibuprofen 400 mg provided significantly faster onset of relief as measured by first perceptible relief, percent attaining complete relief, and superior overall analgesic efficacy compared to acetaminophen 1000 mg for relief of episodic tension-type headache.²²

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 fever.³⁸⁻⁴⁰

Pain of Osteoarthritis

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.¹²⁰⁻¹²¹ These studies support an indication for the relief of pain from inflammation associated with conditions including:

- arthritis
- physical or athletic overexertion (e.g. sprains or strains).

Sore Throat Pain

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

Ibuprofen has also been studied in other pain models including migraine¹¹³⁻¹¹⁹ with equally effective pain relief results.

DETAILED PHARMACOLOGY

Animal Pharmacology

After single oral doses of 20 to 150 mg/kg of C¹⁴ 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

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 A₂ (TXA₂), are important factors in normal platelet aggregation. Cyclooxygenase inhibition reduces TXA₂ 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 TXA₂ synthesis inhibition is involved in this effect.

Human Pharmacology

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 as 2-(2-hydroxy-2-methylpropyl)phenylpropionic acid (metabolite A) and 2-(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

Effect of Ibuprofen on Platelet Aggregation, Bleeding and Clotting Times in Normal Volunteers

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. 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 be made for regular ibuprofen use, and no clinically relevant effect is considered to be likely for occasional ibuprofen use.

MICROBIOLOGY

Not applicable.

TOXICOLOGY

Single Dose Toxicity Studies

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

The LD₅₀ 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 were 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.

Carcinogenic Potential

Thirty male and thirty 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 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 clycopia. 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 Fetus

Rabbits and rats in late pregnancy were given single oral doses of 60 and 20 mg/kg respectively of C¹⁴ 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

REFERENCES

1. Insel, PA. Analgesic-antipyretic and anti-inflammatory agents and drugs employed in the treatment of gout. In Molinoff PB, Ruddon RW, editors. Goodman & Gilman's The Pharmacological Basis of Therapeutics. New York: McGraw-Hill, 1996:617-657.
2. Nozu K: Flurbiprofen: Highly potent inhibitor of prostaglandin synthesis. *Biochim Biophys Acta* 1978; 529: 493-496.
3. Moncada S, Vane JR: Mode of action of aspirin-like drugs. *Intern Med* 1979; 24: 1-22.
4. Adams SS, Buckler JW: Ibuprofen and flurbiprofen. *Clinics Rheum Dis* 1979; 5: 359-379.
5. Brown RD, Wilson JT, Kearns GL, Eichler VF, Johnson VA, Bertrand KM: Single-dose pharmacokinetics of ibuprofen and acetaminophen in febrile children. *J Clin Pharmacol* 1992; 32: 231-241.
6. Nahata MC, Durrell DE, Powell DA, Gupta N: Pharmacokinetics of ibuprofen in febrile children. *Eur J Clin Pharmacol* 1991; 40: 427-428.
7. Walson PD, Galletta G, Braden NF, Alexander L. Ibuprofen, acetaminophen, and placebo treatment of febrile children. *Clin Pharmacol Ther* 1989;46:9-17.
8. Davies NM: Clinical pharmacokinetics of ibuprofen. The first 30 years. *Clin Pharmacokinet* 1998; 34: 101-154.
9. Rudy AC, Knight PM, Brater DG, Hall SD: Enantioselective disposition of ibuprofen in elderly persons with and without renal impairment. *J Pharmacol Exp Ther* 1995; 273: 88-93.
10. Mills RFN, Adams SS, Cliffe EE, et al: The metabolism of ibuprofen. *Xenobiotica* 1973; 3(9):589.
11. Giachetti C, Zanolo G, Canali S: Topical administration of ibuprofen in man. Simultaneous determination of the drug and its metabolites in urine by high resolution gas chromatography. *J High Res Chromatogr Commun* 1985; 8: 465-468.
12. Brooks CJW, Gilbert MT: Studies of urinary metabolites of 2-(4-isobutylphenyl)propionic acid by gas-liquid chromatography-mass spectrometry (GC-MS). *J Chromatogr* 1974; 99: 541-551.
13. Leeman TD, Tanson C, Bonnabry C, Dayer P: A major role for cytochrome P450_{TB} (CYP2C subfamily) in the actions of non-steroidal anti-inflammatory drugs. *Drugs Exp Clin Res* 1993; 19: 189-195.
14. Dollery C: Ibuprofen. In *Therapeutic Drugs*, 1st ed, Churchill Livingstone, 11-14. 1991.
15. Albert KS, Gillespie WR, Wagner JG, Pau A, Lockwood GF: Effects of age on the clinical pharmacokinetics of ibuprofen. *Am J Med* 1984; 77: 47-50.
16. Walson PD: Ibuprofen versus paracetamol for the treatment of fever in children. *Br J Clin Pract* 1990; 70: 19-21.
17. Albert KS, Gernaat RN: Pharmacokinetics of ibuprofen. *Am J Med* 1984; 77: 40-46.
18. Walter K, Dilger C: Ibuprofen in human milk. *Br J Pharmacol* 1997; 44: 211-212.
19. Schachtel BP, Fillingim JM, Thoden WR, Lane AC, Baybutt RI: Sore throat pain in the evaluation of mild analgesics. *Clin Pharmacol Ther* 1988; 44: 704-711.
20. Schachtel BP, Furey SA, Thoden WR: Nonprescription ibuprofen and acetaminophen in the treatment of tension-type headache. *J Clin Pharmacol* 1996; 36: 1120-1125.

21. Schachtel BP, Thoden WR: Onset of action of ibuprofen in the treatment of muscle-contraction headache. *Headache* 1988; 28:471-474.
22. Packman EW, Doyle G, Koronkiewicz K, Jayawardena S, Cooper SA: Onset of analgesia of ibuprofen liquisgels (400 mg) compared to acetaminophen caplets (1000 mg) in the treatment of tension headache. *J Clin Pharmacol* 1998; 38: 876.
23. Cooper SA, Schachtel BP, Goldman E, Gelb S, Cohn P: Ibuprofen and acetaminophen in the relief of acute pain: A randomized, double-blind, placebo-controlled study. *J Clin Pharmacol* 1989; 29: 1026-1030.
24. Cooper SA: The relative efficacy of ibuprofen in dental pain. *Compend Contin Educ Dent* 1986; 7(8): 578-597
25. Forbes JA, Kehm CJ, Grodin CD, Beaver WT: Evaluation of ketorolac, ibuprofen, acetaminophen and an acetaminophen –codeine combination in post-operative oral surgery pain. *Pharmacotherapy* 1990; 10:94S-105S.
26. Forbes JA, Edquist IA, Smith FG, Schwartz MK, Beaver WT: Evaluation of bromfenac, aspirin, and ibuprofen in postoperative oral surgery pain. *Pharmacotherapy* 1991; 11: 64-70.
27. Forbes JA, Beaver WT, Jones KF, Edquist IA, Gongloff Cm, Smith WK, Smith FG, Schwartz MK: Analgesic efficacy of bromfenac, ibuprofen, and aspirin in postoperative oral surgery pain. *Clin Pharmacol Ther* 1992; 51:343-352.
28. Jain AK, Ryan JR, McMahon FG, Kuebel JO, Walters PG, Noveck C: Analgesic efficacy of low-dose ibuprofen in dental extraction pain. *Pharmacotherapy* 1986; 6: 318-322.
29. Mehlisch DR, Sollecito WA, Helfrick JF, Leibold DG, Marcowitz R, Schow CE, Schultz R, Waite DE: multicenter clinical trial of ibuprofen and acetaminophen in the treatment of post-operative dental pain. *J Am Dent Assoc* 1990; 121: 257-263.
30. Ngan P, Wilson S, Shanfeld JS, Amini H: The effect of ibuprofen on the level of discomfort in patients undergoing orthodontic treatment. *Am J Orthodon Dent Orthop* 1994; 106: 88-95.
31. Braun RP, Lockhart EA, Bruno P: Delayed-onset muscle soreness (DOMS)- a new pain model to compare OTC analgesics. *Med Sci Sports Exer* 1994; 26: S14.
32. Corson SL and Bolognese RJ: Ibuprofen therapy for dysmenorrhea. *J Reprod Med* 1978;20(5):246-252.
33. Dawood MY: Over-the-counter (OTC) analgesics for the relief of menstrual cramps. *J Clin Pharmacol* 1994; 34: 1014.
34. Shapiro SS and Diem K: The effect of ibuprofen in the treatment of dysmenorrhea. *Curr Ther Res* 1981; 30(3):327-334.
35. Larkin RM, Van Orden DE, Poulson AM, et al: Dysmenorrhea: Treatment with an antiprostaglandin. *Obstet and Gynecol* 1979; 54(4):456-460.
36. Milsom I, Andersch B: Effect of ibuprofen, naproxen sodium, and paracetamol on intrauterine pressure and menstrual pain in dysmenorrhea. *Br J Obstet Gynaecol* 1984; 91: 1129-1135.
37. Morrison JC, Long FW, Forman EK, et al: Analgesic efficacy of ibuprofen for treatment of primary dysmenorrhea. *South Med J* 1980; 73(8):999-1002.
38. Minor MG, Schachtel BP: Antipyretic efficacy of ibuprofen 200 mg in adults with acute upper respiratory tract infection (URI). *J Clin Pharmacol* 1990; 30: 846.

39. Jain AK, Vargas R, McMahon FG: The antipyretic effect of over-the-counter dosages of aspirin, acetaminophen and ibuprofen in endotoxin-induced fever. *Clin Pharmacol Ther* 1993; 53: 153.
40. Thoden WR, Lockhart EA: Antipyretic efficacy of ibuprofen and naproxen in flu-like upper respiratory illness. *J Clin Pharmacol* 1995; 35: 929.
41. Czaykowski D, Fratarcangelo P, Rosefsky J: Evaluation of the antipyretic efficacy of single dose ibuprofen suspension compared to acetaminophen elixir in children. *Pediatr Res* 1994; 35: 141A.
42. Kauffman RE, Sawyer LA, Scheinbaum ML: Antipyretic efficacy of ibuprofen vs acetaminophen. *AJDC* 1992; 146: 622-625.
43. Kauffman RE, Nelson MV: effect of age on ibuprofen pharmacokinetics and antipyretic response. *J Pediatr* 1992; 121: 969-973.
44. Nahata MC, Powell DA, Durrell DE, Miller MA: Efficacy of ibuprofen in pediatric patients with fever. *Int J Clin Pharmacol Ther Toxicol* 1996; 30: 94-96.
45. Walson PD, Galletta G, Chomilo F, Braden NJ, Sawyer LA, Scheinbaum ML: Comparison of multidose ibuprofen and acetaminophen therapy in febrile children. *AJDC* 1992; 146: 626-632.
46. Aksoylar S, Aksit S, Caglayan S, Yaprak I, Bakiler R, Cetin F: Evaluation of sponge and antipyretic medication to reduce body temperature in febrile children. *Acta Paediatr* 1997; 39: 215-217.
47. Autret E, Breart G, Jonville AP, Courcier S, Lasalle C, Goehrs JM: Comparative efficacy and tolerance of ibuprofen syrup and acetaminophen syrup in children with pyrexia associated with infectious diseases and treated with antibiotics. *Eur J Clin Pharmacol* 1994; 46: 197-201.
48. Autret E, Reboul-Marty J, Henry-Launois B, Laborde C, Courcier S, Goehrs JM, Languilat G, Launois R: Evaluation of ibuprofen versus aspirin and paracetamol on efficacy and comfort in children with fever. *Eur J Clin Pharmacol* 1997; 51: 367-371.
49. Joshi YM, Sovani VB, Joshi VV, Navrange JR, Benakappa DG, Shivananda P, Sankaranarayanan VS: Comparative evaluation of the antipyretic efficacy of ibuprofen and paracetamol. *Indian Pediatr* 1990; 27: 803-806.
50. Kauffman RE, Sawyer LA, Scheinbaum ML: Antipyretic efficacy of ibuprofen vs. acetaminophen. *Am J Dis Child* 1992; 146: 622-625.
51. Kelley MT, Walson PD, Edge JH, Cox S, Mortensen ME: Pharmacokinetics and pharmacodynamics of ibuprofen isomers and acetaminophen in febrile children.
52. Khubchandani RP, Ghatikar KN, Keny S, Usgaonkar NGS: Choice of antipyretic in children. *J Assoc Physicians India* 1995; 43: 614-616.
53. Marriott SC, Stephenson TJ, Hull D, Pownall R, Smith CM, Butler AA: A dose ranging study of ibuprofen suspension as an antipyretic. *Arch Dis Child* 1991; 66: 1037-1042.
54. McIntyre J, Hull D: Comparing efficacy and tolerability of ibuprofen and paracetamol in fever. *Arch Dis Child* 1996; 74: 164-167.
55. Nahata MC, Powell DA, Durrell DE, Miller MA, Gupta A: Efficacy of ibuprofen in pediatric patients with fever. *Int J Clin Pharmacol Ther Toxicol* 1992; 30: 94-96.
56. Sidler J, Frey B, Baerlocher K: A double-blind comparison of ibuprofen and paracetamol in juvenile pyrexia. *Br J Clin Pract* 1991; 70: 22-25.

57. Starha J, Coupek P, Kopecna L, Brazdova L, Vintrova O: Ibuprofen as an antipyretic drug in childhood. *Cesko Slov Pediatr* 1994; 49:424-427.
58. Van Esch A, Van Steensel-Moll HA, Steyerberg EW, Offringa M, Habbema JDF, Derksen-Lubsen G: Antipyretic efficacy of ibuprofen and acetaminophen in children with febrile seizures. *Arch Pediatr Adolesc Med* 1995; 149:632-637.
59. Vauzelle-Kervroedan F, d'Athis P, Pariente-Khayat A, Debregeas S, Olive G, Pons G: Equivalent antipyretic activity of ibuprofen and paracetamol in febrile children. *J Pediatr* 1997; 131: 683-687.
60. Walson PD, Galletta G, Chomilo F, Braden NJ, Sawyer LA, Scheinbaum ML: Comparison of multidose ibuprofen and acetaminophen therapy in febrile children. *Am J Dis Child* 1992; 146: 626-632.
61. Wilson JT, Brown RD, Kearns GL, Eichler VF, Johnson VA, Bertrand KM, Lowe BA: Single-dose placebo-controlled comparative study of ibuprofen and acetaminophen in children. *J Pediatr* 1991; 119: 803-811.
62. Lockhart EA, Thoden WR, Furey SA, Schachtel BP: Ibuprofen and streptococcal sore throat pain in children. *Clin Pharmacol Ther* 1993; 53: 147.
63. Schachtel BP, King SA, Thoden WR: Pain relief in children; A placebo-controlled model. *Clin Pharmacol Ther* 1991; 49: 154.
64. Schachtel BP, Thoden WR: A placebo-controlled model for assaying systemic analgesics in children. *Clin Pharmacol Ther* 1993; 53:593-601.
65. Schachtel BP, Thoden WR: Assaying analgesic response in children: A double-blind, placebo-controlled model involving earache. *Pediatr Res* 1991; 29: 124A.
66. Bertin L, Pons G, d'Athis P, Duhamel JF, Maudelonde C, Lasfargues G, Guillot M, Marsac A, Debregeas B, Olive G: A randomized, double-blind, multicentre controlled trial of ibuprofen versus acetaminophen and placebo for symptoms of acute otitis media in children. *Fund Clin Pharmacol* 1996; 10:387-392.
67. Hamalainen MJ, Hoppu K, Valkeina E, Santavuori P: Ibuprofen or acetaminophen for the acute treatment of migraine in children: A double-blind, randomized, placebo-controlled, crossover study. *Neurology* 1997; 48: 103-107.
68. Greene JJ, Brown SR, Romeo DA, Schachtel BP: Efficacy and safety of ibuprofen (10 mg/kg) (IBU), acetaminophen (15 mg/kg) (APAP) and placebo (PBO) in the relief of orthodontic pain in children. *J Clin Pharmacol* 1995; 35: 929.
69. Diez-Domingo J, Planelles MV, Baldo JM, Ballester A, Nunez F, Jubert A, Dominguez-Granados R: Ibuprofen prophylaxis for adverse reactions to diphtheria-tetanus-pertussis vaccination: a randomized trial. *Curr Ther Res* 1998; 59: 579-588.
70. Bertin L, Pons G, d'Athis P, Lasfargues G, Maudelonde C, Duhamel JF, Olive G: Randomized, double-blind, multicenter, controlled trial of ibuprofen versus acetaminophen (paracetamol) and placebo for treatment of symptoms of tonsillitis and pharyngitis in children. *J Pediatr* 1991; 119:811-814.
71. St. Charles CS, Matt BH, Hamilton MM, Katz BP: A comparison of ibuprofen versus acetaminophen with codeine in the young tonsillectomy patient. *Otolaryngol Head Neck Surg* 1997; 117: 76-82.
72. Lohokare SK, Jog V: Comparative study of suspensions of ibuprofen and paracetamol in soft tissue injuries in children. *J Pain Symp Mgmt* 1991; 6: 158.

73. Garcia Rodriguez LA, Williams R, Derby LE, Dean AD, Herschel J: Acute liver injury associated with non-steroidal anti-inflammatory drugs and the role of risk factors. *Arch Intern Med* 1994; 154: 311-316.
74. Jorgenson HS, Christensen HR, Kampmann JP: Interaction between digoxin and indomethacin or ibuprofen. *Br J Clin Pharmacol* 1991; 31(1): 108-110.
75. Penner JA, Abbrecht PH: Lack of interaction between ibuprofen and warfarin. *Curr Ther Res* 1975;18:862-871.
76. Slattery JT, Levy G: Effect of ibuprofen on protein binding of warfarin in human serum. *J Pharm Sci* 1977-66:1060.
77. Johnson AG, Nguyen TV, Day RO: Do non-steroidal anti-inflammatory drugs affect blood pressure? *Ann Intern Med* 1994; 121: 289-300.
78. Pope JG, Anderson JJ, Felson DT: A meta-analysis of the effects of non-steroidal anti-inflammatory drugs on blood pressure. *Arch Intern Med* 1993; 153:477-484.
79. Davies JG, Rawlins DC, Busson M: Effect of ibuprofen on blood pressure control by propranolol and benzofluazide. *J Intern Med Res* 1988; 16: 173-181.
80. Houston MC, Weir M, Gray J, Ginsberg D, Szeto C, Kathleen PM, Sugimoto D, Lefkowitz M, Runde M: The effects of non-steroidal anti-inflammatory drugs on blood pressure of patients with hypertension controlled by verapamil. *Arch Intern Med* 1995; 155: 1049-1054.
81. Fommei E, Ghione S, Palla L, Ragazzini A, Gazzetti P, Palombo C, Giaconi S: Inhibition of prostaglandins and angiotensin II: Effects on renal function in hypertensive patients. *Agents Actions Suppl* 1987; 22: 183-189.
82. Cook ME, Wallin JD, Thakur VD, Kadowitz PJ, McNamara DB, Garcia MM, Lipani JJ, Poland M: Comparative effects of nabumetone, sulindac and ibuprofen on renal function. *J Rheumatol* 1997; 24: 1137-1144.
83. Minuz P, Lechi A, Arosio E, Degan M, Capuzzo MG, Lechi C, Corsato M, Dalla Riva A, Velo GP: antihypertensive activity of enalapril. Effect of ibuprofen and different salt intakes. *J Clin Hypertens* 1987; 3: 645-653.
84. Gontarz N, Small RE, Comstock TJ, Stalker DJ, Johnson SM, Willis BE: Effects of antacid suspension on the pharmacokinetics of ibuprofen. *Clin Pharm* 1987; 7(5):413-416.
85. Nierenberg DW: Competitive inhibition of methotrexate accumulation in rabbit kidney slices by non-steroidal anti-inflammatory drugs. *J Pharmacol Exper Ther* 1983;226(1):1-6.
86. Ragheb M, Alvin C: Ibuprofen can increase serum lithium in lithium treated patients. *J Clin Psychiatry* 1987; 48: 161-163.
87. Rainsford KD, Roberts SC, Brown S: Ibuprofen and paracetamol: relative safety in non-prescription dosages. *J Pharm Pharmacol* 1997; 49: 345-376.
88. Doyle G, Furey S, Berlin R, Cooper S, Jayawardena S, Ashraf E, Baird L: Gastrointestinal safety and tolerance of ibuprofen maximum over-the-counter use. *Aliment Pharmacol Ther* 1999; 13: 897-906.
89. Furey SA, Waksman JA, Dash BH: Nonprescription ibuprofen: side effect profile. *Pharmacotherapy* 1992; 12: 403-407.
90. DeArmond B, Francisco CA, Lin JS, Huang FY, Halladay S, Bartizek RD, Skare KL: Safety profile of over-the-counter naproxen sodium. *Clin Therap* 1995; 17: 587-601.

91. Kellstein DE, Waksman JA, Binstok G, Furey SA, Cooper SA: The safety profile of nonprescription ibuprofen in multiple-dose use: a meta-analysis. *J Clin Pharmacol* 1999;39: 520-532.
92. Rainsford KD, Quadir M: Gastrointestinal damage and bleeding from non-steroidal anti-inflammatory drugs. I. Clinical and 3epidemiological aspects. *Inflammopharmacology* 1995; 3: 169-190.
93. Strom BL: Gastrointestinal tract bleeding associated with naproxen sodium vs ibuprofen. *Arch Intern Med* 1997; 157: 2636-2631.
94. Gutthann SA, Garcia-Rodriguez LA, Duque-Oliart A, Varas-Lorenzo C: Low-dose diclofenac, naproxen, and ibuprofen cohort study. *Pharmacoepidemiology* 199; 19: 854-859.
95. Committee on Safety of Medicines (CSM) Update: Non-steroidal anti-inflammatory drugs and serious gastrointestinal adverse reactions. *Br Med J* 1986; 2:292.
96. Ewell A, Toth F, Wolfe B, Perelson A, Paul K: Thirteen year secular trend analysis of manufacturer-received Advil[®] spontaneous adverse experience reports. *Pharmacoepidemiol Drug Safety* 1998; 7: S101.
97. Moore N, Van Ganse E, Le Parc JM, Wall R, Schneid H, Farhan M, Verriere F, Pelen F: The PAIN study: paracetamol, aspirin and ibuprofen new tolerability study. *Clin Drug Invest* 1999; 18: 89-98.
98. Ashraf E, Ford, L, Geetha R, Cooper S: Safety profile of ibuprofen suspension in young children. *Inflammopharmacology* 1999, in press.
99. Lesko SM, Mitchell AA: An assessment of the safety of pediatric ibuprofen. 1995; 273(12): 929-933.
100. Lesko SM, Mitchell AA: Renal function after short-term ibuprofen use in infants and children. *Pediatrics* 1997; 100: 954-957.
101. Lesko SM, Mitchell AA: The safety of acetaminophen and ibuprofen among children less than two years old. *Pediatrics* 1999 104 (4): 39-49.
102. Jenkinson ML, Fitzpatrick R, Streete PJ, Volans GN: The relationship between plasma ibuprofen concentrations and toxicity in acute ibuprofen overdose. *Human Toxicol* 1988; 7:319-324.
103. McElwee NE, Veltri JC, Bradford DC, Rollins DE: A prospective, population-based study of acute ibuprofen overdose: Complications are rare and routine serum levels not warranted. *Ann Emerg Med* 1990; 19: 657-662.
104. Veltri JC, Rollins DE: A comparison of the frequency and severity of poisoning cases for ingestion of acetaminophen, aspirin, and ibuprofen. *Am J Emerg Med* 1988; 6: 104-107.
105. Adams SS, Bough RG, Cliffe EE, Lessel B, Mills RFN: Absorption, distribution and toxicity of ibuprofen. *Toxicol Appl Pharmacol* 1969; 15: 310-330.
106. Lillehei TJ, Metke MP, Dawnajee MK, Tago M, Lim MF, Kaye MP: Reduction of platelet deposition in aorto-coronary artery Gore-Tex bypass grafts in dogs by platelet inhibitors. *Circulation* 1980; 62: Suppl 3;53.
107. Dipasquale G, Mellace D: Inhibition of arachidonic acid induced mortality in rabbits with several non-steroidal anti-inflammatory agents. *Agents Actions* 1977; 7: 481-485.
108. Adesuyi SA, Ellis EF: The effect of ibuprofen dose on rabbit platelet aggregation and aortic PGI₂ synthesis. *Thromb Res* 1982; 28: 581-585.

109. Utsunomiya T, Krausz MM, Dunham B, Valeri CR, Levine L, Shepro D, Hechtman HB: Modification of inflammatory response to aspiration with ibuprofen. *Am J Physiol* 1982; 243: H903-910.
110. Imai H, Muramatsu Y, Tsurumi K, Fujimura H: Platelet aggregation and liposome as a model system. *Jap J Pharmacol* 1981; 31:92P.
111. Adams SS, Bough RG, Cliffe EE, Dickinson W, Lessel B, McCullough KF, Mills RFN, Nicholson JS, Williams GAH: Some aspects of the pharmacology, metabolism and toxicology of ibuprofen. *Rheum Phys Med Suppl* 1970: 9-14.
112. USP I: 2002: p.426-427.
113. Codispoti JR, Prior MJ, Fu M, Harte CM, Nelson EB: Efficacy of Nonprescription Doses of Ibuprofen for Treating Migraine Headache. A Randomized Controlled Trial. *Headache* 2001; 41: 665-679
114. Diener HC, Bussone G, de Liano H, Eikermann A, Englert R, Floeter T, Gallai V, Gobel H, Hartung E, Jimenez MD, Lange R, Manzoni GC, Mueller-Schwefe G, Nappi G, Pinessi L, Prat J, Puca FM, Titus F, Voelker M: Placebo-controlled comparison of effervescent acetylsalicylic acid, sumatriptan and ibuprofen in the treatment of migraine attacks. *Cephalgia* 2004; 24: 947-954.
115. Misra UK, Jose M, Kalita J: Rofecoxib versus ibuprofen for acute treatment of migraine: a randomised placebo-controlled trial. *Postgrad Med J* 2004; 80: 720-723.
116. Saper J, Dahlof C, So Y, Tfelt-Hansen P, Malbecq W, Loeys T, Barraclough E, Klipfel M, Lines C, Visser H, Reines S, Yuen E: Rofecoxib in the Acute Treatment of Migraine: A Randomized Controlled Clinical Trial. *Headache* 2006; 46: 264-275.
117. Suthisisang C, Poolsup N, Kittikulsuth W, Pudchakan P, Wiwatpanich P: Efficacy of Low-Dose Ibuprofen in Acute Migraine Treatment: Systemic Review and Meta-Analysis. *Ann Pharmacother* 2007; 41: 1782-1791.
118. Misra UK, Kalita J, Yadav RK: Rizatriptan vs. ibuprofen in migraine: a randomised placebo-controlled trial. *J Headache Pain* 2007; 8: 175-179.
119. Rabie R, Derry S, Moore RA, McQuay HJ: Ibuprofen with or without an antiemetic for acute migraine headaches in adults (review). *The Cochrane Collaboration*. 2010; Issue 10.
120. Schiff M, Minic M: Comparison of the Analgesic Efficacy and Safety of Nonprescription Doses of Naproxen Sodium and Ibuprofen in the Treatment of Osteoarthritis of the Knee. *J Rheumatol* 2004; 31: 1373-1383.
121. Boureau F, Schenid H, Zeghari N, Wall R, Bourgeois P: The IPSO study: ibuprofen, paracetamol study in osteoarthritis. A randomised comparative clinical study comparing the efficacy and safety of ibuprofen and paracetamol analgesic treatment of osteoarthritis of knee or hip. *Ann Rheum Dis*. 2004 Sep; 63: 1028-1034.
122. Malmstrom K, Daniels S, Kotey P, Seidenberg BC, Desjardins PJ. Comparison of rofecoxib and celecoxib, two cyclooxygenase-2 inhibitors, in postoperative dental pain: A randomized, placebo active comparator controlled clinical trial. *Clin Therap* 1999; 21 (10): 1653-63
123. Malmstrom K, Fricke JR, Kotey P, Kress B, Morrison B. A comparison of rofecoxib versus celecoxib in treating pain after dental surgery: a single center, randomized, double blind, placebo and active comparator controlled, parallel group single dose study using the dental impaction pain model. *Clin Therap* 2002; 24(10):1549-60

124. Malmstrom K, Sapre A, Coughlin H, Agrawal NGB, Mazenko RS, Fricke Jr. JR. Etoricoxib in acute pain associated with dental surgery: A randomized, double blind, placebo and active comparator controlled dose ranging study. *Clin Ther* 2004;26(5):667-79
125. Zelenakas K, Fricke Jr. JR, Jayawardene S, Kellstein D. Analgesic efficacy of single oral doses of lumiracoxib and ibuprofen in patients with postoperative dental pain. *Int J Clin Pract* 2004;58(3):251-6
126. Forbes JA, Barkaszi BA, Ragland RN, Hankle JJ. Analgesic effect of fendosal, ibuprofen and aspirin in postoperative oral surgery pain. *Pharmacotherapy* 1984;4:385-391.
127. Fricke JR, Halladay SC, Francisco CA. Efficacy and safety of naproxen sodium and ibuprofen for pain relief after oral surgery. *Curr Ther Research* 1993; 54(6):619-27
128. Morrison BW, Christensen S, Yuan W, Brown J, Amlani S, Seidenberg B. Analgesic efficacy of the cyclooxygenase-2-specific inhibitor rofecoxib in post-dental surgery pain: a randomised, controlled trial. *Clin Ther* 1999; 21(6): 943-53
129. Whitehall-Robins Healthcare Study AI-95-01: A double blind, placebo controlled, parallel study of ibuprofen 600 mg and ibuprofen 400 mg in the treatment of dental pain
130. Advil® Liqui-gels / Advil® Extra Strength Liqui-gels Product Monograph, Pfizer Consumer Healthcare, a division of Pfizer Canada Inc. October 23, 2012.

PART III: CONSUMER INFORMATION

**Ibuprofen Capsules,
400mg**

This leaflet is part III of a three-part "Product Monograph" published when Ibuprofen Capsules, 400 mg was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Ibuprofen Capsules, 400 mg. Contact your doctor or pharmacist if you have any questions about the drug.



What the medication is used for:

Temporary relief of mild to moderate migraine headaches including associated symptoms of nausea, and sensitivity to light and sound.

Fast and effective relief of muscle aches and pain, joint and body pain, backache, muscle sprains and strains, pain of inflammation associated with conditions including arthritis and physical or athletic overexertion (e.g. sprains or strains), headache including tension headache, dental pain, menstrual pain, aches and pain due to the common cold and flu and for reduction of fever. Clinical studies show long lasting pain relief for up to 8 hours.

What it does:

Ibuprofen reduces pain and fever.
Liquid-fast migraine relief.

When it should not be used:

Do not take Ibuprofen Capsules, 400 mg if you have or are:

- peptic ulcer disease or gastrointestinal bleeding,
- taking acetylsalicylic acid (ASA) or any other nonsteroidal anti-inflammatory medication including any other ibuprofen product,
- allergic/hypersensitive to ASA, ibuprofen, other salicylates, other non-steroidal anti-inflammatory drugs (NSAIDs) or any of its ingredients (Refer to the non-medicinal ingredients on outer carton or composition section),
- nasal polyps (swelling of the inside of the nose), or allergic manifestations such as asthma, anaphylaxis (sudden severe life threatening allergic reaction), urticaria/hives, rhinitis (stuffed or runny nose that may be due to allergies), skin rash or other allergic symptoms,
- dehydrated (significant fluid loss) due to vomiting, diarrhea or lack of fluid intake,
- diagnosed with severe high blood pressure or have severe coronary artery disease,
- serious liver or kidney disease.
- Systemic Lupus Erythematosus
- or if you are pregnant or nursing

What the medicinal ingredients are: Ibuprofen (present as free acid and potassium salt).

What the important nonmedicinal ingredients are: Gelatin, iron oxide black, lecithin, medium chain triglycerides, polyethylene glycol, potassium hydroxide, propylene glycol, purified water, sorbitan, sorbitol.

What dosage forms it comes in:

Each liquid filled capsule contains ibuprofen 400mg (present as free acid and potassium salt)

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- Caution in patients prone to gastrointestinal tract irritation, including those with a history of peptic ulcer.

BEFORE you use Ibuprofen Capsules, 400 mg talk to your doctor or pharmacist if:

- you have peptic ulcers, diabetes, high blood pressure, heart failure or thyroid disease, asthma, kidney or liver disease, glaucoma, blood clotting disorder (such as hemophilia), any other serious disease, are under doctor's care for any serious condition, are pregnant or nursing or are taking any other drug including over the counter drugs.

Use with caution in the elderly.

INTERACTIONS WITH THIS MEDICATION

Do not use Ibuprofen 400 mg if you are taking:

- Daily low dose ASA (81 – 325 mg), without talking to a doctor or pharmacist. Ibuprofen may interfere with the preventive benefits of ASA.
- ASA or other anti-inflammatory medication.

Drugs that may interact with Ibuprofen 400 mg include: acetaminophen, anticoagulants (blood thinners), digoxin, oral antidiabetic agents and insulin, diuretics, methotrexate, lithium, protein-bound drugs including probenecid, thyroxine, antibiotics (e.g. cyclosporine), phenytoin, corticosteroids or benzodiazepenes, other NSAIDs, or medications for high blood pressure. Tell your doctor or pharmacist what prescription drugs you are taking or plan to take.

PROPER USE OF THIS MEDICATION

Usual dose:

For migraine headaches: Adults and children over 12: Take 1Ibuprofen 400 mg at the first sign of symptoms and

every 6-8 hours as needed. Do not exceed 3 capsules in 24 hours, unless directed by a doctor.

For all other uses: Adults and children over 12: Take 1 capsule every 6-8 hours as needed. Do not exceed 3 capsules in 24 hours, unless directed by a doctor.

Do not use longer than 3 days for a fever or 5 days for pain relief. Do not give to children under 12.

Overdose:

In case of overdose, call a Poison Control Center or a doctor immediately, even if there are no symptoms.

Missed Dose:

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

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

If abdominal pain, heartburn, nausea or vomiting, bloating, diarrhea or constipation, ringing or buzzing in the ears, nervousness, sleeplessness, dizziness or any change in vision, itching, fluid retention, skin rashes, skin reddening, blisters, blood in vomit, bloody or black stools, or any other side effect or unexplained symptoms develop while taking Ibuprofen 400 mg, discontinue use immediately and contact a doctor.

Side effects may be minimized by using the smallest dose for the shortest duration of time.

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

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 0701E
Ottawa, ON K1A 0K9

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

HOW TO STORE IT

Store at room temperature (15°C-30°C). Protect from light, and moisture

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

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found by contacting the sponsor, Bionpharma Inc., New Jersey, USA at 1-888-235-2466.

This leaflet was prepared by Bionpharma Inc.

Product monograph available to doctors and pharmacists upon request.

Last revised: December 13, 2016