PRODUCT MONOGRAPH

IBUPROFEN MENSTRUAL PAIN RELIEF

Ibuprofen Tablets USP

400 mg

Analgesic, Antipyretic Agent

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PRODUCT MONOGRAPH

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Ibuprofen Tablets USP

400 mg

THERAPEUTIC CLASSIFICATION

Analgesic, Antipyretic Agent

ACTIONS AND CLINICAL PHARMACOLOGY

Ibuprofen is a member of the class of agents commonly known as nonsteroidal anti-inflammatory drugs (NSAID). Consistent with this classification, ibuprofen exhibits anti-inflammatory activity at higher dosage ranges. At lower adult single doses relevant to a nonprescription dosage strength (200 mg to 400 mg) ibuprofen relieves pain of mild to moderate intensity and reduces fever. Analogous to ASA, the prototype of this class, this analgesic/antipyretic activity of ibuprofen occurs at lower doses than necessary for anti-inflammatory effects which are thought to require sustained administration of higher individual doses.

Ibuprofen is rapidly absorbed after oral administration, with peak serum or plasma levels generally appearing within 1½ to 2 hours. Oral absorption is estimated to be 80% of the dose. Both the rate of absorption and peak plasma concentrations are reduced when the drug is taken with food, but, bioavailability as measured by total area under the concentration-time curve is minimally altered. Ibuprofen has an elimination half-life of approximately 2 hours. It is rapidly metabolized through oxidation and glucuronic acid conjugation with urinary excretion of the inactive metabolites usually complete within 24 hours. Less than 10% is excreted unchanged in the urine. Clinical studies indicate a duration of clinical effect for up to 8 hours for fever and 6+ hours for pain.

Studies demonstrate no significant alterations in ibuprofen pharmacokinetics in the elderly. Ibuprofen pharmacokinetics has also been studied in patients with alcoholic liver disease who have been assessed to have fair to poor hepatic function. Results suggest that, despite the liver being the primary organ of metabolism of ibuprofen, its kinetic parameters are not substantially altered by this condition.

The basic mechanism of the pharmacological actions of ibuprofen, like other NSAIDs, has not been precisely determined. It is generally thought to be related to the inhibition of prostaglandin synthesis (Cox I and II).

INDICATIONS AND CLINICAL USE

IBUPROFEN MENSTRUAL PAIN RELIEF (ibuprofen) is indicated for fast and effective relief of headaches, menstrual pain, toothache (dental pain), pain due to arthritis, minor aches and pains in muscles, bones and joints, such as sprains or strains, backache, the aches and pain due to the common cold and for the reduction of fever.

CONTRAINDICATIONS

IBUPROFEN MENSTRUAL PAIN RELIEF (ibuprofen) should not be used in patients who have previously exhibited hypersensitivity to it or in individuals who are known to have a sensitivity (manifested as asthma, bronchospasm, hypotension, angioedema, laryngeal edema, swelling, shock or urticaria) to ASA or other nonsteroidal anti-inflammatory drugs.

IBUPROFEN MENSTRUAL PAIN RELIEF should not be used during pregnancy. Ibuprofen levels in breast milk are extremely low and are unlikely to affect a nursing infant; however,

because its safety under these conditions has not been established, consult a doctor before use in nursing mothers.

IBUPROFEN MENSTRUAL PAIN RELIEF is contraindicated in patients with systemic lupus erythematosus as an anaphylaxis-like reaction with fever may occur, particularly when ibuprofen has been administered previously. Aseptic meningitis has also been reported.

IBUPROFEN MENSTRUAL PAIN RELIEF should not be used in patients with acute peptic ulcer or gastrointestinal bleeding.

WARNINGS

Anaphylactoid reactions have occurred after administration of ibuprofen to patients with known ASA or other NSAID sensitivity manifested as asthma, swelling, shock or hives.

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

PRECAUTIONS

Occasionally, serious gastrointestinal side effects have been associated with the anti-inflammatory uses of ibuprofen (see WARNINGS). Minor gastrointestinal complaints have also been reported during the clinical use of ibuprofen at analgesic doses. The administration of ibuprofen with food or milk is recommended since occasional and mild heartburn, upset stomach

or stomach pain may occur with its use. Patients should be advised to seek the consultation of a physician if gastrointestinal side effects occur consistently, persist, or appear to worsen.

Ibuprofen, like other nonsteroidal anti-inflammatory agents, can inhibit platelet aggregation but the effect is quantitatively less than that seen with ASA. Ibuprofen has been shown to prolong bleeding time (but within the normal range) in normal subjects. Because this prolonged bleeding effect may be exaggerated in patients with underlying hemostatic defects, ibuprofen should be avoided by persons with intrinsic coagulation defects and by those on anticoagulant therapy.

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

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

Patients taking ibuprofen should be cautioned to report to their physician signs or symptoms of gastrointestinal intolerance and/or bleeding, blurred vision or other ocular symptoms, skin rash, tinnitus, dizziness, weight gain, edema or respiratory difficulties.

If ibuprofen is taken in conjunction with prolonged corticosteroid therapy and it is decided to discontinue steroid therapy, the corticosteroid should be tapered slowly to avoid exacerbation of disease or adrenal insufficiency.

Particular caution should be observed in elderly patients taking ibuprofen, as they are more likely to be taking other medications or have pre-existing disease states that can increase the likelihood of the complications that have been associated with ibuprofen. Elderly patients appear to be more susceptible to the CNS reactions; cognitive dysfunction (forgetfulness, inability to concentrate, a feeling of separation from the surroundings) in such patients has been reported.

Pregnancy: No evidence specifically identifies exposure to analgesic doses of ibuprofen as a cause of harm to either mother or fetus during pregnancy. Nonsteroidal anti-inflammatory drugs in general, however, are known to affect the action of prostaglandin synthetase, which could alter a variety of the physiological functions of prostaglandins or platelets during delivery such as facilitating uterine contraction in the mother, closure of the ductus arteriosus in the fetus, and platelet-related hemostasis. Patients should therefore be advised not to use ibuprofen during pregnancy without the advice of a physician, particularly during the last trimester. Clinical information is limited on the effects of ibuprofen in pregnancy.

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

Patients with Special Diseases and Conditions

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

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

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

Long-term ingestion of combinations of analgesics has been associated with analgesic nephropathy. It is therefore appropriate that patients be discouraged from long-term, unsupervised consumption of analgesics, particularly in combination. Patients should therefore be directed to consult a physician if their underlying condition requires administration of ibuprofen for more than 5 days. Ibuprofen usually should not be administered along with acetaminophen or ASA.

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

Drug Interactions

The platelet inhibiting effects of ibuprofen, although less potent and of shorter duration than those induced by ASA, warrant cautionary supervision by a physician before co-administration of ibuprofen and anticoagulants.

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

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

Other Anti-inflammatory Agents (NSAIDs): The addition of ibuprofen to a pre-existent prescribed NSAID regimen in patients with a condition such as rheumatoid arthritis may result in increased risk of adverse effects.

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

Acetaminophen: Although interactions have not been reported, concurrent use with ibuprofen is not advisable.

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

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

ADVERSE REACTIONS

Experience reported with prescription use of ibuprofen has included the following adverse reactions (see Table 1). **Note:** Reactions listed in Table 1 as unknown causal relationship are those where a causal relationship could not be established; however, in these rarely reported events, the possibility of a relationship to ibuprofen also cannot be excluded. The adverse reactions most frequently seen with ibuprofen therapy involve the gastrointestinal system.

TABLE 1: Adverse Effects

Adverse Effect	Incidence 3-9%	Incidence 1-3%	Incidence Less than 1%
Gastrointestinal	• nausea • epigastric pain • heartburn	• diarrhea • abdominal distress • nausea and vomiting • indigestion • constipation • abdominal cramp and pain • gastrointestinal tract fullness (bloating or flatulence)	• gastric or duodenal ulcer with bleeding and/or perforation • gastrointestinal hemorrhage • hepatitis • melena • jaundice • abnormal liver function (SGOT, serum bilirubin and alkaline phosphatase)
	The generally modest elevations of serum transaminase activity that have been observed are usually without clinical sequelae but severe, potentially fatal toxic hepatitis can occur.		
Central Nervous System	• dizziness	• headache • nervousness	• depression • insomnia
	Also reported but with unknown causal relationship: • paresthesia • hallucinations • dream abnormalities • aseptic meningitis in patients with systemic lupus erythematosus or other connective tissue disease • aseptic meningitis and meningioencephalitis, in 1 case accompanied by eosinophilia in the cerebrospinal fluids, in patients who took ibuprofen intermittently and did not have any connective tissue disease • cognitive dysfunction has been observed in elderly patients who took ibuprofen		
Dermatologic	• rash (including maculopapular type)	• pruritus	• vesiculobullous eruptions • urticaria • erythema multiforme
	Also reported but with unknown causal relationship: • alopecia • Stevens-Johnson syndrome		
Special Senses		• tinnitus	• amblyopia (blurred and/or diminished vision, scotomata and/or changes in colour vision) Any patient with eye complaints during ibuprofen therapy should have an ophthalmological examination
	Also reported but with unknown causal relationship: • conjunctivitis • diplopia • optic neuritis		
Metabolic		• decreased appetite • edema • fluid retention	
	Fluid retention generally responds promptly to drug discontinuation		

Adverse Effect	Incidence 3-9%	Incidence 1-3%	Incidence Less than 1%
Hematologic			• leukopenia and decreases in hemoglobin and hematocrit
	Also reported but with unknown causal relationship, rare cases of: • hemolytic anemia • thrombocytopenia • granulocytopenia • bleeding episodes (e.g. purpura, epistaxis, hematuria, menorrhagia) • autoimmune hematological anemia occurred in one patient taking 400 mg of ibuprofen three times a day for ten days • fatal aplastic anemia was reported in one patient who took 600 mg per day for eight months		
Cardiovascular			• congestive heart failure in patients with marginal cardiac function • elevated blood pressure Conditions such as congestive heart failure and hypertension may be aggravated by sodium retention and edema caused by ibuprofen in such patients
	Also reported but with unknown causal relationship, rare cases of: • arrhythmias (sinus tachycardia, sinus bradycardia, palpitations		
Allergic			• anaphylaxis (see Contraindications)
	Also reported but with unknown causal relationship, rarely: • fever • serum sickness • lupus erythematosus syndrome		
Endocrine	Reported but with unknown causal relationship, rare cases of: • gynecomastia • hypoglycemic reaction • menstrual delays of up to 2 weeks and dysfunctional uterine bleeding in 9 patients taking ibuprofen 400 mg 3 times a day for 3 days before menses		
Renal	Reported but with unknown causal relationship: • decreased creatine clearance • polyuria • azotemia Like other NSAIDs, ibuprofen inhibits renal prostaglandin synthesis, which may decrease renal function and cause sodium retention. Renal blood flow glomerular filtration rate decreased in patients with mild impairment of renal functions who took 1,200 mg/day of ibuprofen for 1 week. • renal papillary necrosis A number of factors appear to increase the risk of renal toxicity (see Precautions)		

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Symptoms

A clear pattern of clinical features associated with accidental or intentional overdose of ibuprofen has not been established. Reported cases of overdose have often been complicated by co-ingestion or additional suicidal gestures. The range of symptoms observed has included nausea, vomiting, abdominal pain, drowsiness, nystagmus, diplopia, headache, tinnitus, impaired renal function, coma and hypotension. A review of 4 fatalities associated with ibuprofen overdose indicates other contributing factors co-existed so it would be difficult to identify the toxicity of ibuprofen as a specific cause of death.

Postingestion blood levels may be useful to confirm a diagnosis and to quantify the degree of exposure but otherwise have not been helpful in predicting clinical outcome. Generally, full recovery can be expected with appropriate symptomatic management.

The following cases of overdose have been reported. A 19-month-old child, 1.5 hours after the ingestion of seven to ten 400 mg caplets of ibuprofen presented apnea, cyanosis and responded only to painful stimuli. After treatment with O_2, $NaHCO_3$, infusion of dextrose and normal saline, the child was responsive and 12 hours after ingestion appeared completely recovered. Blood levels of ibuprofen reached 102.9 µg/mL, 8.5 hours after the accident. Two other children weighing approximately 10 kg, had taken an estimated 120 mg/kg. There were no signs of acute intoxication or late sequelae. In 1 child the ibuprofen blood level at 90 minutes after ingestion was approximately 700 µg/mL. A 19-year-old male who ingested 8 000 mg of ibuprofen reported dizziness and nystagmus. He recovered with no reported sequelae after parenteral hydration and 3 days of bed rest.

For perspective, therapeutic doses (200 to 400 mg) in adults result in average peak serum levels of 22.4 to 35.7 µg/mL.

Treatment: Appropriate interventions to decontaminate the gastrointestinal tract may be beneficial within the first 4 hours after ingestion. Routine symptomatic and supportive treatment is then recommended. Physicians should contact the Regional Poison Control Centre for additional guidance about ibuprofen overdose management.

DOSAGE AND ADMINISTRATION

For mild to moderate pain or fever

Adults: 400 mg (1 caplet) as required every 4 hours, not to exceed 1200 mg (3 caplets), in 24 hours unless directed by a physician.

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

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

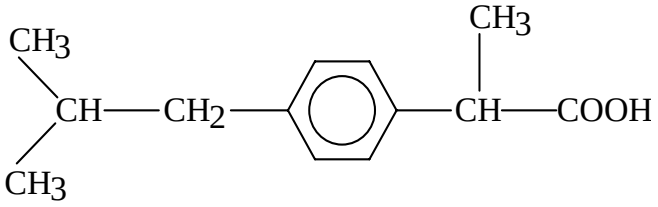
PHARMACEUTICAL INFORMATION

Drug Substance

Proper/Common Name: Ibuprofen

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

Structural Formula:



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

Molecular Weight: 206.28

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

Melting Point: ~75°C

Composition

In addition to ibuprofen, each caplet contains the following non-medicinal ingredients (alphabetical): colloidal silicon dioxide, croscarmellose sodium, hydroxypropyl cellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol and titanium dioxide. The caplets also contain the colouring agent red ferric oxide.

Stability and Storage Recommendations

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

AVAILABILITY OF DOSAGE FORMS

IBUPROFEN MENSTRUAL PAIN RELIEF 400 mg Tablets: Each reddish-brown, capsule-shaped, biconvex, film-coated caplet engraved ‘IBU 400’ on one side contains 400 mg of ibuprofen. Available in bottles of 16.

INFORMATION FOR THE CONSUMER

IBUPROFEN MENSTRUAL PAIN RELIEF

Ibuprofen Tablets USP

400 mg

For temporary relief of menstrual pain (dysmenorrhea), toothache (dental pain), minor aches and pains in muscles, bones and joints, fever and headache and pain due to arthritis or rheumatism.

How should IBUPROFEN MENSTRUAL PAIN RELIEF be taken?

You may take 400 mg (1 caplet) every 4 hours to a maximum daily dose of 1200 mg (3 caplets) unless otherwise directed by your doctor or dentist. Take with food or milk if desired. IBUPROFEN MENSTRUAL PAIN RELIEF should not be taken for pain for more than 5 consecutive days or for fever, if not improved, for more than 3 days without first consulting your doctor or dentist.

Who should not use IBUPROFEN MENSTRUAL PAIN RELIEF?

Do not take this product if you are allergic to ibuprofen or products containing acetylsalicylic acid (ASA), other salicylates, other anti-inflammatory drugs, or if you have ASA-sensitive asthma. Do not take this product while taking ASA, other ibuprofen-containing products or any other pain or fever medicine. IBUPROFEN MENSTRUAL PAIN RELIEF should not be used by children under 12 years of age, except as recommended by a doctor or dentist.

What precautions should be followed when using IBUPROFEN MENSTRUAL PAIN RELIEF?

Consult your doctor, dentist or pharmacist before taking this drug if you suffer from peptic ulcers, high blood pressure, asthma, heart failure, kidney or liver disease, alcoholism, have a history of stomach bleeding, have any other serious disease or condition, are pregnant or nursing, or are taking any other drug.

If any of the following reactions develop during treatment, see your doctor: skin rash or itching, dizziness, any change in vision, ringing or buzzing in the ears, nausea, vomiting, abdominal pain or diarrhea, heartburn, bloating, constipation, fluid retention. Always tell any other doctor, dentist or pharmacist you consult that you are taking this medicine.

Keep this medication out of the reach of children.

What should be done in the case of an overdose of IBUPROFEN MENSTRUAL PAIN RELIEF?

Contact a Poison Control Centre or doctor at once, even if there are no symptoms.

Where should I store this medicine?

Store at room temperature: avoid high humidity, direct light and heat (40°C or 104°F). Do not keep medicine that is outdated (after the expiry date).

PHARMACOLOGY

Animal Studies

Pharmacokinetics

Several aspects of the pharmacokinetics of ibuprofen have been studied in vivo in rats, rabbits, dogs and baboons.

Studies in rats indicate that while limited absorption of ibuprofen occurs in the stomach, the principal site of absorption is the intestine. Single dose studies using C^{14} labelled ibuprofen in rats, rabbits and dogs show rapid absorption rates. Tissue disposition studies performed in rats after both single and repeated doses of 20 mg/kg of C^{14} labelled ibuprofen demonstrate broad distribution with accumulation of radioactivity in the thyroid, adrenals, ovaries, fat and skin. Transplacental passage of ibuprofen was also noted with similar plasma levels measured in both the pregnant rats and fetuses.[17]

Protein binding studies with plasma levels of 20 mcg/mL indicate the percent bound in rats 96%, dogs 99%, baboons 95% and man 99%.[18]

Four metabolites of ibuprofen have been found in the plasma of rabbits, three in rats, none in dogs, two in baboons and two in man, with the liver suggested as the principal organ of metabolism.[17-18] Excretion of metabolites was noted to varying degrees through both urine and feces indicating species variability in the bile and kidney excretion ratios.

Pharmacodynamics

While the mechanism of action of ibuprofen is not definitely known, it is generally believed to involve the inhibition of prostaglandin synthesis. Inhibition of prostaglandin biosynthesis prevents sensitization of tissues by prostaglandins to other inflammatory, pain and thermoregulatory mediators, hence accounting for the activity of ibuprofen and other non-steroidal anti-inflammatory drugs against pain, inflammation and fever. [10]

Inhibition of prostaglandin synthesis by ibuprofen has been demonstrated in several different experimental models: bull seminal vesicle microsomes,[19] stomach, duodenum, kidney and brain of the rat,[20] microsomal preparations from rabbit brain and kidney medulla. [21]

The analgesic efficacy of ibuprofen has been demonsrated in several animal models: phenylbenzoquinone-induced writhing in the mouse, acetylcholine-induced writhing in the mouse, the Randall-Selitto inflamed paw model in the rat, the mouse hot plate and adjuvant-induced arthritis model in the rat.[22-24]

The antipyretic activity of ibuprofen has been demonstrated in yeast-induced fever in rats.[22-24]

Human Studies

Pharmacokinetics

Absorption

The pharmacokinetics of ibuprofen has also been studied in humans. *In vivo* studies indicate that ibuprofen is well absorbed orally with peak plasma levels usually occurring within 1 to 2 hours.

A single 200 mg oral dose study in 6 fasting healthy men produced a peak plasma concentration of 15.0 mcg/mL at 0.75 hr [25]. Another study using a single oral 400 mg dose in humans produced a peak serum level of 31.9 ± 8.8 mcg/mL at 0.5 hours after ingestion, and at 16 hours serum concentrations had dropped to 1 mcg/mL [26]. Comparable serum levels and time to peak 1 to 2 hours were confirmed by other investigations with 200 mg and 400 mg doses [27-28]. A multiple dose study of administration of 200 mg three times a day for 2 weeks showed no evidence of accumulation of ibuprofen [18].

Distribution

Protein binding studies involving ibuprofen added to human serum albumin [29] and equilibrium dialysis using plasma from human subjects receiving ibuprofen [18] indicate ibuprofen is highly bound (>99% bound at 20 g/mL) to plasma proteins.

Tissue distribution of ibuprofen is also extensive in humans. Studies comparing synovial fluid levels with serum concentrations indicated that equilibration time post-ingestion occurred within approximately 3 to 5 hours [28].

Metabolism and Elimination

Ibuprofen is extensively metabolized in humans with approximately 84% recoverable in the urine, primarily as conjugated hydroxy- and carboxy- metabolites, with only approximately 1% excreted unchanged. Ibuprofen has a biphasic plasma elimination time curve; the apparent serum half-life is approximately 1-1/2 to 2 hours [11]. The excretion of ibuprofen is virtually complete 24 hours after the last dose.

The two major metabolites of ibuprofen in humans have been found to have no activity in the ultraviolet erythema test in guinea pigs and in the acetylcholine-induced mouse writhing test at doses of 10 mg/kg and 15 mg/kg respectively [23].

Pharmacodynamics

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

Dental Pain

In adults, the effects of a drug on post-surgical dental extraction pain serves as a standard model for relief of pain of mild to moderate intensity. Ibuprofen 200 mg and 400 mg has been clearly demonstrated to provide pain relief significantly superior to placebo. When compared to the "standard" non-prescription analgesics, ibuprofen 200 mg is found to be comparable to ASA 650 mg [2, 30].

Dysmenorrhea

Non-steroidal anti-inflammatory drugs which inhibit prostaglandin synthesis such as ibuprofen are particularly suitable for management of primary dysmenorrhea. Menstrual pain is now thought to result from abnormal uterine activity which is secondary to increased production and release of endometrial prostaglandins at the time of menstruation. Several adequate and well-controlled clinical trials provide substantial evidence of the safety and efficacy of ibuprofen at doses of 200 to 400 mg in relieving pain of menstrual cramps [31-33].

A summary of trials of ibuprofen in the treatment of dysmenorrhea indicates the usual dose administered to be 400 mg. The few studies which are available at a 200 mg dosage indicate superiority of both ibuprofen 200 mg and 400 mg compared with ASA 650 mg [34].

Pain of Osteoarthritis

Several controlled clinical studies 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 [35-39]. Collectively, these studies support an indication for the temporary relief of minor pains of arthritis and, in conjunction with single dose analgesia studies, support the broader indication: for the temporary relief of minor aches and pains.

Headache

Ibuprofen has also been used satisfactorily in the management of headache. The efficacy of 200 mg of ibuprofen has been reported to be significantly superior to placebo and ASA 650 mg in the treatment of muscle contraction headaches [5]. No differences in the frequency of side effects were found in the treatment groups. Similar results were reported in a study with patients referred to a Headache Clinic with frequent muscle contraction headache [40].

Soft Tissue Injury

Several studies also document the efficacy of analgesic doses of ibuprofen in the treatment of soft tissue injuries such as muscular aches or athletic injuries [41-42].

Fever

Studies of its efficacy in the management of fever in adults demonstrate ibuprofen to be an effective antipyretic with a duration of action of up to eight hours when administered at a dose of 7.5 mg/kg [7-9].

TOXICOLOGY

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

Acute Toxicity Studies

Single-dose acute toxicity studies indicate that ibuprofen in lethal doses depresses the central nervous system of rodents and that large doses are ulcerogenic in both rodents and non-rodents. Ulcerogenesis may occur with both parenteral and oral administration indicating that the mechanism may have both a systemic as well as topical component.

Acute toxicity of ibuprofen in the rodent was studied in a number of models.

Single graded doses of ibuprofen were administered by oral intubation or by intraperitoneal or subcutaneous injection to groups of 10 male albino mice and male albino rats. Gross reactions were observed and mortalities recorded over a period of 14 days. The LD_{50} values determined by this method were 800 mg/kg orally and 320 mg/kg intraperitoneally in the mouse and 1600 mg/kg orally and 1300 mg/kg subcutaneously in the rat. Acute signs of poisoning were prostration in mice, and sedation, prostration, loss of righting reflex and 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 [17].

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

Table 1 - Acute Toxicity in Rodents (LD_{50})

Species	Route	LD_{50} Range (mg/kg)
Albino Mice [17,22]	Oral	800 - 1000
	Intraperitoneal	320
Albino Rats [17]	Oral	1600
	Subcutaneous	1300
Sprague Dawley Rat [43]		1050
Long Evans Rat [44]		1000

In a comparison of several non-steroidal anti-inflammatory drugs (NSAIDs) including ibuprofen, male rats were sacrificed and the stomachs removed and examined for ulceration either 3 or 24 hours after oral administration of various single doses of ibuprofen [45]. Using a standard scoring technique, a mean score for each dosage group was calculated and the ulcerogenic potential was expressed as a minimum ulcerogenic dose. The minimum oral ulcerogenic dose for ibuprofen in rats was calculated to be 6 to 13 mg/kg.

Another group studied the production of gastrointestinal lesions in the rat comparing ulcerogenic doses of ibuprofen and other NSAIDs after oral or intravenous administration [44]. Both male and female Long Evans rats were used in all experiments. Prior to drug administration, the animals were fasted for 8 hours. After treatment they were fed a normal diet and sacrificed after 17 hours.

Gastric and intestinal mucosa was examined for presence of ulcers. The ulcerogenic dose in 50% of treated animals (UD_{50}) was calculated. The UD_{50} following oral administration of ibuprofen was determined to be 70 mg/kg while for intravenous ibuprofen it was 210 mg/kg. The intestinal UD_{50} was 88 mg/kg following oral and 172 mg/kg with intravenous administrations. A calculated "severity index" of gastric lesions was higher by the oral than the IV route at all doses tested. Similar studies of the ulcerogenic potential of ibuprofen are summarized in the following Table 2.

Table 2 – Single Dose Ulcerogenicity Studies in Rodents

Species	Route	UD_{50}† (mg/kg)	MUD†† (mg/kg)
Long Evans Rat [44]	Oral	70	50
	IV	210	
Sprague Dawley Rat [45]	Oral		6-13

† Ulcerogenic dose in 50% treated animals
†† Minimum ulcerogenic dose

Acute toxicity has also been studied in dogs.

Various single oral doses of ibuprofen were administered to dogs with subsequent hematologic examination and biochemical analyses of blood and urine, and examination of feces for occult blood [17]. Gross examination of the major organs occurred after the animals were sacrificed. No ill effects were seen following doses of 20 or 50 mg/kg. Oral doses of 125 mg/kg or greater produced emesis, scouring, albuminuria, fecal blood loss and erosions in the gastric antrum and pylorus.

Multiple Dose Toxicity Studies

Multiple dose ulcerogenicity studies of ibuprofen have also been conducted.

Rats were dosed by the oral route for a specific number of consecutive days, then sacrificed for examination. The ulcerogenic effect of oral ibuprofen was graded and reported by various scoring systems such as percent of animals in whom ulcers were produced by a specific dose, or the UD_{50}.

In one typical such study, Long Evans rats were administered comparative NSAIDs orally once a day for 5 days [44]. The gastric and small intestinal mucosa were then examined for ulceration. The UD_{5O}, MUD and potency ratio of the drugs tested were calculated. The minimal ulcerogenic doses of ibuprofen were 25 mg/kg for the stomach and 50 mg/kg for the intestine.

Similar studies of multiple dose ulcerogenic potential of ibuprofen are summarized in the following Table 3.

Table 3 – Multiple Oral Dose Toxicity Studies

Species	Daily Dose (mg/kg)	Duration	Ulcerogenic Factor
Albino Rat [46]	400	30 hours	Ulcers in 100%
Albino Rat [22]		4 days	UD_{50}=455 mg/kg/day UD_{28}=240 mg/kg/day
Long Evans Rat [44]		5 days	MUD = 25-50 mg/kg/day
Sprague Dawley Rat [47]	5.8 –225	10 days	None
Albino Rat [17]	7.5 180	26 weeks 26 weeks	None Ulcers in 20%
Dog [17]	4 8 16	30 days 30 days 30 days	None 100% 100%

No other organ systems were generally noted to be significantly affected by these chronic administration studies. In one 30 day study [48], Wistar rats receiving 157 mg/kg/day ibuprofen had serum transaminase levels approximately double of those of a control, untreated group. Lower doses of ibuprofen in the same study had no significant effect on the activity of these enzymes.

Chronic toxicity studies in dogs demonstrated no gross or clinical signs of toxicity at 4, 8 or 16 mg/kg/day for 30 days [17]. However, in all dogs given 8 or 16 mg/kg/day, postmortem examination revealed gastric ulcers or erosions. No lesions were observed in dogs given 4 mg/kg/day.

A more complete assessment of chronic toxicity of ibuprofen in dogs studied the effects of administration of oral doses of 0, 2, 4 or 16 mg/kg/day over 26 weeks [17]. Periodic blood, urine and fecal sample analyses were performed. Histologic examination of selected organs and tissues was performed at the completion of the study. During the 26 week period, some reversible signs of gastrointestinal disturbance characterized by frequent vomiting, diarrhea, occasional passage of fresh blood and weight loss occurred in the 2 female dogs but not the males receiving 16 mg/kg ibuprofen. Occult blood was irregularly detected in fecal samples but urinalysis, liver function tests and other hematologic and blood biochemical values were not altered significantly. Gross examination of organs was normal except for ulcerative lesions in the gastrointestinal tract of organs of all dogs receiving 16 mg/kg/day. Dogs given 2 and 4 mg/kg/day suffered no adverse reactions or gastrointestinal damage.

Carcinogenicity

A study to evaluate the potential carcinogenic activity of ibuprofen involved administration of a minimum of 100 mg/kg/day to mice for 80 weeks and 60 mg/kg/day to rats for 2 years [49]. The proportion of animals with tumours of all types examined did not differ from those in the control group. The studies confirm that in the rat and mouse, ibuprofen does not induce tumors of the liver or other organs. Further, despite prolonged treatment, no other drug-induced hepatic lesions were seen in either species.

Teratogenicity and Reproduction Studies

Teratogenicity studies of ibuprofen have been conducted in rabbits and rats [17]. Results of the experiments indicate that ibuprofen is not teratogenic when given in toxic doses to rabbits nor is there embryotoxic or teratogenic activity in pregnant rats even when administered in ulcerogenic doses. Effects of ibuprofen on circular strips of fetal lamb ductus arteriosus indicate that exposure may produce contraction of the ductus [50]. Such an effect might be anticipated because of the known prostaglandin inhibiting properties of ibuprofen.

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