PRODUCT MONOGRAPH

ADVIL® MINI-GELS

Ibuprofen Capsules 200 mg (free acid and potassium salt)
Analgesic/Antipyretic

GlaxoSmithKine Consumer Healthcare Inc.
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ADVIL® MINI-GELS

Ibuprofen Capsules

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
oral	Capsule/ 200 mg	none *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

Adults and children 12 years and over

Advil® Mini-Gels is indicated for:

- headache pain including tension headache;
- 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. [24-23, 118 -125]

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): Advil® 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.

- Advil® should not be used in patients with the complete or partial syndrome of nasal polyps, or in whom asthma, anaphylaxis, urticarial/angioedema, rhinitis or other allergic manifestations are precipitated by ASA or other nonsteroidal anti-inflammatory agents. Fatal anaphylactoid reactions have occurred in such individuals. As well, individuals with the above medical problems are at risk of a severe reaction even if they have taken NSAIDs in the past without any adverse effects.

- 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 should not be used right before or after heart surgery.

- 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.

- Known hyperkalemia (see Warning and Precautions – Renal – Fluid and Electrolyte Balance)

- Children and adolescents (see Indications)

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*

General

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

(ADVIL®) is NOT recommended for use with other NSAIDs because of the absence of any evidence demonstrating synergistic benefits and the potential for additive adverse reactions. (See **Drug Interactions – *Drug/Drug Interactions – Acetylsalicylic acid (ASA) or other NSAIDs***)

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.

Clinical trial and epidemiological data suggest that use of ibuprofen, particularly at high doses (2400 mg or more daily) and in long-term treatment may be associated with a small increased risk of arterial thrombotic events (for e.g., myocardial infarction or stroke). Overall, epidemiological studies do not suggest that low dose ibuprofen (e.g., ≤1200 mg daily) is associated with an increased risk of myocardial infarction. [133,134]

Long term continuous use may increase the risk of heart attack or stroke.[126]

Dependence/Tolerance

Not applicable.

Ear/Nose/Throat

Patients with complete or partial syndrome of nasal polyps should not use Advil® (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. Advil® 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.

Advil® 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, Advil® should be discontinued immediately, appropriate treatment instituted and the patient monitored closely.

No studies, to date, have identified any group of patients not at risk of developing ulceration and bleeding. The major risk factors are a prior history of serious GI events and increasing age. Possible risk factors include other factors such as *Helicobacter pylori* infection, excess alcohol intake, smoking, female gender and concomitant oral steroid and anticoagulant, anti-coagulants, anti-platelet agents (including ASA) or selective serotonin reuptake inhibitors (SSRI's) 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 Advil® 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 Advil® 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 such as those on anti-coagulants or suffering from haemophillia or platelet disorder should be carefully observed when ibuprofen is administered. Numerous studies have shown that the concomitant use of NSAIDs and anti-coagulants increases the risk of bleeding. Concurrent therapy with warfarin requires close monitoring of the international normalized ratio (INR). Even with therapeutic INR monitoring, increased bleeding may occur. (See Drug Interactions)

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

Immune
In occasional cases, with some NSAIDs, the symptoms of aseptic meningitis (stiff neck, severe headaches, nausea and vomiting, fever or clouding of consciousness) have been observed. Patients with autoimmune disorders (systemic lupus erythematosus, mixed connective tissue diseases, etc.) seem to be pre-disposed. Therefore, in such patients, the physician must be vigilant to the development of this complication.

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

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 tubulointerstitial nephritis with hematuria, proteinuria, and occasionally nephrotic syndrome.

A second form of renal toxicity has been seen in patients with prerenal conditions leading to the reduction in renal blood flow or blood volume, where the renal prostaglandins have a supportive role in the maintenance of renal perfusion. In these patients, administration of a nonsteroidal anti-inflammatory drug may cause a dose dependent reduction in prostaglandin formation and

may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics, and the elderly. Discontinuation of nonsteroidal anti-inflammatory therapy is usually followed by recovery to the pre-treatment state.

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

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

Respiratory
ASA-induced asthma is an uncommon but very important indication of ASA and NSAID sensitivity. It occurs more frequently in patients with asthma who have nasal polyps.

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
In rare cases, serious skin reactions such as Stevens-Johnson syndrome, toxic epidermal necrolysis, exfoliative dermatitis, DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms), AGEP (Acute Generalized Exanthematous Pustulosis) and erythema multiforme have been associated with the use of some NSAIDs. Because the rate of these reactions is low, they have usually been noted during post-marketing surveillance in patients taking other medications also associated with the potential development of these serious skin reactions. Thus, causality is NOT clear. These reactions are potentially life threatening but may be reversible if the causative agent is discontinued and appropriate treatment instituted. Patients should be advised that if they experience a skin rash they should discontinue their NSAID and contact their physician for assessment and advice, including which additional therapies to discontinue.

Special Populations

Pregnant Women:
ADVIL® is CONTRAINDICATED for use during the third trimester of pregnancy because of risk of premature closure of the ductus arteriosus and the potential to prolong parturition (see Toxicology).

Caution should be exercised in prescribing ADVIL® to women who are trying to conceive, during the first and second trimesters of pregnancy, or if breastfeeding (see Toxicology).

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.[5] One study showed an ibuprofen concentration of 13 ng/mL 30 minutes after ingesting 400 mg.[14] 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: The safety and efficacy of ibuprofen in children <12 years of age have not been demonstrated for the products mentioned in this monograph.

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. The chance of stomach bleeding is higher if you are: age 60 or older, have had stomach ulcers or bleeding problems, take a blood thinner or steroid drug, take with other drugs containing an NSAID like acetylsalicyclic acid (ASA), ibuprofen, naproxen, or prescription anti-inflammatory drugs, have 3 or more alcoholic drinks every day while using this product. 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 Advil® 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 (1992-1999) (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.[83] 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.[84] Gastrointestinal adverse experiences were similar in the placebo and ibuprofen groups (67 out of 413, 16% with placebo vs. 161 out of 833, 19% with ibuprofen). There was no difference between the two groups in the proportion of discontinuing due to a gastrointestinal event. Gastrointestinal adverse experiences reported by ≥1% of subjects were: dyspepsia, abdominal pain, nausea, diarrhoea, flatulence, and constipation. Seventeen (1.4%) subjects had positive occult blood tests: their frequency was comparable between treatments. When used as directed to treat episodic pain, non-prescription ibuprofen at the maximum dose of 1200 mg/day for 10 days, is well-tolerated.

In two multi-trial analyses[885, 86]a meta analysis,[87] and a literature review,[83]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,[91] France and the United States,[92] 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 trial[93] 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.

Overview

Advil® is not recommended for concomitant use with any other NSAIDs, including ASA. Documented or possible drug interactions with Advil® 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 Advil® is not advisable: it may increase the risk of adverse renal effect.

Acetylsalicylic acid (ASA) or other NSAIDs

The use of Advil® in addition to any other NSAID, including ASA, is not recommended due to the absence of any evidence demonstrating synergistic benefits and 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.[109], keeping in mind that combination NSAID therapy is associated with additive adverse reactions.

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.

Antacids [80]

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

Combinations of ACE inhibitors, angiotensin-II antagonists, or diuretics with NSAIDs might have an increased risk for acute renal failure and hyperkalemia. Blood pressure and renal function (including electrolytes) should be monitored more closely in this situation, as occasionally there can be a substantial increase in blood pressure.

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[73,74]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 al[75]showed that ibuprofen 1600 mg/day for 14 days did not attenuate the antihypertensive effect of two β-adrenergic blockers. Houston et al.[76] 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.[77] 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.[78] In contrast, Minuz[79] 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[71, 72]

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 Advil® to patients on anticoagulants.

Digoxin[70]
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.

Glucocorticoids:
Some studies have shown that the concomitant use of NSAIDs and oral glucocorticoids increases the risk of GI adverse events such as ulceration and bleeding. This is especially the case in older (> 65 years of age) individuals.

H-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.

Lithium[82]
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.

Methotrexate[81]
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.

Selective Serotonin Reuptake Inhibitors (SSRIs)[127, 128]
Studies report an increased risk of gastrointestinal (GI) ulceration and bleeding when Ibuprofen as well as other NSAIDs are taken concomitantly with selective serotonin reuptake inhibitors (SSRIs) than when either class of drugs is taken alone (See Warnings and Precautions – Gastrointestinal).

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, 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 Advil®.

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 Advil® for individual patients are 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

Advil® Mini-Gels:

Adults and Children 12 years and over: Take 1 (every 4 hours) or 2 (every 6-8 hours) capsules as needed. Do not exceed 6 capsules in 24 hours, unless directed by a physician.

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 Overdose [98-100]
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.[108] 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 seizureand 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 catalysing 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.[18]

Pharmacokinetics
Absorption: Ibuprofen is rapidly and almost completely absorbed. Peak serum concentration occurs within 1-2 hours in adults.[4] Advil® Mini-Gels contain solubilized ibuprofen which has

peak serum concentrations at 60 minutes. 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.[5] At therapeutic concentrations ibuprofen is highly bound to whole human plasma and to site II of purified albumin.[5] 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., 1μg/mL) of detection.[13] 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.[14] 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%.[6] S-(+) ibuprofen is believed to be the pharmacologically more active enantiomer. Two major metabolites, 2-[4-(2-carboxypropyl)phenyl] propionic acid and 2-[4-(2-hydroxy-2-methylpropyl]propionic acid, have been identified in plasma and urine.[7] The metabolites 1-hydroxyibuprofen and 3-hydroxyibuprofen have also been found in urine in very small concentrations.[8, 9] Cytochrome P450 (CYP) 2C9 has been identified as the most important catalyst for formation of all oxidative metabolites of R-(-) and S-(+) ibuprofen.[10] Approximately 80% of a dose is recovered in urine, primarily as carboxymetabolites and conjugated hydroxymetabolites.[5] Ibuprofen does not appear to induce the formation of drug metabolising enzymes in the rat. [7]

Excretion: Ibuprofen's plasma half-life in adults is 1.5-2.0 hours.[11] 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.[5]

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.[12] Furthermore, there was no statistically significant difference between the two populations in the urinary excretion pattern of the drug and its major metabolites.

STORAGE AND STABILITY

Advil® Mini-Gels should be stored in tightly-closed containers under room temperature (15-30°C) conditions.

SPECIAL HANDLING INSTRUCTIONS

Not applicable.

DOSAGE FORMS, COMPOSITION AND PACKAGING

For Adults:

Each green transparent gelatin capsule Advil® Mini-Gels, contains 200 mg ibuprofen as free acid and potassium salt.

Advil® Liqui-Gels Minis are available in bottles of 30, 70, and 110 and professional sample pouches of 2.

Advil® Mini-Gels Non-medicinal ingredients: FD&C green no. 3, gelatin, medium chain triglycerides, pharmaceutical ink, polyethylene glycol, potassium hydroxide, purified water, sorbitan, sorbitol.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

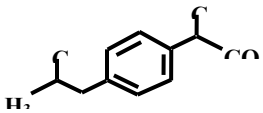
Proper name: Ibuprofen

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

Other names: p-isobutylhydratropic acid
2-(4-isobutylphenyl)-propionic acid

Molecular formula and molecular mass: $C_{13}H_{18}0_2$; 206.28 daltons

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

Advil® Mini-Gels (fasted) and Advil® Liqui-Gels (fasted):

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

ADVIL® MINI-GELS CAPSULES
(2 x 200 mg)
From Measured Data

Geometric Mean
Arithmetic Mean (CV%)

PARAMETER	TEST	REFERENCE*	% RATIO OF GEOMETRIC MEANS	90% CONFIDENCE INTERVAL
AUC_T (µg·hr//mL)	131.91 135.12 (22.54)	132.85 136.21 (23.82)	99.29	(96.44 – 102.23)
AUC_I (µg·hr/mL)	133.21 136.47 (22.57)	134.13 137.51 (23.77)	99.32	(96.59 – 102.13)
C_{max} (µg/mL)	41.66 42.80 (23.95)	45.96 47.10 (22.04)	90.66	(82.91 – 99.13)
T_{max}** (hr)	1.00 [0.35, 3.00]	0.81 [0.33, 2.00]		
$T_{½}$*** (hr)	2.09 (17.30)	2.06 (15.63)		

*Reference product: Pfizer Consumer Healthcare, a division of Pfizer Canada Inc. (2 x 200 mg) Advil® Liqui-Gels DIN 02241769.
** Expressed as median [Range] only
*** 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 pain[109], headache[110,111]and muscle aches[112]

in adults. The antipyretic efficacy of ibuprofen has been demonstrated in adults at doses of 200 and 400 mg[113-115].

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.[19] Several other comparative dental studies have described similar results.[20-26]

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. [22-23, 118-125]

The results of the trials utilized the primary end points of total pain relief at 8 hours (TOTPAR8) [118-120, 123, 124], Pain Intensity Difference (PID) [22, 121], and Sum of Pain Intensity Differences (SPID) [23, 122-123,125] 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 [118-120, 124] 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) [118-120].

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 hours[121]. 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) [121].

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 ($p<0.05$).[22-23, 122-123, 125]

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.[27]

Headache
A double-blind, randomized study showed that ibuprofen 400 mg relieved headache pain significantly better than acetaminophen 1000 mg and placebo.[16] 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.[17] 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.[8]

Dysmenorrhea
Several studies demonstrate the significant effect of ibuprofen compared to placebo or other active analgesics on uterine pain and cramping.[28-33]

Fever
The antipyretic efficacy of ibuprofen has been demonstrated in adult fever.[34-36]

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.[116-117] 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.[15]

Ibuprofen has also been studied in other pain models including migraine[109-115] with equally effective pain relief results.

DETAILED PHARMACOLOGY

Animal Pharmacology

After single oral doses of 20 to 150 mg/kg of C^{14} labelled ibuprofen rats, the peak plasma level occurred at or before the earliest time examined (20 minutes in the 20 mg/kg group and 45 minutes in the 150 mg/kg group) and peak levels occurred with 45 minutes of dosing in nearly all tissues examined. The concentration in plasma and tissue decreased to very low levels by six hours after the 20 mg/kg dose and by 17 hours after the 150 mg/kg dose. Sixteen to 38% of the daily dose of ibuprofen was excreted in the urine.[101]

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.[101]

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.[102] The drug's protective action against fatal pulmonary embolism in rabbits injected intravenously with arachidonic acid may also relate to platelet inhibition.[103, 104] Various prostaglandins and thromboxane A_2 (TXA_2), are important factors in normal platelet aggregation. Cyclooxygenase inhibition reduces TXA_2 production and release, thereby reducing platelet aggregation.[105] Ibuprofen may also reduce platelet membrane fluidity, which reduces aggregation,[106] but it is not known to what extent TXA_2 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 at 2-4', (2-hydroxy-2-methylpropyl) phenylpropionic acid (metabolite A) and 2-4' (2-carboxpropyl) phenylpropionic acid (metabolite B). About 1/3 of the dose was excreted in the urine of patients as metabolite B, 1/10 as unchanged ibuprofen and 1/10 as metabolite A. The remainder of the dose could not be identified in the urine.[101]

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.[101]

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

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

Acute signs of poisoning were prostration in mice, and sedation, prostration, loss of righting reflex and laboured respiration in rats. Death occurred within 3 days from perforated gastric ulcers in mice and intestinal ulceration in rats, irrespective of the route of administration. Following single ibuprofen doses of 125 mg/kg and above to dogs effects were observed including emesis, transient albuminuria, faecal blood loss and erosions in the gastric antrum and pylorus; no ill effects were seen with 20 or 50 mg/kg doses.

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

Rats receiving ibuprofen for 26 weeks grew normally except for males on 180 mg/kg/day, which gained significantly less weight than the controls. One male rat receiving 180 mg/kg/day died due to intestinal lesions and the death was thought to be treatment-related. Both males and females receiving 180 mg/kg/day were anaemic; leukocyte count and plasma glutamic pyruvic

transaminase activities were not significantly altered. The organ to body weight ratio of males given 180 mg/kg/day was typically greater than normal. For some organs, this was because the males weighed less than the controls. Organs that were enlarged were the liver, kidney, and spleen. The same organs were also enlarged in females receiving 180 mg/kg/day, although these females were similar in body weight to the controls. In addition, the combined seminal vesicle and prostate weight was subnormal and uterine weight was increased. The thyroid gland of males receiving 180, 60, 20 mg/kg/day exhibited a slight increase in weight, which was the same for the three doses, however no such increase was observed in the females. There were no significant histological changes observed in rat tissues except for the presence of intestinal ulcers in 1 male and 3 females receiving 180 mg/kg/day.

The above experiment was adapted to establish whether the effects of ibuprofen treatment on rats were reversible when dosing ended.[101] 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.

Genotoxicity

Ibuprofen has shown no genotoxicity in the in vitro bacterial mutation assay in the presence and absence of S9 using *Salmonella* Typhimurium TA1535, TA1538, TA97a, TA100 and TA102.[129, 130] It was also tested in an in vivo sister chromatid exchange assay in the bone marrow cells of mice dosed orally or intraperitoneal and showed weak genotoxicity in the sister chromatid assay.

There was no difference in the occurrence of chromosomal aberrations in cultured human lymphocytes in patients before or after treatment with ibuprofen.[131] A recent study in mouse bone marrow cells suggested a potential for chromosomal aberrations after oral dosing.[132] Overall, it was not genotoxic in vitro but was weakly mutagenic in vivo.

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.[107]

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 cyclopia. The results of this experiment indicate that ibuprofen is not teratogenic when given in toxic doses to rabbits.[101]

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.[101]

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 C^{14} labelled ibuprofen. Rabbits were killed three hours after dosing and rats killed 1.5 hours after dosing when maternal and foetal blood was collected. Similar concentrations of radioactive ibuprofen were detected in both the mother and foetus indicating that the drug and its metabolites readily crossed the placental barrier into the foetal circulation.[101]

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PART III: CONSUMER INFORMATION

Advil® MINI-GELS
Ibuprofen Capsules, 200mg (as free acid and potassium salt)

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

ABOUT THIS MEDICATION

What the medication is used for:

Fast and effective temporary 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.

What it does:
Advil® Mini-Gels (Ibuprofen) is a non-steroidal anti-inflammatory drug (NSAID) that can reduce the chemicals produced by your body which cause pain and inflammation.

When it should not be used:
Do not take Advil® Mini-Gels if you have or are:

- **active or recurrent stomach ulcer, gastrointestinal (GI) bleeding, or active inflammatory bowel disease (e.g. Crohn's, colitis),**
- **taking acetylsalicylic acid (ASA) or any other non-steroidal 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 Advil® Mini-Gels ingredients (Refer to the nonmedicinal 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,**
- **right before or after heart surgery,**
- **serious liver or kidney disease,**
- **Systemic Lupus Erythematosus,**
- **or if you are in your third trimester of pregnancy.**

Advil® Mini-Gels should NOT be used in patients under 12 years of age since the safety and effectiveness have NOT been established. Children under 12 should use Children's Advil.

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

What the important nonmedicinal ingredients are:
FD&C green no. 3, gelatin, medium chain triglycerides, pharmaceutical ink, polyethylene glycol, potassium hydroxide, purified water, sorbitan, sorbitol.

What dosage forms it comes in:
Each liquid filled capsule contains ibuprofen 200mg (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. The chance of stomach bleeding is higher if you are: age 60 or older, have had stomach ulcers or bleeding problems, take a blood thinner or steroid drug, take with other drugs containing an NSAID like ASA, ibuprofen, naproxen, or prescription anti-inflammatory drugs, have 3 or more alcoholic drinks every day while using this product.

BEFORE you use Advil® Mini-Gels talk to your doctor or pharmacist if:

- **you have previous or current stomach ulcers, diabetes, high blood pressure, heart failure, heart disease 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 trying to conceive, are in your first or second trimester of pregnancy, are breastfeeding or are taking any other drug including over the counter drugs.**

Use with caution in the elderly.

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

INTERACTIONS WITH THIS MEDICATION

Do not use Advil® Mini-Gels 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.**

Talk to your doctor or pharmacist if you are taking other medication (prescription or non-prescription) such as any of the following (NOT a complete list): acetaminophen,

anticoagulants (blood thinners), digoxin, oral antidiabetic agents and insulin, diuretics, methotrexate, lithium, protein-bound drugs including probenecid, thyroxine, antibiotics, cyclosporine, phenytoin, corticosteroids or benzodiazepines, 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:
Adults and children 12 years and over: Take 1 (every 4 hours) or 2 (every 6-8 hours) capsules as needed. Do not exceed 6 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. Children under 12 should use Children's Advil®.

Overdose:

In case of overdose, call a Poison Control Centre 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 time.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Take with food or milk if upset stomach occurs.

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, shortness of breath, wheezing, any trouble breathing or chest tightness, hives, swelling or itching, skin rashes, skin reddening, blisters, blood in vomit, bloody or black stools, jaundice (yellowing of the eyes or skin due to liver problem), or any other side effect or unexplained symptoms develop while taking Advil® Mini-Gels, 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 Advil® Mini-Gels, contact your doctor or pharmacist.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- **Visiting the Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by or**
- **Calling toll-free at 1-866-234-2345.**

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

HOW TO STORE IT

Store at room temperature (15°-30°C).

Keep out of reach of children. This package contains enough medicine to seriously harm a child. Advil® Mini-Gels 30s are available with child resistant cap.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found by contacting the sponsor, GlaxoSmithKline Consumer Healthcare Inc. Mississauga, ON L5N 6L4, at: 1-888-275-9938 or www.advil.ca.

This leaflet was prepared by GlaxoSmithKline Consumer Healthcare Inc.

Product monograph available to doctors and pharmacists upon request.

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