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IBUPROFEN ORAL SUSPENSION USP
100 mg/5 mL
FORM NO. 1270-IN
Rev. 5/08 VC3115

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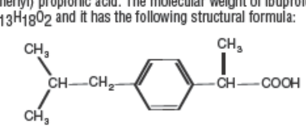
℞ Only

Cardiovascular Risk
- NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk (See **WARNINGS**).
- Ibuprofen Oral Suspension is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery (see **WARNINGS**).

Gastrointestinal Risk
- NSAIDs cause an increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events (See **WARNINGS**).

DESCRIPTION
The active ingredient in Ibuprofen Oral Suspension USP is ibuprofen, which is a member of the propionic acid group of nonsteroidal anti-inflammatory drugs (NSAIDs). Ibuprofen is a racemic mixture of [+]S- and [-]R-enantiomers. It is a white to off-white crystalline powder, with a melting point of 74° to 77°C. It is practically insoluble in water (< 0.1 mg/mL), but readily soluble in organic solvents such as ethanol and acetone. Ibuprofen has a pKa of 4.43 ± 0.03 and an n-octanol/water partition coefficient of 11.7 at pH 7.4. The chemical name for ibuprofen is (±)-2-(p-isobutylphenyl) propionic acid. The molecular weight of ibuprofen is 206.28. Its molecular formula is $C_{13}H_{18}O_2$ and it has the following structural formula:



Ibuprofen Oral Suspension USP is a sucrose-sweetened, orange-colored, berry-flavored suspension containing 100 mg of ibuprofen in 5 mL (20 mg/mL). Inactive ingredients include: citric acid anhydrous, glycerin, hypromellose, polysorbate 80, purified water, sodium benzoate, sucrose, xanthan gum, D&C yellow #10 and FD&C red #40, and artificial flavors (strawberry/vanillin).

CLINICAL PHARMACOLOGY
Pharmacodynamics - Ibuprofen is a nonsteroidal anti-inflammatory drug (NSAID) that possesses anti-inflammatory, analgesic and antipyretic activity. Its mode of action, like that of other NSAIDs, is not completely understood, but may be related to prostaglandin synthetase inhibition. After absorption of the racemic ibuprofen, the [-]R-enantiomer undergoes interconversion to the [+]S-form. The biological activities of ibuprofen are associated with the [+]S-enantiomer.

Pharmacokinetics - Ibuprofen is a racemic mixture of [-]R-and [+]S-isomers. *In vivo* and *in vitro* studies indicate that the [+]S-isomer is responsible for clinical activity. The [-]R-form, while thought to be pharmacologically inactive, is slowly and incompletely (~60%) interconverted into the active [+]S species in adults. The degree of interconversion in children is unknown, but is thought to be similar. The [-]R-isomer serves as a circulating reservoir to maintain levels of active drug. Ibuprofen is well absorbed orally, with less than 1% being excreted in the urine unchanged. It has a biphasic elimination time curve with a plasma half-life of approximately 2 hours. Studies in febrile children have established the dose-proportionality of 5 and 10 mg/kg doses of ibuprofen. Studies in adults have established the dose-proportionality of ibuprofen as a single oral dose from 50 to 600 mg for total drug and up to 1200 mg for free drug.

Absorption - *In vivo* studies indicate that ibuprofen is well absorbed orally from the suspension formulation, with peak plasma levels usually occurring within 1 to 2 hours (see Table 1).

Table 1
Pharmacokinetic Parameters of Ibuprofen Oral Suspension
[Mean values (% coefficient of variation)]

Dose	200 mg (2.8 mg/kg) in Adults	10 mg/kg in Febrile Children
Formulation	Suspension	Suspension
Number of Patients	24	18
AUC_{inf} (mcg•h/mL)	64 (27%)	155 (24%)
C_{max} (mcg/mL)	19 (22%)	55 (23%)
T_{max} (h)	0.79 (69%)	0.97 (57%)
Cl/F (mL/h/kg)	45.6 (22%)	68.6 (22%)

Legend: AUC_{inf} = Area-under-the-curve to infinity
T_{max} = Time-to-peak plasma concentration
C_{max} = Peak plasma concentration
Cl/F = Clearance divided by fraction at drug absorbed

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

H-2 Antagonists - In studies with human volunteers, coadministration of cimetidine or ranitidine with ibuprofen had no substantive effect on ibuprofen serum concentrations.

Food Effects - Absorption is most rapid when ibuprofen is given under fasting conditions. Administration of ibuprofen with food affects the rate but not the extent of absorption. When taken with food, T_{max} is delayed by approximately 30 to 60 minutes, and peak levels are reduced by approximately 30 to 50%.

Distribution - Ibuprofen, like most drugs of its class, is highly protein bound (>99% bound at 20 mcg/mL). Protein binding is saturable and at concentrations >20 mcg/mL binding is non-linear. Based on oral dosing data there is an age- or fever-related change in volume of distribution for ibuprofen. Febrile children <11 years old have a volume of approximately 0.2 L/kg while adults have a volume of approximately 0.12 L/kg. The clinical significance of these findings is unknown.

Metabolism - Following oral administration, the majority of the dose was recovered in the urine within 24 hours as the hydroxy-(25%) and carboxypropyl-(37%) phenylpropionic acid metabolites. The percentages of free and conjugated ibuprofen found in the urine were approximately 1% and 14%, respectively. The remainder of the drug was found in the stool as both metabolites and unabsorbed drug.

Elimination - Ibuprofen is rapidly metabolized and eliminated in the urine. The excretion of ibuprofen is virtually complete 24 hours after the last dose. It has a biphasic plasma elimination time curve with a half-life of approximately 2.0 hours. There is no difference in the observed terminal elimination rate or half-life between children and adults, however, there is an age- or fever-related change in total clearance. This suggests that the observed change in clearance is due to changes in the volume of distribution of ibuprofen (see Table 1 for Cl/F values).

Clinical Studies - Controlled clinical trials comparing doses of 5 and 10 mg/kg ibuprofen suspension and 10-15 mg/kg of acetaminophen elixir have been conducted in children 6 months to 12 years of age with fever primarily due to viral illnesses. In these studies there were no differences between treatments in fever reduction for the first hour and maximum fever reduction occurred between 2 and 4 hours. Response after 1 hour was dependent on both the level of temperature elevation as well as the treatment. In children with baseline temperatures at or below 102.5°F both ibuprofen doses and acetaminophen were equally effective in their maximum effect. In children with temperatures above 102.5°F, the ibuprofen 10 mg/kg dose was more effective. By 6 hours, children treated with ibuprofen 5 mg/kg tended to have recurrence of fever, whereas children treated with ibuprofen 10 mg/kg still had significant fever reduction at 8 hours. In control groups treated with 10 mg/kg acetaminophen, fever reduction resembled that seen in children treated with 5 mg/kg of ibuprofen, with the exception that temperature elevation tended to return 1-2 hours earlier.

In patients with primary dysmenorrhea, ibuprofen has been shown to reduce elevated levels of prostaglandin activity in the menstrual fluid and to reduce testing and active intrauterine pressure, as well as the frequency of uterine contractions. The probable mechanism of action is to inhibit prostaglandin synthesis rather than simply to provide analgesia.

INDICATIONS AND USAGE
Carefully consider the potential benefits and risks of Ibuprofen Oral Suspension and other treatment options before deciding to use ibuprofen. Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals (see **WARNINGS**).

In Pediatric Patients, Ibuprofen Oral Suspension is indicated:
- For reduction of fever in patients aged 6 months up to 2 years of age.
- For relief of mild to moderate pain in patients aged 6 months up to 2 years of age.
- For relief of signs and symptoms of juvenile arthritis.

In Adults, Ibuprofen Oral Suspension is indicated:
- For treatment of primary dysmenorrhea.
- For relief of the signs and symptoms of rheumatoid arthritis and osteoarthritis.

Since there have been no controlled trials to demonstrate whether there is any beneficial effect or harmful interaction with the use of ibuprofen in conjunction with aspirin, the combination cannot be recommended (see **PRECAUTIONS - Drug Interactions**).

CONTRAINDICATIONS
Ibuprofen is contraindicated in patients with known hypersensitivity to ibuprofen.

Ibuprofen should not be given to patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs. Severe, rarely fatal, anaphylactic-like reactions to NSAIDs have been reported in such patients (see **WARNINGS – Anaphylactoid Reactions**, and **PRECAUTIONS – Preexisting Asthma**).

Ibuprofen is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery (see **WARNINGS**).

WARNINGS
CARDIOVASCULAR EFFECTS
Cardiovascular Thrombotic Events
Clinical trials of several COX-2 selective and nonselective NSAIDs of up to three years duration have shown an increased risk of serious cardiovascular (CV) thrombotic events, myocardial infarction, and stroke, which can be fatal. All NSAIDs, both COX-2 selective and nonselective, may have a similar risk. Patients with known CV disease or risk factors for CV disease may be at greater risk. To minimize the potential risk for an adverse CV event in patients treated with an NSAID, the lowest effective dose should be used for the shortest duration possible. Physicians and patients should remain alert for the development of such events, even in the absence of previous CV symptoms. Patients should be informed about the signs and/or symptoms of serious CV events and the steps to take if they occur.

There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious CV thrombotic events associated with NSAID use. The concurrent use of aspirin and an NSAID does increase the risk of serious GI events (see **GI WARNINGS**).

Two large, controlled, clinical trials of a COX-2 selective NSAID for the treatment of pain in the first 10-14 days following CABG surgery found an increased incidence of myocardial infarction and stroke (see **CONTRAINDICATIONS**).

Hypertension
NSAIDs, including ibuprofen, can lead to onset of new hypertension or worsening of pre-existing hypertension, either of which may contribute to the increased incidence of CV events. Patients taking thiazides or loop diuretics may have impaired response to these therapies when taking NSAIDs. NSAIDs, including ibuprofen, should be used with caution in patients with hypertension. Blood pressure (BP) should be monitored closely during the initiation of NSAID treatment and throughout the course of therapy.

Congestive Heart Failure and Edema
Fluid retention and edema have been observed in some patients taking NSAIDs. Ibuprofen should be used with caution in patients with fluid retention or heart failure.

Gastrointestinal Effects – Risk of Ulceration, Bleeding, and Perforation
NSAIDs, including ibuprofen, can cause serious gastrointestinal (GI) adverse events including inflammation, bleeding, ulceration, and perforation of the stomach, small intestine, or large intestine, which can be fatal. These serious adverse events can occur at any time, with or without warning symptoms, in patients treated with NSAIDs. Only one in five patients, who develop a serious upper GI adverse event on NSAID therapy, is symptomatic. Upper GI ulcers, gross bleeding, or perforation caused by NSAIDs occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year. These trends continue with longer duration of use, increasing the likelihood of developing a serious GI event at some time during the course of therapy. However, even short-term therapy is not without risk.

NSAIDs should be prescribed with extreme caution in those with a prior history of ulcer disease or gastrointestinal bleeding. Patients with a *prior history of peptic ulcer disease and/or gastrointestinal bleeding* who use NSAIDs have a greater than 10-fold risk for developing a GI bleed compared to patients with neither of these risk factors. Other factors that increase the risk for GI bleeding in patients treated with NSAIDs include concomitant use of oral corticosteroids or anticoagulants, longer duration of NSAID therapy, smoking, use of alcohol, older age, and poor general health status. Most spontaneous reports of fatal GI events are in elderly or debilitated patients and therefore, special care should be taken in treating this population.

To minimize the potential risk for an adverse GI event in patients treated with an NSAID, the lowest effective dose should be used for the shortest possible duration. Patients and physicians should remain alert for signs and symptoms of GI ulceration and bleeding during NSAID therapy and promptly initiate additional evaluation and treatment if a serious GI adverse event is suspected. This should include discontinuation of the NSAID until a serious GI adverse event is ruled out. For high risk patients, alternate therapies that do not involve NSAIDs should be considered.

Renal Effects
Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory 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, secondarily, in renal blood flow, which 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 ACE inhibitors, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state.

Advanced Renal Disease
No information is available from controlled clinical studies regarding the use of ibuprofen in patients with advanced renal disease. Therefore, treatment with ibuprofen is not recommended in these patients with advanced renal disease. If ibuprofen therapy must be initiated, close monitoring of the patient's renal function is advisable.

Anaphylactoid Reactions
As with other NSAIDs, anaphylactoid reactions may occur in patients without known prior exposure to ibuprofen. Ibuprofen should not be given to patients with the aspirin triad. This symptom complex typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking aspirin or other NSAIDs (see **CONTRAINDICATIONS** and **PRECAUTIONS – Preexisting Asthma**). Emergency help should be sought in cases where an anaphylactoid reaction occurs.

Skin Reactions
NSAIDs, including ibuprofen, can cause serious skin adverse events such as exfoliative dermatitis, Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. These serious events may occur without warning. Patients should be informed about the signs and symptoms of serious skin manifestations and use of the drug should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.

Pregnancy
In late pregnancy, as with other NSAIDs, ibuprofen should be avoided because it may cause premature closure of the ductus arteriosus.

PRECAUTIONS
General
Ibuprofen cannot be expected to substitute for corticosteroids or to treat corticosteroid insufficiency. Abrupt discontinuation of corticosteroids may lead to disease exacerbation. Patients on prolonged corticosteroid therapy should have their therapy tapered slowly if a decision is made to discontinue corticosteroids. The pharmacological activity of ibuprofen in reducing fever and inflammation may diminish the utility of these diagnostic signs in detecting complications of presumed noninfectious, painful conditions.

Hepatic Effects
Borderline elevations of one or more liver tests may occur in up to 15% of patients taking NSAIDs including ibuprofen. These laboratory abnormalities may progress, may remain unchanged, or may be transient with continuing therapy. Notable elevations of ALT or AST (approximately three or more times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials with NSAIDs. In addition, rare cases of severe hepatic reactions, including jaundice and fatal fulminant hepatitis, liver necrosis and hepatic failure, some of them with fatal outcomes have been reported.

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 a more severe hepatic reaction while on therapy with ibuprofen. If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), ibuprofen should be discontinued.

Hematological Effects
Anemia is sometimes seen in patients receiving NSAIDs, including ibuprofen. This may be due to fluid retention, occult or gross GI blood loss, or an incompletely described effect upon erythropoiesis. Patients on long-term treatment with NSAIDs, including ibuprofen, should have their hemoglobin or hematocrit checked if they exhibit any signs or symptoms of anemia.

In two postmarketing clinical studies the incidence of a decreased hemoglobin level was greater than previously reported. Decrease in hemoglobin of 1 gram or more was observed in 17.1% of 193 patients on 1600 mg ibuprofen daily (osteoarthritis), and in 22.8% of 189 patients taking 2400 mg of ibuprofen daily (rheumatoid arthritis). Positive stool occult blood tests and elevated serum creatinine levels were also observed in these studies.

NSAIDs inhibit platelet aggregation and have been shown to prolong bleeding time in some patients. Unlike aspirin, their effect on platelet function is quantitatively less, of shorter duration, and reversible. Patients receiving ibuprofen who may be adversely affected by alterations in platelet function, such as those with coagulation disorders or patients receiving anticoagulants, should be carefully monitored.

Preexisting Asthma
Patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin-sensitive asthma has been associated with severe bronchospasm, which can be fatal. Since cross reactivity, including bronchospasm, between aspirin and other nonsteroidal anti-inflammatory drugs has been reported in such aspirin-sensitive patients, ibuprofen should not be administered to patients with this form of aspirin sensitivity and should be used with caution in patients with preexisting asthma.

Aseptic Meningitis
Aseptic meningitis, with fever and coma, has been observed on rare occasions in patients on ibuprofen therapy. Although it is probably more likely to occur in patients with systemic lupus erythematosus and related connective tissue diseases, it has been reported in patients who do not have an underlying chronic disease.

Diabetics
Ibuprofen oral suspension contains 0.3 g sucrose and 1.6 calories per mL, or 1.5 g sucrose and 8 calories per teaspoon, which should be taken into consideration when treating diabetic patients with this product.

Information for Patients:
Patients should be informed of the following information before initiating therapy with an NSAID and periodically during the course of ongoing therapy. Patients should also be encouraged to read the NSAID Medication Guide that accompanies each prescription dispensed.

1. Ibuprofen, like other NSAIDs, may cause serious CV side effects, such as MI or stroke, which may result in hospitalization, and even death. Although serious CV events can occur without warning symptoms, patients should be alert for the signs and symptoms of chest pain, shortness of breath, weakness, slurring of speech, and should ask for medical advice when observing any indicative sign or symptoms. Patients should be apprised of the importance of this follow-up (see **WARNINGS, Cardiovascular Effects**).
2. Ibuprofen, like other NSAIDs, can cause GI discomfort and, rarely, serious GI side effects, such as ulcers and bleeding, which may result in hospitalization or even death. Although serious GI tract ulcerations and bleeding can occur without warning symptoms, patients should be alert for signs and symptoms of ulcerations and bleeding, and should ask for medical advice when observing any indicative sign or symptoms including epigastric pain, dyspepsia, melena, and hematemesis. Patients should be apprised of the importance of this follow-up (see **WARNINGS, Gastrointestinal Effects-Risk of Ulceration, Bleeding, and Perforation**).
3. Ibuprofen, like other NSAIDs, can cause serious skin side effects such as exfoliative dermatitis, SJS, and TEN, which may result in hospitalizations and even death. Although serious skin reactions may occur without warning, patients should be alert for the signs and symptoms of skin rash and blisters, fever, or other signs of hypersensitivity such as itching, and should ask for medical advice when observing any indicative signs or symptoms. Patients should be advised to stop the drug immediately if they develop any type of rash or contact their physicians as soon as possible.
4. Patients should promptly report signs and symptoms of unexplained weight gain or edema to their physicians.
5. Patients should be informed of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, pruritis, jaundice, right upper quadrant tenderness, and "flu-like" symptoms). If these occur, patients should be instructed to stop therapy and seek immediate medical therapy.
6. Patients should be informed of the signs of an anaphylactoid reaction (e.g. difficulty breathing, swelling of the face or throat). If these occur, patients should be instructed to seek immediate emergency help (see **WARNINGS**).
7. In late pregnancy, as with other NSAIDs, ibuprofen should be avoided because it may cause premature closure of the ductus arteriosus.

Laboratory Tests
Because serious GI tract ulcerations and bleeding can occur without warning symptoms, physicians should monitor for signs or symptoms of GI bleeding. Patients on long-term treatment with NSAIDs should have their CBC and a chemistry profile checked periodically. If clinical signs and symptoms consistent with liver or renal disease develop, systemic manifestations occur (e.g., eosinophilia, rash, etc.) or if abnormal liver tests persist or worsen, ibuprofen should be discontinued.

Drug Interactions
ACE-Inhibitors
Reports suggest that NSAIDs may diminish the antihypertensive effect of ACE-inhibitors. This interaction should be given consideration in patients taking NSAIDs concomitantly with ACE-inhibitors.

Aspirin
As with other NSAIDs, concomitant administration of ibuprofen and aspirin is not generally recommended because of the potential of increased adverse effects.

Diuretics
Clinical studies, as well as post marketing 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 NSAIDs, the patient should be observed closely for signs of renal failure (see **WARNINGS, Renal Effects**), as well as to assure diuretic efficacy.

Lithium
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. (Read circulars for lithium preparation before use of such concurrent therapy.)

Methotrexate
NSAIDs have been reported to competitively inhibit methotrexate accumulation in rabbit kidney slices. This may indicate that they could enhance the toxicity of methotrexate. Caution should be used when NSAIDs are administered concomitantly with methotrexate.

Warfarin
Several short-term controlled studies failed to show that ibuprofen significantly affected prothrombin times or a variety of other clotting factors when administered to individuals on warfarin-type anticoagulants. However, because bleeding has been reported when ibuprofen and other NSAIDs have been administered to patients on warfarin-type anticoagulants, the physician should be cautious when administering ibuprofen to patients on anticoagulants. The effects of warfarin and NSAIDs on GI bleeding are synergistic, such that the users of both drugs together have a risk of serious GI bleeding higher than users of either drug alone.

Pregnancy
Teratogenic Effects — Pregnancy Category C: 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. There are no adequate and well-controlled studies in pregnant women. Ibuprofen should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects
Because of the known effects of nonsteroidal anti-inflammatory drugs on the fetal cardiovascular system (closure of ductus arteriosus), use during pregnancy (particularly late pregnancy) should be avoided.

Labor and Delivery
In rat studies with NSAIDs, as with other drugs known to inhibit prostaglandin synthesis, an increased incidence of dystocia, delayed parturition, and decreased pup survival occurred. The effects of ibuprofen on labor and delivery in pregnant women are unknown. Therefore, administration of ibuprofen is not recommended during labor and delivery.

Nursing Mothers
It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from ibuprofen, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use
Safety and effectiveness of ibuprofen in pediatric patients below the age of 6 months have not been established (see **CLINICAL PHARMACOLOGY - Clinical Studies**). Dosing of ibuprofen in children 6 months or older should be guided by their body weight (see **DOSAGE AND ADMINISTRATION**).

Geriatric Use
As with any NSAIDs, caution should be exercised in treating the elderly (65 years and older).

ADVERSE REACTIONS
In patients taking ibuprofen or other NSAIDs, the most frequently reported adverse experiences occurring in approximately 1-10% of patients are: Abnormal renal function, anemia, dizziness, edema, elevated liver enzymes, fluid retention, gastrointestinal experiences (including abdominal pain, bloating, constipation, diarrhea, dyspepsia, epigastric pain, flatulence, heartburn, nausea, vomiting), headaches, increased bleeding time, nervousness, pruritus, rashes (including maculopapular) and tinnitus.

Additional adverse experiences reported occasionally include:
Body as a whole - fever, infection, sepsis
Cardiovascular system - congestive heart failure in patients with marginal cardiac function, hypertension, tachycardia, syncope
Digestive system - dry mouth, duodenitits, esophagitis, gastric or duodenal ulcer with bleeding and/or perforation, gastritis, gastrointestinal bleeding, glossitis, hematemesis, hepatitis, jaundice, melena, rectal bleeding
Hemic and lymphatic system - ecchymosis, eosinophilia, leukopenia, purpura, stomatitis, thrombocytopenia
Metabolic and nutritional - weight changes
Nervous system - anxiety, asthenia, confusion, depression, dream abnormalities, drowsiness, insomnia, malaise, paresthesia, somnolence, tremors, vertigo
Respiratory system - asthma, dyspnea
Skin and appendages - alopecia, photosensitivity, sweat
Special senses - blurred vision
Urogenital system - cystitis, dysuria, hematuria, interstitial nephritis, oliguria/polyuria, proteinuria, acute renal failure in patients with pre-existing significantly impaired renal function

Other adverse reactions, which occur rarely are:
Body as a whole - anaphylactic reactions, anaphylactoid reactions, appetite changes
Cardiovascular system - arrhythmia, cerebrovascular accident, hypotension, myocardial infarction, palpitations, vasculitis
Digestive system - eructation, gingival ulcer, hepatorenal syndrome, liver necrosis, liver failure, pancreatitis
Hemic and lymphatic system - agranulocystosis, hemolytic anemia, aplastic anemia, lymphadenopathy, neutropenia, pancytopenia
Metabolic and nutritional - hyperglycemia
Nervous system - convulsions, coma, emotional lability hallucinations, aseptic meningitis
Respiratory - apnea, respiratory depression, pneumonia, rhinitis
Skin and appendages - angioedema, toxic epidermal necrosis, erythema multiforme, exfoliative dermatitis, Stevens Johnson syndrome, urticaria, vesiculobullous eruptions
Special senses - amblyopia (blurred and/or diminished vision, scotomata and/or changes in color vision), conjunctivitis, dry eyes, hearing impairment
Urogenital - azotemia, decreased creatinine clearance, glomerulitis, renal papillary necrosis, tubular necrosis

OVERDOSAGE
The toxicity of ibuprofen overdose is dependent upon the amount of drug ingested and the time elapsed since ingestion, though individual response may vary, which makes it necessary to evaluate each case individually. Although uncommon, serious toxicity and death have been reported in the medical literature with ibuprofen overdosage. The most frequently reported symptoms of ibuprofen overdose include abdominal pain, nausea, vomiting, lethargy and drowsiness. Other central nervous system symptoms include headache, tinnitus, CNS depression and seizures. Metabolic acidosis, coma, acute renal failure and apnea (primarily in very young children) may rarely occur. Cardiovascular toxicity, including hypotension, bradycardia, tachycardia and atrial fibrillation also have been reported.

The treatment of acute ibuprofen overdose is primarily supportive. Management of hypotension, acidosis and gastrointestinal bleeding may be necessary. In cases of acute overdose, the stomach should be emptied through ipecac-induced emesis or lavage. Emesis is most effective if initiated within 30 minutes of ingestion. Orally administered activated charcoal may help in reducing the absorption and reabsorption of ibuprofen.

In children, 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. Children ingesting 100 to 200 mg/kg may be managed with induced emesis and a minimal observation time of four hours. Children ingesting 200 to 400 mg/kg of ibuprofen should have immediate gastric emptying and at least four hours observation in a health care facility. Children ingesting greater than 400 mg/kg require immediate medical referral, careful observation and appropriate supportive therapy. Ipecac-induced emesis is not recommended in overdoses greater than 400 mg/kg because of the risk for convulsions and the potential for aspiration of gastric contents.

In adult patients the history of 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.

DOSAGE AND ADMINISTRATION
Carefully consider the potential benefits and risks of ibuprofen oral suspension and other treatment options before deciding to use ibuprofen oral suspension. Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals (see **WARNINGS**).

After observing the response to initial therapy with ibuprofen oral suspension, the dose and frequency should be adjusted to suit an individual patient's needs.

Pediatric Patients
Fever Reduction: For reduction of fever in children, 6 months up to 2 years of age, the dosage should be adjusted on the basis of the initial temperature level (see **CLINICAL PHARMACOLOGY**). The recommended dose is 5 mg/kg if the baseline temperature is less than 102.5ºF, or 10 mg/kg if the baseline temperature is 102.5ºF or greater. The duration of fever reduction is generally 6 to 8 hours. The recommended maximum daily dose is 40 mg/kg.
Analgesia: For relief of mild to moderate pain in children 6 months up to 2 years of age, the recommended dosage is 10 mg/kg, every 6 to 8 hours. The recommended maximum daily dose is 40 mg/kg. Doses should be given so as not to disturb the child's sleep pattern.
Juvenile Arthritis: The recommended dose is 30 to 40 mg/kg/day divided into three to four doses (see *Individualization Of Dosage*). Patients with milder disease may be adequately treated with 20 mg/kg/day.
In patients with juvenile arthritis, doses above 50 mg/kg/day are not recommended because they have not been studied and doses exceeding the upper recommended dose of 40 mg/kg/day may increase the risk of causing serious adverse events. The therapeutic response may require from a few days to several weeks to be achieved. Once a clinical effect is obtained, the dosage should be lowered to the smallest dose of ibuprofen oral suspension needed to maintain adequate control of symptoms.
Pediatric patients receiving doses above 30 mg/kg/day or if abnormal liver function tests have occurred with previous NSAID treatments should be carefully followed for signs and symptoms of early liver dysfunction.

Adults
Primary Dysmenorrhea: For the treatment of primary dysmenorrhea, beginning with the earliest onset of such pain, ibuprofen oral suspension should be given in a dose of 400 mg every 4 hours, as necessary, for the relief of pain.
Rheumatoid Arthritis And Osteoarthritis: Suggested dosage: 1200-3200 mg daily (300 mg q.i.d. or 400 mg, 600 mg or 800 mg t.i.d. or q.i.d.). Individual patients may show a better response to 3200 mg daily, as compared with 2400 mg, although in well-controlled clinical trials patients on 3200 mg did not show a better mean response in terms of efficacy. Therefore, when treating patients with 3200 mg/day, the physician should observe sufficient increased clinical benefits to offset potential increased risk.
Individualization Of Dosage: The dose of ibuprofen oral suspension should be tailored to each patient, and may be lowered or raised from the suggested doses depending on the severity of symptoms either at time of initiating drug therapy or as the patient responds or fails to respond.
One fever study showed that, after the initial dose of ibuprofen oral suspension, subsequent doses may be lowered and still provide adequate fever control.
In a situation when low fever would require the ibuprofen oral suspension 5 mg/kg dose in a child with pain, the dose that will effectively treat the predominant symptom should be chosen.
In chronic conditions, a therapeutic response to ibuprofen therapy is sometimes seen in a few days to a week, but most often is observed by two weeks. After a satisfactory response has been achieved, the patient's dose should be reviewed and adjusted as required.
Patients with rheumatoid arthritis seem to require higher doses than do patients with osteoarthritis. The smallest dose of ibuprofen oral suspension that yields acceptable control should be employed.
Ibuprofen oral suspension may be used in combination with gold salts and/or corticosteroids.

HOW SUPPLIED
Ibuprofen Oral Suspension USP, 100 mg/5 mL
Orange-colored, berry-flavored suspension
- Bottles of 4 fl oz (118 mL)
- Bottles of ONE PINT (473 mL)

Shake well before using. Store at controlled room temperature 15° to 30°C (59° to 86°F).
Dispense in a well-closed container as defined in the USP.

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Medication Guide for Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)
(See the end of this Medication Guide for a list of prescription NSAID medicines.)

What is the most important information I should know about medicines called Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)?

NSAID medicines may increase the chance of a heart attack or stroke that can lead to death. This chance increases:
- with longer use of NSAID medicines
- in people who have heart disease

NSAID medicines should never be used right before or after a heart surgery called a "coronary artery bypass graft (CABG)."

NSAID medicines can cause ulcers and bleeding in the stomach and intestines at any time during treatment. Ulcers and bleeding:
- can happen without warning symptoms
- may cause death

The chance of a person getting an ulcer or bleeding increases with:
- taking medicines called "corticosteroids" and "anticoagulants"
- longer use
- smoking
- drinking alcohol
- older age
- having poor health

NSAID medicines should only be used:
- exactly as prescribed
- at the lowest dose possible for your treatment
- for the shortest time needed

What are Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)?
NSAID medicines are used to treat pain and redness, swelling, and heat (inflammation) from medical conditions such as:
- different types of arthritis
- menstrual cramps and other types of short-term pain

Who should not take a Non-Steroidal Anti-Inflammatory Drug (NSAID)?
Do not take an NSAID medicine:
- if you had an asthma attack, hives, or other allergic reaction with aspirin or any other NSAID medicine
- for pain right before or after heart bypass surgery

Tell your healthcare provider:
- about all your medical conditions.
- about all of the medicines you take. NSAIDs and some other medicines can interact with each other and cause serious side effects. **Keep a list of your medicines to show to your healthcare provider and pharmacist.**
- if you are pregnant. **NSAID medicines should not be used by pregnant women late in their pregnancy.**
- if you are breastfeeding. **Talk to your doctor.**

What are the possible side effects of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)?

Serious side effects include:	Other side effects include:
• heart attack • stroke • high blood pressure • heart failure from body swelling (fluid retention) • kidney problems including kidney failure • bleeding and ulcers in the stomach and intestine • low red blood cells (anemia) • life-threatening skin reactions • life-threatening allergic reactions	• stomach pain • constipation • diarrhea • gas • heartburn • nausea • vomiting *Continued on reverse side*

Continued

Serious side effects include:	Other side effects include:
• liver problems including liver failure • asthma attacks in people who have asthma	• dizziness

Get emergency help right away if you have any of the following symptoms:
- shortness of breath or trouble breathing
- chest pain
- weakness in one part or side of your body
- slurred speech
- swelling of the face or throat

Stop your NSAID medicine and call your healthcare provider right away if you have any of the following symptoms:
- nausea
- more tired or weaker than usual
- itching
- your skin or eyes look yellow
- stomach pain
- flu-like symptoms
- vomit blood
- there is blood in your bowel movement or it is black and sticky like tar
- unusual weight gain
- skin rash or blisters with fever
- swelling of the arms and legs, hands and feet

These are not all the side effects with NSAID medicines. Talk to your healthcare provider or pharmacist for more information about NSAID medicines.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

Other information about Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)
- Aspirin is an NSAID medicine but it does not increase the chance of a heart attack. Aspirin can cause bleeding in the brain, stomach, and intestines. Aspirin can also cause ulcers in the stomach and intestines.
- Some of these NSAID medicines are sold in lower doses without a prescription (over-the-counter). Talk to your healthcare provider before using over-the-counter NSAIDs for more than 10 days.

NSAID medicines that need a prescription

Generic Name	Tradename
Celecoxib	Celebrex
Diclofenac	Cataflam, Voltaren, Arthrotec (combined with misoprostol)
Diflunisal	Dolobid
Etodolac	Lodine, Lodine XL
Fenoprofen	Nalfon, Nalfon 200
Flurbirofen	Ansaid
Ibuprofen	Motrin, Tab-Profen, Vicoprofen* (combined with hydrocodone), Combunox (combined with oxycodone)
Indomethacin	Indocin, Indocin SR, Indo-Lemmon, Indomethagan
Ketoprofen	Oruvail
Ketorolac	Toradol
Mefenamic Acid	Ponstel
Meloxicam	Mobic
Nabumetone	Relafen
Naproxen	Naprosyn, Anaprox, Anaprox DS, EC-Naproxyn, Naprelan, Naprapac (copackaged with lansoprazole)
Oxaprozin	Daypro
Piroxicam	Feldene
Sulindac	Clinoril
Tolmetin	Tolectin, Tolectin DS, Tolectin 600

*Vicoprofen contains the same dose of ibuprofen as over-the-counter (OTC) NSAIDs, and is usually used for less than 10 days to treat pain. The OTC NSAID label warns that long term continuous use may increase the risk of heart attack or stroke.

This Medication Guide has been approved by the U.S. Food and Drug Administration.