

IBUPROFEN- ibuprofen tablet, film coated
Aphena Pharma Solutions - Tennessee, LLC

IBU™ Tablets

BOXED WARNING

Cardiovascular Thrombotic Events

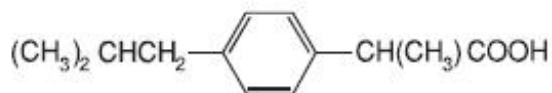
1. Nonsteroidal anti-inflammatory drugs (NSAIDs) cause an increased risk of serious cardiovascular thrombotic events, including myocardial infarction and stroke, which can be fatal. This risk may occur early in treatment and may increase with duration of use. (See **WARNINGS** and **PRECAUTIONS**).
1. IBU tablets are contraindicated in the setting of coronary artery bypass graft (CABG) surgery (See **CONTRAINDICATIONS** and **WARNINGS**).

Gastrointestinal Risk

1. 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

IBU tablets contain the active ingredient ibuprofen, which is (\pm) -2 - (*p* - isobutylphenyl) propionic acid. Ibuprofen is a white powder with a melting point of 74-77° C and is very slightly soluble in water (<1 mg/mL) and readily soluble in organic solvents such as ethanol and acetone. The structural formula is represented below:



IBU, a nonsteroidal anti-inflammatory drug (NSAID), is available in 400 mg, 600 mg, and 800 mg tablets for oral administration. Inactive ingredients: carnauba wax, colloidal silicon dioxide, croscarmellose sodium, hypromellose, magnesium stearate, microcrystalline cellulose, polydextrose, polyethylene glycol, polysorbate, titanium dioxide.

CLINICAL PHARMACOLOGY

IBU tablets contain ibuprofen which possesses analgesic and antipyretic activities. Its mode of action, like that of other NSAIDs, is not completely understood, but may be related to prostaglandin synthetase inhibition.

In clinical studies in patients with rheumatoid arthritis and osteoarthritis, Ibuprofen tablets have been shown to be comparable to aspirin in controlling pain and inflammation and to be associated with a statistically significant reduction in the milder gastrointestinal side effects (see **ADVERSE REACTIONS**). Ibuprofen may be well tolerated in some patients who have had gastrointestinal side

effects with aspirin, but these patients when treated with IBU tablets should be carefully followed for signs and symptoms of gastrointestinal ulceration and bleeding. Although it is not definitely known whether ibuprofen causes less peptic ulceration than aspirin, in one study involving 885 patients with rheumatoid arthritis treated for up to one year, there were no reports of gastric ulceration with ibuprofen whereas frank ulceration was reported in 13 patients in the aspirin group (statistically significant $p < .001$).

Gastroscopic studies at varying doses show an increased tendency toward gastric irritation at higher doses. However, at comparable doses, gastric irritation is approximately half that seen with aspirin. Studies using ^{51}Cr -tagged red cells indicate that fecal blood loss associated with ibuprofen tablets in doses up to 2400 mg daily did not exceed the normal range, and was significantly less than that seen in aspirin-treated patients.

In clinical studies in patients with rheumatoid arthritis, ibuprofen has been shown to be comparable to indomethacin in controlling the signs and symptoms of disease activity and to be associated with a statistically significant reduction of the milder gastrointestinal (see **ADVERSE REACTIONS**) and CNS side effects.

Ibuprofen may be used in combination with gold salts and/or corticosteroids.

Controlled studies have demonstrated that ibuprofen is a more effective analgesic than propoxyphene for the relief of episiotomy pain, pain following dental extraction procedures, and for the relief of the symptoms of primary dysmenorrhea.

In patients with primary dysmenorrhea, ibuprofen has been shown to reduce elevated levels of prostaglandin activity in the menstrual fluid and to reduce resting 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.

Pharmacodynamics

In a healthy volunteer study, ibuprofen 400 mg given once daily, administered 2 hours prior to immediate-release aspirin (81 mg) for 6 days, showed an interaction with the antiplatelet activity of aspirin as measured by % serum thromboxane B_2 (Tx B_2) inhibition at 24 hours following the day-6 aspirin dose [53%]. An interaction was still observed, but minimized, when ibuprofen 400 mg given once-daily was administered as early as 8 hours prior to the immediate-release aspirin dose [90.7%]. However, there was no interaction with the antiplatelet activity of aspirin when ibuprofen 400 mg, given once daily, was administered 2 hours after (but not concomitantly, 15 min, or 30 min after) the immediate-release aspirin dose [99.2%].

In another study, where immediate-release aspirin 81 mg was administered once daily with ibuprofen 400 mg given three times daily (1, 7, and 13 hours post-aspirin dose) for 10 consecutive days, the mean % serum thromboxane B_2 (Tx B_2) inhibition suggested no interaction with the antiplatelet activity of aspirin [98.3%]. However, there were individual subjects with serum Tx B_2 inhibition below 95%, with the lowest being 90.2%.

When a similarly designed study was conducted with enteric-coated aspirin, where healthy subjects were administered enteric-coated aspirin 81 mg once daily for 6 days and ibuprofen 400 mg three times daily (2, 7 and 12 h post-aspirin dose) for 6 days, there was an interaction with the antiplatelet activity at 24 hours following the day-6 aspirin dose [67%]. [See Precautions/Drug Interactions].

Pharmacokinetics

The ibuprofen in IBU tablets is rapidly absorbed. Peak serum ibuprofen levels are generally attained one to two hours after administration. With single doses up to 800 mg, a linear relationship exists between amount of drug administered and the integrated area under the serum drug concentration vs time curve. Above 800 mg, however, the area under the curve increases less than proportional to increases in dose. There is no evidence of drug accumulation or enzyme induction.

The administration of Ibuprofen tablets either under fasting conditions or immediately before meals yields quite similar serum ibuprofen concentration-time profiles. When Ibuprofen is administered immediately after a meal, there is a reduction in the rate of absorption but no appreciable decrease in the extent of absorption. The bioavailability of the drug is minimally altered by the presence of food.

A bioavailability study 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.

Ibuprofen is rapidly metabolized and eliminated in the urine. The excretion of ibuprofen is virtually complete 24 hours after the last dose. The serum half-life is 1.8 to 2.0 hours.

Studies have shown that following ingestion of the drug, 45% to 79% of the dose was recovered in the urine within 24 hours as metabolite A (25%), (+)-2-[p-(2hydroxymethyl-propyl) phenyl] propionic acid and metabolite B (37%), (+)-2-[p-(2carboxypropyl)phenyl]propionic acid; the percentages of free and conjugated ibuprofen were approximately 1% and 14%, respectively.

INDICATIONS AND USAGE

Carefully consider the potential benefits and risks of Ibuprofen tablets 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**).

IBU tablets are indicated for relief of the signs and symptoms of rheumatoid arthritis and osteoarthritis.

IBU tablets are indicated for relief of mild to moderate pain.

IBU tablets are also indicated for the treatment of primary dysmenorrhea.

Controlled clinical trials to establish the safety and effectiveness of IBU tablets in children have not been conducted.

CONTRAINDICATIONS

IBU tablets are contraindicated in patients with known hypersensitivity to ibuprofen.

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

IBU tablets are contraindicated 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, including myocardial infarction (MI), and stroke, which can be fatal. Based on available data, it is unclear that the risk for CV thrombotic events is similar for all NSAIDs. The relative increase in serious CV thrombotic events over baseline conferred by NSAID use appears to be similar in those with and without known CV disease or risk factors for CV disease. However, patients with known CV disease or risk factors had a higher absolute incidence of excess serious CV thrombotic events, due to their increased baseline rate. Some observational studies found that this increased risk of serious CV thrombotic events began as early as the first weeks of treatment. The increase in CV thrombotic risk has been observed most consistently at

higher doses.

To minimize the potential risk for an adverse CV event in NSAID-treated patients, use the lowest effective dose for the shortest duration possible. Physicians and patients should remain alert for the development of such events, throughout the entire treatment course, even in the absence of previous CV symptoms. Patients should be informed about the 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, such as ibuprofen, increases the risk of serious gastrointestinal (GI) events (see WARNINGS).

Status Post Coronary Bypass Graft (CABG) Surgery 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. NSAIDs are contraindicated in the setting of CABG (see CONTRAINDICATIONS).

Post-MI Patients Observational studies conducted in the Danish National Registry have demonstrated that patients treated with NSAIDs in the post-MI period were at increased risk of reinfarction, CV-related death, and all-cause mortality beginning in the first week of treatment. In this same cohort, the incidence of death in the first year post MI was 20 per 100 person years in NSAID-treated patients compared to 12 per 100 person years in non-NSAID exposed patients. Although the absolute rate of death declined somewhat after the first year post-MI, the increased relative risk of death in NSAID users persisted over at least the next four years to follow-up.

Avoid the use of Ibuprofen in patients with a recent MI unless the benefits are expected to outweigh the risk of recurrent CV thrombotic events. If Ibuprofen is used in patients with a recent MI, monitor patients for signs of cardiac ischemia.

Hypertension

NSAIDs including IBU tablets, can lead to onset of new hypertension or worsening of preexisting 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 IBU tablets, 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.

Heart Failure and Edema

The Coxib and traditional NSAID Trialists' Collaboration meta-analysis of randomized controlled trials demonstrated an approximately two-fold increase in hospitalizations for heart failure in COX-2 selective-treated patients and nonselective NSAID-treated patients compared to placebo-treated patients. In a Danish National Registry study of patients with heart failure, NSAID use increased the risk of MI, hospitalization for heart failure, and death. Additionally, fluid retention and edema have been observed in some patients treated with NSAIDs. Use of ibuprofen may blunt the CV effects of several therapeutic agents used to treat these medical conditions [e.g., diuretics, ACE inhibitors, or angiotensin receptor blockers (ARBs)] [See DRUG INTERACTIONS]. Avoid the use of IBU tablets in patients with severe heart failure unless the benefits are expected to outweigh the risk of worsening heart failure. If IBU tablets is used in patients with severe heart failure, monitor patients for signs of worsening heart failure.

Gastrointestinal Effects - Risk of Ulceration, Bleeding, and Perforation

NSAIDs, including IBU tablets, 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 increased risk for developing a GI bleed compared to patients treated with neither of these risk factors. Other factors that increase the risk of 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 ulcerations and bleeding during NSAID therapy and promptly initiate additional evaluation and treatment if a serious GI 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 NSAID 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 tablets in patients with advanced renal disease. Therefore, treatment with IBU tablets is not recommended in these patients with advanced renal disease. If IBU tablet therapy must be initiated, close monitoring of the patients renal function is advisable.

Anaphylactoid Reactions

As with other NSAIDs, anaphylactoid reactions may occur in patients without known prior exposure to IBU tablets. IBU tablets 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 IBU tablets, 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, IBU tablets should be avoided because it may cause premature

closure of the ductus arteriosus.

PRECAUTIONS

General

IBU tablets 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 IBU tablets 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 IBU tablets. 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, 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 with abnormal liver test values, should be evaluated for evidence of the development of a more severe hepatic reaction while on therapy with IBU tablets. If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), IBU tablets should be discontinued.

Hematological effects

Anemia is sometimes seen in patients receiving NSAIDs, including IBU tablets. 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 IBU tablets, 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 IBU tablets 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 NSAIDs has been reported in such aspirin-sensitive patients, IBU tablets should not be administered to patients with this form of aspirin sensitivity and should be used with caution in patients with preexisting asthma.

Ophthalmological effects.

Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported. If a patient develops such complaints while receiving IBU tablets, the drug should be discontinued, and

the patient should have an ophthalmologic examination which includes central visual fields and color vision testing.

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. If signs or symptoms of meningitis develop in a patient on IBU tablets, the possibility of its being related to IBU tablets should be considered.

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

- **Cardiovascular Thrombotic Events:** Advise patients to be alert for the symptoms of cardiovascular thrombotic events, including chest pain, shortness of breath, weakness, or slurring of speech, and to report any of these symptoms to their health care provider immediately [see WARNINGS].
- IBU tablets, like other NSAIDs, can cause GI discomfort and, rarely, serious GI side effects, such as ulcers and bleeding, which may result in hospitalization and even death. Although serious GI tract ulcerations and bleeding can occur without warning symptoms, patients should be alert for the signs and symptoms of ulcerations and bleeding, and should ask for medical advice when observing any indicative signs 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**).
- IBU tablets, like other NSAIDs, can cause serious skin side effects such as exfoliative dermatitis, SJS and TEN, which may result in hospitalization 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 sign or symptoms. Patients should be advised to stop the drug immediately if they develop any type of rash and contact their physicians as soon as possible.
- **Heart Failure and Edema:** Advise patients to be alert for the symptoms of congestive heart failure including shortness of breath, unexplained weight gain, or edema and to contact their health care provider if such symptoms occur [see WARNINGS].
- Patients should be informed of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, pruritus, jaundice, right upper quadrant tenderness and “flu-like” symptoms). If these occur, patients should be instructed to stop therapy and seek immediate medical therapy.
- 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**).
- In late pregnancy, as with other NSAIDs, IBU tablets 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 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 abnormal liver tests persist or worsen, IBU tablets 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:

Pharmacodynamic studies have demonstrated interference with the antiplatelet activity of aspirin when ibuprofen 400 mg, given three times daily, is administered with enteric-coated low-dose aspirin. The interaction exists even following a once-daily regimen of ibuprofen 400 mg, particularly when ibuprofen is dosed prior to aspirin. The interaction is alleviated if immediate-release low-dose aspirin is dosed at least 2 hours prior to a once-daily regimen of ibuprofen; however, this finding cannot be extended to enteric-coated low-dose aspirin [see Clinical Pharmacology/Pharmacodynamics].

Because there may be an increased risk of cardiovascular events due to the interference of ibuprofen with the antiplatelet effect of aspirin, for patients taking low-dose aspirin for cardio protection who require analgesics, consider use of an NSAID that does not interfere with the antiplatelet effect of aspirin, or non-NSAID analgesics, where appropriate.

When IBU tablets are administered with aspirin, its protein binding is reduced, although the clearance of free IBU tablets is not altered. The clinical significance of this interaction is not known; however, as with other NSAIDs, concomitant administration of ibuprofen and aspirin is not generally recommended because of the potential for increased adverse effects.

Diuretics

Clinical studies, as well as post marketing observations, have shown that Ibuprofen tablets 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 PRECAUTIONS, 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-type anticoagulants

Several short-term controlled studies failed to show that Ibuprofen tablets significantly affected prothrombin times or a variety of other clotting factors when administered to individuals on coumarin-type anticoagulants. However, because bleeding has been reported when IBU tablets and other NSAIDs have been administered to patients on coumarin-type anticoagulants, the physician should be cautious when administering IBU tablets 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.

H-2 Antagonists

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

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 NSAIDs on the fetal cardiovascular system (closure of ductus arteriosus), use during 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 IBU tablets on labor and delivery in pregnant women are unknown.

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 IBU tablets, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness of IBU tablets in pediatric patients have not been established.

Geriatric Use

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

ADVERSE REACTIONS

The most frequent type of adverse reaction occurring with ibuprofen tablets is gastrointestinal. In controlled clinical trials the percentage of patients reporting one or more gastrointestinal complaints ranged from 4% to 16%.

In controlled studies when ibuprofen tablets were compared to aspirin and indomethacin in equally effective doses, the overall incidence of gastrointestinal complaints was about half that seen in either the aspirin- or indomethacin-treated patients.

Adverse reactions observed during controlled clinical trials at an incidence greater than 1% are listed in the table. Those reactions listed in Column one encompass observations in approximately 3,000 patients. More than 500 of these patients were treated for periods of at least 54 weeks.

Still other reactions occurring less frequently than 1 in 100 were reported in controlled clinical trials and from marketing experience. These reactions have been divided into two categories: Column two of the table lists reactions with therapy with ibuprofen tablets where the probability of a causal relationship exists; for the reactions in Column three, a causal relationship with ibuprofen tablets has not been established.

Reported side effects were higher at doses of 3200 mg/day than at doses of 2400 mg or less per day in clinical trials of patients with rheumatoid arthritis. The increases in incidence were slight and still within

the ranges reported in the table.

Incidence Greater than 1% (but less than 3%) Probable Causal Relationship*	Precise Incidence Unknown (but less than 1%) Probable Causal Relationship**	Precise Incidence Unknown (but less than 1%) Causal Relationship Unknown**
GASTROINTESTINAL Nausea*, epigastric pain*, heartburn*, diarrhea, abdominal distress, nausea and vomiting, indigestion, constipation, abdominal cramps or Pain, fullness of GI tract (bloating and flatulence)	Gastric or duodenal ulcer with bleeding and/or perforation, gastrointestinal hemorrhage, melena, gastritis, hepatitis, jaundice, abnormal liver function tests; pancreatitis	
CENTRAL NERVOUS SYSTEM Dizziness*, headache, nervousness	Depression, insomnia, confusion, emotional lability, somnolence, aseptic meningitis with fever and coma (see PRECAUTIONS)	Paresthesias, hallucinations, dream abnormalities, pseudotumor cerebri
DERMATOLOGIC Rash*, (including maculopapular type), pruritus	Vesiculobullous eruptions, urticaria, erythema multiforme, Stevens-Johnson syndrome, alopecia	Toxic epidermal necrolysis, photoallergic skin reactions
SPECIAL SENSES Tinnitus	Hearing loss, amblyopia (blurred and/or diminished vision, scotomata and/or changes in color vision) (see PRECAUTIONS)	Conjunctivitis, diplopia, optic neuritis, cataracts
HEMATOLOGIC	Neutropenia, agranulocytosis, aplastic anemia, hemolytic anemia (sometimes Coombs positive), thrombocytopenia with or without purpura, eosinophilia, decreases in hemoglobin and hematocrit (see PRECAUTIONS)	Bleeding episodes (eg epistaxis, menorrhagia)
METABOLIC/ENDOCRINE Decreased appetite		Gynecomastia, hypoglycemic reaction, acidosis
CARDIOVASCULAR Edema, fluid retention (generally responds promptly to drug discontinuation) (see PRECAUTIONS)	Congestive heart failure in patients with marginal cardiac function, elevate blood pressure, palpitations	Arrhythmias (sinus tachycardia, sinus bradycardia)
ALLERGIC	Syndrome of abdominal pain, fever, chills, nausea and vomiting; anaphylaxis; bronchospasm (see CONTRAINDICATIONS)	Serum sickness, lupus erythematosus syndrome, Henoch-Schonlein vasculitis, angioedema
RENAL	Acute renal failure (see PRECAUTIONS), decreased creatinine clearance, polyuria, azotemia, cystitis, Hematuria	Renal papillary necrosis
MISCELLANEOUS	Dry eyes and mouth, gingival ulcer, rhinitis	

* Reactions occurring in 3% to 9% of patients treated with IBU. (Those reactions occurring in less than 3% of the patients are unmarked.)
 ** Reactions are classified under "Probable Causal Relationship (PCR)" if there has been one positive rechallenge or if three or more cases occur which might be causally related. Reactions are classified under "Causal Relationship Unknown" if seven or more events have been reported but the criteria for PCR have not been met.

OVERDOSAGE

Approximately 11/2 hours after the reported ingestion of from 7 to 10 Ibuprofen tablets (400 mg), a 19-month old child weighing 12 kg was seen in the hospital emergency room, apneic and cyanotic, responding only to painful stimuli. This type of stimulus, however, was sufficient to induce respiration. Oxygen and parenteral fluids were given; a greenish-yellow fluid was aspirated from the stomach with no evidence to indicate the presence of ibuprofen. Two hours after ingestion the child's condition seemed stable; she still responded only to painful stimuli and continued to have periods of apnea lasting from 5 to 10 seconds. She was admitted to intensive care and sodium bicarbonate was administered as well as infusions of dextrose and normal saline. By four hours post-ingestion she could be aroused easily, sit by herself and respond to spoken commands. Blood level of ibuprofen was 102.9 µg/mL approximately 8 1/2 hours after accidental ingestion. At 12 hours she appeared to be completely recovered.

In two other reported cases where children (each weighing approximately 10 kg) accidentally, acutely ingested approximately 120 mg/kg, there were no signs of acute intoxication or late sequelae. Blood level in one child 90 minutes after ingestion was 700 µg/mL —about 10 times the peak levels seen in absorption-excretion studies. A 19-year old male who had taken 8,000 mg of ibuprofen over a period of a few hours complained of dizziness, and nystagmus was noted. After hospitalization, parenteral hydration and three days bedrest, he recovered with no reported sequelae.

In cases of acute overdosage, the stomach should be emptied by vomiting or lavage, though little drug will likely be recovered if more than an hour has elapsed since ingestion. Because the drug is acidic and is excreted in the urine, it is theoretically beneficial to administer alkali and induce diuresis. In addition to supportive measures, the use of oral activated charcoal may help to reduce the absorption and reabsorption of Ibuprofen tablets.

DOSAGE AND ADMINISTRATION

Carefully consider the potential benefits and risks of IBU tablets and other treatment options before

deciding to use IBU tablets. 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 IBU tablets, the dose and frequency should be adjusted to suit an individual patient's needs. Do not exceed 3200 mg total daily dose. If gastrointestinal complaints occur, administer IBU tablets with meals or milk.

Rheumatoid arthritis and osteoarthritis, including flare-ups of chronic disease:

Suggested Dosage: 1200 mg-3200 mg daily (400 mg, 600 mg or 800 mg tid or qid). 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. The dose should be tailored to each patient, and may be lowered or raised depending on the severity of symptoms either at time of initiating drug therapy or as the patient responds or fails to respond. In general, patients with rheumatoid arthritis seem to require higher doses of IBU tablets than do patients with osteoarthritis.

The smallest dose of IBU tablets that yields acceptable control should be employed. A linear blood level dose-response relationship exists with single doses up to 800 mg (See CLINICAL PHARMACOLOGY for effects of food on rate of absorption).

The availability of three tablet strengths facilitates dosage adjustment. In chronic conditions, a therapeutic response to therapy with IBU tablets 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.

Mild to moderate pain:

400 mg every 4 to 6 hours as necessary for relief of pain. In controlled analgesic clinical trials, doses of Ibuprofen tablets greater than 400 mg were no more effective than the 400 mg dose.

Dysmenorrhea:

For the treatment of dysmenorrhea, beginning with the earliest onset of such pain, IBU tablets should be given in a dose of 400 mg every 4 hours as necessary for the relief of pain.

HOW SUPPLIED

IBU tablets are available in the following strengths, colors and sizes:

400 mg (white, oval, debossed 4I)

Unit Dose Box of 100 NDC 0904-5853-61

Bottle of 100 Tablets NDC 0904-5853-60

Bottle of 500 Tablets NDC 0904-5853-40

600 mg (white, caplet, debossed 6I)

Unit Dose Box of 100 NDC 0904-5854-61

Bottle of 100 Tablets NDC 0904-5854-60

Bottle of 500 Tablets NDC 0904-5854-40

800 mg (white, caplet, debossed 8I)

Unit Dose Box of 100 NDC 0904-5855-61

Bottle of 100 Tablets NDC 0904-5855-60

Bottle of 500 Tablets NDC 0904-5855-40

Store at room temperature. Avoid excessive heat 40°C (104°F).

Manufactured by:

Dr. Reddy's Laboratories Louisiana, LLC

Shreveport, LA 71106 USA

Distributed By:

MAJOR® PHARMACEUTICALS

17177 N Laurel Park Dr., Suite 233

Livonia, MI 48152

Revised: April 2019

MEDICATION GUIDE

Medication Guide for Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

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

NSAIDs can cause serious side effects, including:

• **Increased risk of a heart attack or stroke that can lead to death.** This risk may happen early in treatment and may increase:

- with increasing doses of NSAIDs
- with longer use of NSAIDs

Do not take NSAIDs right before or after a heart surgery called a "coronary artery bypass graft (CABG)."

Avoid taking NSAIDs after a recent heart attack, unless your healthcare provider tells you to. You may have an increased risk of another heart attack if you take NSAIDs after a recent heart attack.

• **Increased risk of bleeding, ulcers, and tears (perforation) of the esophagus (tube leading from the mouth to the stomach), stomach and intestines:**

- anytime during use
- without warning symptoms
- that may cause death

The risk of getting an ulcer or bleeding increases with:

- past history of stomach ulcers, or stomach or intestinal bleeding with use of NSAIDs
- taking medicines called "corticosteroids", "anticoagulants", "SSRIs", or "SNRIs"
- increasing use of NSAIDs
- longer use of NSAIDs
- smoking
- drinking alcohol
- older age
- poor health

- advanced liver disease
- bleeding problems

NSAIDs should only be used:

- exactly as prescribed
- at the lowest dose possible for your treatment
- for the shortest time needed

What are NSAIDs?

NSAIDs 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 NSAIDs?

Do not take NSAIDs:

- if you had an asthma attack, hives, or other allergic reaction with aspirin or any other NSAIDs
- right before or after heart bypass surgery

Before taking NSAIDs, tell your healthcare provider about all your medical conditions, including if you:

- have liver or kidney problems
- have high blood pressure
- have asthma
- are pregnant or plan to become pregnant. Talk to your healthcare provider if you are considering taking NSAIDs during pregnancy. **You should not take NSAIDs after 29 weeks or pregnancy.**
- are breastfeeding or plan to breast feed

Tell your healthcare provider about all of the medicines you take, including prescription or over-the-counter medicines, vitamins or herbal supplements. NSAIDs and some other medicines can interact with each other and cause serious side effects. **Do not start taking any new medicine without talking to your healthcare provider first.**

What are the possible side effects of NSAIDs?

NSAIDs can cause serious side effects, including:

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

- new or worse high blood pressure • low red blood cells (anemia)
- heart failure • life-threatening skin reactions
- liver problems including liver failure • life-threatening allergic reactions
- kidney problems including kidney failure
- **Other side effects of NSAIDs include:** stomach pain, constipation, diarrhea, gas, heartburn, nausea, vomiting, and dizziness.

Get emergency help right away if you have any of the following symptoms:

- shortness of breath or trouble breathing • slurred speech
- chest pain • swelling of the face or throat
- weakness in one part or side of your body

Stop your NSAID medicine and call your healthcare provider right away if you have any of the following symptoms:

- nausea • vomit blood
- more tired or weaker than usual • there is blood in your bowel movement or it is black and sticky like tar
- diarrhea • unusual weight gain
- itching • skin rash or blisters with fever
- your skin or eyes look yellow • swelling of the arms, legs, hands and feet
- indigestion or stomach pain • flu-like symptoms

If you take too much of your NSAIDs, call your healthcare provider or get medical help right away.

These are not all the possible side effects of NSAIDs. For more information, ask your healthcare provider or pharmacist about NSAIDs.

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

Other information about NSAIDs

- Aspirin is an NSAID 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 NSAIDs 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.

General information about the safe and effective use of NSAIDs

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use NSAIDs for a condition for which it was not prescribed. Do not give NSAIDs to other people, even if they have the same symptoms that you have. It may harm them.

If you would like more information about NSAIDs, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about NSAIDs that is written for professionals.

IBU™ Ibuprofen Tablets USP 400 mg, 600 mg, and 800 mg Rx - ANDA# 075682

Manufacturing facility: Dr. Reddy's Laboratories Louisiana, LLC - Shreveport, LA 71106 USA

Distributed by: Dr. Reddy's Laboratories, Inc.

For more info, call/contact: 1-888-375-3784

Distributed By:

MAJOR® PHARMACEUTICALS

17177 N Laurel Park Dr., Suite 233

Livonia, MI 48152

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

Revised: April 2019

Repackaging Information

Please reference the **How Supplied** section listed above for a description of individual tablets. This drug product has been received by Aphenia Pharma - TN in a manufacturer or distributor packaged configuration and repackaged in full compliance with all applicable cGMP regulations. The package

configurations available from Aphenia are listed below:

Count	400 mg
90	71610-414-60
180	71610-414-80
270	71610-414-92
500	71610-414-74

Store between 20°-25°C (68°-77°F). See USP Controlled Room Temperature. Dispense in a tight light-resistant container as defined by USP. Keep this and all drugs out of the reach of children.

Repackaged by:

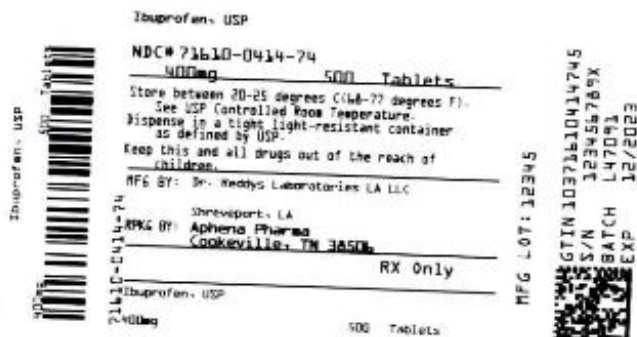


Cookeville, TN 38506

20200430JH

PRINCIPAL DISPLAY PANEL - 400 mg

NDC 71610-414 - Ibuprofen, USP 400 mg Tablets - Rx Only



IBUPROFEN

ibuprofen tablet, film coated

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:71610-414(NDC:0904-5853)
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
IBUPROFEN (UNII: WK2XYI10QM) (IBUPROFEN - UNII:WK2XYI10QM)	IBUPROFEN	400 mg

Inactive Ingredients

Ingredient Name	Strength
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
COPOVIDONE K25-31 (UNII: D9C330MD8B)	
SODIUM STARCH GLYCOLATE TYPE A POTATO (UNII: 5856J3G2A2)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
POLYSORBATE 80 (UNII: 6OZP39ZG8H)	

Product Characteristics

Color	WHITE	Score	no score
Shape	OVAL	Size	14mm
Flavor		Imprint Code	4I
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:71610-414-60	90 in 1 BOTTLE; Type 0: Not a Combination Product	07/30/2020	
2	NDC:71610-414-80	180 in 1 BOTTLE; Type 0: Not a Combination Product	07/30/2020	
3	NDC:71610-414-92	270 in 1 BOTTLE; Type 0: Not a Combination Product	07/30/2020	
4	NDC:71610-414-74	500 in 1 BOTTLE; Type 0: Not a Combination Product	04/15/2020	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA075682	06/10/2009	

Labeler - Aphenia Pharma Solutions - Tennessee, LLC (128385585)

Establishment

Name	Address	ID/FEI	Business Operations
Aphenia Pharma Solutions - Tennessee, LLC		128385585	REPACK(71610-414)