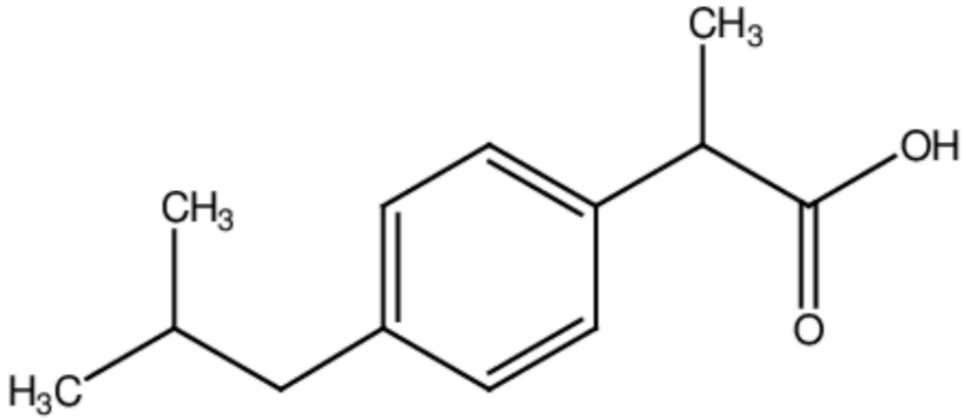
Approved Date: December 28th, 2007
Revision Date: December 1st, 2015

Package Insert of Ibuprofen Sustained-release Capsules

Please read the package insert carefully and use according to doctor's instructions.

[Drug Name]
Generic Name: Ibuprofen Sustained-release Capsules
Chinese Pinyin: Bulofen Huanshi Jiaonang

[Active Ingredients]
The active pharmaceutical ingredient (API) of this product is ibuprofen.
Chemical Name of the API: (±) - 2 - (p -isobutylphenyl) propionic acid.
Chemical Structure:



Molecular Formula: $C_{13}H_{18}O_2$
Molecular Weight: 206.29

[Inactive Ingredients]
Sucrose pellets, Polyethylene glycol, Hydroxypropyl Methylcellulose, Titanium Oxide, Alcohol, Purified Water.

[Properties]
This product contains white granule pellets.

[Drug Class]
This product is a non-steroidal anti-inflammatory drug (NSAID).

[Indications]
JIUBAOFEN capsules are indicated for the relief of mild to moderate pain, like headache, migraine, toothache, muscle pain, neuropathic pain andthe signs and symptoms of rheumatoid arthritis, osteoarthritis. JIUBAOFEN also indicated for relieve the fever caused by common cold or flu.

[Strength]
300 mg

[Dosage and Administration]

Oral administration. Adult: one capsule at a time, twice a day (one in the morning and one in the night).

[Adverse Reactions]

The most frequent type of adverse reaction occurring with IBUPROFEN 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 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 where the probability of a causal relationship exists: for the reactions in Column three, a causal relationship with IBUPROFEN has not been established.

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 liability, somnolence, aseptic meningitis with fever and coma	Paresthesias, hallucinations, dream, abnormalities, pseudo-tumor
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)	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	Bleeding episodes (eg epistaxis, menorrhagia)
METABOLIC/ENDOCRINE		
Decreased appetite		Gynecomastia, hypoglycemic reaction, acidosis

CARDIOVASCULAR		
Edema, fluid retention (generally responds promptly to drug discontinuation)	Congestive heart failure in patients with marginal cardiac function, elevated blood pressure, palpitations	Arrhythmias (sinus tachycardia, sinus bradycardia)
ALLERGIC		
	Syndrome of abdominal pain, fever, chills, nausea and vomiting; anaphylaxis; bronchospasm	Serum sickness, lupus erythematosus syndrome. Henoch-Schonlein vasculitis, angioedema
RENAL		
	Acute renal failure, decreased creatinine clearance, polyuria, azotemia, cystitis, Hematuria	Renal papillary necrosis
MISCELLANEOUS		
	Dry eyes and mouth, gingival ulcer, rhinitis	

[Contraindications]
JIUBAOFEN are contraindicated in patients with known hypersensitivity to Ibuprofen.
JIUBAOFEN 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.
JIUBAOFEN are contraindicated for the treatment of perioperative pain in the setting of coronary artery bypass graft (CABG) surgery.

[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, 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 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 NSAIDs 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.

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 IBUPROFEN, 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 IBUPROFEN, the possibility of its being related to IBUPROFEN should be considered.

[Use in Pregnant and Lactation]
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 IBUPROFEN 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 IBUPROFEN, 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 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).

[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
When IBUPROFEN are administered with aspirin, its protein binding is reduced, although the clearance of free IBUPROFEN 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 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, 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.

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 capsules 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 IBUPROFEN and other NSAIDs have been administered to patients on coumarin-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.

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

[Over-Dosage]

Approximately t½ hours after the reported ingestion of from 7 to 10 MOTRIN 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 8½ 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 bed rest, 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 MOTRIN tablets.

[Pharmacology and Toxicology]

Clinical Pharmacology

JIUBAOFEN 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, JIUBAOFEN 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. JIUBAOFEN may be well tolerated in some patients who have had gastrointestinal side effects with aspirin, but these patients when treated with JIUBAOFEN should be carefully followed for signs and symptoms of gastrointestinal ulceration and bleeding. Although it is not definitely known whether JIUBAOFEN 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 JIUBAOFEN 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 51Cr-tagged red cells indicate that fecal blood loss associated with JIUBAOFEN 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, JIUBAOFEN have 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 and CNS side effects.

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

Controlled studies have demonstrated that JIUBAOFEN are 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, JIUBAOFEN have 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.

The ibuprofen in JIUBAOFEN 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 JIUBAOFEN either under fasting conditions or immediately before meals yields quite similar serum ibuprofen concentration-time profiles. When JIUBAOFEN are 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 JIUBAOFEN were 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.

[Storage]
Seal and store away from direct sunlight.

[Packaging]
Aluminum-plastic blister packaging, 6 tablets/plate, two plates/carton
Aluminum-plastic blister packaging, 6 tablets/plate, three plates/carton
Aluminum-plastic blister packaging, 6 tablets/plate, four plates/carton
Aluminum-plastic blister packaging, 10 tablets/plate, one plate/carton
Aluminum-plastic blister packaging, 10 tablets/plate, two plates/carton
Aluminum-plastic blister packaging, 10 tablets/plate, three plates/carton

[Shelf-Life]
24 months

[Executive Standard]
Chinese Pharmacopoeia 2015 Edition Second Part

[Approval Number]
Guo Yao Zhun Zi H20074172

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