

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use IBUPROFEN and FAMOTIDINE TABLETS safely and effectively. See full prescribing information for IBUPROFEN and FAMOTIDINE TABLETS.

IBUPROFEN and FAMOTIDINE tablets, for oral use

Initial U.S. Approval: 2011

WARNING: RISK OF SERIOUS CARDIOVASCULAR AND GASTROINTESTINAL EVENTS

See full prescribing information for complete boxed warning.

- 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 (5.1)

- Ibuprofen and famotidine tablet is contraindicated in the setting of coronary artery bypass graft (CABG) surgery (4, 5.1)
- NSAIDs cause an increased risk of serious gastrointestinal (GI) 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 and patients with a prior history of peptic ulcer disease and/or GI bleeding are at greater risk for serious GI events (5.2)

RECENT MAJOR CHANGES

- Warnings and Precautions, Serious Skin Reactions (5.11)

07/2024

INDICATIONS AND USAGE

Ibuprofen and famotidine tablet, a combination of a nonsteroidal anti-inflammatory drug (NSAID) ibuprofen and the histamine H₂-receptor antagonist famotidine, is indicated for the relief of signs and symptoms of rheumatoid arthritis and osteoarthritis and to decrease the risk of developing upper gastrointestinal ulcers, which in the clinical trials was defined as a gastric and/or duodenal ulcer, in patients who are taking ibuprofen for those indications. The clinical trials primarily enrolled patients less than 65 years of age without a prior history of gastrointestinal ulcer. Controlled trials do not extend beyond 6 months. (1)

DOSE AND ADMINISTRATION

- One ibuprofen and famotidine tablet administered orally three times per day. (2)
- Use ibuprofen at the lowest effective dosage for the shortest duration consistent with individual patient treatment goals. (2)
- Do not substitute ibuprofen and famotidine tablet with the single-ingredient products of ibuprofen and famotidine. (2)

DOSE FORMS AND STRENGTHS

- Ibuprofen and Famotidine Tablets: 800 mg ibuprofen and 28.6 mg famotidine. (3)

CONTRAINDICATIONS

- Known hypersensitivity to ibuprofen or famotidine or any components of the drug product. (4)
- History of asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs. (4)

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FULL PRESCRIBING INFORMATION

WARNING: RISK OF SERIOUS CARDIOVASCULAR AND GASTROINTESTINAL EVENTS

Cardiovascular Thrombotic Events

- 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 (5.1)].*
- Ibuprofen and famotidine tablet is contraindicated in the setting of coronary artery bypass graft (CABG) surgery *[see Contraindications (4)]* and *Warnings and Precautions (5.1)]*.

Gastrointestinal Bleeding, Ulceration, and Perforation

- NSAIDs cause an increased risk of serious gastrointestinal (GI) 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 and patients with a prior history of peptic ulcer disease and/or GI bleeding are at greater risk for serious GI events *[see Warnings and Precautions (5.2)]*.

1. INDICATIONS AND USAGE

Ibuprofen and famotidine tablet, a combination of the NSAID ibuprofen and the histamine H₂-receptor antagonist famotidine, is indicated for the relief of signs and symptoms of rheumatoid arthritis and osteoarthritis and to decrease the risk of developing upper gastrointestinal ulcers, which in the clinical trials was defined as a gastric and/or duodenal ulcer, in patients who are taking ibuprofen for those indications. The clinical trials primarily enrolled patients less than 65 years of age without a prior history of gastrointestinal ulcer. Controlled trials do not extend beyond 6 months *[see Clinical Studies (14), Use in Specific Populations (8.5)]*.

2. DOSE AND ADMINISTRATION

Carefully consider the potential benefits and risks of ibuprofen and famotidine tablets and other treatment options before deciding to use ibuprofen and famotidine tablets. Use ibuprofen at the lowest effective dosage for the shortest duration consistent with individual patient treatment goals *[see Warnings and Precautions (5)]*.

The recommended daily dose of ibuprofen and famotidine 800 mg/28.6 mg is a single tablet administered orally three times per day. Ibuprofen and famotidine tablets should be swallowed whole, and should be taken with or without food. Do not chew, divide, or crush tablets.

Patients should be instructed that if a dose is missed, it should be taken as soon possible. However, if the next scheduled dose is due, the patient should not take the missed dose, and should be instructed to take the next dose on time. Patients should be instructed not to take 2 doses at one time to make up for a missed dose.

Do not substitute ibuprofen and famotidine tablet with the single-ingredient products of ibuprofen and famotidine.

3. DOSE FORMS AND STRENGTHS

Ibuprofen and famotidine tablets: 800 mg/28.6 mg are Blue/Light blue coated Modified Oval shaped tablets debossed with T396 on one side and an engraved circle on the other side.

4. CONTRAINDICATIONS

Ibuprofen and famotidine tablet is contraindicated in the following patients:

- Known hypersensitivity (e.g., anaphylactic reactions and serious skin reactions) to ibuprofen or famotidine or any components of the drug product *[see Warnings and Precautions (5.8, 5.11)]*.
- History of asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs. Severe, sometimes fatal, anaphylactic reactions to NSAIDs have been reported in such patients *[see Warnings and Precautions (5.8, 5.10)]*.
- In the setting of coronary artery bypass graft (CABG) surgery *[see Warnings and Precautions (4)]*.
- Ibuprofen and famotidine tablet should not be administered to patients with a history of hypersensitivity to other H₂-receptor antagonists. Cross sensitivity with other H₂-receptor antagonists has been observed.

5. WARNINGS AND PRECAUTIONS

5.1 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 and Precautions (5.2)]*.

Status Post Coronary Artery 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 (4)]*.

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 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 of follow-up.

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

5.2 Gastrointestinal Bleeding, Ulceration, and Perforation
NSAIDs, including ibuprofen, cause serious gastrointestinal (GI) adverse events including inflammation, bleeding, ulceration, and perforation of the esophagus, 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 occurred in approximately 1% of patients treated for 3–6 months, and in about 2%–4% of patients treated for one year. However, even short-term NSAID therapy is not without risk.

Risk Factors for GI Bleeding, Ulceration, and Perforation
Patients with a prior history of peptic ulcer disease and/or GI bleeding who used NSAIDs had a greater than 10-fold increased risk of developing a GI bleed compared to patients without these risk factors. Other factors that increase the risk of GI bleeding in patients treated with NSAIDs include longer duration of NSAID therapy; concomitant use of oral corticosteroids, aspirin, anticoagulants, or selective serotonin reuptake inhibitors (SSRIs); smoking; use of alcohol; older age; or poor general health status. Most postmarketing reports of fatal GI events occurred in elderly or debilitated patients. Additionally, patients with advanced liver disease and/or coagulopathy are at increased risk for GI bleeding.

NSAIDs should be given with care to patients with a history of inflammatory bowel disease (ulcerative colitis, Crohn's disease) as their condition may be exacerbated.

Strategies to Minimize the GI Risks in NSAID-treated patients:

- Use the lowest effective dosage for the shortest possible duration.
- Avoid administration of more than one NSAID at a time.
- Avoid use in patients at higher risk unless benefits are expected to outweigh the increased risk of bleeding. For such patients, as well as those with active GI bleeding, consider alternate therapies other than NSAIDs.
- Remain alert for signs and symptoms of GI ulceration and bleeding during NSAID therapy.
- If a serious GI adverse event is suspected, promptly initiate evaluation and treatment, and discontinue ibuprofen and famotidine tablet until a serious GI adverse event is ruled out.
- In the setting of concomitant use of low-dose aspirin for cardiac prophylaxis, monitor patients more closely for evidence of GI bleeding *[see Drug Interactions (7)]*.

- In the setting of CABG surgery. (4)
- Known hypersensitivity to other H₂-receptor antagonists. (4)

- Hepatotoxicity:** Inform patients of warning signs and symptoms of hepatotoxicity. Discontinue if abnormal liver tests persist or worsen or if clinical signs and symptoms of liver disease develop. (5.4)
- Hypertension:** Patients taking some antihypertensive medications may have impaired response to these therapies when taking NSAIDs. Monitor blood pressure. (5.5, 7)
- Heart Failure and Edema:** Avoid use of ibuprofen and famotidine tablets in patients with severe heart failure unless benefits are expected to outweigh risk of worsening heart failure. (5.6)
- Active Bleeding:** Active and clinically significant bleeding from any source can occur; discontinue ibuprofen and famotidine tablet if active bleeding occurs. (5.3)
- Renal Toxicity:** Monitor renal function in patients with renal or hepatic impairment, heart failure, dehydration, or hypovolemia. Avoid use of ibuprofen and famotidine tablet in patients with advanced renal disease unless benefits are expected to outweigh risk of worsening renal function. (5.7)
- Anaphylactic Reactions:** Seek emergency help if an anaphylactic reaction occurs. (5.8)
- Exacerbation of Asthma Related to Aspirin Sensitivity:** Ibuprofen and famotidine tablet is contraindicated in patients with aspirin-sensitive asthma. Monitor patients with preexisting asthma (without aspirin-sensitivity). (5.10)
- Serious Skin Reactions:** Discontinue ibuprofen and famotidine tablet at first appearance of skin rash or other signs of hypersensitivity (5.11).
- Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS):** Discontinue and evaluate clinically (5.12).
- Fetal Toxicity:** Limit use of NSAIDs, including ibuprofen and famotidine tablet, between about 20 to 30 weeks in pregnancy due to the risk of oligohydramnios/fetal renal dysfunction. Avoid use of NSAIDs in women at about 30 weeks gestation and later in pregnancy due to the risks of oligohydramnios/fetal renal dysfunction and premature closure of the fetal ductus arteriosus (5.13, 8.1).
- Hematologic Toxicity:** Monitor hemoglobin or hematocrit in patient with any signs or symptoms of anemia. (5.14)

Most common adverse reactions (≥1% and greater than ibuprofen alone) are nausea, diarrhea, constipation, upper abdominal pain, and headache. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Camber Pharmaceuticals, Inc., at 1-866-495-8330 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

See full prescribing information for a list of clinically important drug interactions. (7)

USE IN SPECIFIC POPULATIONS

- Pregnancy:** Use of NSAIDs during the third trimester of pregnancy increases the risk of premature closure of the fetal ductus arteriosus. Avoid use of NSAIDs in pregnant women starting at 30 weeks gestation. (5.13, 8.1)
- Females and Males of Reproductive Potential:** NSAIDs are associated with reversible infertility. Consider withdrawal of ibuprofen and famotidine tablet in women who have difficulties conceiving. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 10/24

6. ADVERSE REACTIONS

- Clinical Trials Experience
- Postmarketing Experience
- Use in Specific Populations
- Pregnancy
- Lactation
- Females and Males of Reproductive Potential
- Pediatric Use
- Geriatric Use
- Renal Insufficiency

10. OVERDOSAGE

12. CLINICAL PHARMACOLOGY

- Mechanism of Action
- Pharmacodynamics

13. NONCLINICAL TOXICOLOGY

- Carcinogenesis, Mutagenesis, and Impairment of Fertility

14. CLINICAL STUDIES

15. HOW SUPPLIED/STORAGE AND HANDLING

17. PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

5.3 Active Bleeding

When active and clinically significant bleeding from any source occurs in patients receiving ibuprofen and famotidine tablet, the treatment should be withdrawn. Patients with initial hemoglobin values of 10 g or less who are to receive long-term therapy should have hemoglobin values determined periodically.

5.4 Hepatotoxicity

Elevations of ALT or AST (three or more times the upper limit of normal [ULN]) have been reported in approximately 1% of NSAID-treated patients. In some cases, elevations were sometimes fatal, cases of severe hepatic injury, including fulminant hepatitis, liver necrosis, and hepatic failure have been reported.

Elevations of ALT or AST (less than three times ULN) may occur in up to 15% of patients treated with NSAIDs including ibuprofen.

Inform patients of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, diarrhea, pruritus, jaundice, right upper quadrant tenderness, and “flu-like” symptoms). If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), discontinue ibuprofen and famotidine tablet immediately, and perform a clinical evaluation of the patient.

5.5 Hypertension

NSAIDs, including ibuprofen and famotidine tablet, can lead to new onset of hypertension or worsening of pre-existing hypertension, either of which may contribute to the increased incidence of CV events. Patients taking antihypertensive agents (ACE inhibitors, thiazide diuretics, or loop diuretics may have impaired response to these therapies when taking NSAIDs *[see Drug Interactions (7)]*.

Monitor blood pressure (BP) during the initiation of NSAID treatment and throughout the course of therapy.

5.6 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 (7)]*.

Avoid the use of ibuprofen and famotidine tablet in patients with severe heart failure unless the benefits are expected to outweigh the risk of worsening heart failure. If ibuprofen and famotidine tablet is used in patients with severe heart failure, monitor patients for signs and symptoms of worsening heart failure.

5.7 Renal Toxicity and Hyperkalemia

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 an 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, dehydration, hypovolemia, heart failure, liver dysfunction, those taking diuretics and ACE-inhibitors or ARBs, and the elderly. Discontinuation of NSAID therapy was usually followed by recovery to the pretreatment state.

No information is available from controlled clinical studies regarding the use of ibuprofen and famotidine tablet in patients with advanced renal disease. The renal effects of ibuprofen and famotidine tablet may hasten the progression of renal dysfunction in patients with pre-existing renal disease.

Correct volume status in dehydrated or hypovolemic patients prior to initiating ibuprofen and famotidine tablet. Monitor renal function in patients with renal or hepatic impairment, heart failure, dehydration, or heart failure. Avoid use of ibuprofen and famotidine tablet *[see Drug Interactions (7)]*. Avoid the use of ibuprofen and famotidine tablet in patients with advanced renal disease unless the benefits are expected to outweigh the risk of worsening renal failure. If ibuprofen and famotidine tablet is used in patients with advanced renal disease, monitor patients for signs of worsening renal function.

Hyperkalemia

Increases in serum potassium concentration, including hyperkalemia, have been reported with use of NSAIDs, even in some patients with normal renal impairment. In patients with normal renal function, these effects have been attributed to a hyporeninemic-hypaldosteronism state.

5.8 Anaphylactic Reactions

Ibuprofen has been associated with anaphylactic reactions in patients with and without known hypersensitivity to ibuprofen and in patients with aspirin-sensitive asthma *[see Contraindications (4), Warnings and Precautions (5.8)]*.

Seek emergency help if an anaphylactic reaction occurs.

5.9 Seizures

Seizure activity (CNS) adverse effects including seizures, delirium, and coma have been reported with famotidine in patients with moderate (creatinine clearance <50 mL/min) and severe renal insufficiency (creatinine clearance <10 mL/min), and the dosage of the famotidine component in ibuprofen and famotidine tablet is fixed. Therefore, ibuprofen and famotidine tablet is not recommended in patients with creatinine clearance < 50 mL/min.

5.10 Exacerbation of Asthma Related to Aspirin Sensitivity

A subpopulation of patients with asthma may have aspirin-sensitive asthma which may include chronic rhinosinusitis complicated by nasal polyps; severe, potentially fatal bronchospasm; and/or intolerance to aspirin and other NSAIDs. Because cross-reactivity between aspirin and other NSAIDs has been reported in such aspirin-sensitive patients, ibuprofen and famotidine tablet is contraindicated in patients with this form of aspirin sensitivity *[see Contraindications (4)]*. When ibuprofen and famotidine tablet is used in patients with preexisting asthma (without known aspirin sensitivity), monitor patients for changes in the signs and symptoms of asthma.

5.11 Serious Skin Reactions

NSAIDs, including ibuprofen, can cause serious skin adverse reactions such as exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. NSAIDs can also cause fixed drug eruption (FDE). FDE may present as a more severe variant known as generalized bullous fixed drug eruption (GBFDE), which can be life-threatening. These serious events may occur without warning. Inform patients about the signs and symptoms of serious skin reactions and to discontinue the use of ibuprofen and famotidine tablet at the first appearance of skin rash or any other sign of hypersensitivity. Ibuprofen and famotidine tablet is contraindicated in patients with previous serious skin reactions to NSAIDs *[see Contraindications (4)]*.

5.12 Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) has been reported in patients taking NSAIDs such as ibuprofen and famotidine tablet. The renal effects of ibuprofen and famotidine tablet, DRESS typically, although not exclusively, presents with fever, rash, lymphadenopathy, and/or facial swelling. Other clinical manifestations may include hepatitis, nephritis, hematological abnormalities, myocarditis, or myositis. Sometimes symptoms of DRESS may resemble an acute viral infection. Eosinophilia is often present. Because this disorder is variable in its presentation, other organ systems not noted here may be involved. It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, discontinue ibuprofen and famotidine tablet and evaluate the patient immediately.

5.13 Fetal Toxicity

Premature Closure of Fetal Ductus Arteriosus:

Avoid use of NSAIDs, including ibuprofen and famotidine tablet, in pregnant women at about 30 weeks gestation and later. NSAIDs, including ibuprofen and famotidine tablet, increase the risk of premature closure of the fetal ductus arteriosus at approximately this gestational age.

Oligohydramnios/Neonatal Renal Impairment:
Use of NSAIDs, including ibuprofen and famotidine tablet, at about 20 weeks gestation or later in pregnancy may cause fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation. Oligohydramnios is often, but not always, reversible with treatment discontinuation. Complications of prolonged oligohydramnios may, for example, include limb contractures and delayed lung maturation. In some postmarketing cases of impaired neonatal renal function, invasive procedures such as exchange transfusion or dialysis were required.

If NSAID treatment is necessary between about 20 weeks and 30 weeks gestation, limit ibuprofen and famotidine tablet use to the lowest effective dose and shortest duration possible. Consider ultrasound monitoring of amniotic fluid if ibuprofen and famotidine tablet treatment is needed for a pregnant woman. Discontinue ibuprofen and famotidine tablet if oligohydramnios occurs and follow up according to clinical practice *[see Use in Specific Populations (8.1)]*.

5.14 Hematologic Toxicity

Anemia has occurred in NSAID-treated patients. This may be due to occult or gross blood loss, fluid retention, or an incompletely described effect on erythropoiesis. If a patient treated with ibuprofen and famotidine tablet has any signs or symptoms of anemia, monitor hemoglobin or hematocrit.

NSAIDs, including ibuprofen and famotidine tablet, may increase the risk of bleeding events. Co-morbid conditions such as coagulation disorders or concomitant use of warfarin, and other anticoagulants, antiplatelet agents (e.g., aspirin), serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) may increase the risk. Monitor these patients for signs of bleeding *[see Drug Interactions (7)]*.

5.15 Masking of Inflammation and Fever

The pharmacological activity of ibuprofen and famotidine tablet in reducing inflammation, and possibly fever, may diminish the utility of diagnostic signs in detecting infections.

5.16 Laboratory Monitoring

Because serious GI bleeding, hepatotoxicity, and renal injury can occur without warning symptoms or signs, consider monitoring patients on long-term NSAID treatment with a CBC and chemistry profile periodically *[see Warnings and Precautions (5.2, 5.4, 5.7)]*.

5.17 Concomitant NSAID Use

Ibuprofen and famotidine tablet contains ibuprofen as one of its active ingredients. It should not be used with other ibuprofen-containing products.

The concomitant use of NSAIDs, including aspirin, with ibuprofen and famotidine tablet may increase the risk of adverse reactions *[see Adverse Reactions (6), Drug Interactions (7), Clinical Studies (14)]*.

5.18 Asseptic Meningitis

Asseptic meningitis with fever and coma has been observed on rare occasions in patients on ibuprofen, which is a component of ibuprofen and famotidine tablet. Although it is probably more likely to occur in patients with systemic lupus erythematosus (SLE) 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 and famotidine tablet, the possibility of its being related to ibuprofen should be considered.

5.19 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 and famotidine tablet, the drug should be discontinued, and the patient should have an ophthalmologic examination which includes central visual fields and color vision testing.

6. ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the labeling:

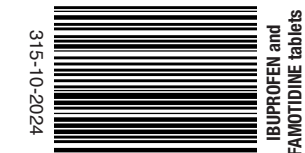
- Cardiovascular Thrombotic Events *[see Warnings and Precautions (5.1)]*
- GI Bleeding, Ulceration, and Perforation *[see Warnings and Precautions (5.2)]*
- Hepatotoxicity *[see Warnings and Precautions (5.4)]*
- Hypertension *[see Warnings and Precautions (5.5)]*
- Heart Failure and Edema *[see Warnings and Precautions (5.6)]*
- Renal Toxicity and Hyperkalemia *[see Warnings and Precautions (5.7)]*
- Anaphylactic Reactions *[see Warnings and Precautions (5.8)]*
- Seizures *[see Warnings and Precautions (5.9)]*
- Serious Skin Reactions *[see Warnings and Precautions (5.11)]*
- Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) *[see Warnings and Precautions (5.12)]*
- Fetal Toxicity *[see Warnings and Precautions (5.13)]*
- Hematologic Toxicity *[see Warnings and Precautions (5.14)]*
- Metabolism and Nutrition Disorders: decreased appetite *[see Warnings and Precautions (5.10)]*
- Ophthalmological Effects *[see Warnings and Precautions (5.19)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of ibuprofen and famotidine tablet was evaluated in 1022 patients in controlled clinical studies, including 508 patients treated for at least 6 months and 107 patients treated for approximately 1 year. Patients treated with ibuprofen and famotidine tablet ranged in age from 39 to 80 years (median age 55 years), with 67% female, 79% Caucasian, 18% African-American, and 3% other races. Two randomized, active-controlled clinical studies (Study 301 and Study 303) were conducted for the reduction of the risk of development of ibuprofen-associated, upper gastrointestinal ulcers in patients who required use of ibuprofen, which included 1022 patients on ibuprofen and famotidine tablet and 511 patients on ibuprofen alone. Approximately 15% of patients were on low-dose aspirin. Patients were assigned randomly, in a 2:1 ratio, to treatment with either ibuprofen and famotidine or ibuprofen 800 mg three times a day for 12 consecutive weeks.

Three serious cases of acute renal failure were observed in patients treated with ibuprofen and famotidine tablet in the two controlled



	Ibuprofen and famotidine tablet % (n/N)	Ibuprofen % (n/N)	P-value ^a
Primary endpoint			
Gastric ulcer*	8.7% (39/447)	17.6% (38/216)	0.0004
Gastric ulcer**	17.4% (78/447)	31.0% (67/216)	<0.0001
Secondary endpoint			
Upper gastrointestinal ulcer*	10.1% (45/447)	21.3% (46/216)	<0.0001
Upper gastrointestinal ulcer**	18.6% (83/447)	34.3% (74/216)	<0.0001

* Cochran-Mantel-Haenszel test
** Classifying early terminated patients as NOT having an ulcer
*** Classifying patients who early terminated due to an adverse event, were test to follow-up, discontinued due to the discretion of the sponsor or the investigator, or did not have an endoscopy performed within 14 days of their last dose of study drug, as having an ulcer

Subgroup analyses of patients who used low-dose aspirin (less than or equal to 325 mg daily), were 65 years and older, or had a prior history of gastrointestinal ulcer are summarized as follows:

Of the 1022 patients in clinical studies of ibuprofen and famotidine tablet, 15% (213 patients) used low-dose aspirin and the results were consistent with the overall findings of the study. In these clinical studies 16% of patients who used low-dose aspirin who were treated with ibuprofen and famotidine tablet developed an upper gastrointestinal ulcer compared to 35% of those patients who received only ibuprofen.

The clinical trials primarily enrolled patients less than 65 years without a prior history of gastrointestinal ulcer. Of the 1022 patients in clinical studies of ibuprofen and famotidine tablet, 18% (249 patients) were 65 years of age or older. In these clinical studies, 23% of patients 65 years of age and older who were treated with ibuprofen and famotidine tablet developed an upper gastrointestinal ulcer compared to 27% of those patients who received only ibuprofen (see *Use in Specific Populations (8.3)*).

Of the 1022 patients in clinical studies of ibuprofen and famotidine tablet, 6% had a prior history of gastrointestinal ulcer. In these clinical studies, 25% of patients with a prior history of gastrointestinal ulcer who were treated with ibuprofen and famotidine tablet developed an upper gastrointestinal ulcer compared to 24% of those patients who received only ibuprofen.

16. HOW SUPPLIED/STORAGE AND HANDLING
Ibuprofen and famotidine tablets, 800 mg/26.6 mg, are Blue/Light blue coated Modified Oval shaped tablets debossed with T396 on one side and an engraved circle on the other side and supplied as:

NDC Number	Size
31722-315-90	Bottle of 90 tablets
Storage	Store at 25°C (77°F); excursions permitted to 15°C - 30°C (59°F - 86°F). [See USP Controlled Room Temperature]

17. PATIENT COUNSELING INFORMATION
Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Inform patients, families, or caregivers of the following before initiating therapy with ibuprofen and famotidine tablet and periodically during the course of ongoing therapy.

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 and Precautions (5.1)*).

Gastrointestinal Bleeding, Ulceration, and Perforation
Advise patients to report symptoms of ulcerations and bleeding, including epigastric pain, dyspepsia, melena, and hematemesis to their health care provider. In the setting of concomitant use of low-dose aspirin for cardiac prophylaxis, inform patients of the increased risk for and the signs and symptoms of GI bleeding (see *Warnings and Precautions (5.2)*).

Hepatotoxicity
Inform patients 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, instruct patients to stop ibuprofen and famotidine tablet and seek immediate medical therapy (see *Warnings and Precautions (5.4)*).

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 and Precautions (5.6)*).

Anaphylactic Reactions
Inform patients of the signs of an anaphylactic reaction (e.g., difficulty breathing, swelling of the face or throat). Instruct patients to seek immediate emergency help if these occur (see *Contraindications (4)*, *Warnings and Precautions (5.8)*).

Serious Skin Reactions, Including DRESS
Advise patients to stop taking ibuprofen and famotidine tablet immediately if they develop any type of rash or fever and contact their health care provider as soon as possible (see *Warnings and Precautions (5.11, 5.12)*).

Fertility
Advise females of reproductive potential who desire pregnancy that NSAIDs, including ibuprofen and famotidine tablet, may be associated with a reversible delay in ovulation (see *Use in Specific Populations (8.3)*).

Fetal Toxicity
Inform pregnant women to avoid use of ibuprofen and famotidine tablet with other NSAIDs starting at 30 weeks gestation because of the risk of the premature closure of the fetal ductus arteriosus. If treatment with ibuprofen and famotidine tablet is needed for a pregnant woman between about 20 to 30 weeks gestation, advise her that she may need to be monitored for oligohydramnios (see *Warnings and Precautions (5.13)* and *Use in Specific Populations (8.1)*).

Avoid Concomitant Use of NSAIDs
Inform patients that the concomitant use of ibuprofen and famotidine tablet with other NSAIDs or salicylates (e.g., diflunisal, salsalate) is not recommended due to the increased risk of gastrointestinal toxicity, and little or no increase in efficacy (see *Warnings and Precautions (5.2, 5.7)*, *Drug Interactions (7)*). Alert patients that NSAIDs may be present in the "over the counter" medications for treatment of colds, fever, or insomnia.

Use of NSAIDs and Low-Dose Aspirin
Inform patients not to use low-dose aspirin concomitantly with ibuprofen and famotidine tablet until they talk to their health care provider (see *Drug Interactions (7)*).

Nephrotoxicity
Patients should be monitored for development of nephrotoxicity (e.g., azotemia, hypertension, and/or proteinuria). If these patients should be instructed to stop therapy and seek immediate medical therapy.

Creatinine Clearance
Ibuprofen and famotidine tablet is not recommended in patients with creatinine clearance <50 mL/min because of seizures, delirium, coma and other CNS effect.

Taking Ibuprofen and famotidine tablet
Inform patients that ibuprofen and famotidine tablets should be swallowed whole, and should not be cut to supply a lower dose. Advise patient not to chew, divide, or crush tablets (see *Dosage and Administration (2)*).

Patients should be instructed that if a dose is missed, it should be taken as soon as possible. However, if the next scheduled dose is due, the patient should not take the missed dose, and should be instructed to take the next dose on time. Patients should be instructed not to take 2 doses at one time to make up for a missed dose.

Manufactured by:
Ascend Pharmaceuticals, Inc.
Central Islip, NY 11722

Manufactured for:
Camber Pharmaceuticals, Inc.
Piscataway, NJ 08854

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Medication Guide IBUPROFEN and FAMOTIDINE (eye-BYOO-proe-fen and fa-MOE-ti-deen) tablets, for oral use

What is the most important information I should know about ibuprofen and famotidine tablet?
Ibuprofen and famotidine tablet 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 medicine containing NSAIDs
 - with longer use of medicine containing NSAIDs
- Do not take ibuprofen and famotidine tablet right before or after a heart surgery called a "coronary artery bypass graft (CABG)."
- Do not take ibuprofen and famotidine tablet 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 ibuprofen and famotidine tablet 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 the use of NSAIDs
- taking medicines called "corticosteroids", "anticoagulants", "SSRIs", or "SNRIs"
- increasing doses of NSAIDs
- longer use of NSAIDs
- smoking
- drinking alcohol
- older age
- poor health
- advanced liver disease
- bleeding problems

You should take ibuprofen and famotidine tablet exactly as prescribed, at the lowest dose possible and for the shortest time needed. Ibuprofen and famotidine tablet contains a non-steroidal anti-inflammatory drug NSAID (ibuprofen). Do not use ibuprofen and famotidine tablet with other medicines to lessen pain or fever or with other medicines for colds or sleeping problems without talking to your healthcare provider first, because they may contain an NSAID also.

Ibuprofen and famotidine tablet may help your acid-related symptoms, but you could still have serious stomach problems. Talk with your healthcare provider.

Ibuprofen and famotidine tablet contains ibuprofen, an NSAID and famotidine, a histamine H₂-receptor blocker medicine.

What is ibuprofen and famotidine tablet?
Ibuprofen and famotidine tablet is a prescription medicine used to:

- relieve the signs and symptoms of rheumatoid arthritis and osteoarthritis.
- decrease the risk of developing ulcers of the stomach and upper intestines (upper gastrointestinal ulcers) in people taking ibuprofen for rheumatoid arthritis and osteoarthritis.

It is not known if ibuprofen and famotidine tablet is safe and effective in children.

Do not take ibuprofen and famotidine tablet:

- if you are allergic to ibuprofen, famotidine, any other histamine H₂-receptor blocker, or any of the ingredients in ibuprofen and famotidine tablet. See the end of this Medication Guide for a complete list of ingredients.
- if you have had an asthma attack, hives, or other allergic reaction with aspirin or any other NSAIDs.
- right before or after heart bypass surgery.

Before taking ibuprofen and famotidine tablet, tell your healthcare provider about all of your medical conditions, including if you:

- have liver or kidney problems.
- have high blood pressure.
- have heart problems.
- have asthma.
- have bleeding problems.
- are pregnant or plan to become pregnant. Taking ibuprofen and famotidine tablet at about 20 weeks of pregnancy or later may harm your unborn baby. If you need to take ibuprofen and famotidine tablet when you are between 20 and 30 weeks of pregnancy, your healthcare provider may need to monitor the amount of fluid in your womb around your baby. **You should not take ibuprofen and famotidine tablet after about 30 weeks of pregnancy.**
- are breastfeeding or plan to breast feed. Ibuprofen and famotidine can pass into your breast milk. Talk to your healthcare provider about the best way to feed your baby if you take ibuprofen and famotidine tablet.

Tell your healthcare provider about all of the medicines you take, including prescription and over-the-counter medicines, vitamins and herbal supplements. Ibuprofen and famotidine tablet 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.**

Each ibuprofen and famotidine tablet contains ibuprofen (800 mg) and famotidine, USP (26.6 mg). The inactive ingredients in ibuprofen and famotidine tablet include: microcrystalline cellulose, pregelatinized starch, silicon dioxide, magnesium stearate, Hydroxy Propyl Methyl Cellulose, Glycerin, croscarmellose sodium, FD&C Blue#1, tac, povidone, FD&C Blue#2.

12. CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
Ibuprofen and famotidine tablet is a fixed-combination tablet of ibuprofen and famotidine. The ibuprofen component has analgesic, anti-inflammatory, and antipyretic properties. The mechanism of action of the ibuprofen component of ibuprofen and famotidine tablet, like that of other NSAIDs, is not completely understood but involves inhibition of cyclooxygenase (COX-1 and COX-2).

Ibuprofen is a patent inhibitor of prostaglandin synthesis *in vitro*. Ibuprofen concentrations reached during therapy have produced *in vivo* effects. Prostaglandins sensitize afferent nerves and potentiate the action of bradykinin in inducing pain in animal models. Prostaglandins are mediators of inflammation. Because ibuprofen is an inhibitor of prostaglandin synthesis, its mode of action may be due to an increase of prostaglandins in peripheral tissues.

Famotidine is a competitive inhibitor of histamine H₂-receptors. The primary clinically important pharmacologic activity of famotidine is inhibition of gastric secretion. Both the acid concentration and volume of gastric secretion are suppressed by famotidine, while changes in pepsin secretion are proportional to volume output.

Systemic effects of famotidine in the CNS, cardiovascular, respiratory, or endocrine systems were not noted in clinical pharmacology studies. Also, no antiandrogenic effects were noted. Serum hormone levels, including prolactin, cortisol, thyroxine (T₄), and testosterone, were not altered after treatment with famotidine.

12.2 Pharmacodynamics
In a healthy volunteer study, ibuprofen 400 mg given once daily, administered 2 hours prior to immediate-release aspirin (81 mg) on 6 days, showed an interaction with the antiplatelet activity of aspirin as measured by % serum thromboxane B2 (TxB2) 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 (30.7%). 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 (98.2%).

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 B2 (TxB2) inhibition suggested no interaction with the antiplatelet activity of aspirin (98.3%). However, there were individual subjects with serum TxB2 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 *Drug Interactions (7)*).

12.3 Pharmacokinetics
Absorption
Ibuprofen and famotidine are rapidly absorbed after a single dose administration of ibuprofen and famotidine tablet. Mean C_{max} values for ibuprofen are 45 µg/mL and are reached approximately 1.9 hours after oral administration of ibuprofen and famotidine tablet. The C_{max} and AUC_{0-24h} values for the 800 mg of ibuprofen contained in a ibuprofen and famotidine tablet are bioequivalent to the values for 800 mg of ibuprofen administered alone. C_{max} values for famotidine were 61 ng/mL and are reached at approximately 2 hours after oral administration of ibuprofen and famotidine tablet.

A high-fat meal reduced famotidine C_{max} and AUC by approximately by 15% and 11%, respectively, and reduced ibuprofen AUC by approximately 14% but did not change C_{max}. Food delayed famotidine T_{max} and ibuprofen T_{max} by approximately 1 hour and 0.2 hour, respectively.

Distribution
Ibuprofen is extensively bound to plasma proteins.

Fifteen to 20% of famotidine in plasma is protein bound.

Elimination
Metabolism
The only metabolite of famotidine identified in man is the S-oxide.

Excretion
Ibuprofen is eliminated from the systemic circulation with a mean half-life (t_{1/2}) value of 2 hours following administration of a single dose of ibuprofen and famotidine tablet.

Ibuprofen is rapidly metabolized and eliminated in the urine. The excretion of ibuprofen is virtually complete 24 hours after the last dose.

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-(2-hydroxyethyl-propyl) phenyl] propionic acid and metabolite B (37%), (+)-2-[p-(2-carboxypropyl) phenyl] propionic acid; the percentages of free and conjugated ibuprofen were approximately 1% and 14%, respectively.

Famotidine is eliminated from the systemic circulation with a mean t_{1/2} value of 4 hours following administration of a single dose of ibuprofen and famotidine tablet.

Famotidine is eliminated by renal (65-70%) and metabolic (30-35%) routes. Renal clearance is 250-450 mL/min, indicating some tubular excretion. Twenty-five to 30% of an oral dose and 65-70% of an intravenous dose are recovered in the urine as unchanged compound.

Specific Populations
Pediatrics: The pharmacokinetics of ibuprofen or famotidine after administration of ibuprofen and famotidine tablet have not been evaluated in a pediatric population considering the doses of ibuprofen and famotidine in ibuprofen and famotidine tablet are targeted for use in an adult population.

Hepatic impairment: The effects of hepatic impairment on the pharmacokinetics of ibuprofen or famotidine after administration of ibuprofen and famotidine tablet have not been evaluated (see *Warnings and Precautions (5.4)*).

Renal impairment: There is a close relationship between creatinine clearance values and the elimination t_{1/2} of famotidine, which is a component of ibuprofen and famotidine tablets. In patients with creatinine clearance <50 mL/min, the elimination t_{1/2} of famotidine is increased and may exceed 20 hours. Therefore, ibuprofen and famotidine tablet is not recommended in patients with creatinine clearance < 50 mL/min (see *Warnings and Precautions (5.7)*).

Drug Interaction Studies
Co-administration of ibuprofen (800 mg) and famotidine (40 mg) increased ibuprofen C_{max} by 15.6% but did not affect its AUC, and increased famotidine AUC and C_{max} by 16% and 22%, respectively.

Aspirin: When NSAIDs were administered with aspirin, the protein binding of NSAIDs were reduced, although the clearance of free NSAID was not altered. The clinical significance of this interaction is not known. See Table 3 for clinically significant drug interactions of NSAIDs with aspirin (see *Drug Interaction (7)*).

Probenecid, an inhibitor of Organic Anion Transporter 1 (OAT1) and OAT3
In vitro studies indicate that famotidine is a substrate for OAT1 and OAT3. Following coadministration of probenecid (1500 mg) with a single oral 20 mg dose of famotidine in 8 healthy subjects, the serum AUC_{0-10h} of famotidine increased from 424 to 768 ng•h/mL and the maximum serum concentration (C_{max}) increased from 73 to 113 ng/mL. Renal clearance, urinary excretion rate and amount of famotidine excreted unchanged in urine were decreased. The clinical relevance of this interaction is unknown.

Metformin: Famotidine is a selective inhibitor of multidrug and toxin extrusion transporter 1 (MATE-1) but no clinical significant interaction with metformin, a substrate for MATE-1, was observed.

13. NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility
Carcinogenesis
Studies to evaluate the potential effects of ibuprofen and famotidine tablet on carcinogenicity, mutagenicity, or impairment of fertility have not been conducted.

In a 106-week study in rats and a 92-week study in mice, famotidine was given at oral doses of up to 2000 mg/kg/day (approximately 122 and 243 times the recommended human dose, respectively, based on body surface area). There was no evidence of carcinogenic potential for famotidine.

Mutagenesis
Famotidine was negative in the microbial mutagen test (Ames test) using *Saimonella typhimurium* and *Escherichia coli* with or without rat liver enzyme activation at concentrations up to 10,000 µg/plate. In *in vivo* mouse micronucleus test and a chromosomal aberration test with famotidine, no evidence of a mutagenic effect was observed.

In published studies, ibuprofen was not mutagenic in the *in vitro* bacterial reverse mutation assay (Ames assay).

Impairment of Fertility
In studies of famotidine in rats at oral doses of up to 2000 mg/kg/day (approximately 243 times the recommended human dose, based on body surface area), fertility and reproductive performance were not affected.

In a published study, dietary administration of ibuprofen to male and female rats 8-weeks prior to and during mating at dose levels of 20 mg/kg (0.06-times the MRHD based on body surface area comparison) did not impact male or female fertility or litter size.

In other studies, adult mice were administered ibuprofen intraperitoneally at a dose of 5.6 mg/kg/day (0.0085-times the MRHD based on body surface area comparison) for 35 or 60 days in males and 35 days in females. There was no effect on sperm motility or viability in males but decreased ovulation was reported in females.

14. CLINICAL STUDIES
Two multicenter, double-blind, active-controlled, randomized, 24-week studies of ibuprofen and famotidine tablet were conducted in patients who were expected to receive blind, active-blind administration of an NSAID for at least the coming 6 months for conditions such as the following: osteoarthritis, rheumatoid arthritis, chronic low back pain, chronic regional pain syndrome, and chronic soft tissue pain. Patients were assigned randomly, in approximately a 2:1 ratio, to treatment with either ibuprofen and famotidine tablet or ibuprofen (800 mg) three times a day for 24 consecutive weeks. A total of 1533 patients were enrolled and ranged in age from 39 to 80 years (median age 55 years) with 68% females. Race was distributed as follows: 79% Caucasian, 18% African-American, and 3% Other. Approximately 15% of the patients in Studies 301 and 303 were taking concurrent low-dose aspirin (less than or equal to 325 mg daily), 18% were 65 years of age or older, and 6% had a history of previous upper gastrointestinal ulcer. Although H. pylori status was negative at baseline, H. pylori status was not reassessed during the trials.

Studies 301 and 303 compared the incidence of upper gastrointestinal (gastric and/or duodenal) ulcer formation in a total 930 patients taking ibuprofen and famotidine tablet and 452 patients taking ibuprofen only, either as a primary or secondary endpoint. In both trials, ibuprofen and famotidine was associated with a statistically significant reduction in the risk of developing upper gastrointestinal ulcers compared to taking ibuprofen only during the 6 month study period. The data are presented below in tables 4 and 5. Two analyses for each endpoint were conducted. In one analysis patients who terminated early, without an endoscopic evaluation within 14 days of their last dose of study drug, were classified as not having an ulcer. In the second analysis, those patients were classified as having an ulcer. Both analyses exclude patients who terminated study prior to the first scheduled endoscopy at 8 weeks.

	Ibuprofen and famotidine tablet % (n/N)	Ibuprofen % (n/N)	P-value ^a
Primary endpoint			
Upper gastrointestinal ulcer*	10.5% (40/380)	20.0% (38/190)	0.002
Upper gastrointestinal ulcer**	22.9% (87/380)	32.1% (61/190)	0.020
Secondary endpoint			
Gastric ulcer*	9.7% (37/380)	17.9% (34/190)	0.005
Gastric ulcer**	22.4% (85/380)	30.0% (57/190)	0.052

* Cochran-Mantel-Haenszel test
** Classifying early terminated patients as NOT having an ulcer
*** Classifying patients who early terminated due to an adverse event, were test to follow-up, discontinued due to the discretion of the sponsor or the investigator, or did not have an endoscopy performed within 14 days of their last dose of study drug, as having an ulcer

Table 5: Overall Incidence Rate of Patients Who Developed at Least One Gastric or Upper Gastrointestinal Ulcer - Study 303

	Ibuprofen and famotidine tablet % (n/N)	Ibuprofen % (n/N)	P-value ^a
Primary endpoint			
Gastric ulcer*	8.7% (39/447)	17.6% (38/216)	0.0004
Gastric ulcer**	17.4% (78/447)	31.0% (67/216)	<0.0001
Secondary endpoint			
Upper gastrointestinal ulcer*	10.1% (45/447)	21.3% (46/216)	<0.0001
Upper gastrointestinal ulcer**	18.6% (83/447)	34.3% (74/216)	<0.0001

* Cochran-Mantel-Haenszel test
** Classifying early terminated patients as NOT having an ulcer
*** Classifying patients who early terminated due to an adverse event, were test to follow-up, discontinued due to the discretion of the sponsor or the investigator, or did not have an endoscopy performed within 14 days of their last dose of study drug, as having an ulcer

Table 6: Overall Incidence Rate of Patients Who Developed at Least One Gastric or Upper Gastrointestinal Ulcer - Study 302

	Ibuprofen and famotidine tablet % (n/N)	Ibuprofen % (n/N)	P-value ^a
Primary endpoint			
Gastric ulcer*	8.7% (39/447)	17.6% (38/216)	0.0004
Gastric ulcer**	17.4% (78/447)	31.0% (67/216)	<0.0001
Secondary endpoint			
Upper gastrointestinal ulcer*	10.1% (45/447)	21.3% (46/216)	<0.0001
Upper gastrointestinal ulcer**	18.6% (83/447)	34.3% (74/216)	<0.0001

* Cochran-Mantel-Haenszel test
** Classifying early terminated patients as NOT having an ulcer
*** Classifying patients who early terminated due to an adverse event, were test to follow-up, discontinued due to the discretion of the sponsor or the investigator, or did not have an endoscopy performed within 14 days of their last dose of study drug, as having an ulcer

famotidine tablet, can cause premature closure of the fetal ductus arteriosus (see *Data*).

Oligohydramnios/Neonatal Renal Impairment
If an NSAID is necessary at about 20 weeks gestation or later in pregnancy, limit the use to the lowest effective dose and shortest duration possible. If ibuprofen and famotidine tablet treatment is needed for a pregnant woman, consider monitoring with ultrasound for oligohydramnios. If oligohydramnios occurs, discontinue ibuprofen and famotidine tablet and follow up according to clinical practice (see *Data*).

Labor or Delivery
There are no studies on the effects of ibuprofen and famotidine tablet during labor or delivery. In animal studies, NSAIDs, including ibuprofen, inhibit prostaglandin synthesis, cause delayed parturition, and increase the incidence of stillbirth.

Data
Human Data
When used to delay preterm labor, inhibitors of prostaglandin synthesis, including NSAIDs such as ibuprofen, may increase the risk of neonatal complications such as necrotizing enterocolitis, patent ductus arteriosus and intracranial hemorrhage. Ibuprofen treatment given in late pregnancy to delay parturition has been associated with persistent pulmonary hypertension, renal dysfunction and abnormal prostaglandin E levels in preterm infants.

Ibuprofen
Premature Closure of Fetal Ductus Arteriosus:
Published literature reports that the use of NSAIDs at about 30 weeks of gestation and later in pregnancy may cause premature closure of the fetal ductus arteriosus.

Oligohydramnios/Neonatal Renal Impairment:
Published studies and postmarketing reports describe maternal NSAID use at about 20 weeks gestation or later in pregnancy associated with fetal renal dysfunction leading to oligohydramnios, and in some cases, neonatal renal impairment. These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation. In many cases, but not all, the decrease in amniotic fluid was transient and reversible with cessation of the drug. There have been a limited number of case reports of maternal NSAID use and neonatal renal dysfunction without oligohydramnios, some of which were irreversible. Some cases of neonatal renal dysfunction required treatment with invasive procedures, such as dialysis or extracorporeal membrane oxygenation or bypass.

Methodological limitations of these postmarketing studies and reports include lack of a control group; limited information regarding dose, duration, and timing of drug exposure; and concomitant use of other medications. These limitations preclude establishing a reliable estimate of the risk of adverse fetal and neonatal outcomes with maternal NSAID use. Because the published safety data on neonatal outcomes involved mostly preterm infants, the generalizability of certain reported risks to the full-term infant exposed to NSAIDs through maternal use is uncertain.

When used to delay preterm labor, inhibitors of prostaglandin synthesis, including NSAIDs such as ibuprofen, may increase the risk of other neonatal complications such as necrotizing enterocolitis and intracranial hemorrhage. Ibuprofen treatment given in late pregnancy to delay parturition has been associated with persistent pulmonary hypertension, renal dysfunction, and abnormal prostaglandin E levels in preterm infants.

Animal Data
Animal reproduction studies have not been conducted with ibuprofen and famotidine tablet.

Ibuprofen
In a published study, female rabbits given 7.5, 20, or 60 mg/kg ibuprofen (0.04, 0.12, or 0.36-times the maximum recommended human daily dose of 3200 mg of ibuprofen based on body surface area) from Gestation Days 1 to 29, no clear treatment-related adverse developmental effects were noted. Doses of 20 and 60 mg/kg were associated with significant maternal toxicity (stomach ulcers, gastric lesions). In the same publication, female rats were administered 7.5, 20, 60, 180 mg/kg ibuprofen (0.02, 0.06, 0.18, 0.54-times the maximum daily dose) did not result in clear adverse developmental effects. Maternal toxicity (gastrointestinal lesions) was noted at 20 mg/kg and above.

In a published study, rats were orally dosed with 300 mg/kg ibuprofen (0.912-times the maximum human daily dose of 3200 mg based on body surface area) during Gestation Days 9 and 10 (critical time points for heart development in rats). Ibuprofen treatment resulted in an increase in the incidence of membranous ventricular septal defects. This dose was associated with significant maternal toxicity including gastrointestinal toxicity. One incidence each of a membranous ventricular septal defect and gastroschisis was noted in fetuses from rabbits treated with 500 mg/kg (1.5-times the maximum human daily dose) from Gestation Day 9-11.

Famotidine
Reproductive studies with famotidine have been performed in rats and rabbits at oral doses of up to 2000 and 500 mg/kg/day (approximately 243 and 122 times the recommended human dose of 80 mg per day, respectively, based on body surface area) and in both species at intravenous doses of up to 200 mg/kg/day (about 24 and 49 times the recommended human dose of 80 mg per day, respectively, based on body surface area), and have revealed no significant evidence of harm to the fetus due to famotidine. While no direct fetotoxic effects have been observed, sporadic abortions occurring only in mothers displaying marked decreased food intake were seen in some rabbits at oral doses of 200 mg/kg/day (approximately 49 times the recommended human dose of 80 mg per day, respectively, based on body surface area) or higher. Animal reproduction studies are not always predictive of human response.

8.2 Lactation
Risk Summary
In a published study, human breast milk was analyzed for the presence of ibuprofen and famotidine tablet. Limited data from published literature report famotidine is present in human milk in low amounts. Published literature also reports the presence of ibuprofen in human milk in low amounts. No information is available on the effects of famotidine or