

# DUEXIS<sup>®</sup>

(ibuprofen and famotidine) Tablets  
800 mg/26.6 mg

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use DUEXIS<sup>®</sup> safely and effectively. See full prescribing information for DUEXIS.

DUEXIS (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.

- **Ibuprofen, a component of DUEXIS, may increase the risk of serious cardiovascular (CV) thrombotic events, myocardial infarction, and stroke, which can be fatal. Risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk. (5.1)**
- **DUEXIS is contraindicated for the treatment of perioperative pain in the setting of coronary artery bypass graft (CABG) surgery. (4, 5.1)**
- **NSAIDs, including ibuprofen, a component of DUEXIS, increase the risk of serious gastrointestinal (GI) adverse reactions including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. Reactions can occur at any time without warning symptoms. Elderly patients are at greater risk. (5.4)**

## INDICATIONS AND USAGE

DUEXIS, a combination of the NSAID ibuprofen and the histamine H<sub>2</sub>-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)

## DOSAGE AND ADMINISTRATION

- One DUEXIS tablet administered orally three times per day (2)

## DOSAGE FORMS AND STRENGTHS

- Tablets: 800 mg ibuprofen and 26.6 mg famotidine (3)

## CONTRAINDICATIONS

- Pre-existing asthma, urticaria, or allergic reactions after taking aspirin or other NSAIDs (4)
- Use during the perioperative period in the setting of coronary artery bypass graft surgery (4)
- Starting at 30 weeks gestation, DUEXIS should not be used by pregnant women as premature closure of the ductus arteriosus in the fetus may occur. (4)
- Known hypersensitivity to other H<sub>2</sub>-receptor antagonists (4)

## FULL PRESCRIBING INFORMATION: CONTENTS\*

### WARNING: RISK OF SERIOUS CARDIOVASCULAR AND GASTROINTESTINAL EVENTS

#### 1 INDICATIONS AND USAGE

#### 2 DOSAGE AND ADMINISTRATION

#### 3 DOSAGE FORMS AND STRENGTHS

#### 4 CONTRAINDICATIONS

#### 5 WARNINGS AND PRECAUTIONS

- 5.1 Cardiovascular Thrombotic Events
- 5.2 Hypertension
- 5.3 Congestive Heart Failure and Edema
- 5.4 Risk of Gastrointestinal Ulceration, Bleeding, and Perforation
- 5.5 Active Bleeding
- 5.6 Renal Injury
- 5.7 Seizures
- 5.8 Anaphylaxis
- 5.9 Skin Reactions
- 5.10 Pregnancy
- 5.11 Hepatic Injury
- 5.12 Anemia
- 5.13 Inhibition of Platelet Aggregation
- 5.14 Preexisting Asthma
- 5.15 Concomitant NSAID Use
- 5.16 Aseptic Meningitis
- 5.17 Corticosteroid Treatment
- 5.18 Masking of Inflammation and Fever
- 5.19 Visual Disturbances

#### 6 ADVERSE REACTIONS

- 6.1 Clinical Trials Experience
- 6.2 Postmarketing Experience

## WARNINGS AND PRECAUTIONS

- **Hypertension:** Hypertension can occur with NSAID treatment; monitor blood pressure closely during treatment with DUEXIS. (5.2)
- **Congestive heart failure and edema:** Fluid retention and edema can occur with NSAID treatment; use DUEXIS with caution in patients with fluid retention or heart failure. (5.3)
- **Active Bleeding:** Active and clinically significant bleeding from any source can occur; discontinue DUEXIS if active bleeding occurs (5.5)
- **Renal Injury:** Long-term administration of NSAIDs can result in renal papillary necrosis and other renal injury; use DUEXIS with caution in patients at risk (e.g., the elderly, those with renal impairment, heart failure, liver impairment, and those taking diuretics or ACE inhibitors). (5.6)
- **Anaphylaxis:** Anaphylaxis may occur in patients with the aspirin triad or in patients without prior exposure to DUEXIS; discontinue DUEXIS immediately if an anaphylactoid reaction occurs. (5.8)
- **Serious skin reactions:** Includes exfoliative dermatitis, Stevens-Johnson Syndrome, and toxic epidermal necrolysis, which can be fatal; discontinue DUEXIS if rash or other signs of local skin reaction occur. (5.9)
- **Hepatic Injury:** Hepatic injury ranging from transaminase elevations to liver failure can occur; discontinue DUEXIS immediately if abnormal liver tests persist or worsen, if clinical signs and symptoms of liver disease develop or if systemic manifestations occur. (5.11)

## ADVERSE REACTIONS

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 Horizon Pharma USA, Inc. at (1-866-479-6742) or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

## DRUG INTERACTIONS

- **Warfarin-type anticoagulants:** Concomitant use of NSAIDs and anticoagulants (e.g., warfarin) increases the risk of serious GI bleeding. (7.1)
- **Aspirin:** Concomitant administration with other NSAIDs, including aspirin, may increase the risk of adverse reactions, including GI bleeding. (7.2)
- **ACE-inhibitors and diuretics:** Ibuprofen, a component of DUEXIS, may reduce the effectiveness of these drugs (7.3, 7.4)
- **Lithium:** Ibuprofen, a component of DUEXIS, may increase lithium levels (7.5)

## USE IN SPECIFIC POPULATIONS

- **Nursing mothers:** Use with caution, as it is not known if ibuprofen is excreted in human milk and famotidine is excreted in human milk. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: October 2011  
0140DUEX01

## 7 DRUG INTERACTIONS

- 7.1 Warfarin-Type Anticoagulants
- 7.2 Aspirin
- 7.3 ACE-Inhibitors
- 7.4 Diuretics
- 7.5 Lithium
- 7.6 Methotrexate
- 7.7 Selective Serotonin Reuptake Inhibitors (SSRIs)
- 7.8 Cholestyramine

## 8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.2 Labor and Delivery
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 8.6 Renal Insufficiency

## 10 OVERDOSAGE

## 11 DESCRIPTION

## 12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics

## 13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

## 14 CLINICAL STUDIES

## 16 HOW SUPPLIED/STORAGE AND HANDLING

## 17 PATIENT COUNSELING INFORMATION

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

## FULL PRESCRIBING INFORMATION

### WARNING: RISK OF SERIOUS CARDIOVASCULAR AND GASTROINTESTINAL EVENTS

#### Cardiovascular Risk

- NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk [see *Warnings and Precautions* (5.1)].
- NSAIDs, including DUEXIS, are contraindicated for treatment of perioperative pain in the setting of coronary artery bypass graft (CABG) surgery [see *Warnings and Precautions* (5.1)].

#### Gastrointestinal Risk

- NSAIDs cause an increased risk of serious gastrointestinal adverse reactions including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These reactions can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events [see *Warnings and Precautions* (5.4)].

## 1 INDICATIONS AND USAGE

Carefully consider the potential benefits and risks of DUEXIS and other treatment options before deciding to use DUEXIS. Use the shortest duration consistent with individual patient treatment goals [see *Warnings and Precautions* (5), *Drug Interactions* (7) and *Use in Specific Populations* (8)].

DUEXIS, a combination of the NSAID ibuprofen and the histamine H<sub>2</sub>-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) and *Use in Specific Populations* (8.5)].

## 2 DOSAGE AND ADMINISTRATION

The recommended daily dose of DUEXIS (ibuprofen and famotidine) 800 mg/26.6 mg is a single tablet administered orally three times per day.

DUEXIS tablets should be swallowed whole, and should not be cut to supply a lower dose. 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.

## 3 DOSAGE FORMS AND STRENGTHS

DUEXIS (ibuprofen and famotidine) tablets, 800 mg/26.6 mg, are light blue, oval, biconvex, film-coated tablets debossed with "HZT" on one side.

## 4 CONTRAINDICATIONS

- DUEXIS should not be given to patients who have experienced asthma, urticaria, or allergic reactions after taking aspirin or other NSAIDs. Severe, rarely fatal, anaphylaxis with NSAIDs have been reported in such patients [see *Warnings and Precautions* (5.7, 5.12) and *Drug Interactions* (7.2)].
- DUEXIS is contraindicated for the treatment of perioperative pain in the setting of coronary artery bypass graft (CABG) surgery [see *Warnings and Precautions* (5.2)].
- DUEXIS is contraindicated in patients in late stages of pregnancy [see *Warnings and Precautions* (5.9)].
- DUEXIS should not be administered to patients with a history of hypersensitivity to other H<sub>2</sub>-receptor antagonists. Cross sensitivity with other H<sub>2</sub>-receptor antagonists has been observed.

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Cardiovascular Thrombotic Events

Clinical trials of several COX-2 selective and nonselective NSAIDs, including ibuprofen, which is a component of DUEXIS tablets, of up to 3 years duration have shown an increased risk of serious cardiovascular (CV) thrombotic events, myocardial infarction, and stroke, which can be fatal. All NSAIDs, both COX-2 selective and nonselective, may have a similar risk. Patients with known CV disease or risk factors for CV disease may be at greater risk. To minimize the potential risk for an adverse CV event in patients treated with an NSAID, the lowest effective dose should be used for the shortest duration possible. Physicians and patients should remain alert for the development of such events, even in the absence of previous CV symptoms. Patients should be informed about the signs and/or symptoms of serious CV events and the steps to take if they occur.

There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious CV thrombotic events associated with NSAID use. The concurrent use of aspirin and an NSAID does increase the risk of serious GI events [see *Warnings and Precautions* (5.13)].

Two large, controlled clinical trials of a COX-2 selective NSAID for the treatment of pain in the first 10-14 days following CABG surgery found an increased incidence of myocardial infarction and stroke [see *Contraindications* (4)].

### 5.2 Hypertension

NSAIDs, including ibuprofen, which is a component of DUEXIS tablets, can lead to onset of new hypertension or worsening of pre-existing hypertension, either of which may contribute to the increased incidence of CV events. Patients taking thiazides or loop diuretics may have impaired response to these therapies when taking NSAIDs. NSAIDs, including DUEXIS, 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 [see *Drug Interactions* (7.1, 7.4)].

### 5.3 Congestive Heart Failure and Edema

Fluid retention and edema have been observed in some patients taking NSAIDs. DUEXIS should be used with caution in patients with fluid retention or heart failure.

### 5.4 Risk of Gastrointestinal Ulceration, Bleeding, and Perforation

NSAIDs, including ibuprofen, which is a component of DUEXIS tablets, can cause serious gastrointestinal (GI) adverse reactions including inflammation, bleeding, ulceration, and perforation of the stomach, small intestine, or large intestine, which can be fatal. These serious adverse reactions 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 1 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, including DUEXIS, should be prescribed with extreme caution in those with a prior history of ulcer disease or GI bleeding. Patients with a prior history of peptic ulcer disease and/or GI 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, including DUEXIS, include concomitant use of oral corticosteroids, anticoagulants, antiplatelet drugs (including low-dose aspirin), longer duration of NSAID therapy, smoking, use of alcohol, older age, and poor general health status. Most spontaneous reports of fatal GI reactions are in elderly or debilitated patients, and, therefore, special care should be taken in treating this population with DUEXIS.

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

Epidemiological studies of the case-control and cohort design have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding. In two studies, concurrent use of an NSAID, COX-2 inhibitor, or aspirin potentiated the risk of bleeding [see *Drug Interactions* (7.2, 7.7)]. Although these studies focused on upper gastrointestinal bleeding, bleeding at other sites cannot be ruled out.

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.

Because serious GI tract ulcers 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 complete blood count (CBC) and chemistry profile checked periodically.

Symptomatic response to therapy with DUEXIS does not preclude the presence of gastric malignancy.

### 5.5 Active Bleeding

When active and clinically significant bleeding from any source occurs in patients receiving DUEXIS, 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.

## 5.6 Renal Injury

Long-term administration of NSAIDs, including ibuprofen, which is a component of DUEXIS tablets, 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, heart failure, liver dysfunction, those taking diuretics and angiotensin-converting enzyme (ACE) inhibitors, and the elderly. If clinical signs (e.g., azotemia, hypertension, and/or proteinuria) and symptoms consistent with renal disease develop, DUEXIS should be discontinued. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state [see *Adverse Reactions (6.1) and Use in Specific Populations (8.6)*].

## 5.7 Seizures

Central nervous system (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 DUEXIS is fixed. Therefore, DUEXIS is not recommended in patients with creatinine clearance < 50 mL/min.

## 5.8 Anaphylaxis

Anaphylaxis may occur in patients without known prior exposure to ibuprofen, which is a component of DUEXIS tablets. DUEXIS 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 (4) and Warnings and Precautions (5.12)*]. Emergency help should be sought in cases where anaphylaxis, which may have a fatal outcome, occurs.

## 5.9 Skin Reactions

NSAIDs, including ibuprofen, which is a component of DUEXIS tablets, can cause serious skin adverse reactions 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 [see *Contraindications (4) and Adverse Reactions (6)*].

## 5.10 Pregnancy

Starting at 30 weeks gestation, DUEXIS should be avoided by pregnant women because it may cause premature closure of the ductus arteriosus [see *Contraindications (4) and Use in Specific Population (8.1)*].

## 5.11 Hepatic Injury

Borderline elevations of one or more liver tests may occur in up to 15% of patients taking NSAIDs, including ibuprofen, which is a component of DUEXIS tablets. These laboratory abnormalities may progress, may remain unchanged, or may be transient with continuing therapy. Notable elevations of alanine aminotransferase (ALT) or aspartate aminotransferase (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 DUEXIS. If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), DUEXIS should be discontinued.

## 5.12 Anemia

Anemia is sometimes seen in patients receiving NSAIDs, including ibuprofen which is a component of DUEXIS 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 DUEXIS, should have their hemoglobin or hematocrit checked if they exhibit any signs or symptoms of anemia.

## 5.13 Inhibition of Platelet Aggregation

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 DUEXIS who may be adversely affected by alterations in platelet function, such as those with coagulation disorders or patients receiving anticoagulants, should be carefully monitored.

## 5.14 Pre-existing 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, DUEXIS should not be administered to patients with this form of aspirin sensitivity and should be used with caution in patients with pre-existing asthma.

## 5.15 Concomitant NSAID Use

DUEXIS 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 DUEXIS may increase the risk of adverse events [see *Adverse Reactions (6)*, *Drug Interactions (7.2)*, and *Clinical Studies (14)*].

## 5.16 Aseptic Meningitis

Aseptic meningitis with fever and coma has been observed on rare occasions in patients on ibuprofen, which is a component of DUEXIS. 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 DUEXIS, the possibility of its being related to ibuprofen should be considered.

## 5.17 Corticosteroid Treatment

DUEXIS 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 and the patient should be observed closely for any evidence of adverse effects, including adrenal insufficiency and exacerbation of symptoms of arthritis.

## 5.18 Masking of Inflammation and Fever

The pharmacological activity of DUEXIS in reducing fever and inflammation may diminish the utility of these diagnostic signs in detecting complications of presumed noninfectious, noninflammatory painful conditions.

## 5.19 Visual Disturbances

Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported. If a patient develops such complaints while receiving DUEXIS, 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 elsewhere in the labeling:

- Cardiovascular events [see *Boxed Warning and Warnings and Precautions (5.1)*]
- Gastrointestinal effects [see *Boxed Warning and Warnings and Precautions (5.4)*]
- Renal injury [see *Warnings and Precautions (5.6)*]
- Seizures [see *Warnings and Precautions (5.7)*]
- Anaphylaxis [see *Warnings and Precautions (5.8)*]
- Skin reactions [see *Warnings and Precautions (5.9)*]
- Corticosteroid treatment [see *Warnings and Precautions (5.17)*]
- Masking of inflammation and fever [see *Warnings and Precautions (5.18)*]
- Hepatic injury [see *Warnings and Precautions (5.11)*]
- Hematological effects [see *Warnings and Precautions (5.13)*]
- Pre-existing asthma [see *Warnings and Precautions (5.14)*]
- Aseptic meningitis [see *Warnings and Precautions (5.16)*]

## 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 DUEXIS 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 DUEXIS 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 DUEXIS 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 DUEXIS or ibuprofen 800 mg three times a day for 24 consecutive weeks

Three serious cases of acute renal failure were observed in patients treated with DUEXIS in the two controlled clinical trials. All three patients recovered to baseline levels after discontinuation of DUEXIS. Additionally, increases in serum creatinine were observed in both treatment arms in the two clinical studies. Many of these patients were taking concomitant diuretics and/or angiotensin-converting enzyme inhibitors, or angiotensin receptor blockers. There were patients with a normal baseline serum creatinine level who developed abnormal values in the controlled trials as presented in Table 1.

**Table 1: Shift table of serum creatinine, normal\*\* to abnormal\*\*\* in controlled studies**

Study 301				Study 303	
Baseline	Post-Baseline*	DUEXIS N=414 % (n)	Ibuprofen N=207 % (n)	DUEXIS N=598 % (n)	Ibuprofen N=296 % (n)
Normal**	Abnormal***	4% (17)	2% (4)	2%(15)	4% (12)

\*At any point after baseline level

\*\*serum creatinine normal range is 0.5 – 1.4 mg/dL or 44-124 micromol/L

\*\*\*serum creatinine >1.4 mg/dL

### Most Commonly Reported Adverse Reactions

The most common adverse reactions (≥2%), from pooled data from the two controlled studies are presented in Table 2.

**Table 2: Incidence of Adverse Reactions in Controlled Studies**

	DUEXIS N=1022	Ibuprofen N=511
	%	%
<b>Blood and lymphatic system disorders</b>		
Anemia	2	1
<b>Gastrointestinal disorders</b>		
Nausea	6	5
Dyspepsia	5	8
Diarrhea	5	4
Constipation	4	4
Abdominal pain upper	3	3
Gastroesophageal reflux disease	2	3
Vomiting	2	2
Stomach discomfort	2	2
Abdominal pain	2	2
<b>General disorders and administration site conditions</b>		
Edema peripheral	2	2
<b>Infections and infestations</b>		
Upper respiratory tract infection	4	4
Nasopharyngitis	2	3
Sinusitis	2	3
Bronchitis	2	1
Urinary tract infection	2	2
Influenza	2	2
<b>Musculoskeletal and connective tissue disorders</b>		
Arthralgia	1	2
Back pain	2	1
<b>Nervous system disorders</b>		
Headache	3	3
<b>Respiratory, thoracic and mediastinal disorders</b>		
Cough	2	2
Pharyngolaryngeal pain	2	1
<b>Vascular disorders</b>		
Hypertension	3	2

DUEXIS (ibuprofen and famotidine) tablets 800 mg/26.6 mg administered orally three times per day.

Ibuprofen 800 mg administered orally three times per day.

In controlled clinical studies, the discontinuation rate due to adverse events for patients receiving DUEXIS and ibuprofen alone were similar. The most common adverse reactions leading to discontinuation from DUEXIS therapy were nausea (0.9%) and upper abdominal pain (0.9%).

There were no differences in types of related adverse reactions seen during maintenance treatment up to 12 months compared to short-term treatment.

## 6.2 Postmarketing Experience

### Ibuprofen

The following adverse reactions have been identified during post-approval use of ibuprofen. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These reports are listed below by body system:

Cardiac disorders: myocardial infarction

Gastrointestinal disorders: nausea, vomiting, diarrhea, abdominal pain

General disorders and administration site conditions: pyrexia, pain, fatigue, asthenia, chest pain, drug ineffective, edema peripheral

Musculoskeletal and connective tissue disorders: arthralgia

Nervous system disorders: headache, dizziness

Psychiatric disorders: depression, anxiety

Renal and urinary disorders: renal failure acute

Respiratory, thoracic, and mediastinal disorders: dyspnea

Vascular disorders: hypertension

### Famotidine

The following adverse reactions have been identified during post-approval use of famotidine. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These reports are listed below by body system:

Blood and lymphatic system disorders: anemia, thrombocytopenia

Gastrointestinal disorders: nausea, diarrhea, vomiting, abdominal pain

General disorders and administration site conditions: pyrexia, condition aggravated, asthenia, drug ineffective, chest pain, fatigue, pain, edema peripheral

Hepatobiliary disorders: hepatic function abnormal

Infections and infestations: pneumonia, sepsis

Investigations: platelet count decreased, aspartate aminotransferase increased, alanine aminotransferase increased, hemoglobin decreased

Metabolism and nutrition disorders: decreased appetite

Nervous system disorders: dizziness, headache

Respiratory, thoracic, and mediastinal disorders: dyspnea

Vascular disorders: hypotension

## 7 DRUG INTERACTIONS

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.

Studies with famotidine in man, in animal models, and in vitro have shown no significant interference with the disposition of compounds metabolized by the hepatic microsomal enzymes, e.g., cytochrome P450 system. Compounds tested in man include warfarin, theophylline, phenytoin, diazepam, aminopyrine and antipyrine. Indocyanine green as an index of hepatic drug extraction has been tested, and no significant effects have been found.

### 7.1 Warfarin-Type Anticoagulants

Several short-term controlled studies failed to show that ibuprofen significantly affected prothrombin times or a variety of other clotting factors when administered to individuals on coumarin-type anticoagulants. However, because bleeding has been reported when ibuprofen and other NSAIDs have been administered to patients on coumarin-type anticoagulants, prescribers 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 [see *Warnings and Precautions* (5.4, 5.14)].

### 7.2 Aspirin

When ibuprofen, which is a component of DUEXIS tablets, is 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. As with other NSAIDs, the concurrent use of aspirin and DUEXIS may increase the risk of adverse events [see *Warnings and Precautions* (5.1, 5.4), *Adverse Reactions* (6), and *Clinical Studies* (14)].

### 7.3 ACE-Inhibitors

Reports suggest that ibuprofen, a component of DUEXIS, may diminish the antihypertensive effect of ACE-inhibitors. This interaction should be given consideration in patients taking DUEXIS concomitantly with ACE-inhibitors. During concomitant therapy with DUEXIS, the patient should be observed closely for signs of renal failure [see *Warnings and Precautions* (5.6)].

### 7.4 Diuretics

Clinical studies, as well as postmarketing observations, have shown that ibuprofen, which is a component of DUEXIS, 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 DUEXIS, the patient should be observed closely for signs of renal failure [see *Warnings and Precautions* (5.6)], as well as to assure diuretic efficacy.

## 7.5 Lithium

Ibuprofen, which is a component of DUEXIS tablets, produced an elevation of plasma lithium levels and a reduction in renal lithium clearance in a study of 11 normal volunteers. The mean minimum lithium concentration increased 15% and the renal clearance of lithium was decreased by 20% during this period of concomitant ibuprofen drug administration. This effect has been attributed to inhibition of renal prostaglandin synthesis by ibuprofen. Thus, when ibuprofen and lithium are administered concurrently, patients should be observed carefully for signs of lithium toxicity.

## 7.6 Methotrexate

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

## 7.7 Selective Serotonin Reuptake Inhibitors (SSRIs)

There is an increased risk of gastrointestinal bleeding when selective serotonin reuptake inhibitors (SSRIs) are combined with NSAIDs including COX-2 selective inhibitors. Caution should be used when NSAIDs are administered concomitantly with SSRIs [see *Warnings and Precautions (5.4)*].

## 7.8 Cholestyramine

As with other NSAIDs, concomitant administration of cholestyramine can delay the absorption of ibuprofen, a component of DUEXIS.

# 8 USE IN SPECIFIC POPULATIONS

## 8.1 Pregnancy

### Teratogenic Effects

Pregnancy Category C. Animal reproduction studies have not been conducted with DUEXIS. Reproductive studies conducted with ibuprofen in rats and rabbits have not demonstrated evidence of developmental abnormalities. 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, respectively, based on body surface area) and in both species at intravenous (I.V.) doses of up to 200 mg/kg/day, and have revealed no significant evidence of impaired fertility or 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 based on body surface area) or higher. There are no adequate and well-controlled studies in pregnant women. Animal reproduction studies are not always predictive of human response. DUEXIS should be used during 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 [see *Warnings and Precautions (5.10)*].

## 8.2 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 DUEXIS on labor and delivery in pregnant women are unknown.

## 8.3 Nursing Mothers

It is not known whether ibuprofen is excreted in human milk.

Famotidine is secreted into breast milk of lactating rats. Transient growth depression was observed in young rats suckling from mothers treated with maternotoxic doses of at least 300 times the usual human dose of famotidine. Famotidine is detectable in human milk. Because of the potential for serious adverse reactions in nursing infants from DUEXIS, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

## 8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

## 8.5 Geriatric Use

The clinical trials primarily enrolled patients less than 65 years of age. Of the 1022 patients in clinical studies of DUEXIS, 18% (249 patients) were 65 years of age or older. Efficacy results in patients who are greater than or equal to 65 years of age are summarized in the CLINICAL STUDIES section [see *Clinical Studies (14)*].

Famotidine is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection and adjusting dose interval, and it may be useful to monitor renal function [see *Warnings and Precautions (5.6)*].

As with any NSAIDs, caution should be exercised in treating the elderly (65 years old and older). Experience indicates that geriatric patients may be particularly sensitive to certain adverse effects of NSAIDs. Elderly or debilitated patients seem to tolerate peptic ulceration or bleeding less well when these events do occur. Most spontaneous reports of fatal GI events are in the geriatric population [see *Warnings and Precautions (5.4)*].

Ibuprofen is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. Geriatric patients may be at a greater risk for the development of a form of renal toxicity precipitated by reduced prostaglandin formation during administration of NSAIDs [see *Warnings and Precautions (5.6)*].

## 8.6 Renal Insufficiency

In adult patients with renal insufficiency (creatinine clearance < 50 mL/min), the elimination half-life of famotidine is increased. Since CNS adverse effects have been reported in patients with creatinine clearance < 50 mL/min and the dosage of the famotidine component in DUEXIS is fixed, DUEXIS is not recommended in these patients [see *Warnings and Precautions (5.7)*].

# 10 OVERDOSAGE

No data are available with regard to overdose of DUEXIS. Findings related to the individual active substances are listed below.

## Ibuprofen

Approximately 1 1/2 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 4 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 8.5 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 3 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 1 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.

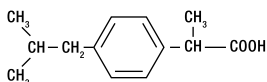
## Famotidine

The adverse reactions in overdose cases are similar to the adverse reactions encountered in normal clinical experience. Oral doses of up to 640 mg/day have been given to adult patients with pathological hypersecretory conditions with no serious adverse effects. In the event of overdosage, treatment should be symptomatic and supportive. Unabsorbed material should be removed from the GI tract, the patient should be monitored, and supportive therapy should be employed.

## 11 DESCRIPTION

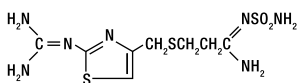
DUEXIS (ibuprofen and famotidine) is supplied as a tablet for oral administration which combines the nonsteroidal anti-inflammatory agent, ibuprofen, and the histamine H<sub>2</sub>-receptor antagonist, famotidine.

Ibuprofen is (±)-2-(*p*-isobutylphenyl)propionic acid. Its chemical formula is C<sub>13</sub>H<sub>18</sub>O<sub>2</sub> and molecular weight is 206.28. Ibuprofen is a white powder that is very slightly soluble in water (<1 mg/mL) and readily soluble in organic solvents such as ethanol and acetone. Its structural formula is:



Famotidine is *N*'-(aminosulfonyl)-3-[[[2-[(diaminomethylene)amino]-4-thiazolyl]methyl]thio]propanimidamide. Its chemical formula is C<sub>8</sub>H<sub>15</sub>N<sub>7</sub>O<sub>2</sub>S<sub>3</sub> and molecular weight is 337.45.

Famotidine is a white to pale yellow crystalline compound that is freely soluble in glacial acetic acid, slightly soluble in methanol, very slightly soluble in water, and practically insoluble in ethanol. Its structural formula is:



Each DUEXIS tablet contains ibuprofen, USP (800 mg) and famotidine, USP (26.6 mg) and the following inactive ingredients: microcrystalline cellulose, anhydrous lactose, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate, purified water, povidone, titanium dioxide, polyethylene glycol, polysorbate 80, polyvinyl alcohol, hypromellose, talc, FD&C Blue #2/Indigo Carmine Aluminum Lake, and FD&C Blue #1/Bright Blue FCF Aluminum Lake.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

DUEXIS is fixed-combination tablet of ibuprofen and famotidine. Ibuprofen 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.

Famotidine is a competitive inhibitor of histamine H<sub>2</sub>-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 (T<sub>4</sub>), and testosterone, were not altered after treatment with famotidine.

### 12.2 Pharmacodynamics

No pharmacodynamic studies were conducted.

### 12.3 Pharmacokinetics

#### Absorption

Ibuprofen and famotidine are rapidly absorbed after a single dose administration of DUEXIS. Mean C<sub>max</sub> values for ibuprofen are 45 µg/mL and are reached approximately 1.9 hours after oral administration of DUEXIS. The C<sub>max</sub> and AUC<sub>0-24hours</sub> values for the 800 mg of ibuprofen contained in a DUEXIS tablet are bioequivalent to the values for 800 mg of ibuprofen administered alone. C<sub>max</sub> values for famotidine were 61 ng/mL and are reached at approximately 2 hours after oral administration of DUEXIS.

A high-fat meal reduced famotidine C<sub>max</sub> and AUC by approximately 15% and 11%, respectively, and reduced ibuprofen AUC by approximately 14% but did not change C<sub>max</sub>. Food delayed famotidine T<sub>max</sub> and ibuprofen T<sub>max</sub> 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.

#### 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<sub>1/2</sub>) value of 2 hours following administration of a single dose of DUEXIS.

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-hydroxymethyl-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<sub>1/2</sub> value of 4 hours following administration of a single dose of DUEXIS.

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.

#### Special Populations

Gender: The effects of gender on the pharmacokinetics of ibuprofen or famotidine after administration of DUEXIS have not been evaluated.

Age: The effects of age on the pharmacokinetics of ibuprofen or famotidine after administration of DUEXIS have not been evaluated.

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

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

Hepatic impairment: The effects of hepatic impairment on the pharmacokinetics of ibuprofen or famotidine after administration of DUEXIS have not been evaluated [see *Warnings and Precautions* (5.11)].

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies to evaluate the potential effects of DUEXIS 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.

Famotidine was negative in the microbial mutagen test (Ames test) using *Salmonella 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 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.

## 14 CLINICAL STUDIES

Two multicenter, double-blind, active-controlled, randomized, 24-week studies of DUEXIS were conducted in patients who were expected to require daily 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 DUEXIS 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 DUEXIS (ibuprofen and famotidine) and 452 patients taking ibuprofen only, either as a primary or secondary endpoint. In both trials, DUEXIS 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 3 and 4. 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.

**Table 3: Overall Incidence Rates of Patients Who Developed at Least One Upper Gastrointestinal or Gastric Ulcer - Study 301**

	DUEXIS % (n/N)	Ibuprofen % (n/N)	P-value <sup>a</sup>
<b>Primary endpoint</b>			
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
<b>Secondary endpoint</b>			
Gastric ulcer*	9.7% (37/380)	17.9% (34/190)	0.005
Gastric ulcer**	22.4% (85/380)	30.0% (57/190)	0.052

<sup>a</sup>Cochran-Mantel-Haenszel test

\*Classifying early terminated patients as NOT having an ulcer

\*\*Classifying patients who early terminated due to an adverse event, were lost 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 4: Overall Incidence Rate of Patients Who Developed at Least One Gastric or Upper Gastrointestinal Ulcer - Study 303**

	DUEXIS % (n/N)	Ibuprofen % (n/N)	P-value <sup>a</sup>
<b>Primary endpoint</b>			
Gastric ulcer*	8.7% (39/447)	17.6% (38/216)	0.0004
Gastric ulcer**	17.4% (78/447)	31.0% (67/216)	<0.0001
<b>Secondary endpoint</b>			
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

<sup>a</sup>Cochran-Mantel-Haenszel test

\*Classifying early terminated patients as NOT having an ulcer

\*\*Classifying patients who early terminated due to an adverse event, were lost 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 DUEXIS, 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 DUEXIS 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 DUEXIS, 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 DUEXIS developed an upper gastrointestinal ulcer compared to 27% of those patients who received only ibuprofen [see *Use in Specific Populations (8.5)*].

Of the 1022 patients in clinical studies of DUEXIS, 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 DUEXIS developed an upper gastrointestinal ulcer compared to 24% of those patients who received only ibuprofen.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

DUEXIS (ibuprofen and famotidine) tablets, 800 mg/26.6 mg, are light blue, oval, biconvex, film-coated tablets debossed with "HZT" on one side and supplied as:

<b>NDC Number</b>	<b>Size</b>
75987-010-03	Bottle of 90 tablets

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). [See USP Controlled Room Temperature]

## 17 PATIENT COUNSELING INFORMATION

"See FDA-approved patient labeling (Medication Guide)"

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.

- DUEXIS, like other NSAIDs, may cause serious CV side effects, such as MI or stroke, which may result in hospitalization and even death [see *Warnings and Precautions (5.1)*].
- DUEXIS, 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 [see *Warnings and Precautions (5.4)*].
- DUEXIS, like other NSAIDs, can cause serious skin side effects such as exfoliative dermatitis, Stevens Johnson Syndrome, and Toxic epidermal necrolysis, which may result in hospitalization and even death. Patients should be advised to stop the drug immediately if

they develop any type of rash and contact their physicians as soon as possible.

- Patients should be monitored for development of nephrotoxicity (e.g., azotemia, hypertension, and/or proteinuria). If these occur, patients should be instructed to stop therapy and seek immediate medical therapy.
- DUEXIS is not recommended in patients with creatinine clearance < 50 mL/min because of the seizures, delirium, coma and other CNS effect.
- Patients should promptly report signs or symptoms of unexplained weight gain or edema to their physicians.
- 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 anaphylaxis (e.g., difficulty breathing, swelling of the face or throat). If these occur, patients should be instructed to seek immediate emergency help [see *Warnings and Precautions (5.7)*].
- Patients should be informed that in late pregnancy, as with other NSAIDs, DUEXIS should be avoided because it may cause premature closure of the ductus arteriosus.
- DUEXIS tablets should be swallowed whole, and should not be cut to supply a lower dose. Do not 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 possible. However, if the next schedule 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.

Distributed by:  
Horizon Pharma USA, Inc.  
1033 Skokie Boulevard, Suite 355  
Northbrook, IL 60062

Manufactured by:  
Pharmaceutics International, Inc.  
10819 Gilroy Road  
Hunt Valley, MD 21031  
sanofi-aventis Canada  
2150 St-Ezear Blvd. West  
Laval, Québec H7L 4A8  
Canada

## Medication Guide

### **DUEXIS® (due ex is)**

#### **(ibuprofen and famotidine) tablets**

Read this Medication Guide before you start taking DUEXIS and each time you get a refill. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or your treatment.

#### **What is the most important information I should know about DUEXIS?**

**DUEXIS contains ibuprofen [a nonsteroidal anti-inflammatory drug (NSAID)] and famotidine. NSAID-containing medicines, such as DUEXIS, may increase the chance of a heart attack or stroke that can lead to death.**

This chance increases:

- with longer use of NSAID medicines
- in people who have heart disease

**NSAID-containing medicines, such as DUEXIS, should never be used right before or after a heart surgery called a coronary artery bypass graft (CABG).**

**NSAID-containing medicines, such as DUEXIS can cause ulcers and bleeding in the stomach and intestines at any time during treatment.**

#### **Ulcers and bleeding:**

- can happen without warning symptoms
- may cause death

**The chance of a person getting an ulcer or bleeding with NSAIDs increases with:**

- taking medicines called steroid hormones (corticosteroids) and blood thinners (anticoagulants)
- longer use of the NSAID
- smoking
- drinking alcohol
- older age
- having poor health

**NSAID-containing medicines, such as DUEXIS, should only be used:**

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

#### **What are Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)?**

NSAID medicines are used to treat pain and redness, swelling, and heat (inflammation) from medical conditions such as:

- different types of arthritis (rheumatoid arthritis and osteoarthritis)

#### **Who should not take a Non-Steroidal Anti-Inflammatory Drug (NSAID)?**

##### **Do not take an NSAID medicine:**

- If you had an asthma attack, hives, or other allergic reaction with aspirin or any other NSAID medicine
- For pain right before or after heart bypass surgery

##### **Tell your healthcare provider:**

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

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

##### **Serious side effects include:**

- heart attack
- stroke
- high blood pressure
- heart failure from body swelling (fluid retention)
- kidney problems including kidney failure
- bleeding and ulcers in the stomach and intestine
- low red blood cells (anemia)
- life-threatening skin reactions
- life-threatening allergic reactions
- liver problems including liver failure
- asthma attacks in people who have asthma

##### **Other side effects include:**

- stomach pain
- constipation
- diarrhea
- gas
- heartburn
- nausea
- vomiting
- dizziness

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

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

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

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

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

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

##### **Other information about Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)**

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

## NSAID medicines that need a prescription

Generic Name	Requires Prescription
Celecoxib	Celebrex
Diclofenac	Cataflam, Voltaren, Arthrotec (combined with misoprostol)
Difunisal	Dolobid
Etodolac	Lodine, Lodine XL
Fenoprofen	Nalfon, Nalfon 200
Flurbiprofen	Ansaid
Ibuprofen	Motrin, Tab-Profen, Vicoprofen (combined with hydrocodone), Combunox (combined with oxycodone), DUEXIS (combined with famotidine)
Indomethacin	Indocin, Indocin SR, Indo-Lemmon, Indomethagan
Ketoprofen	Orudis, Orudis KT, Oruvail
Ketorolac	Toradol
Mefanamic Acid	Ponstel
Meloxicam	Mobic
Nabumetone	Relafen
Naproxen	Naprosyn, Anaprox, Anaprox DS, Prevacid NapraPAC (Prevacid copackaged with Naprosyn), Vimovo (combined with esomeprazole)
Oxaprozin	Daypro
Enteric coated naproxen	EC-Naproxen, Naprelan
Piroxicam	Feldene
Sulindac	Clinoril
Tolmetin	Tolectin, Tolectin DS, Tolectin 600

## What is DUEXIS?

DUEXIS contains 2 medicines:

1. Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID). Please read the above information regarding the benefits and risks of NSAIDs, including ibuprofen, a component of DUEXIS.
2. Famotidine is a histamine 2 (H<sub>2</sub>)-receptor antagonist, a medicine that may help reduce stomach acid.

DUEXIS is a prescription medicine used to:

- relieve 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 who are taking ibuprofen for rheumatoid arthritis and osteoarthritis. DUEXIS was studied mostly in people less than 65 years of age and who did not have a prior history of ulcers of the stomach and upper intestines.

It is not known if DUEXIS is safe or effective in children.

## Who should not take DUEXIS?

### Do not take DUEXIS:

- If you had an asthma attack, hives, or other allergic reaction after taking aspirin or other NSAID medicine.
- For pain right before or after heart bypass surgery.
- If you are in the late stages of pregnancy (after 30 weeks of pregnancy).
- If you are allergic to any other histamine 2 (H<sub>2</sub>)-receptor antagonist.

## What should I tell my healthcare provider before taking DUEXIS?

### Before you take DUEXIS, tell your healthcare provider if you:

- have high blood pressure (hypertension)
- have heart problems
- have a history of stomach ulcers
- have or had bleeding problems
- have liver or kidney problems
- have ulcerative colitis or Crohn's disease (inflammatory bowel disease or IBD)
- have any other medical conditions
- are pregnant or plan to become pregnant. DUEXIS should not be used by pregnant women late their pregnancy. **See "What is the most important information I should know about DUEXIS?"**
- are breast-feeding or plan to breast-feed. DUEXIS can pass into your milk and may harm your baby. You should not breast-feed while taking DUEXIS. Talk to your healthcare provider about the best way to feed your baby if you take DUEXIS.

Tell your healthcare provider about all of the medicines you take including prescription and nonprescription medicines, vitamins, and herbal supplements. Since DUEXIS contains ibuprofen, talk to your healthcare provider before taking any other NSAID containing products.

Using DUEXIS with other medicines can cause serious side effects. DUEXIS may affect the way other medicines work and other medicines may affect how DUEXIS works.

Especially, tell your doctor if you take:

- Aspirin
- Warfarin (Coumadin)

## How should I take DUEXIS?

- Take DUEXIS exactly as your healthcare provider tells you to take it.
- Your healthcare provider will tell you how many DUEXIS to take and when to take them.
- Do not stop DUEXIS without first talking to your healthcare provider.
- Swallow DUEXIS tablets whole. Do not crush, split or chew DUEXIS tablets.
- If you forget to take a dose of DUEXIS, take it as soon as you remember. If it is almost time for your next dose, do not take the missed dose. Take the next dose on time. Do not take 2 doses at one time to make up for a missed dose.
- If you take too much DUEXIS, tell your healthcare provider or go to the nearest hospital emergency room right away.

If you take more DUEXIS than your doctor recommends, call your Poison Control Center at 1-800-222-1222.

- Your doctor may do certain tests from time to time to check you for side effects of DUEXIS.

## What are the possible side effects of DUEXIS?

### DUEXIS may cause serious side effects.

See "What is the most important information I should know about DUEXIS?"

- **Stroke or Heart Attack.** If you have heart disease you may be at risk for a heart attack or stroke while taking DUEXIS. Call your healthcare provider or get medical help right away if you have any of these signs and symptoms:

### Signs and symptoms of a Stroke

- numbness or weakness of the face, arm or leg, especially on one side of the body
- sudden confusion, trouble speaking or understanding
- sudden trouble seeing in one or both eyes
- sudden trouble walking, dizziness, loss of balance or coordination
- sudden, severe headache

## Signs and symptoms of a Heart Attack

- chest discomfort in the center of your chest that lasts for more than few minutes, or that goes away or comes back
- chest discomfort that feels like uncomfortable pressure or squeezing
- chest fullness or pain
- pain or discomfort in your arms, back, neck, jaw or stomach
- shortness of breath with or without chest discomfort
- break out in a cold sweat
- nausea or vomiting
- **New or worsening high blood pressure (hypertension).** Your healthcare provider should check your blood pressure while you are taking DUEXIS.
- **Heart problems** such as congestive heart failure. Tell your healthcare provider about any swelling of your body, hands or feet, sudden weight gain or trouble breathing.
- **Active bleeding.** Tell your doctor if you have signs of active bleeding including:
  - passing black sticky bowel movements (stools)
  - having bloody diarrhea
  - vomiting or coughing up blood or dark particles that look like coffee grounds
- **Kidney problems.** Long term use of NSAIDS, including ibuprofen which is a medicine in DUEXIS can cause kidney problems. Your healthcare provider should do blood test to check your kidneys.
- **Serious allergic reactions.** Tell your healthcare provider or get medical help right away if you get:
  - swelling of your lips, tongue, or face
  - throat tightness
  - rash
  - problems breathing or swallowing
- **Serious skin reactions.** NSAIDS, including ibuprofen which is a medicine in DUEXIS can cause a serious skin reaction called Stevens-Johnson Syndrome, toxic epidermal necrolysis or other serious skin reactions that may affect any part of your body. These serious skin reactions may be life threatening and you may need to be treated in a hospital. Stop taking DUEXIS and call your healthcare provider right away if you have any of these symptoms:
  - skin rash or acne
  - dry skin
  - itching
  - blisters on your skin
  - blisters or sores in your mouth
  - peeling of your skin fever
  - muscle or joint aches
  - redness or swelling of your face, hands, or soles of your feet
- **Liver problems.** Tell your healthcare provider right away if you have any of these following symptoms of liver problems:
  - dark (tea colored) urine
  - yellowing of your skin or whites of your eyes
  - light-colored bowel movements (stools)
  - fever
  - nausea (feeling sick to your stomach)
  - feel unwell or like you have the flu
  - pain or tenderness on your right side below your ribs
  - tiredness
  - loss of appetite
- **Low red blood cell count (anemia).** Symptoms of anemia include shortness of breath and tiredness.
- **Meningitis.** Ibuprofen, one of the medicines in DUEXIS may cause meningitis, a serious brain problem. Call your healthcare provider right away if you have any of the following symptoms of meningitis:

- headache
- fever
- nausea
- vomiting
- stiff neck
- rash
- unusual sensitivity to light
- muscle pains
- chills
- confusion
- drowsiness

- **Eye problems.** Tell your healthcare provider if you develop blurred or decreased vision, changes in color vision, or any other problems with your eyes.

- nausea
- constipation
- diarrhea
- upper stomach (abdominal) pain
- vomiting
- throat irritation, pain or swelling
- back pain

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

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

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

## How should I store DUEXIS?

- Store DUEXIS at 59°F to 86°F (15°C to 30°C).
- Keep DUEXIS in the original container and keep the bottle tightly closed.
- Keep DUEXIS dry.

## Keep DUEXIS and all medicines out of the reach of children.

### General information about DUEXIS.

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

This Medication Guide summarizes the most important information about DUEXIS. If you would like more information, ask your healthcare provider. You can ask your healthcare provider or pharmacist for information that is written for healthcare professionals.

For more information, go to [www.DUEXIS.com](http://www.DUEXIS.com) or call 1-866-479-6742

## What are the ingredients in DUEXIS?

**Active ingredients:** ibuprofen and famotidine

**Inactive ingredients:** microcrystalline cellulose, anhydrous lactose, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate, purified water, povidone, titanium dioxide, polyethylene glycol, polysorbate 80, polyvinyl alcohol, talc, FD&C Blue #2/Indigo Carmine Aluminum Lake and FD&C Blue #1/Brilliant Blue FDF Aluminum Lake

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

**Horizon Pharma USA, Inc.**  
**1033 Skokie Blvd. Ste. 355**  
**Northbrook, Illinois 60062**

April 2011