FLURBIPROFEN- flurbiprofen tablet, film coated
Bryant Ranch Prepack

FLURBIPROFEN TABLETS USP, 100 mg
0711
Rx only

Cardiovascular Risk

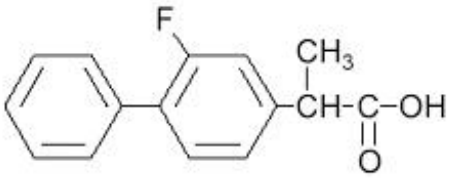
- NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk (see **WARNINGS**).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

Gastrointestinal Risk

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

DESCRIPTION

Flurbiprofen is a member of the phenylalkanoic acid derivative group of non-steroidal anti-inflammatory drugs. Flurbiprofen tablets USP are round, blue, film-coated tablets for oral administration. Flurbiprofen is a racemic mixture of (+)S- and (-)R- enantiomers. Flurbiprofen is a white or slightly yellow crystalline powder. It is slightly soluble in water at pH 7.0 and readily soluble in most polar solvents. The chemical name is [1,1'-biphenyl]-4-acetic acid,2-fluoro-α-methyl-, (±)-. It has the following structural formula:



$C_{15}H_{13}FO_2$ M.W. 244.26

Each tablet, for oral administration, contains 100 mg flurbiprofen. In addition, each tablet contains the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, titanium dioxide, and FD&C Blue #1 aluminum lake.

CLINICAL PHARMACOLOGY

Pharmacodynamics

Flurbiprofen tablets contain flurbiprofen, a non-steroidal anti-inflammatory drug that exhibits anti-inflammatory, analgesic, and antipyretic activities in animal models. The mechanism of action of

flurbiprofen, like that of other non-steroidal anti-inflammatory drugs, is not completely understood but may be related to prostaglandin synthetase inhibition.

Pharmacokinetics

Absorption

The mean oral bioavailability of flurbiprofen from flurbiprofen tablets 100 mg is 96% relative to an oral solution. Flurbiprofen is rapidly and non-stereoselectively absorbed from flurbiprofen tablets, with peak plasma concentrations occurring at about 2 hours (see **Table 1**). Administration of flurbiprofen tablets with either food or antacids may alter the rate but not the extent of flurbiprofen absorption. Ranitidine has been shown to have no effect on either the rate or extent of flurbiprofen absorption from flurbiprofen tablets.

Distribution

The apparent volume of distribution (Vz/F) of both R- and S-flurbiprofen is approximately 0.12 L/kg. Both flurbiprofen enantiomers are more than 99% bound to plasma proteins, primarily albumin. Plasma protein binding is relatively constant for the typical average steady-state concentrations (≤ 10 mcg/mL) achieved with recommended doses. Flurbiprofen is poorly excreted into human milk. The nursing infant dose is predicted to be approximately 0.1 mg/day in the established milk of a woman taking flurbiprofen tablets 200 mg/day (see **PRECAUTIONS**, **Nursing Mothers**).

Metabolism

Several flurbiprofen metabolites have been identified in human plasma and urine. These metabolites include 4’-hydroxy-flurbiprofen, 3’,4’-dihydroxy-flurbiprofen, 3’-hydroxy-4’-methoxy-flurbiprofen, their conjugates, and conjugated flurbiprofen. Unlike other arylpropionic acid derivatives (e.g., ibuprofen), metabolism of R-flurbiprofen to S-flurbiprofen is minimal. *In vitro* studies have demonstrated that cytochrome P4502C9 (CYP2C9) plays an important role in the metabolism of flurbiprofen to its major metabolite, 4’hydroxy-flurbiprofen (see **CLINICAL PHARMACOLOGY**, **Special Populations**). The 4’-hydroxy- flurbiprofen metabolite showed little anti-inflammatory activity in animal models of inflammation. *In vitro* studies also demonstrated glucuronidation of both enantiomers of flurbiprofen and 4'-hydroxy-flurbiprofen. UGT2B7 is the predominant UGT isoenzyme responsible for the glucuronidation. Flurbiprofen does not induce enzymes that alter its metabolism.

The total plasma clearance of unbound flurbiprofen is not stereoselective, and clearance of flurbiprofen is independent of dose when used within the therapeutic range.

Excretion

Following dosing with flurbiprofen tablets, less than 3% of flurbiprofen is excreted unchanged in the urine, with about 70% of the dose eliminated in the urine as flurbiprofen, 4'-hydroxy-flurbiprofen, and their acyl-glucuronide conjugates. Because renal elimination is a significant pathway of elimination of flurbiprofen metabolites, dosing adjustment in patients with moderate or severe renal dysfunction may be necessary to avoid accumulation of flurbiprofen metabolites. The mean terminal disposition half-lives ($t_{½}$) of R- and S-flurbiprofen are similar, about 4.7 and 5.7 hours, respectively. There is little accumulation of flurbiprofen following multiple doses of flurbiprofen tablets.

Table 1: Mean (SD) R,S-Flurbiprofen Pharmacokinetic Parameters Normalized to a 100 mg Dose of Flurbiprofen Tablets

Pharmacokinetic	Normal Healthy Adults*	Geriatric Arthritis Patients†	End Stage Renal Disease	Alcoholic Cirrhosis Patients‡

Pharmacokinetic Parameter	(18 to 40 years) N = 15	Patients† (65 to 83 years) N = 13	Disease Patients* (23 to 42 years) N = 8	Patients‡ (31 to 61 years) N = 8
Peak Concentration (Tg/mL)	14 (4)	16 (5)	9§	9§
Time of Peak Concentration (h)	1.9 (1.5)	2.2 (3)	2.3§	1.2§
Urinary Recovery of Unchanged Flurbiprofen (% of Dose)	2.9 (1.3)	0.6 (0.6)	0.02 (0.02)	NA¶
Area Under the Curve (AUC)# (Tg h/mL)	83 (20)	77 (24)	44§	50§
Apparent Volume of Distribution (Vz/F, L)	14 (3)	12 (5)	10§	14§
Terminal Disposition Half-life (t½, h)	7.5 (0.8)	5.8 (1.9)	3.3Þ	5.4Þ

* 100 mg single-dose
† Steady-state evaluation of 100 mg every 12 hours
‡ 200 mg single-dose
§ Calculated from mean parameter values of both flurbiprofen enantiomers
¶ Not available
# AUC from 0 to infinity for single doses and from 0 to the end of the dosing interval for multiple-doses
Þ Value for S-flurbiprofen

Special Populations

Pediatric

The pharmacokinetics of flurbiprofen have not been investigated in pediatric patients.

Race

No pharmacokinetic differences due to race have been identified.

Geriatric

Flurbiprofen pharmacokinetics were similar in geriatric arthritis patients, younger arthritis patients, and young healthy volunteers receiving flurbiprofen tablets, 100 mg as either single or multiple doses.

Hepatic Insufficiency

Hepatic metabolism may account for > 90% of flurbiprofen elimination, so patients with hepatic disease may require reduced doses of flurbiprofen tablets compared to patients with normal hepatic function.

The pharmacokinetics of R- and S-flurbiprofen were similar, however, in alcoholic cirrhosis patients (N = 8) and young healthy volunteers (N = 8) following administration of a single 200 mg dose of flurbiprofen tablets.

Flurbiprofen plasma protein binding may be decreased in patients with liver disease and serum albumin concentrations below 3.1g/dL (see **PRECAUTIONS**, **Hepatic Effects**).

Poor Metabolizers of CYP2C9 Substrates

Patients who are known or suspected to be poor CYP2C9 metabolizers based on previous history/experience with other CYP2C9 substrates (such as warfarin and phenytoin) should be administered flurbiprofen with caution as they may have abnormally high plasma levels due to reduced metabolic clearance.

Renal Insufficiency

Renal clearance is an important route of elimination for flurbiprofen metabolites, but a minor route of elimination for unchanged flurbiprofen (≤ 3% of total clearance). The unbound clearances of R- and S-flurbiprofen did not differ significantly between normal healthy volunteers (N = 6, 50 mg single dose) and patients with renal impairment (N = 8, inulin clearances ranging from 11 to 43 mL/min, 50 mg multiple doses). Flurbiprofen plasma protein binding may be decreased in patients with renal impairment and serum albumin concentrations below 3.9 g/dL. Elimination of flurbiprofen metabolites may be reduced in patients with renal impairment (see **WARNINGS**, **Renal Effects**).

Flurbiprofen is not significantly removed from the blood into dialysate in patients undergoing continuous ambulatory peritoneal dialysis.

Drug-Drug Interactions

(see also PRECAUTIONS, **Drug Interactions)**

Antacids

Administration of flurbiprofen tablets to volunteers under fasting conditions or with antacid suspension yielded similar serum flurbiprofen-time profiles in young adult subjects (n = 12). In geriatric subjects (n = 7), there was a reduction in the rate but not the extent of flurbiprofen absorption.

Aspirin

Concurrent administration of flurbiprofen tablets and aspirin resulted in 50% lower serum flurbiprofen concentrations. This effect of aspirin (which is also seen with other non-steroidal anti-inflammatory drugs) has been demonstrated in patients with rheumatoid arthritis (n = 15) and in healthy volunteers (n = 16) (see **PRECAUTIONS**, **Drug Interactions**).

Beta-Adrenergic Blocking Agents

The effect of flurbiprofen on blood pressure response to propranolol and atenolol was evaluated in men with mild uncomplicated hypertension (n = 10). Flurbiprofen pretreatment attenuated the hypotensive effect of a single dose of propranolol but not atenolol. Flurbiprofen did not appear to affect the beta-blocker-mediated reduction in heart rate. Flurbiprofen did not affect the pharmacokinetic profile of either drug (see **PRECAUTIONS**, **Drug Interactions**).

Cimetidine, Ranitidine

In normal volunteers (n = 9), pretreatment with cimetidine or ranitidine did not affect flurbiprofen pharmacokinetics, except for a small (13%) but statistically significant increase in the area under the serum concentration curve of flurbiprofen in subjects who received cimetidine.

Digoxin

In studies of healthy males (n = 14), concomitant administration of flurbiprofen and digoxin did not change the steady state serum levels of either drug.

Diuretics

Studies in healthy volunteers have shown that, like other non-steroidal anti-inflammatory drugs, flurbiprofen can interfere with the effects of furosemide. Although results have varied from study to study, effects have been shown on furosemide-stimulated diuresis, natriuresis, and kaliuresis. Other non-steroidal anti-inflammatory drugs that inhibit prostaglandin synthesis have been shown to interfere with thiazide and potassium-sparing diuretics (see **PRECAUTIONS**, **Drug Interactions**).

Lithium

In a study of 11 women with bipolar disorder receiving lithium carbonate at a dosage of 600 to 1200 mg/day, administration of 100 mg flurbiprofen tablets every 12 hours increased plasma lithium concentrations by 19%. Four of 11 patients experienced a clinically important increase (> 25% or > 0.2 mmol/L). Non-steroidal anti-inflammatory drugs have also been reported to decrease the renal clearance of lithium by about 20% (see **PRECAUTIONS**, **Drug Interactions**).

Methotrexate

In a study of six adult arthritis patients, coadministration of methotrexate (10 to 25 mg/dose) and flurbiprofen tablets (300 mg/day) resulted in no observable interaction between these two drugs.

Oral Hypoglycemic Agents

In a clinical study, flurbiprofen was administered to adult diabetics who were already receiving glyburide (n = 4), metformin (n = 2), chlorpropamide with phenformin (n = 3), or glyburide with phenformin (n = 6). Although there was a slight reduction in blood sugar concentrations during concomitant administration of flurbiprofen and hypoglycemic agents, there were no signs or symptoms of hypoglycemia.

INDICATIONS AND USAGE

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

Flurbiprofen tablets are indicated:

- For relief of the signs and symptoms of rheumatoid arthritis.
- For relief of the signs and symptoms of osteoarthritis.

CONTRAINDICATIONS

Flurbiprofen tablets are contraindicated in patients with known hypersensitivity to flurbiprofen.

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

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

WARNINGS

Cardiovascular Effects

Cardiovascular Thrombotic Events

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

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

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

Hypertension

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

Congestive Heart Failure and Edema

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

Gastrointestinal Effects - Risk of Ulceration, Bleeding, and Perforation

NSAIDs, including flurbiprofen tablets, can cause serious gastrointestinal (GI) adverse events including inflammation, bleeding, ulceration, and perforation of the stomach, small intestine, or large intestine, which can be fatal. These serious adverse events can occur at any time, with or without warning symptoms, in patients treated with NSAIDs. Only one in five patients, who develop a serious upper GI adverse event on NSAID therapy, is symptomatic. Upper GI ulcers, gross bleeding, or perforation caused by NSAIDs occur in approximately 1% of patients treated for 3 to 6 months, and in about 2 to 4% of patients treated for one year. These trends continue with longer duration of use, increasing the likelihood of developing a serious GI event at some time during the course of therapy. However, even short-term therapy is not without risk. NSAIDs should be prescribed with extreme caution in those with a prior history of ulcer disease or gastrointestinal bleeding. Patients with a *prior history of peptic ulcer disease and/or gastrointestinal bleeding* who use NSAIDs have a greater than 10 fold increased risk for developing a GI bleed compared to patients treated with neither of these risk factors. Other factors that increase the risk of GI bleeding in patients treated with NSAIDs include concomitant use of oral corticosteroids or anticoagulants, longer duration of NSAID therapy, smoking, use of alcohol, older age, and poor general health status. Most spontaneous reports of fatal GI events are in elderly or debilitated patients and therefore, special care should be taken in treating this population.

To minimize the potential risk for an adverse GI event in patients treated with an NSAID, the lowest effective dose should be used for the shortest possible duration. Patients and physicians should remain alert for signs and symptoms of GI ulcerations and bleeding during NSAID therapy and promptly initiate additional evaluation and treatment if a serious GI event is suspected. This should include

discontinuation of the NSAID until a serious GI adverse event is ruled out. For high-risk patients, alternate therapies that do not involve NSAIDs should be considered.

Renal Effects

Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of a non-steroidal anti-inflammatory drug may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state.

Advanced Renal Disease

In clinical studies, the elimination half-life of flurbiprofen was unchanged in patients with renal impairment. Flurbiprofen metabolites are eliminated primarily by the kidneys. Elimination of 4'-hydroxy-flurbiprofen was reduced in patients with moderate to severe renal impairment. Therefore, treatment with flurbiprofen tablets is not recommended in these patients with advanced renal disease. If flurbiprofen tablet therapy must be initiated, close monitoring of the patient's renal function is advisable (see **CLINICAL PHARMACOLOGY**).

Anaphylactoid Reactions

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

Skin Reactions

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

Pregnancy

In late pregnancy, as with other NSAIDs, flurbiprofen tablets should be avoided because they may cause premature closure of the ductus arteriosus.

PRECAUTIONS

General

Flurbiprofen tablets cannot be expected to substitute for corticosteroids or to treat corticosteroid insufficiency. Abrupt discontinuation of corticosteroids may lead to disease exacerbation. Patients on prolonged corticosteroid therapy should have their therapy tapered slowly if a decision is made to discontinue corticosteroids.

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

Hepatic Effects

Borderline elevations of one or more liver tests may occur in up to 15% of patients taking non-steroidal anti-inflammatory drugs, including flurbiprofen tablets. These laboratory abnormalities may progress, may remain unchanged, or may be transient with continuing therapy. Notable elevations of ALT or AST (approximately three or more times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials with non-steroidal anti-inflammatory drugs. 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 flurbiprofen tablets. If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), flurbiprofen tablets should be discontinued.

Hematological Effects

Anemia is sometimes seen in patients receiving non-steroidal anti-inflammatory drugs, including flurbiprofen tablets. This may be due to fluid retention, GI blood loss, or an incompletely described effect upon erythropoiesis. Patients on long-term treatment with non-steroidal anti-inflammatory drugs, including flurbiprofen tablets, should have their hemoglobin or hematocrit checked periodically even if they do not exhibit any signs or symptoms of anemia.

Non-steroidal anti-inflammatory drugs 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. Flurbiprofen tablets do not generally affect platelet counts, prothrombin time (PT), or partial thromboplastin time (PTT). Patients receiving flurbiprofen tablets who may be adversely affected by alterations in platelet function, such as those with coagulation disorders or patients receiving anticoagulants, should be carefully monitored.

Preexisting Asthma

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

Vision Changes

Blurred and/or diminished vision has been reported with the use of flurbiprofen tablets and other non-steroidal anti-inflammatory drugs. Patients experiencing eye complaints should have ophthalmologic examinations.

Information for Patients

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

- Flurbiprofen tablets, like other NSAIDs, may cause CV side effects, such as MI or stroke, which may result in hospitalization and even death. Although serious CV events can occur without warning symptoms, patients should be alert for the signs and symptoms of chest pain, shortness of breath, weakness, slurring of speech, and should ask for medical advice when observing any indicative sign or symptoms. Patients should be apprised of the importance of this follow-up (see **WARNINGS**, **Cardiovascular Effects**).

- Flurbiprofen tablets, like other NSAIDs, can cause GI discomfort and, rarely, serious GI side effects, such as ulcers and bleeding, which may result in hospitalization and even death. Although serious GI tract ulcerations and bleeding can occur without warning symptoms, patients should be alert for the signs and symptoms of ulcerations and bleeding, and should ask for medical advice when observing any indicative sign or symptoms including epigastric pain, dyspepsia, melena, and hematemesis. Patients should be apprised of the importance of this follow-up (see **WARNINGS**, **Gastrointestinal Effects - Risk of Ulceration, Bleeding, and Perforation**).
- Flurbiprofen tablets, like other NSAIDs, can cause serious skin side effects such as exfoliative dermatitis, SJS and TEN, which may result in hospitalization and even death. Although serious skin reactions may occur without warning, patients should be alert for the signs and symptoms of skin rash and blisters, fever, or other signs of hypersensitivity such as itching, and should ask for medical advice when observing any indicative sign or symptoms. Patients should be advised to stop the drug immediately if they develop any type of rash and contact their physicians as soon as possible.
- 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 an anaphylactoid reaction (e.g., difficulty breathing, swelling of the face or throat). If these occur, patients should be instructed to seek immediate emergency help (see **WARNINGS**, **Anaphylactoid Reactions**).
- In late pregnancy, as with other NSAIDs, flurbiprofen tablets should be avoided because they may cause premature closure of the ductus arteriosus.

Laboratory Tests

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

Drug Interactions

ACE-Inhibitors

Reports suggest that non-steroidal anti-inflammatory drugs may diminish the antihypertensive effect of ACE-inhibitors. This interaction should be given consideration in patients taking non-steroidal anti-inflammatory drugs concomitantly with ACE-inhibitors.

Anticoagulants

The effects of warfarin and NSAIDs on GI bleeding are synergistic, such that users of both drugs together have a risk of serious GI bleeding higher than users of either drug alone. The physician should be cautious when administering flurbiprofen tablets to patients taking warfarin or other anticoagulants.

Aspirin

Concurrent administration of aspirin lowers serum flurbiprofen concentrations (see **CLINICAL PHARMACOLOGY**, **Drug-Drug Interactions**). The clinical significance of this interaction is not known; however, as with other NSAIDs, concomitant administration of flurbiprofen and aspirin is not generally recommended because of the potential for increased adverse effects.

Beta-Andrenergic Blocking Agents

Flurbiprofen attenuated the hypotensive effect of propranolol but not atenolol (see **CLINICAL PHARMACOLOGY**, **Drug-Drug Interactions**). The mechanism underlying this interference is unknown. Patients taking both flurbiprofen and a beta-blocker should be monitored to ensure that a satisfactory hypotensive effect is achieved.

Diuretics

Clinical studies, as well as postmarketing observations, have shown that flurbiprofen tablets can reduce the natriuretic effect of furosemide and thiazides in some patients. This response has been attributed to inhibition of renal prostaglandin synthesis. During concomitant therapy with NSAIDs, the patient should be observed closely for signs of renal failure (see **WARNINGS**, **Renal Effects**), as well as diuretic efficacy.

Lithium

NSAIDs have produced an elevation of plasma lithium levels and a reduction in renal lithium clearance. The mean minimum lithium concentration increased 15% and the renal clearance was decreased by approximately 20%.

These effects have been attributed to inhibition of renal prostaglandin synthesis by the non-steroidal anti-inflammatory drug. Thus, when non-steroidal anti-inflammatory drugs and lithium are administered concurrently, subjects should be observed carefully for signs of lithium toxicity.

Methotrexate

Non-steroidal anti-inflammatory drugs have been reported to competitively inhibit methotrexate accumulation in rabbit kidney slices. This may indicate that they could enhance the toxicity of methotrexate. Caution should be used when non-steroidal anti-inflammatory drugs are administered concomitantly with methotrexate.

Pregnancy

Teratogenic Effects

Pregnancy category C

Reproductive studies conducted in rats and rabbits have not demonstrated evidence of developmental abnormalities. However, animal reproduction studies are not always predictive of human response. There are no adequate and well-controlled studies in pregnant women. Flurbiprofen tablets should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects

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

Labor and Delivery

In rat studies with non-steroidal anti-inflammatory drugs, as with other drugs known to inhibit prostaglandin synthesis, an increased incidence of dystocia, delayed parturition, and decreased pup survival occurred. The effects of flurbiprofen on labor and delivery in pregnant women are unknown.

Nursing Mothers

Concentrations of flurbiprofen in breast milk and plasma of nursing mothers suggest that a nursing infant could receive approximately 0.10 mg flurbiprofen per day in the established milk of a woman taking flurbiprofen tablets, 200 mg/day. Because of possible adverse effects of prostaglandin-inhibiting drugs

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

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

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

Clinical experience with flurbiprofen suggests that elderly patients may have a higher incidence of gastrointestinal complaints than younger patients, including ulceration, bleeding, flatulence, bloating, and abdominal pain. **To minimize the potential risk for gastrointestinal events, the lowest effective dose should be used for the shortest possible duration** (see **WARNINGS**, **Gastrointestinal Effects - Risk of Ulceration, Bleeding, and Perforation**). Likewise, elderly patients are at greater risk of developing renal decompensation (see **WARNINGS**, **Renal Effects**).

The pharmacokinetics of flurbiprofen do not seem to differ in elderly patients from those in younger individuals (see **CLINICAL PHARMACOLOGY**, **Special Populations**). The rate of absorption of flurbiprofen was reduced in elderly patients who also received antacids, although the extent of absorption was not affected (see **CLINICAL PHARMACOLOGY**, **Drug-Drug Interactions**).

ADVERSE REACTIONS

Table 2: Reported adverse events in patients receiving flurbiprofen tablets or other non-steroidal anti-inflammatory drugs

Reported in patients treated with flurbiprofen tablets			**Reported in patients treated with other products but not flurbiprofen tablets**
Incidence of 1% or greater[*]	**Incidence < 1% - Causal Relationship Probable**[†]	**Incidence < 1% - Causal Relationship Unknown**[†]	
BODY AS A WHOLE edema	anaphylactic reaction chills fever		< **1%:** death infection sepsis
CARDIOVASCULAR SYSTEM	congestive heart failure hypertension vascular diseases vasodilation	angina pectoris arrhythmias myocardial infarction	< **1%:** hypotension palpitations syncope tachycardia vasculitis
DIGESTIVE SYSTEM abdominal pain constipation diarrhea dyspepsia/heartburn elevated liver enzymes flatulence GI bleeding nausea vomiting	bloody diarrhea esophageal disease gastric/peptic ulcer disease gastritis jaundice (cholestatic and noncholestatic) hematemesis hepatitis stomatitis/glossitis	appetite changes cholecystitis colitis dry mouth exacerbation of inflammatory bowel disease periodontal abscess small intestine inflammation with loss of	> **1%:** GI perforation GI ulcers (gastric/duodenal) **< 1%:** eructation liver failure pancreatitis

	stomatitis/glossitis	blood and protein	
HEMIC AND LYMPHATIC SYSTEM	aplastic anemia (including agranulocytosis or pancytopenia) decrease in hemoglobin and hematocrit ecchymosis/purpura eosinophilia hemolytic anemia iron deficiency anemia leukopenia thrombocytopenia	lymphadenopathy	> **1%:** anemia increased bleeding time < **1%:** melena rectal bleeding
METABOLIC AND NUTRITIONAL SYSTEM body weight changes	hyperuricemia	hyperkalemia	< **1%:** hyperglycemia
NERVOUS SYSTEM headache nervousness and other manifestations of central nervous system (CNS) stimulation (e.g., anxiety, insomnia, increased reflexes, tremor) symptoms associated with CNS inhibition (e.g., amnesia, asthenia, depression, malaise, somnolence)	ataxia cerebrovascular ischemia confusion paresthesia twitching	convulsion cerebrovascular accident emotional lability hypertonia meningitis myasthenia subarachnoid hemorrhage	< **1%:** coma dream abnormalities drowsiness hallucinations
RESPIRATORY SYSTEM rhinitis	asthma epistaxis	bronchitis dyspnea hyperventilation laryngitis pulmonary embolism pulmonary infarct	< **1%:** pneumonia respiratory depression
SKIN AND APPENDAGES rash	angioedema eczema exfoliative dermatitis photosensitivity pruritus toxic epidermal necrolysis urticaria	alopecia dry skin herpes simplex/zoster nail disorder sweating	< **1%:** erythema multiforme Stevens Johnson syndrome
SPECIAL SENSES changes in vision	conjunctivitis	changes in taste corneal opacity ear disease glaucoma retinal	> **1%:** pruritus < **1%:** hearing

dizziness/vertigo tinnitus	parosmia	hemorrhage retrobulbar neuritis transient hearing loss	< **1%:** hearing impairment
UROGENITAL SYSTEM signs and symptoms suggesting urinary tract infection	hematuria interstitial nephritis renal failure	menstrual disturbances prostate disease vaginal and uterine hemorrhage vulvovaginitis	> **1%:** abnormal renal function < **1%:** dysuria oliguria polyuria proteinuria
* from clinical trials † from clinical trials, postmarketing surveillance, or literature			

OVERDOSAGE

Symptoms following acute overdoses with non-steroidal anti-inflammatory drugs are usually limited to lethargy, drowsiness, nausea, vomiting, and epigastric pain, which are generally reversible with supportive care. Gastrointestinal bleeding can occur. Hypertension, acute renal failure, respiratory depression and coma may occur, but are rare. Anaphylactoid reactions have been reported with therapeutic ingestion of non-steroidal anti-inflammatory drugs, and may occur following an overdose.

Patients should be managed by symptomatic and supportive care following overdose with a non-steroidal anti-inflammatory drug. There are no specific antidotes. Emesis and/or activated charcoal (60 to 100 g in adults, 1 to 2 g/kg in children) and/or osmotic cathartic may be indicated in patients seen within 4 hours of ingestion with symptoms, or following a large overdose (5 to 10 times the usual dose). Forced diuresis, alkalization of urine, hemodialysis, or hemoperfusion may not be useful due to high protein binding.

DOSAGE AND ADMINISTRATION

Carefully consider the potential benefits and risks of flurbiprofen tablets USP and other treatment options before deciding to use flurbiprofen tablets USP. Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals (see **WARNINGS**).

After observing the response to initial therapy with flurbiprofen tablets USP, the dose and frequency should be adjusted to suit an individual patient's needs.

For relief of the signs and symptoms of rheumatoid arthritis or osteoarthritis, the recommended starting dose of flurbiprofen tablets USP is 200 to 300 mg per day, divided for administration two, three, or four times a day. The largest recommended single dose in a multiple-dose daily regimen is 100 mg.

HOW SUPPLIED

Flurbiprofen tablets USP, 100 mg are round, blue, film-coated tablets debossed “93”-“711” available in bottles of 100 and 500.

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

TEVA PHARMACEUTICALS USA

Sellersville, PA 18960

Rev. I 9/2010

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

Rx only

(See the end of this Medication Guide for a list of prescription NSAID medicines.)

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

NSAID medicines may increase the chance of a heart attack or stroke that can lead to death. This chance increases:

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

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

NSAID medicines can cause ulcers and bleeding in the stomach and intestines at any time during treatment. Ulcers and bleeding:

- can happen without warning symptoms
- may cause death

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

- taking medicines called "corticosteroids" and "anticoagulants"
- longer use
- smoking
- drinking alcohol
- older age
- having poor health

NSAID medicines should only be used:

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

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

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

- different types of arthritis
- menstrual cramps and other types of short-term pain

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

Do not take an NSAID medicine:

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

Tell your healthcare provider:

- about all 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 doctor.**

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.

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

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

NSAID medicines that need a prescription

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

Sulindac	Clinoril
Tolmetin	Tolectin, Tolectin DS, Tolectin 600

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

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

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

Manufactured By:

TEVA PHARMACEUTICALS USA

Sellersville, PA 18960

Rev. B 7/2009

Flurbiprofen 100mg Tablet

FLURBIPROFEN

flurbiprofen tablet, film coated

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG LABEL	**Item Code (Source)**	NDC:63629-1250(NDC:0093-0711)
Route of Administration	ORAL	**DEA Schedule**	

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
FLURBIPROFEN (FLURBIPROFEN)	FLURBIPROFEN	100 mg

Inactive Ingredients

Ingredient Name	Strength
SILICON DIOXIDE	
CROSCARMELLOSE SODIUM	
HYPROMELLOSES	
LACTOSE MONOHYDRATE	
MAGNESIUM STEARATE	
CELLULOSE, MICROCRYSTALLINE	
POLYETHYLENE GLYCOLS	
POLYSORBATE 80	
TITANIUM DIOXIDE	
FD&C BLUE NO. 1	
ALUMINUM OXIDE	

Product Characteristics

Color	BLUE	**Score**	no score
Shape	ROUND	**Size**	10mm
Flavor		**Imprint Code**	93;711
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:63629-1250-1	20 in 1 BOTTLE		
2	NDC:63629-1250-2	30 in 1 BOTTLE		
3	NDC:63629-1250-3	14 in 1 BOTTLE		
4	NDC:63629-1250-4	90 in 1 BOTTLE		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA074431	06/02/1995	

Labeler - Bryant Ranch Prepack (171714327)

Registrant - Bryant Ranch Prepack (171714327)

Establishment

Name	Address	ID/FEI	Business Operations
Bryant Ranch Prepack		171714327	REPACK(63629-1250), RELABEL(63629-1250)