Flurbiprofen

Drug Description

Flurbiprofen is a nonsteroidal anti-inflammatory drug (NSAID) of the propionic acid chemical class. The oral formulation is used for the relief of pain and inflammation associated with rheumatoid arthritis and osteoarthritis. Unlabeled uses for oral flurbiprofen include dysmenorrhea and to preserve bone around dental implants. The longer half-life of flurbiprofen versus ketoprofen or fenoprofen allows for twice daily dosing of flurbiprofen in many patients. All NSAIDs including flurbiprofen cause an increased risk of serious gastrointestinal adverse effects including bleeding, ulceration, and perforation of the stomach or intestines and may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke. The lowest effective flurbiprofen dose for the shortest possible duration is recommended, as the risk for adverse effects may increase with duration of use. An ophthalmic form of flurbiprofen (Ocufen®) is available for inhibition of intraoperative miosis and was approved by the FDA in 1986. Flurbiprofen tablets were approved by the FDA in 1988.

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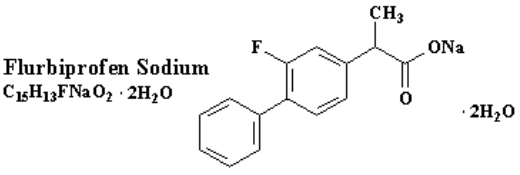
Classifications

- Analgesics
  - Nonsteroidal Antiinflammatory Drugs (NSAIDs)
    - Ophthalmic Nonsteroidal Antiinflammatory Drugs (NSAIDs)
- Musculoskeletal Agents
  - Musculoskeletal Antiinflammatory Agents
    - Nonsteroidal Antiinflammatory Drugs (NSAIDs)
- Ophthalmic Agents
  - Ophthalmic Antiinflammatory Agents
    - Ophthalmic Nonsteroidal Antiinflammatory Drugs (NSAIDs)

Chemical Structures



Mechanism of Action

Mechanism of Action: Flurbiprofen competitively inhibits both cyclooxygenase (COX) isoenzymes, COX-1 and COX-2, by blocking arachidonate binding resulting in analgesic, antipyretic, and anti-inflammatory pharmacologic effects. The enzymes COX-1 and COX-2 catalyze the conversion of arachidonic acid to prostaglandin G_2 (PGG_2), the first step of the synthesis prostaglandins and thromboxanes that are involved in rapid physiological responses. COX isoenzymes are also responsible for a peroxidase reaction, which is not affected by NSAIDs. In addition, NSAIDs do not suppress leukotriene synthesis by lipoxygenase pathways. COX-1 is constitutively expressed in almost all tissues, while COX-2 appears to only be constitutively expressed in the brain, kidney, bones, reproductive organs, and some neoplasms (e.g., colon and prostate cancers). COX-1 is responsible for prostaglandin synthesis in response to stimulation by circulating hormones, as well as maintenance of normal renal function, gastric mucosal integrity, and hemostasis. However, COX-2 is inducible in many cells in response to certain mediators of inflammation (e.g., interleukin-1, tumor necrosis factor, lipopolysaccharide, mitogens, and reactive oxygen intermediates).

- ***Antiinflammatory Activity:*** The antiinflammatory mechanism of flurbiprofen is due to decreased prostaglandin synthesis via inhibition of COX-1 and COX-2. It appears that the antiinflammatory effects may be primarily due to inhibition of the COX-2 isoenzyme. However, COX-1 is expressed at some sites of inflammation. COX-1 is expressed in the joints of rheumatoid arthritis or osteoarthritis patients, especially the synovial lining, and it is the primary enzyme of prostaglandin synthesis in human bursitis. Flurbiprofen is considered a non-selective NSAID, affecting COX-1 and COX-2 to a similar degree.
- ***Analgesic Activity:*** Flurbiprofen is effective in cases where inflammation has caused sensitivity of pain receptors (hyperalgesia). It appears prostaglandins, specifically prostaglandins E and F, are responsible for sensitizing the pain receptors; therefore, NSAIDs have an indirect analgesic effect by inhibiting the production of further prostaglandins and does not directly affect hyperalgesia or the pain threshold. Higher doses are required for analgesic versus antiinflammatory activity.
- ***Antipyretic Activity:*** Flurbiprofen promotes a return to a normal body temperature set point in the hypothalamus by suppressing the synthesis of prostaglandins, specifically PGE_2, in circumventricular organs in and near the hypothalamus. Although not indicated for the management of fever, flurbiprofen may mask fever in some patients, especially with high or chronic dosing.
- ***Ophthalmic Activity:*** Following topical application to the eye, flurbiprofen inhibits miosis by inhibiting the biosynthesis of ocular prostaglandins. Prostaglandins play a role in the miotic response produced during ocular surgery by constricting the iris sphincter independently of cholinergic mechanisms.

In the eye, prostaglandins also have been shown to disrupt the blood-aqueous humor barrier, cause vasodilation, increase vascular permeability, promote leukocytosis, and increase intraocular pressure. The degree of ocular inflammatory response is correlated with prostaglandin-induced increases in ciliary epithelium permeability. When applied topically to the eye, flurbiprofen and other NSAIDs inhibit the synthesis of prostaglandins in the iris, ciliary body, and conjunctiva. Thus, NSAIDs may prevent many of the manifestations of ocular inflammation. Flurbiprofen does not affect intraocular pressure or tonographic aqueous outflow resistance and does not interfere with the action of acetylcholine administered during ocular surgery. Flurbiprofen also does not prevent increases in intraocular pressure or decreases in aqueous outflow induced by topical corticosteroids.

•GI Effects: Gastrointestinal side effects of flurbiprofen are primarily contributed to COX-1 inhibition; however, potential role of COX-2 inhibition in the GI tract has not been fully elucidated.

•Platelet Effects: The inhibition of platelet aggregation seen with flurbiprofen is due to dose-dependent inhibition of COX-1 in platelets leading to decreased levels of platelet thromboxane A_2 and an increase in bleeding time. The inhibition of platelet aggregation is reversible within 24 hours of discontinuation of flurbiprofen. This differs from aspirin, which irreversibly binds to COX-1 in platelets inhibiting this enzyme for the life of the cell.

•Renal Effects: In the kidney, prostaglandins, produced by both COX-1 and COX-2, are important regulators of sodium and water reabsorption through PGE_2 and of renal function and hemodynamics via PGI_2 in response to vasoconstrictive factors (e.g., endothelin-1, a factor that increases peripheral vascular resistance) and through effects on the renin-angiotensin system. In the setting of decreased volume, PGI_2, helps maintain renal blood flow by counteracting other vasoconstrictive autocoids. In conditions where renal blood flow is dependent upon prostaglandin synthesis, administration of NSAIDs can result in significant decreases in renal blood flow leading to acute renal failure. In addition, alterations in sodium and water reabsorption may worsen in increased blood pressure, which can be significant in selected individuals.

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Pharmacokinetics

Pharmacokinetics: Flurbiprofen is administered orally or as an ophthalmic solution. It is not widely distributed after oral administration to humans; the apparent volume of distribution is approximately 0.12 L/kg. Flurbiprofen is poorly excreted into human milk. It is highly protein bound (>= 99%), primarily to albumin. The albumin binding site is apparently different than the binding site of warfarin, sulfonamides, or phenytoin. Flurbiprofen may also bind to erythrocytes. It is metabolized in the liver, via cytochrome P4502C9, to three major metabolites as well as some minor metabolites. Two major metabolites are formed by hydroxylation and the third by hydroxylation and methylation. The principal metabolite, 4'-hydroxyflurbiprofen, has weak prostaglandin inhibitory activity.[41951] Both enantiomers of flurbiprofen and the 4'-hydroxyflurbiprofen metabolite undergo UGT mediated glucouronidation, primarily via UGT2B7.[41951] [41952] After oral administration, less than 3% is excreted unchanged in the urine, with about 70% of the dose eliminated in the urine as flurbiprofen, 4’-hydroxyflurbiprofen, and their acyl-glucuronide conjugates. The elimination half-life in adults is about 5.7 hours (range: 3—9 hours).[41951]

Affected cytochrome P450 (CYP450) enzymes and drug transporter: CYP2C9, UGT2B7
Flurbiprofen is a substrate of the hepatic cytochrome isoenzyme CYP2C9. In addition, flurbiprofen and the flurbiprofen metabolite 4'-hydroxyflurbiprofen undergo UGT mediated glucouronidation, primarily via UGT2B7.[41951][41952]

•Route-Specific Pharmacokinetics

Oral Route

Fluribiprofen, orally administered as a racemic mixture of both R- and S-flurbiprofen, is rapidly and almost completely absorbed. Peak plasma concentrations are attained about 2 hours after dosing. Administration with food affects the rate, but not the extent of absorption.[41951]

Other Route(s)

Ophthalmic Route

Following topical application of flurbiprofen to the eye, peak drug concentrations in ocular tissues and fluids are achieved in about 0.5—1 hour. The extent of ocular absorption and peak aqueous humor concentrations of flurbiprofen do not appear to increase proportionally with the dose. Distribution into human ocular tissues and fluids has not been fully characterized. In rabbits, flurbiprofen is rapidly distributed throughout ocular tissues and fluids, including cornea, external tissues (e.g., sclera, conjunctiva), intraocular tissues (e.g., aqueous humor, iris, ciliary body), lens, and vitreous humor. In rabbits, the ocular distribution half-life is about 15 minutes and the ocular elimination half-life is about 1.5 hours. After topical application of flurbiprofen to the eye, metabolites and unchanged drug are present in urine, indicating systemic absorption. However, the risk of systemic effects appears to be minimal after topical ophthalmic use of the drug.

•Special Populations

Hepatic Impairment

Pharmacokinetic studies of flurbiprofen have not been performed in patients with hepatic dysfunction; however, as more than 90% of drug elimination is via hepatic metabolism, dosage adjustments may be required in patients with hepatic impairment. Further, plasma protein binding of flurbiprofen may be decreased in patients with liver disease and a serum albumin concentration of less than 3.1 g/dL, thus increasing the availability of free drug.[41951]

Renal Impairment

The elimination half-life of flurbiprofen was unchanged in patients with end stage renal disease (ESRD). Flurbiprofen metabolites are primarily eliminated by the kidneys, and elimination of 4'-hydroxyflurbiprofen was markedly reduced in ESRD patients. Therefore, patients with significantly impaired renal function may require a reduction of dosage to avoid accumulation of flurbiprofen metabolites. In addition, flurbiprofen protein binding may be decreased in patients with renal impairment and serum albumin concentrations below 3.9 g/dL.[41951]

Pediatrics
The pharmacokinetics of flurbiprofen have not been investigated in pediatric patients.[41951]

Geriatric
Flurbiprofen pharmacokinetics were similar in geriatric arthritis patients (age 65 to 83 years), younger arthritis patients (age unspecified), and young healthy volunteers (age 18 to 40 years) receiving flurbiprofen 100 mg PO as either single or multiple doses.[41951]

Ethnic Differences
No pharmacokinetic differences due to race/ethnic background have been identified.[41951]

Other
Poor Metabolizers of CYP2C9 Substrates
Patients who are poor CYP2C9 metabolizers may have increased flurbiprofen plasma concentrations and increased systemic exposure due to reduced metabolic clearance; CYP2C9 is the main enzyme involved in the metabolism of flurbiprofen to the minimally active 4'-hydroxyflurbiprofen metabolite. Administer flurbiprofen with caution to patients who are known or suspected poor CYP2C9 metabolizers based on previous history/experience with other CYP2C9 substrates (such as warfarin and phenytoin).[41951]

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Indications

Labeled

- arthralgia
- mild pain
- miosis inhibition
- moderate pain
- myalgia
- osteoarthritis
- rheumatoid arthritis

Off-Label, Recommended

- ankylosing spondylitis †
- bone pain †
- dental implants †
- dental pain †
- dysmenorrhea †
- migraine †
- migraine prophylaxis †
- postoperative ocular inflammation †

† Off-label indication

For the treatment of rheumatoid arthritis:
Oral dosage:
Adults: 200—300 mg/day PO in 2—4 divided doses; do not exceed 100 mg/dose PO. Most experience with rheumatoid arthritis has been with doses divided 3 or 4 times per day.

For the treatment of osteoarthritis:
Oral dosage:
Adults: 200—300 mg/day PO in 2—4 divided doses; do not exceed 100 mg/dose PO.

For the treatment of ankylosing spondylitis†:
Oral dosage:
Adults: 50 mg PO 4 times per day or 100 mg PO twice daily. Adjust dosage according to individual response up to a maximum of 300 mg/day PO in divided doses.[25129]

For the treatment of dysmenorrhea†:
Oral dosage:
Adults: Doses of 50 mg PO 4 times per day or 100 mg PO twice daily have been studied.[25130]

For the acute treatment of migraine† headache:
Oral dosage:
Adults: Doses of 100 mg PO 1—3 times per day have been used. Do not exceed 300 mg PO in any 24 hour period.

For migraine prophylaxis†:
Oral dosage:
Adults: 100 mg PO twice daily.[25428] Clinical practice guidelines classify flurbiprofen as possibly effective for migraine prophylaxis.[58130]

For the preservation of bone around dental implants†:
Oral dosage:
Adults: 100 mg PO twice daily for 3 months has been used to preserve bone around dental implants.[25131]

For the treatment of mild pain and moderate pain including arthralgia, myalgia, bone pain†, and dental pain†:
Oral dosage:

Adults: 50 mg PO 4 times per day or 100 mg PO twice daily. Single doses of 50—100 mg PO have been effective when used after dental surgery.[25132] Do not exceed 300 mg/day.

For intraoperative miosis inhibition:
Ophthalmic dosage:
Adults: A total of 4 drops should be administered by instilling 1 drop into the affected eye every 30 minutes beginning 2 hours before surgery.

For the treatment of postoperative ocular inflammation†:
Ophthalmic dosage:
Adults: 1 drop into the affected eye every 4 hours for 1—3 weeks.

Maximum Dosage Limits
•Adults
300 mg/day PO; not to exceed 100 mg/dose PO.
•Elderly
300 mg/day PO; not to exceed 100 mg/dose PO.
•Adolescents
Safety and efficacy have not been established.
•Children
Safety and efficacy have not been established.

Patients with Hepatic Impairment Dosing
Although specific guidelines are not available, oral dosage reduction may be necessary in patients with hepatic dysfunction.

Patients with Renal Impairment Dosing
CrCl < 10 mL/min: A reduction in oral dosage may be required to avoid accumulation of flurbiprofen metabolites.

†Off-label indication

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Level of Evidence

Indication Under Review: Flurbiprofen for migraine prophylaxis (Adults)

Status: Off-label

Source: Internal

Recommendation

For the use of flurbiprofen for migraine prophylaxis (Adults)

Strength of Recommendation: Equivocal/Weak For
Level of Evidence Rating: Very Low
Date of Review: 11/15/2014

NOTE: For information regarding editorial evaluation of off-label indications and recommendations, see Clinical Pharmacology Help, Editorial Policies

Evidence Summary

Indication	Dosage Regimen	Results/Endpoints	Citation	Level of Evidence
For migraine prophylaxis†	2-week placebo washout period followed by 8 weeks of flurbiprofen 100 mg PO twice daily vs. placebo, then another 2-week washout period before crossing over to other group for 8 weeks.	Mean migraine frequency (attacks/8 weeks): flurbiprofen, 4.39; placebo, 5.73 ($p < 0.1$). Mean migraine duration (hours/8 weeks): flurbiprofen, 51.7; placebo, 87.6 ($p < 0.015$). Mean relief medication dosing frequency (doses/8 weeks): flurbiprofen, 9.7; placebo, 14 ($p < 0.015$). Mean migraine intensity (5-point scale where 1 describes no limitation in daily activities and 5 describes bedridden): flurbiprofen, 2.1; placebo 2.5 ($p < 0.05$). Migraine frequency/8 weeks Duration of migraine attacks; intensity of migraine attacks	Solomon GD, Kunkel RS. Flurbiprofen in the prophylaxis of migraine. Cleve Clin J Med 1993;60:43-8.	Very Low

Discussion

Migraine can cause significant disability and lead to decreased productivity and quality of life. Prophylactic therapy can help reduce the frequency of attacks and therefore headache-related disability.[57980] [57981] The efficacy of flurbiprofen for migraine prophylaxis has been evaluated in 1 randomized, placebo-controlled, crossover trial.[25428] Cautious use is advised due to the risks of adverse gastrointestinal (GI) effects and potential headache progression or medication overuse headache.[25428] [58130] Fenoprofen may not be clinically appropriate in patients with a history of peptic ulcer disease or GI bleeding.[41951] Flurbiprofen may be considered for this indication; however, other therapies may be as or more effective or better tolerated.

Patients with migraine with aura, without aura, or both, as diagnosed by International Headache Society criteria, were included in a double-blind, randomized, placebo-controlled, crossover trial (n = 23) that evaluated the efficacy of flurbiprofen 100 mg PO twice daily. Mean migraine intensity (2.1 vs. 2.5), mean migraine duration (51.7 vs. 87.6 hours/8 weeks), and mean relief medication dosing frequency (9.7 vs. 14 doses/8 weeks) were significantly lower with flurbiprofen vs. placebo. Although mean migraine frequency decreased with flurbiprofen vs. placebo (4.39 vs. 5.73 attacks/8 weeks), the difference was not significant. Adverse effects included hemoccult positive stool test (2), hemoglobin decrease (1), hematocrit decrease (1), abdominal cramps with diarrhea (1), mouth sores (1), and epigastric pain with emesis (1).[25428]

Administration Information

General Administration Information
For storage information, see the specific product information within the How Supplied section.

Route-Specific Administration

Oral Administration

Oral Solid Formulations

- Flurbiprofen tablets should be administered with food to decrease gastrointestinal side effects.

Ophthalmic Administration

- Apply topically to the eye.
- Do not touch the tip of the dropper to the eye, fingertips, or other surface.
- Patients having bilateral ocular surgery who are using flurbiprofen solution for intraoperative miosis inhibition should use 1 bottle for each eye to avoid the potential for cross-contamination.[49155]

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Contraindications / Precautions

Absolute contraindications are italicized

- B *coronary artery bypass graft surgery (CABG)*
- *NSAID hypersensitivity*
- *salicylate hypersensitivity*
- acute bronchospasm
- acute myocardial infarction
- alcoholism
- anemia
- angina
- anticoagulant therapy
- asthma
- bone marrow suppression
- breast-feeding
- cardiac arrhythmias
- cardiac disease
- cardiomyopathy
- cerebrovascular disease
- chemotherapy
- children
- coagulopathy
- coronary artery disease
- corticosteroid therapy
- dental disease
- dental work
- diabetes mellitus
- edema
- geriatric
- B GI bleeding
- GI disease
- B GI perforation
- heart failure
- hematological disease
- hemophilia
- hepatic disease
- hypertension
- immunosuppression
- jaundice
- labor
- B myocardial infarction
- nasal polyps
- neutropenia
- obstetric delivery
- ocular surgery
- peptic ulcer disease
- peripheral vascular disease
- poor metabolizers
- pregnancy
- renal disease
- renal failure
- renal impairment
- rheumatoid arthritis
- B stroke
- surgery
- tachycardia
- thrombocytopenia
- tobacco smoking
- ulcerative colitis
- urticaria

Flurbiprofen is contraindicated in patients with *salicylate hypersensitivity* or *NSAID hypersensitivity* who have experienced asthma, urticaria, or other allergic reactions after taking aspirin or other NSAIDs. Severe, rarely fatal, anaphylactoid reactions to flurbiprofen have been reported in such patients. Flurbiprofen should not be used in asthma patients with aspirin-sensitive asthma or the aspirin triad because of the approximate 5% cross-sensitivity that occurs between aspirin and NSAIDs. The triad typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who experience severe, potentially fatal, acute bronchospasm after taking aspirin or other NSAIDs. The use of NSAIDs, including flurbiprofen, may cause serious and potentially fatal skin reactions including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis. Patients should be instructed to discontinue the medication and contact their health care provider if erythema, rash, blisters, or related skin reactions develop.

Chronic use of oral flurbiprofen can result in gastritis, ulceration with or without GI perforation, and/or GI bleeding, which can occur at any time, often without preceding symptoms. Therefore, oral flurbiprofen should be avoided if possible in patients with a history of or active GI disease including peptic ulcer disease, ulcerative colitis, or GI bleeding.[41951] Patients with a prior history of peptic ulcer disease or GI bleeding who use NSAIDs have a greater than 10-fold increased risk for developing a GI bleed compared to patients with neither of these risk factors. It is recommended not to initiate therapy with maximum doses in these patients due to the likely increase frequency of adverse reactions. Patients at increased risk for NSAID-induced GI bleeding include those receiving concurrent myelosuppressive chemotherapy, corticosteroid therapy, or anticoagulant therapy, tobacco smoking patients, geriatric patients, and patients with alcoholism. All patients receiving prolonged treatment should be routinely monitored for potential GI ulceration and bleeding. Consider therapies besides NSAIDs for high risk patients.

Flurbiprofen should be used cautiously in patients with preexisting hematological disease (e.g., coagulopathy or hemophilia) or thrombocytopenia due to the effect of the drug on platelet function. Like other NSAIDs, flurbiprofen can alter platelet aggregation and prolong bleeding time. Flurbiprofen should also be used with caution in patients undergoing surgery when a high degree of hemostasis is required. There have been reports that ophthalmic administration of flurbiprofen may cause increased bleeding of ocular tissues (including hyphema) in conjunction with ocular surgery. Therefore, flurbiprofen ophthalmic solution should be used with caution in ocular surgery patients with known bleeding tendencies or who are receiving other medications which may prolong bleeding time. NSAIDs should be used with caution in patients with immunosuppression or neutropenia. NSAIDs may mask the signs of infection such as fever or pain in patients with bone marrow suppression.

Anemia may be exacerbated with the use of oral NSAIDs (such as flurbiprofen). This may be due to fluid retention, GI blood loss, or an incompletely described effect upon erythrogenesis. Patients who have initial hemoglobin values of 10 g/dL or less and who are to receive long-term NSAID therapy should have hemoglobin values determined periodically.

Use of flurbiprofen may cause increased bleeding in patients with dental disease. Patients should inform their dentist they are taking flurbiprofen prior to any dental work due to a potential increased risk of bleeding. Patients should be instructed on proper oral hygiene.

Flurbiprofen should be used with caution in patients with pre-existing hepatic disease as drug accumulation and/or increased drug exposure may be possible, and drug-induced hepatotoxicity has been reported. Hepatic metabolism is thought to account for more than 90% of flurbiprofen elimination; patients with hepatic impairment may require a lower dosage. Plasma protein binding may also be decreased in patients with liver disease and a serum albumin concentration of less than 3.1 g/dL, thus increasing the availability of free drug. Severe hepatic reactions have occurred during treatment with flurbiprofen, and patients with hepatic impairment are at an increased risk for developing these complications. Elevations in liver-function tests have been reported in up to 15% of patients receiving NSAID therapy. Flurbiprofen should be discontinued if elevated hepatic enzymes persist or worsen, or if signs or symptoms of hepatic disease, such as jaundice, develop.[41951]

Ocular flurbiprofen should be used with caution in patients with diabetes mellitus, corneal denervation, corneal epithelial defects, xerophthalmia, rheumatoid arthritis, or repeat ocular surgery within a short time period, as these patients may be at greater risk for corneal adverse events. Some ocular adverse effects of flurbiprofen may be sight-threatening.

Patients with significant renal impairment/renal failure (creatinine clearance < 10 ml/min) require oral dosage reduction of flurbiprofen to prevent accumulation of active metabolites (see Dosage). Due to the role of prostaglandins in renal function and hemodynamics, patients with renal disease should be closely observed during therapy with flurbiprofen due to an increased risk for adverse reactions during treatment. Conditions such as congestive heart failure or hypertension can be exacerbated with flurbiprofen. Dosage adjustment may be necessary. Meta-analysis have demonstrated that the effect of NSAIDs on blood pressure is the greatest in hypertensive individuals receiving antihypertensive medication. In addition, normotensive patients receiving antihypertensive therapy had higher increases in blood pressure than subjects with uncontrolled hypertension or normotensive subjects receiving no hypertensive therapy.[27388] Patients with renal impairment, renal failure, hepatic disease, diabetes mellitus, systemic lupus erythematosus (SLE), or congestive heart failure, rheumatoid arthritis, edema, extracellular volume depletion (i.e., hypovolemia or dehydration), sepsis; those taking diuretics or nephrotoxic drugs; and the elderly are at the highest risk for complications related to suboptimal renal perfusion.

Flurbiprofen, like all NSAIDs, may exacerbate hypertension and congestive heart failure and may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. The FDA has warned that the risk of myocardial infarction or stroke can occur as early as the first weeks of using a NSAID, and risk may increase with higher doses and longer duration of use. Data demonstrate that patients treated with NSAIDs were more likely to die in the first year following a myocardial infarction compared to those not treated with NSAIDs. NSAIDs may increase the risk of a cardiovascular thrombotic event in patients with or without underlying heart disease or risk factors for heart disease. Patients with known heart disease or risk factors appear to have a greater likelihood of an event following NSAID use, likely due to a higher baseline risk. Current evidence is insufficient to determine if the risk of an event is higher or lower for any particular NSAID compared to other NSAIDs. There is an increased risk of heart failure with NSAID use.[59937] Caution is recommended when administering flurbiprofen to patients with cardiac disease, cardiomyopathy, cardiac arrhythmias (e.g., tachycardia), significant coronary artery disease (including acute myocardial infarction, angina, or history of myocardial infarction), peripheral vascular disease, cerebrovascular disease (e.g., stroke, transient ischemic attack), hypertension, pre-existing renal disease, or fluid retention. Both fluid retention and edema have been reported in patients receiving flurbiprofen. In addition, clinical practice guidelines state NSAIDs should not be administered to patients presenting with and hospitalized for ST-elevation myocardial infarction (STEMI) due to increased risk of mortality, reinfarction, hypertension, heart failure, and myocardial rupture associated with their use.[34165] Closely monitor blood pressure during flurbiprofen receipt. Use the lowest effective dose

for the shortest duration possible to minimize the potential risk for an adverse cardiovascular event. Inform patients to seek immediate medical attention if they experience any signs or symptoms of a cardiovascular thrombotic event.[59937]

Safe and effective use of flurbiprofen have not been established in children.

Although use should be avoided in late pregnancy, oral formulations of flurbiprofen are classified as FDA pregnancy risk category C throughout most of gestation.[41951] Flurbiprofen ophthalmic solution is classified as FDA pregnancy risk category C because no studies during pregnancy are available in animals or humans.[49155] Use of flurbiprofen should be avoided unless the potential therapeutic benefits justify its use during pregnancy. Systemic flurbiprofen is classified as FDA pregnancy risk category D drug if used during the third trimester due to the potential for prostaglandin synthetase inhibitors to cause *in utero* constriction of the fetal ductus arteriosus. Of 40 babies born with persistent pulmonary hypertension of the newborn (PPHN), 87.5% had the presence of an NSAID in their meconium versus 24.6% of 61 children born without PPHN; the presence of only 4 NSAIDs was examined. In addition to meconium aspiration, asphyxia, respiratory distress syndrome, and group B streptococcal pneumonia, ductus arteriosus constriction by an NSAID appears to be another predisposing factor for PPHN development, as a patent ductus arteriosus was absent in 18 of the 40 infants.[27563] Prostaglandin synthetase inhibitors also have the potential to prolong pregnancy and inhibit labor if taken during the third trimester. There may be an increased risk of neonatal complications, such as necrotizing enterocolitis, patent ductus arteriosus, and intracranial hemorrhage when prostaglandin synthetase inhibitors are used to delay preterm labor.[41951] Therefore, flurbiprofen should be avoided in labor and obstetric delivery due to the potential to adversely affect fetal circulation and inhibit uterine contractions, thereby increasing the risk of uterine hemorrhage. The effects of ophthalmic flurbiprofen preparations during labor and delivery are unknown. Prostaglandin inhibitors may impair fertility and are not recommended in women attempting to conceive.[28331]

According to the manufacturer, systemic flurbiprofen or breast-feeding should be discontinued because of the potential for serious adverse reactions of prostaglandin-inhibiting drugs on nursing infants; use of ophthalmic flurbiprofen during breast-feeding has not been evaluated, however, the ophthalmic formulation is not for chronic use. Flurbiprofen is poorly excreted into human milk following systemic absorption. The manufacturer predicted breast-fed infant exposure is approximately 0.1 mg/day via nursing in the established milk of a woman receiving flurbiprofen 200 mg/day PO (breast milk consumption not stated).[41951] At maternal doses of 150 mg/day orally for 3 days, breast milk flurbiprofen concentrations were reported as undetectable (< 0.05 mcg/mL) in all samples from 11 of the 12 patients studied; breast milk flurbiprofen concentrations were 0.06 mcg/mL after the first dose and 0.07 mcg/mL immediately before the second dose in milk samples from the final patient. Maternal plasma concentrations of flurbiprofen were as expected and ranged from 1.93 +/- 0.44 mcg/mL to 5.28 +/- 1.06 mcg/mL at various time points over the 3 days.[41962] The American Academy of Pediatrics (AAP) has not evaluated the use of flurbiprofen during breast-feeding.[6278] However, alternative analgesic and anti-inflammatory drugs considered to be usually compatible with breast-feeding by the AAP include acetaminophen, ibuprofen, indomethacin, naproxen, and piroxicam. Consider the benefits of breast-feeding, the risk of potential infant drug exposure, and the risk of an untreated or inadequately treated condition. If a breast-feeding infant experiences an adverse effect related to a maternally ingested drug, healthcare providers are encouraged to report the adverse effect to the FDA.

Flurbiprofen is contraindicated for the treatment of peri-operative pain in the setting of *coronary artery bypass graft surgery (CABG)*. An increased incidence of myocardial infarction and stroke was found through analysis of data regarding the use of a COX-2 selective NSAID for the treatment of pain in the first 10—14 days after CABG surgery.

Use systemic flurbiprofen with caution in patients who are known or suspected poor metabolizers of CYP2C9 substrates based on previous history with other CYP2C9 substrates (e.g., warfarin and phenytoin). Patients with impaired CYP2C9 activity may have increased flurbiprofen plasma concentrations due to reduced metabolic clearance; hepatic metabolism is estimated to account for more than 90% of flurbiprofen elimination, in which the isoenzyme CYP2C9 plays an important part.[41951]

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Pregnancy / Breast-feeding

Although use should be avoided in late pregnancy, oral formulations of flurbiprofen are classified as FDA pregnancy risk category C throughout most of gestation.[41951] Flurbiprofen ophthalmic solution is classified as FDA pregnancy risk category C because no studies during pregnancy are available in animals or humans.[49155] Use of flurbiprofen should be avoided unless the potential therapeutic benefits justify its use during pregnancy. Systemic flurbiprofen is classified as FDA pregnancy risk category D drug if used during the third trimester due to the potential for prostaglandin synthetase inhibitors to cause *in utero* constriction of the fetal ductus arteriosus. Of 40 babies born with persistent pulmonary hypertension of the newborn (PPHN), 87.5% had the presence of an NSAID in their meconium versus 24.6% of 61 children born without PPHN; the presence of only 4 NSAIDs was examined. In addition to meconium aspiration, asphyxia, respiratory distress syndrome, and group B streptococcal pneumonia, ductus arteriosus constriction by an NSAID appears to be another predisposing factor for PPHN development, as a patent ductus arteriosus was absent in 18 of the 40 infants.[27563] Prostaglandin synthetase inhibitors also have the potential to prolong pregnancy and inhibit labor if taken during the third trimester. There may be an increased risk of neonatal complications, such as necrotizing enterocolitis, patent ductus arteriosus, and intracranial hemorrhage when prostaglandin synthetase inhibitors are used to delay preterm labor.[41951] Therefore, flurbiprofen should be avoided in labor and obstetric delivery due to the potential to adversely affect fetal circulation and inhibit uterine contractions, thereby increasing the risk of uterine hemorrhage. The effects of ophthalmic flurbiprofen preparations during labor and delivery are unknown. Prostaglandin inhibitors may impair fertility and are not recommended in women attempting to conceive.[28331]

According to the manufacturer, systemic flurbiprofen or breast-feeding should be discontinued because of the potential for serious adverse reactions of prostaglandin-inhibiting drugs on nursing infants; use of ophthalmic flurbiprofen during breast-feeding has not been evaluated, however, the ophthalmic formulation is not for chronic use. Flurbiprofen is poorly excreted into human milk following systemic absorption. The manufacturer predicted breast-fed infant exposure is approximately 0.1 mg/day via nursing in the established milk of a woman receiving flurbiprofen 200 mg/day PO (breast milk consumption not stated).[41951] At maternal doses of 150 mg/day orally for 3 days, breast milk flurbiprofen concentrations were reported as undetectable (< 0.05 mcg/mL) in all samples from 11 of the 12 patients studied; breast milk flurbiprofen concentrations were 0.06 mcg/mL after the first dose and 0.07 mcg/mL immediately before the second dose in milk samples from the final patient. Maternal plasma concentrations of flurbiprofen were as expected and ranged from 1.93 +/- 0.44 mcg/mL to 5.28 +/- 1.06 mcg/mL at various time points over the 3 days.[41962] The American Academy of Pediatrics (AAP) has not

evaluated the use of flurbiprofen during breast-feeding.[6278] However, alternative analgesic and anti-inflammatory drugs considered to be usually compatible with breast-feeding by the AAP include acetaminophen, ibuprofen, indomethacin, naproxen, and piroxicam. Consider the benefits of breast-feeding, the risk of potential infant drug exposure, and the risk of an untreated or inadequately treated condition. If a breast-feeding infant experiences an adverse effect related to a maternally ingested drug, healthcare providers are encouraged to report the adverse effect to the FDA.

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Interactions

Level 1 - Severe

- Cidofovir

Level 2 - Major

- Anticoagulants
- Bisphosphonates
- Desmopressin
- Ethanol
- Flavocoxid, Flavocoxid; Citrated Zinc Bisglycinate
- Ginkgo, Ginkgo biloba
- Methotrexate
- Nonsteroidal antiinflammatory drugs (NSAIDs)
- Pemetrexed
- Salicylates

Level 3 - Moderate

- Adefovir
- Antihypertensive Agents
- Antithymocyte Globulin
- Atazanavir
- Atazanavir; Cobicistat
- Cobicistat; Elvitegravir; Emtricitabine; Tenofovir
- Cobicistat; Elvitegravir; Emtricitabine; Tenofovir Alafenamide
- Corticosteroids
- Cyclosporine
- Digoxin
- Diuretics
- Donepezil
- Entecavir
- Fluconazole
- Galantamine
- Immunosuppressives
- Leflunomide
- Lithium
- Methylsulfonylmethane, MSM
- Pentamidine
- Platelet Inhibitors
- Quinolones
- Radiopaque Contrast Agents
- Rivastigmine
- Selective serotonin reuptake inhibitors (SSRIs)
- Serotonin norepinephrine reuptake inhibitors
- Sodium Phosphate Monobasic Monohydrate; Sodium Phosphate Dibasic Anhydrous
- Tacrine
- Thrombolytic Agents

Level 4 - Minor

- Acetylcholine Chloride
- Aminoglycosides
- Amphotericin B
- Antineoplastic Agents
- Carbachol
- Drospirenone; Ethinyl Estradiol
- Fenofibric Acid
- Feverfew, Tanacetum parthenium
- Foscarnet
- Ganciclovir
- Garlic, Allium sativum
- Ginger, Zingiber officinale
- Ivacaftor
- Lumacaftor; Ivacaftor
- Photosensitizing Agents
- Strontium-89 Chloride
- Sulfinpyrazone
- Vancomycin
- Voriconazole

NOTE: Flurbiprofen is a substrate of the hepatic cytochrome isoenzyme CYP2C9.[41951]. In addition, flurbiprofen and the flurbiprofen metabolite 4'-hydroxyflurbiprofen undergo UGT mediated glucouronidation, primarily via UGT2B7.[41951] [41952]

Because flurbiprofen exerts similar pharmacologic characteristics to other nonsteroidal antiinflammatory drugs (NSAIDs) (including COX-2 inhibitors), additive pharmacodynamic effects, including a potential increase for additive adverse gastrointestinal (GI) effects, may be seen if flurbiprofen is used with other NSAIDs.[6991] The drugs may represent duplicative therapies and generally concurrent use should be avoided. Concurrent use of flurbiprofen with flavocoxid, flavocoxid; citrated zinc bisglycinate, a nutritional supplement with similar pharmacological characteristics to NSAIDs, should be avoided.[8954]

Concomitant use of systemic flurbiprofen with ethanol can enhance the risk of gastrointestinal (GI) side effects.[6991]

Increased adverse gastrointestinal effects (GI) are possible if systemic flurbiprofen is used with systemic corticosteroids.[6991] Although some patients may

need to be given corticosteroids and NSAIDs concomitantly, which can be done successfully for short periods of time without sequelae, prolonged concomitant administration should be avoided. A meta-analysis published in 1991 revealed that concomitant use of corticosteroids increased the risk of adverse GI events due to NSAIDs.[1162] NSAIDs may mask fever, pain, swelling and other signs and symptoms of an infection; use NSAIDs with caution in patients receiving immunosuppressant dosages of corticosteroids. Concomitant use of topical NSAIDs and topical corticosteroids may increase the potential for healing problems, as both classes of drugs may slow or delay healing. Use caution also during the coadministration of ophthalmic NSAIDs (e.g., flurbiprofen ophthalmic) with ophthalmic corticosteroids. The concurrent use of these ophthalmic drugs may slow or delay healing of the affected eye(s). Also, use of an ocular corticosteroid and an ocular NSAID is a potential risk factor for corneal erosion development.[4315]

Because NSAIDs, such as flurbiprofen, can cause GI bleeding,[6991] inhibit platelet aggregation, and prolong bleeding time, additive effects may be seen in patients receiving platelet inhibitors (including aspirin, ASA), anticoagulants (e.g., warfarin), or thrombolytic agents.[1162] [6991] Concomitant use of systemic flurbiprofen with salicylates can enhance the risk of gastrointestinal (GI) side effects.[6991] In addition, concurrent administration of flurbiprofen and aspirin results in about a 50% reduction in serum flurbiprofen concentrations.[6991] Therefore, coadministration of flurbiprofen and aspirin is not recommended.

The concomitant administration of cidofovir and NSAIDs, such as flurbiprofen is contraindicated due to the potential for increased nephrotoxicity. NSAIDs should be discontinued 7 days prior to beginning cidofovir.[5118]

Concomitant use of medicines with potential to alter renal perfusion or function such as flurbiprofen may increase the risk of acute phosphate nephropathy in patients receiving sodium phosphate monobasic monohydrate; sodium phosphate dibasic anhydrous.[8973] [8974]

Chronic coadministration of adefovir with nephrotoxic drugs, such as nonsteroidal antiinflammatory drugs (NSAIDs) may increase the risk of developing nephrotoxicity, even in patients who have normal renal function. The use of adefovir with NSAIDs may be done cautiously. As stated in the current adefovir prescribing information, 'Ibuprofen (800 mg PO three times daily), when given concomitantly with adefovir dipivoxil, increased the adefovir Cmax by 33% and AUC by 23%, as well as urinary recovery. The increase appears to be due to higher oral bioavailability, not a reduction in renal clearance of adefovir. In an *in vitro* investigation, the antiviral effect of adefovir was unaltered and the renal proximal tubule accumulation of adefovir was inhibited by the presence of a NSAID.[4322] Adefovir is efficiently transported by the human renal organic anion transporter 1, and the presence of this transporter appears to mediate the accumulation of the drug in renal proximal tubules. The *in vitro* study suggests that the use of a NSAID with adefovir may potentially reduce the nephrotoxic potential of adefovir. Of course, NSAIDs are associated with nephrotoxicity of their own; therefore, further data on the interaction between NSAIDs and adefovir in humans are needed.[4322]

NSAIDs interfere with lithium excretion and may lead to elevated lithium serum concentrations. Clinically significant interactions rarely occur, but lithium toxicity has been reported. It is thought that prostaglandins are involved in the renal clearance of lithium and that NSAIDs interfere with this process. Increased lithium levels develop over 5—10 days after adding a NSAID and return to pretreatment levels within 7 days of stopping the NSAID. If NSAID therapy is started or stopped in a patient stabilized on lithium, monitor for evidence of lithium toxicity or decreased clinical effects, respectively.[5385]

In general, NSAID therapy can decrease the clearance of methotrexate, resulting in elevated and prolonged serum methotrexate levels. Nonsteroidal antiinflammatory drugs (NSAIDs) should not be administered prior to, concomitantly, or following intermediate or high doses of methotrexate.[5067] Concomitant administration of NSAIDs with high dose methotrexate therapy has been reported to elevate and prolong serum concentrations of methotrexate resulting in deaths from severe hematologic and gastrointestinal toxicity. Caution should be used when NSAIDs are administered concurrently with lower doses of methotrexate. In patients with rheumatoid arthritis, methotrexate has been given concurrently with NSAIDs without apparent problems. It should be noted that the doses of methotrexate used in rheumatoid arthritis are lower than those used in psoriasis or malignant disease; these higher doses may lead to unexpected toxicity in combination with NSAIDs. Concurrent use of NSAIDs may lead to an increased risk of GI bleeding in patients with methotrexate-induced thrombocytopenia or mask fever, pain, swelling and other signs and symptoms of an infection.

Clinical status and serum creatinine and potassium levels should be closely monitored when cyclosporine is given with salicylates or other nonsteroidal antiinflammatory drugs (NSAIDs). Pharmacodynamic interactions have been reported between cyclosporine and NSAIDs, consisting of additive decreases in renal function with concomitant use.[5134] [5936] NSAIDs should be used with caution in patients receiving immunosuppressives as they may mask fever, pain, swelling and other signs and symptoms of an infection.[6144]

Ginkgo is reported to inhibit platelet aggregation [1900] and several case reports describe bleeding complications with ginkgo, Ginkgo biloba, with or without concomitant drug therapy. Ginkgo should be used cautiously in patients receiving drugs that inhibit platelet aggregation or pose a risk for bleeding, such as NSAIDs.[5200] A case of fatal intracerebral bleeding has been reported with the combination of Ginkgo and ibuprofen.[5211] A 71 year-old gentleman had been taking a concentrated Ginkgo biloba extract (Gingium, Germany) 40 mg PO twice daily for a few years; 4 weeks prior to his death, he had started taking ibuprofen (600 mg daily) for osteoarthritic hip pain. The man was found comatose and CT scan revealed a massive intracerebral bleed; no other causative factors were identified.[5211]

Garlic, Allium sativum [2233] and ginger, Zingiber officinale [5200] also have clinically significant effects on platelet aggregation leading to a potential increased risk of bleeding when used with NSAIDs. An increased risk of bleeding may occur when NSAIDs, such as flurbiprofen, are used with agents that cause clinically significant thrombocytopenia due to decreases in platelet aggregation.[6991] Notable interactions may occur with myelosuppressive antineoplastic agents, antithymocyte globulin [6303] and strontium-89 chloride [4694].

There have been reports that acetylcholine chloride and carbachol, when administered topically to the eye, have been ineffective in patients treated with ophthalmic flurbiprofen.[6990] However, clinical studies with acetylcholine and animal studies with acetylcholine or carbachol revealed no interference, and there is no known pharmacologic basis for an interaction.

Preclinical data suggest agents that inhibit prostaglandin synthesis such as NSAIDs could decrease the efficacy of photosensitizing agents used in photodynamic therapy.[6625]

In vitro studies indicate that the M1 metabolite of leflunomide inhibits cytochrome P450 2C9, the enzyme responsible for the metabolism of many NSAIDs.[4709] Leflunomide has inhibited the metabolism of diclofenac *in vitro*. Leflunomide also altered protein binding, increasing the free fraction of both ibuprofen and diclofenac by 13—50%. The clinical significance of these interactions with NSAIDs is unknown. There was extensive concomitant use of NSAIDs in phase III clinical studies of leflunomide in the treatment of rheumatoid arthritis and no clinical differential effects were observed. However, because some NSAIDs have been reported to cause hepatotoxic effects, some caution may be warranted in their use with leflunomide.

Nonsteroidal anti-inflammatory drugs (NSAIDs) may reduce the natriuretic effect of diuretics in some patients. NSAIDS have been associated with an inhibition of prostaglandin synthesis, which may result in reduced renal blood flow leading to renal insufficiency and increases in blood pressure that are often accompanied by peripheral edema and weight gain.[30489] Patients taking diuretics and NSAIDS concurrently are at higher risk of developing renal insufficiency.[48492] If flurbiprofen and a diuretic are used concurrently, carefully monitor the patient for signs and symptoms of decreased renal function and diuretic efficacy.

Nonsteroidal anti-inflammatory drugs (NSAIDs), to varying degrees, have been associated with an elevation in blood pressure. This effect is most significant in patients receiving concurrent antihypertensive agents and long-term NSAID therapy. NSAIDs cause a dose-dependent reduction in prostaglandin formation, which may result in a reduction in renal blood flow leading to renal insufficiency and an increase in blood pressure that are often accompanied by peripheral edema and weight gain.[30489] Patients who rely upon renal prostaglandins to maintain renal perfusion may have acute renal blood flow reduction with NSAID usage. Elderly patients may be at increased risk of adverse effects from combined long-term NSAID therapy and antihypertensive agents, especially diuretics, due to age-related decreases in renal function and an increased risk of stroke and coronary artery disease.[3154] If flurbiprofen and an antihypertensive drug are concurrently used, carefully monitor the patient for signs and symptoms of renal insufficiency and blood pressure control. Doses of antihypertensive medications may require adjustment in patients receiving concurrent NSAIDs.[4087]

It is possible that additive nephrotoxicity may occur in patients who receive NSAIDs such as flurbiprofen concurrently with other nephrotoxic agents.[6144] These include aminoglycosides, amphotericin B [5062], cisplatin [5123], foscarnet [5106], ganciclovir [5173], pentamidine [5612], and parenteral vancomycin [5198].

Nonsteroidal antiinflammatory drugs (NSAIDs) may cause additive pharmacodynamic GI effects with Alzheimer's disease (AD) agents that inhibit cholinesterase (e.g., donepezil [6382], galantamine [5234], rivastigmine [6380], or tacrine [6381]), leading to GI intolerance. Patients receiving concurrent NSAIDs should be monitored closely for symptoms of active or occult gastrointestinal bleeding. While NSAIDs appear to suppress microglial activity, which in turn may slow inflammatory neurodegenerative processes important for the progression of AD [4040], there are no clinical data at this time to suggest that NSAIDs alone [6384] [6386] or as combined therapy with AD agents result in synergistic effects in AD.

Feverfew appears to inhibit prostaglandin synthesis, reportedly at a different step in the prostaglandin pathway than the NSAIDs, which inhibit cyclooxygenase.[2911] [2912] Theoretically, the NSAIDs might decrease the effectiveness of feverfew, Tanacetum parthenium. However, clinical interactions have not been reported.[5314]

Drospirenone has antimineralocorticoid effects; the progestin may increase serum potassium.[4716] Drugs that may have additive effects on serum potassium with drospirenone; ethinyl estradiol (Yasmin) include chronic treatment with NSAIDs, and monitoring of serum potassium in the 1st month of concurrent therapy is recommended.

Voriconazole is known to be an inhibitor of CYP2C9 [4882] and may lead to increased plasma levels of some NSAIDs, including flurbiprofen (CYP2C9 substrate) [4718]. If voriconazole is administered concomitantly with flurbiprofen, monitor for NSAID-induced toxicity, such as GI irritation, GI bleeding or renal dysfunction and adjust the dose of the NSAID if needed.

Fluconazole significantly inhibits the metabolism of flurbiprofen via CYP2C9. The mean systemic exposure of flurbiprofen increased 81% after 100 mg of flurbiprofen was taken after the patients had taken 2 doses of fluconazole 200 mg 8—10 hours apart. The half-life of flurbiprofen increased from 3.3 hours to 5.3 hours. Increased adverse effects of flurbiprofen may occur, especially if the two drugs are used concurrently over several days.[9026]

Sulfinpyrazone is an inhibitor of CYP2C9 and may lead to increased plasma levels of some NSAIDs, including flurbiprofen (CYP2C9 substrate).[4718] In addition, sulfinpyrazone and its metabolites inhibit platelet cyclooxygenase leading to decreased platelet aggregation.[6482] Sulfinpyrazone has been independently associated with GI bleeding in some cases; concurrent therapy with NSAIDs such as flurbiprofen could potentially increase the risk of adverse GI effects. During concurrent therapy, monitor for potential NSAID-induced toxicity, such as GI irritation or bleeding.

Use of pemetrexed with flurbiprofen, a nonsteroidal anti-inflammatory drug (NSAID), may increase the systemic exposure to pemetrexed.[5105] The clearance of pemetrexed is reduced about 20% in patients with normal renal function that also take ibuprofen 400 mg four times daily. Patients with a creatinine clearance between 45 and 79 ml/minute should avoid taking NSAIDs with short elimination half-lives for a period of 2 days before, the day of, and 2 days after pemetrexed administration. Due to an absence of data, NSAIDs with longer half-lives should not be taken by anyone (regardless of renal function status) for a period of 5 days before, the day of, and 2 days after pemetrexed administration. If use of a NSAID is unavoidable, monitor patients for myelosuppression, renal, and gastrointestinal adverse effects from pemetrexed.[5105]

Because the use of other nephrotoxic drugs including nonsteroidal anti-inflammatory drugs (NSAIDs) is an additive risk factor for nephrotoxicity in patients receiving radiopaque contrast agents, NSAID therapy should be withheld, when possible, during radiopaque contrast agent administration.[5423]

Because entecavir is primarily eliminated by the kidneys and nonsteroidal anti-inflammatory agents (NSAIDs) can affect renal function, concurrent administration with NSAIDs may increase the serum concentrations of entecavir and adverse events. The manufacturer of entecavir recommends monitoring for adverse effects when these drugs are coadministered.[8007]

Platelet aggregation may be impaired by selective serotonin reuptake inhibitors (SSRIs) due to platelet serotonin depletion, possibly increasing the risk of a bleeding complication (e.g., gastrointestinal bleeding, ecchymoses, epistaxis, hematomas, petechiae, hemorrhage) in patients receiving nonsteroidal antiinflammatory drugs (NSAIDs).[4987] [28343] Patients should be instructed to monitor for signs and symptoms of bleeding while taking an SSRI concurrently with medications which impair platelet function and to promptly report any bleeding events to the practitioner.

Platelet aggregation may be impaired by serotonin norepinephrine reuptake inhibitors (SNRIs) due to platelet serotonin depletion, possibly increasing the risk of a bleeding complication (e.g., gastrointestinal bleeding, ecchymoses, epistaxis, hematomas, petechiae, hemorrhage) in patients receiving NSAIDs. [5002] [6682] Patients should be instructed to monitor for signs and symptoms of bleeding while taking an SNRI with medications which impair platelet function and to promptly report any bleeding events to the practitioner.

The concomitant administration of quinolones such as norfloxacin, ofloxacin, or levofloxacin and a nonsteroidal anti-inflammatory drug (NSAID) may increase the risk of CNS stimulation and convulsive seizures.[5151] [6695] [6564] Patients with CNS disorders or other risk factors that may predispose them to seizure development or patients taking drugs that lower the seizure threshold may not be appropriate candidates for flurbiprofen or another NSAID usage if they are also taking a quinolone. Use a quinolone with caution in individuals who take a NSAID concomitantly.

Increased effects from concomitant anticoagulant drugs such as increased bruising or blood in the stool have been reported in patients taking methylsulfonylmethane, MSM.[9832] [9834] Although these effects have not been confirmed in published medical literature or during clinical studies, clinicians should consider using methylsulfonylmethane, MSM with caution in patients who are taking anticoagulants or drugs with platelet inhibiting properties including NSAIDs such as flurbiprofen until data confirming the safety of MSM in patients taking these drugs are available. During one of the available, published clinical trials in patients with osteoarthritis, those patients with bleeding disorders or using anticoagulants or antiplatelets were excluded from enrollment.[9832] Patients who choose to consume methylsulfonylmethane, MSM while receiving NSAIDs should be observed for increased bleeding.

Caution is recommended if desmopressin acetate is taken with a drug that may increase the risk of water intoxication with hyponatremia such as a NSAID (e.g., flurbiprofen) (see Adverse Reactions).[10457] A woman who took both desmopressin and ibuprofen was found in a comatose state. As her serum sodium concentration was 121 mmol/L, and her plasma osmolality was low in the presence of a high-normal urine osmolality and normal sodium excretion, she was treated with fluid restriction. Her serum sodium concentration was 124 mmol/L within a day and was 135 mmol/L by the second day. The woman had previously received desmopressin without the development of clinical symptoms of hyponatremia.[10458]

At therapeutic concentrations, fenofibric acid is a mild-to-moderate inhibitor of CYP2C9.[49952] Concomitant use of fenofibric acid with CYP2C9 substrates, such as flurbiprofen [6991], has not been formally studied. Fenofibric acid may theoretically increase plasma concentrations of CYP2C9 substrates and could lead to toxicity for drugs that have a narrow therapeutic range. Monitor the therapeutic effect of flurbiprofen during coadministration with fenofibric acid.

As the use of nonsteroidal antiinflammatory drugs (NSAIDs) are associated with GI irritation, risk of nephrotoxicity, and decreased bone mineral density [40288], exercise caution when administering an NSAID with a bisphosphonate, particularly orally administered bisphosphonates; additive GI and kidney toxicity, and a less than expected bone mineral stabilizing effect may result. In a prospective study, women taking concomitant naproxen and alendronate were significantly more likely to develop gastric ulcers than women receiving either agent alone. In addition, alendronate plus naproxen was poorly tolerated with 69% of patients receiving the combination reporting side effects compared to 23% of those receiving naproxen alone and 54% of those receiving alendronate. In a retrospective study, women taking concomitant NSAIDs and alendronate had a 70% increased risk of developing a GI adverse event, such as gastric ulceration.[5375] During clinical trials of risedronate for osteoporosis, most patients took either NSAIDs or aspirin, and the incidence of adverse upper GI reactions was similar between risedronate-treated (24.5%) and placebo-treated patients (24.8%).[6090] Though patients receiving intravenously administered bisphosphonates have a decreased incidence of GI adverse effects as compared to those taking orally administered bisphosphonates, additive GI irritation and nephrotoxicity are possible if therapy is concurrent with NSAID therapy.[6318] [7799]

Concomitant use of nonsteroidal antiinflammatory drugs (NSAIDs) with digoxin may result in increased serum concentrations of digoxin. NSAIDs may cause a significant deterioration in renal function. A decline in glomerular filtration or tubular secretion may impair the excretion of digoxin. Monitor patients during concomitant treatment for possible digoxin toxicity and reduce digoxin dose as necessary.[28272]

Caution is warranted when atazanavir is administered with flurbiprofen as there is a potential for elevated flubriprofen concentrations. Flurbiprofen is a substrate of uridine glucoronyltransferase (UGT). Atazanavir is an UGT1A1 inhibitor.[41951] [28142]

Caution is warranted when atazanavir; cobicistat is administered with flurbiprofen as there is a potential for elevated flubriprofen concentrations. Flurbiprofen is a substrate of uridine glucoronyltransferase (UGT). Atazanavir is an UGT1A1 inhibitor.[41951] [41952] [58761]

Increased monitoring is recommended if ivacaftor is administered concurrently with CYP2C9 substrates, such as flurbiprofen. *In vitro* studies showed ivacaftor to be a weak inhibitor of CYP2C9. Co-administration may lead to increased exposure to CYP2C9 substrates; however, the clinical impact of this has not yet been determined.[48524] [41951]

Although the clinical significance of this interaction is unknown, concurrent use of flurbiprofen and lumacaftor; ivacaftor may alter flurbiprofen exposure; caution and monitoring are advised if these drugs are used together. Flurbiprofen is a substrate of CYP2C9. *In vitro* data suggest that lumacaftor; ivacaftor may induce and/or inhibit CYP2C9. The net effect of lumacaftor; ivacaftor on CYP2C9-mediated metabolism is not clear, but CYP2C9 substrate exposure may be affected leading to decreased efficacy or increased or prolonged therapeutic effects and adverse events.[41951] [41952] [59891]

The plasma concentrations of flurbiprofen may be decreased when administered concurrently with cobicistat; elvitegravir; emtricitabine; tenofovir disoproxil fumarate. Patients may experience decreased analgesic or anti-inflammatory effects when these drugs are coadministered. Elvitegravir is a CYP2C9 inducer, while flurbiprofen is a CYP2C9 substrate.[41951] [51664]

The plasma concentrations of flurbiprofen may be decreased when administered concurrently with cobicistat; elvitegravir; emtricitabine; tenofovir alafenamide. Patients may experience decreased analgesic or anti-inflammatory effects when these drugs are coadministered. Elvitegravir is a CYP2C9 inducer, while flurbiprofen is a CYP2C9 substrate.[41951] [60269]

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Adverse Reactions

- abdominal pain
- agranulocytosis
- alopecia
- amnesia
- anaphylactoid reactions
- anemia
- angina
- angioedema
- anorexia
- anxiety
- aplastic anemia
- appetite stimulation
- arrhythmia exacerbation
- aseptic meningitis
- asthenia
- ataxia
- blurred vision
- chills
- cholecystitis
- cholestasis
- colitis
- coma
- confusion
- conjunctivitis
- constipation
- corneal opacification
- cystitis
- depression
- diaphoresis
- diarrhea
- dizziness
- drowsiness
- dysgeusia
- dyspepsia
- dysphagia
- dyspnea
- dysuria
- ecchymosis
- edema
- elevated hepatic enzymes
- emotional lability
- eosinophilia
- epistaxis
- eructation
- erythema multiforme
- esophageal stricture
- esophageal ulceration
- esophagitis
- exfoliative dermatitis
- fever
- flatulence
- foreign body sensation
- gastritis
- GI bleeding
- GI perforation
- glossitis
- hallucinations
- headache
- hyperventilation
- hyphema
- hyponatremia
- hypotension
- infection
- insomnia
- interstitial nephritis
- jaundice
- laryngitis
- leukopenia
- lymphadenopathy
- malaise
- melena
- meningitis
- menstrual irregularity
- miosis
- myasthenia
- mydriasis
- myocardial infarction
- nausea
- nephrotic syndrome
- ocular irritation
- ocular pain
- odynophagia
- oliguria
- optic neuritis
- palpitations
- pancreatitis
- pancytopenia
- paresthesias
- parosmia
- peptic ulcer
- peripheral vasodilation
- photophobia
- photosensitivity
- platelet dysfunction
- polyuria
- prolonged bleeding time
- prostatic hypertrophy
- prostatitis
- proteinuria
- pruritus
- pulmonary embolism
- purpura
- pyrosis (heartburn)
- rash (unspecified)
- renal failure (unspecified)
- renal papillary necrosis
- respiratory depression
- retinal hemorrhage
- rhinitis
- seizures
- sinus tachycardia
- Stevens-Johnson syndrome
- stomatitis
- stroke
- syncope
- thrombocytopenia

- hearing loss
- heart failure
- hematemesis
- hematuria
- hemolytic anemia
- hepatic failure
- hepatitis
- hyperglycemia
- hyperkalemia
- hyperreflexia
- hypertension
- hypertonia
- hyperuricemia
- tinnitus
- toxic epidermal necrolysis
- tremor
- urticaria
- vaginal bleeding
- vaginitis
- vasculitis
- vertigo
- vomiting
- weight gain
- xerophthalmia
- xerostomia

The most frequently reported adverse GI reactions (>= 1%) with flurbiprofen include abdominal pain, constipation, diarrhea, dyspepsia, pyrosis (heartburn), flatulence, and nausea and vomiting. Serious gastrointestinal toxicity, such as gastritis (< 1%), GI bleeding (>= 1%), hematemesis (< 1%), bloody diarrhea (< 1%), and gastric or peptic ulcer (< 1%), can occur at any time, with or without symptoms. In patients treated with other NSAIDs, GI perforation and duodenal or gastric ulcers have occurred in > 1% of patients. In patients observed in clinical trials for several months to 2 years, symptomatic GI ulcers, gross bleeding, or perforation occurred in roughly 1% of patients treated with an NSAID for 3—6 months and in 2—4% of patients treated for 1 year. The risk of severe GI events is increased by the presence of the following factors: history of peptic ulcer disease or GI bleed, smoking, alcohol usage, concomitant usage of anticoagulants, or oral corticosteroids, older age, poor general health status, and NSAID duration of use. GI bleeding or erosive gastritis can be minor or life-threatening and may result from a combination of direct irritant action on the stomach mucosa and a prolonged bleeding time, due to changes in platelet aggregation. Older patients appear to be greater affected by GI ulceration or bleeding; most fatal GI events occur in older or debilitated patients. Occult GI bleeding occurs in many patients and is not necessarily correlated with GI distress. Patients on prolonged therapy should undergo regular blood monitoring. Use the lowest effective dose of flurbiprofen for the shortest possible duration. Discontinue flurbiprofen if a serious GI adverse event is suspected. Other adverse GI events that have occurred with flurbiprofen use in < 1% of patients include stomatitis, appetite stimulation, anorexia, colitis, xerostomia, glossitis, exacerbation of inflammatory bowel disease, periodontal abscess, and small intestine inflammation with loss of blood and protein. Eructation (< 1%) is associated with NSAID treatment.[41951]

Rare cases of esophageal disease (< 1%) such as esophagitis have been reported in patients receiving NSAIDs such as flurbiprofen. NSAID-induced esophagitis is characterized by sudden onset odynophagia, retrosternal pain, and dysphagia. Pyrosis (heartburn) may be present. Severe complications such as esophageal ulceration, esophageal stricture, bleeding, and perforation have been reported rarely. Risk factors for NSAID-induced esophageal effects include taking the medication without water and at night. Symptoms usually resolve within days to weeks after stopping the medication.[41951]

As with other NSAIDs, elevated hepatic enzymes may occur in patients who receive flurbiprofen (incidence >= 1%). These abnormalities may progress, remain essentially unchanged, or resolve with continued therapy. Significant elevations of AST (3 times the upper limit of normal) occur in just under 1% of patients who take NSAIDs. Hepatitis (cholestasis and noncholestatic jaundice) has been reported rarely (< 1% of patients). Although severe hepatic reactions are rare, if abnormal liver tests persist or worsen, clinical signs and symptoms consistent with liver disease develop, or systemic manifestations occur (eosinophilia, rash, pyrexia), flurbiprofen should be discontinued. Cholecystitis has also been reported with flurbiprofen use (< 1%). Experience with other NSAIDs suggests that hepatic failure and pancreatitis occur rarely, in < 1% of patients.[41951]

Frequently reported CNS adverse reactions associated with flurbiprofen use in >= 1% of patients during clinical trials include those related to both CNS stimulation (anxiety, insomnia, tremor, and hyperreflexia) and CNS inhibition (amnesia, asthenia, malaise, depression, and somnolence). Changes in vision such as blurred vision, dizziness, vertigo, and tinnitus have also occurred in >= 1% of patients using flurbiprofen. Other adverse effects reported in < 1% of patients with probable drug causality include ataxia, confusion, paresthesias, and twitching; those with questionable causality include convulsions or seizures, emotional lability, hypertonia, meningitis, and myasthenia. Headache occurred in >= 1% of patients during flurbiprofen clinical trials.[41951] Overuse of flurbiprofen by headache-prone patients frequently produces drug-induced rebound headache accompanied by dependence on symptomatic medication, tolerance (refractoriness to prophylactic medication), and withdrawal symptoms. In this case, overuse of flurbiprofen (i.e., simple analgesic) has been defined as taking 3 or more doses per day more often than 5 days per week. The frequency of use may be more important than the dose. Features of a rebound headache include morning headache, end-of-dosing interval headache, or headache improvement with discontinuation of overused medication. Stopping the symptomatic medication may result in a period of increased headache and then headache improvement. Analgesic overuse may be responsible for the transformation of episodic migraine or episodic tension headache into daily headache and may perpetuate the syndrome.[27347] Other CNS effects reported in < 1% of patients taking other NSAIDs include coma, dream abnormalities, drowsiness, and hallucinations. Disorders of the senses, including dysgeusia, parosmia, ear disease, and transient hearing loss have occurred in < 1% of patients taking flurbiprofen.[41951]

It is well known that vasodilatory renal prostaglandins and the potent vasoconstrictor angiotensin II work in concert to maintain renal blood flow. In patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion, renal decompensation from long-term NSAID induced prostaglandin synthesis and decreased blood flow may occur. Renal failure (unspecified), hematuria, and interstitial nephritis occurred in < 1% of patients who received flurbiprofen during clinical trials or post-marketing experience. With other NSAIDs, abnormal renal function (> 1%) including renal papillary necrosis, nephrotic syndrome, dysuria (< 1%), oliguria (< 1%), polyuria (< 1%), proteinuria (< 1%), hyperkalemia (< 1%), and hyperuricemia (< 1%) have been reported. Inhibition of prostaglandin synthesis by NSAIDs potentiates water reabsorption. Edema (peripheral edema) and body weight changes (weight gain) occurred in >= 1% of patients receiving flurbiprofen in clinical trials.[41951] Hyponatremia due to water intoxication has been reported with NSAID use.[33608] [33609] [33610] Monitoring of the patient's fluid status and serum creatinine and blood urea nitrogen concentrations is recommended; treatment is not recommended in advanced renal disease. NSAIDs may increase the risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. Estimates of increased relative risk range from 10—50% or more, based on the drug and dose studied. The risk may increase with increased exposure, as measured in dose or duration. Significant cardiovascular risk has been observed within days to weeks of NSAID initiation. The relative increase in cardiovascular thrombotic events over baseline appears to be similar in patients with or without cardiovascular disease or risk factors for cardiovascular disease; however, patients with known cardiovascular disease or risk factors may be at greater risk because of a higher baseline risk of

events.[59937] Angina, arrhythmia exacerbation, congestive heart failure, hypertension, myocardial infarction, vascular disease, and peripheral vasodilation have been reported in < 1% of patients who received flurbiprofen, while other NSAIDs have rarely (< 1%) been associated with hypotension, palpitations, syncope, sinus tachycardia, and vasculitis. Cerebrovascular ischemia, as well as stroke, including cerebrovascular accidents and subarachnoid hemorrhage, have been reported in < 1%.[41951] Inform patients of the signs and symptoms of CV events, and advise them to seek medical help immediately if such signs or symptoms occur.

Systemic adverse events associated with flurbiprofen therapy in < 1% of patients include chills and fever. Infectious illnesses, such as rhinitis and cystitis occurred in >= 1%. Adverse illnesses associated with other NSAIDs in < 1% of patients include sepsis, other unspecified infection, or death.[41951]

Hematologic abnormalities may occur with flurbiprofen use. Aplastic anemia (including agranulocytosis or pancytopenia), hemolytic anemia, and iron deficiency anemia have been associated with flurbiprofen use in < 1% of patients. As a class, anemia has been observed in > 1% of patients treated with NSAIDs. Other rare events reported with flurbiprofen use in < 1% of patients with probable causality include eosinophilia, leukopenia, and thrombocytopenia. Lymphadenopathy was observed with flurbiprofen use in < 1% of patients; however, a causal relationship is not established.[41951]

Flurbiprofen may cause rash (unspecified), it has previously been reported in >= 1% of patients during clinical trials. In general, all NSAIDs have been associated with severe and occasionally fatal asthmatic and anaphylactic reactions. Other allergic adverse reactions reported in < 1% of patients with probable drug causality include include anaphylactoid reactions, angioedema, eczema, exfoliative dermatitis, photosensitivity, pruritus, toxic epidermal necrolysis, and urticaria. Alopecia, dry skin, herpes simplex/zoster, nail disorders, and diaphoresis also occurred in < 1% of patients who received flurbiprofen; however, a causal relationship has not been established. Stevens-Johnson syndrome, a serious and potentially fatal skin reaction, as well as erythema multiforme have been reported in < 1% of patients with other NSAIDs and may occur with flurbiprofen. Patients should be instructed to discontinue the medication and contact their health care provider if erythema, rash, blisters, or related skin reactions develop.[41951]

NSAIDs, such as flurbiprofen have been shown to cause platelet dysfunction, but this effect is transient and reversible. Since inhibition of platelet aggregation appears to correlate with effective plasma concentrations of the drug, the individual half-life of each NSAID determines the duration of this effect. Vaginal bleeding, uterine hemorrhage, and epistaxis have been reported in < 1% of patients taking flurbiprofen. Melena (< 1%), rectal bleeding (< 1%), and prolonged bleeding time (> 1%) are associated the use of other NSAIDs. There is a probable likelihood that flurbiprofen has caused purpura, ecchymosis, and decreases in hemoglobin and hematocrit in < 1% of patients.[41951]

Flurbiprofen ophthalmic solution is generally well-tolerated following topical application to the eye. Most adverse effects of ocular flurbiprofen administration are related to the eye, but systemic adverse reactions can occur. Additionally, some adverse occular effects have been reported with the use of flurbiprofen tablets. The most common adverse effects following ophthalmic solution application are transient ocular irritation or ocular pain (stinging or burning). Other symptoms following topical application to the eye include pruritus, foreign body sensation, ocular fibrosis, miosis, mydriasis, and other symptoms of ocular irritation (e.g., tearing, xerophthalmia, dull eye pain, photophobia). There have also been reports of ocular hyperemia and increased bleeding of ocular tissues (including hyphema) in conjunction with ocular surgery. Ophthalmic administration of flurbiprofen may result in delayed wound healing. Conjunctivitis, corneal opacification, glaucoma, optic neuritis (specifically retrobulbar neuritis), and retinal hemorrhage have been reported in < 1% of patients taking flurbiprofen tablets.[41951] [49155]

Aseptic meningitis has been reported rarely with NSAID (such as flurbiprofen) therapy. Ibuprofen has been the most common NSAID implicated in this adverse reaction; however, cases have been reported with sulindac, naproxen, tolmetin, diclofenac, ketoprofen, rofecoxib, and piroxicam. Aseptic meningitis from one NSAID does not preclude use of another NSAID; most patients can be treated with another drug without incident. However, one patient with Sjogren's syndrome experienced aseptic meningitis after receipt of naproxen, ibuprofen, and rofecoxib at different times; aseptic meningitis developed about a week after each drug exposure, and the symptoms abated roughly 2 days following each drug cessation.[27710] The occurrence of aseptic meningitis is not related to NSAID chemical class or prostaglandin inhibition. A Type III or IV immunological hypersensitivity reaction is the proposed mechanism of action. Drug-induced aseptic meningitis usually occurs shortly after drug initiation but can occur after years of drug usage. Although NSAID-induced aseptic meningitis is primarily reported in patients with systemic lupus erythematosus (SLE), healthy patients and patients with other disease states such as ankylosing spondylitis, connective tissue disease, osteoarthritis, and rheumatoid arthritis have developed NSAID-induced aseptic meningitis. Symptoms of aseptic meningitis include confusion, drowsiness, general feeling of illness, severe headache, nausea, nuchal rigidity, and photophobia. As aseptic meningitis is a diagnosis of exclusion, the suspected drug should be discontinued and not restarted unless a rechallenge is desired.

Significant events such as pulmonary embolism or pulmonary infarct occurred in < 1% of patients given flurbiprofen; however, a causal relationship is not established. Other adverse respiratory effects reported in < 1% of patients include dyspnea, hyperventilation, laryngitis, and bronchitis. Respiratory depression and pneumonia have been observed in < 1% of patients taking other NSAIDs.[41951]

Menstrual disturbances, which may include menstrual irregularity, as well as prostate disease, which may include prostatic hypertrophy or prostatitis, were reported in < 1% of patients given flurbiprofen. Drug causality has not been established. Vaginitis, such as vulvovaginitis, occurred in < 1%.[41951]

Rare cases of hyperglycemia have been reported in patients taking flurbiprofen tablets (< 1%).[41951]

Revision Date: 7/13/2015 10:38:00 AM

How Supplied

Flurbiprofen Oral tablet

Ansaid 100mg Tablet	(55289-0647)	(PD-RX Pharmaceuticals)	
Ansaid 100mg Tablet	(00009-0305)	(Pfizer US Pharmaceuticals) (off market)	

Ansaid 50mg Tablet (00009-0170) (Pfizer US Pharmaceuticals) (off market)	
Flurbiprofen 100mg Tablet (59762-3724) (Greenstone Ltd) (off market)	
Flurbiprofen 100mg Tablet (00182-2621) (Ivax Corporation a Division of Teva USA) (off market)	
Flurbiprofen 100mg Tablet (00172-4362) (Ivax Pharmaceuticals Inc a Division of Teva USA) (off market)	
Flurbiprofen 100mg Tablet (51079-0815) (Mylan Institutional LLC formerly UDL Laboratories Inc) (off market)	
Flurbiprofen 100mg Tablet (00378-0093) (Mylan Pharmaceuticals Inc)	
Flurbiprofen 100mg Tablet (66267-0486) (NuCare Pharmaceuticals Inc) (off market)	
Flurbiprofen 100mg Tablet (55289-0561) (PD-RX Pharmaceuticals)	
Flurbiprofen 100mg Tablet (50111-0606) (Pliva Inc a Division of Teva USA) (off market)	
Flurbiprofen 100mg Tablet (00781-1129) (Sandoz Inc) (off market)	
Flurbiprofen 100mg Tablet (57664-0165) (Sun Pharmaceutical Industries, Inc.)	
Flurbiprofen 100mg Tablet (00093-0711) (Teva Pharmaceuticals USA Inc)	
Flurbiprofen 50mg Tablet (00781-1031) (Geneva Pharmaceuticals Inc) (off market)	
Flurbiprofen 50mg Tablet (00172-4361) (Ivax Pharmaceuticals Inc a Division of Teva USA) (off market)	
Flurbiprofen 50mg Tablet (00378-0076) (Mylan Pharmaceuticals Inc)	
Flurbiprofen 50mg Tablet (50111-0605) (Pliva Inc a Division of Teva USA) (off market)	
Flurbiprofen 50mg Tablet (57664-0164) (Sun Pharmaceutical Industries, Inc.)	

Flurbiprofen Sodium Ophthalmic drops, solution

Flurbiprofen Sodium 0.03% Ophthalmic Solution (60758-0910) (Actavis Inc, formerly Pacific Pharma)	
Flurbiprofen Sodium 0.03% Ophthalmic Solution (24208-0314) (Bausch and Lomb Pharmaceuticals Inc, a wholly-owned subsidiary of Valeant)	
Ocufen 0.03% Ophthalmic Solution (11980-0801) (Allergan America)	

Monitoring Parameters

- CBC
- LFTs
- serum creatinine/BUN
- stool guaiac

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