PRODUCT MONOGRAPH

FLURBIPROFEN

Flurbiprofen Tablets BP

50 mg and 100 mg

Anti-inflammatory, analgesic agent

AA PHARMA INC.
1165 Creditstone Road, Unit #1
Vaughan, Ontario
L4K 4N7

DATE OF PREPARATION:
April 16, 1991

DATE OF REVISION:
February 7, 2019

Submission Control No. 223098

PRODUCT MONOGRAPH

NAME OF DRUG

FLURBIPROFEN

Flurbiprofen Tablets BP

50 mg and 100 mg

PHARMACOLOGICAL CLASSIFICATION

Anti-inflammatory, analgesic agent

ACTIONS AND CLINICAL PHARMACOLOGY

FLURBIPROFEN (flurbiprofen), a phenylalkanoic acid derivative, is a non-steroidal anti-inflammatory agent which also possesses analgesic and antipyretic activities. Its mode of action, like that of other non-steroidal anti-inflammatory agents, is not known. However, its therapeutic action is not due to pituitary adrenal stimulation. Flurbiprofen is an inhibitor of prostaglandin synthesis. The resulting decrease in prostaglandin synthesis may partially explain the drug's anti-inflammatory effect at the cellular level.

Pharmacokinetics:

Flurbiprofen is well absorbed after oral administration, reaching peak blood levels in approximately 1.5 hours (range 0.5 to 4 hours). Administration of flurbiprofen with food does not alter total drug availability but delays absorption.

Excretion of flurbiprofen is virtually complete 24 hours after the last dose. The elimination half-life is 5.7 hours with 90% of the half-life values from 3-9 hours. There is no evidence of drug accumulation and flurbiprofen does not induce enzymes that alter its metabolism.

Flurbiprofen is rapidly metabolized and excreted in the urine as free and unaltered intact drug (20-25%) and hydroxylated metabolites (60-80%). In animal models of inflammation the metabolites showed no activity. Flurbiprofen is extensively bound (99%) to human plasma protein such as albumin. Mean peak serum concentrations of flurbiprofen were higher in the elderly female patients.

The average maximum serum concentration of flurbiprofen following a 100 mg oral dose in normal volunteers (n=184) was 15.2 mcg/ml with 90% of the values between 10 and 22 mcg/ml. In geriatric subjects (n=7) between the ages of 58 and 77 years, 100 mg of flurbiprofen resulted in an average peak drug level of 18.0 mcg/ml and an average elimination half-life of 6.5 hours (range 3-10 hours). In geriatric rheumatoid arthritis

patients (n=13) between the ages of 65 and 83 years receiving 100 mg flurbiprofen, the average maximum blood level was 12.7 mcg/ml and the average elimination half-life was 5.6 hours (range 4-10 hours).

In a study assessing flurbiprofen pharmacokinetics in end stage renal disease (ESRD), mean urinary recovery of a 100 mg dose was 73% in 48 hours for 9 normal subjects and 17% in 96 hours for 8 ESRD patients undergoing continuous ambulatory peritoneal dialysis. Plasma concentrations of flurbiprofen were about 40% lower in the ESRD patients; the elimination half-life of flurbiprofen was unchanged. Elimination of the 4'-hydroxy-flurbiprofen metabolite was markedly reduced in the ESRD patients. The pharmacokinetics of flurbiprofen in patients with decreased renal function but not ESRD have not been determined.

The pharmacokinetics of flurbiprofen in patients with hepatic disease have not been determined.

Comparative Bioavailability:

A bioavailability study was performed using normal human volunteers. The rate and extent of absorption after a single oral dose of 100 mg flurbiprofen in the form of Flurbiprofen 100 mg and Ansaid 100 mg was measured and compared. The results can be summarized as follows:

	Ansaid	Flurbiprofen	Percentage of Ansaid
AUC_T* (mcg.hrs/ml)	72.85 (20)	73.90 (17)	+1.4
AUC_I* (mcg.hrs/ml)	75.50 (21)	76.62 (19)	+1.4
C_{max}* (mcg/ml)	14.05 (25)	14.95 (13)	+6.4
T_{max}** (hrs)	1.49 (0.85)	1.35 (0.89)	-
$t_{1/2}$** (hrs)	5.37 (0.77)	5.48 (0.79)	-

* Geometric means (CV)

** Arithmetic means (SD)

INDICATIONS AND CLINICAL USE

FLURBIPROFEN (flurbiprofen) is indicated for the relief of signs and symptoms of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis.

FLURBIPROFEN is indicated for the relief of pain associated with dysmenorrhoea.

FLURBIPROFEN is also indicated for the relief of mild to moderate pain accompanied by inflammation (eg. bursitis, tendinitis, soft-tissue trauma).

CONTRAINDICATIONS

FLURBIPROFEN (flurbiprofen) should not be used in patients with active or recent history of inflammatory diseases of the gastrointestinal system such as peptic ulcer, gastritis, regional enteritis or ulcerative colitis.

Flurbiprofen is contraindicated in patients with a known or suspected history of hypersensitivity to the drug.

FLURBIPROFEN should be used in patients in whom acute asthmatic attacks, urticaria, rhinitis or other allergic manifestations are precipitated by ASA or other non-steroidal anti-inflammatory agents. Fatal anaphylactoid reactions have occurred in such individuals.

WARNINGS

General:

Peptic ulceration, perforation and gastrointestinal bleeding, sometimes severe and occasionally fatal have been reported during therapy with non-steroidal anti-inflammatory drugs (NSAIDs) including flurbiprofen.

FLURBIPROFEN (flurbiprofen) should be given under close medical supervision to patients prone to gastrointestinal tract irritation particularly those with a history of peptic ulcer, diverticulosis or other inflammatory disease of the gastrointestinal tract. In these cases the physician must weigh the benefits of treatment against the possible hazards.

Patients taking any NSAID including this drug should be instructed to contact a physician immediately if they experience symptoms or signs suggestive of peptic ulceration or gastrointestinal bleeding. These reactions can occur without warning symptoms or signs and at any time during the treatment.

Elderly, frail and debilitated patients appear to be at higher risk from a variety of adverse reactions from non-steroidal anti-inflammatory drugs (NSAIDs). For such patients, consideration should be given to a starting dose lower than usual, with individual adjustment when necessary and under close supervision. See "Precautions" for further advice.

Pregnancy and Lactation:

The safe use of flurbiprofen in pregnancy and lactation has not been established. Although no teratogenic effects were seen in animal studies, parturition was delayed and prolonged, and there was an increase in the number of stillbirths. Flurbiprofen has been found to cross the placental barrier, and is secreted in breast milk. Therefore the use of this drug is not recommended during pregnancy and lactation.

Use in Children:

The safety and efficacy of FLURBIPROFEN (flurbiprofen) has not been established in children, and therefore the use in this age group is not recommended.

Pre-existing Asthma:

About 10% of patients with asthma may have ASA-sensitive asthma. The use of ASA in patients with ASA-sensitive asthma has been associated with severe bronchospasm which can be fatal. Since cross-reactivity, including bronchospasm, between ASA and other nonsteroidal anti-inflammatory drugs has been reported in such ASA-sensitive patients, Flurbiprofen should not be administered to patients with this form of ASA-sensitivity and should be used with caution in all patients with pre-existing asthma.

PRECAUTIONS

As with all NSAIDs, flurbiprofen should be used with caution in the elderly, particularly women and the dosage should be adjusted individually.

Gastrointestinal System:

If peptic ulceration is suspected or confirmed, or if gastrointestinal bleeding or perforation occurs FLURBIPROFEN (flurbiprofen) should be discontinued, an appropriate treatment instituted and the patient closely monitored.

There is no definitive evidence that the concomitant administration of histamine H_2-receptor antagonists and/or antacids will either prevent the occurrence of gastrointestinal side effects or allow continuation of flurbiprofen therapy when and if these adverse reactions appear.

Renal Function:

As with other non-steroidal anti-inflammatory drugs, long-term administration of flurbiprofen to animals has resulted in renal papillary necrosis and other abnormal renal pathology. In humans, there have been reports of acute interstitial nephritis with hematuria, proteinuria and occasionally nephrotic syndrome.

A second form of renal toxicity has been seen in patients with prerenal conditions leading to the reduction in renal blood flow or blood volume, where the renal prostaglandins have a supportive role in the maintenance renal perfusion. In these patients, administration of a non-steroidal anti-inflammatory drug may cause a dose-dependent reduction in prostaglandin formation and 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 the elderly. Discontinuation of non-steroidal anti-inflammatory therapy is usually followed by recovery to the pre-treatment state.

Flurbiprofen and its metabolites are eliminated primarily by the kidneys, therefore the drug should be used with great caution in patients with impaired renal function. In these cases lower doses of FLURBIPROFEN should be anticipated and patients carefully monitored.

During long-term therapy kidney function should be monitored periodically.

Hepatic Function:

As with other non-steroidal anti-inflammatory drugs, borderline elevations of one or more liver tests may occur. These abnormalities may progress, may remain essentially unchanged, or may be transient with continued therapy. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of more severe hepatic reaction while on therapy with this drug. Severe hepatic reactions including jaundice and cases of fatal hepatitis have been reported with this drug as with other non-steroidal anti-inflammatory drugs. Although such reactions are rare, if abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g. eosinophilia, rash, etc.), FLURBIPROFEN should be discontinued.

During long-term therapy, liver function tests should be monitored periodically. If this drug is to be used in the presence of impaired liver function, it must be done under strict observation.

Fluid and Electrolyte Balance:

Fluid retention and edema have been observed in patients treated with flurbiprofen. Therefore, as with many other non-steroidal anti-inflammatory drugs, the possibility of precipitating congestive heart failure in elderly patients or those with compromised cardiac function should be borne in mind. FLURBIPROFEN should be used with caution in patients with heart failure, hypertension or other conditions predisposing to fluid retention.

Serum electrolytes should be monitored periodically during long-term therapy, especially in those patients at risk.

Hematology:

Drugs inhibiting prostaglandin biosynthesis do interfere with platelet function to some degree; therefore, patients who may be adversely affected by such an action should be carefully observed when FLURBIPROFEN is administered.

Blood dyscrasias associated with the use of non-steroidal anti-inflammatory drugs are rare, but could be with severe consequences.

Flurbiprofen inhibits collagen-induced platelet aggregation. As it has been shown that flurbiprofen prolongs bleeding time, it should be used with caution in patients with potential for abnormal bleeding. Safety of flurbiprofen in combination with anticoagulants has not been established and if such use is necessary, special caution should be used.

Infection:

In common with other anti-inflammatory drugs, FLURBIPROFEN may mask the usual signs of infection.

Ophthalmology:

Blurred and/or diminished vision has been reported with the use of flurbiprofen and other non-steroidal anti-inflammatory drugs. If such symptoms develop this drug should be discontinued and an ophthalmologic examination performed; ophthalmic examination should be carried out at periodic intervals in any patient receiving this drug for an extended period of time.

Drug Interactions:

Acetylsalicylic Acid (ASA):

Concomitant oral administration of flurbiprofen and ASA indicates that flurbiprofen has no significant effect on the pharmacokinetics and metabolism of ASI. However concomitant administration of ASA decreases flurbiprofen peak serum levels, as well as the rate and amount of flurbiprofen absorbed.

Digoxin:

Flurbiprofen does not change the rate of elimination of digoxin and the rate of elimination of flurbiprofen is not altered by co-administration of digoxin. However, digoxin absorption may be delayed during co-administration of flurbiprofen.

Anticoagulants, Sulfonamides and Phenytoin:

In a short term study, flurbiprofen given with phenprocoumon did not affect prothrombin time. but the bleeding time increased slightly, although it remained in the normal range.

Flurbiprofen is extensively protein bound (99%) to human serum albumin. Less than 10% of the primary binding sites were estimated to be occupied at therapeutic drug concentrations. *In vitro* studies suggest that flurbiprofen binds to a different primary site on albumin (Type II) than drugs such as anticoagulants, sulfonamides and phenytoin (Type I). However, patients with such combination therapy should be monitored.

Oral Hypoglycaemic Drugs:

Co-administration of flurbiprofen with glibenclamide, metformin, chlorpropamide or phenformin did not lead to interaction effects of any clinical significance. A tendency towards a reduction in blood sugar levels occurred over a 24 hour period, but no hypoglycaemic reactions occurred. No interaction in terms of blood sugar or immunoreactive insulin occurred following co-administration of flurbiprofen and tolbutamide.

Diuretics:

Flurbiprofen antagonizes the action of intravenous or oral furosemide.

Antihypertensives:

No significant alterations in the pharmacokinetics of either propranolol or atenolol followed pre-treatment with placebo or flurbiprofen. However, pre-treatment with flurbiprofen

attenuated the effects of propranolol on blood pressure but not on heart rate. The hypotensive effect caused by atenolol was attenuated to a lesser degree following flurbiprofen pre-treatment.

Antacids:

The pharmacokinetics of a single oral dose of flurbiprofen are not altered by the concomitant administration of a magnesium and aluminum hydroxide antacid formulation.

Cimetidine, Ranitidine:

In normal volunteers (n=9), pretreatment with cimetidine or ranitidine did not affect flurbiprofen pharmacokinetics, except that a small (11%) but statistically significant increase in the area under the serum concentration curve of flurbiprofen resulted with cimetidine.

Clinical Laboratory Tests:

Flurbiprofen and Thyroid Function Tests:

Flurbiprofen does not modify the laboratory parameters of thyroid function.

ADVERSE REACTIONS

The most common adverse reactions encountered with non-steroidal anti-inflammatory drugs are gastrointestinal, of which peptic ulcer, with or without bleeding, is the most severe. Fatalities have occurred on occasion, particularly in the elderly.

Adverse reaction information was derived from patients who received flurbiprofen in blinded-controlled and open-label clinical trials, and from world wide marketing experience and from publications. In the tables below, rates of the more common events (greater than 1%) and many of the less common events (less than 1%) represent clinical study results. Of the 4123 patients in premarketing studies, 2954 were treated for at least 1 month, 1448 for at least 3 months, 948 for at least 6 months, 356 for at least 1 year, and 100 for at least 2 years. The adverse reaction figures represent the percent of treated patients (N=4123) reporting an adverse reaction.

Reactions listed in column *2* of the following table occurred in <1% of patients in the clinical trials or were reported during post-marketing experience from other countries. Reactions listed in column 3 have been reported in patients taking flurbiprofen under circumstances that do not permit a clear attribution of the reaction to flurbiprofen.

INCIDENCE GREATER THAN 1%	INCIDENCE LESS THAN 1% (CAUSAL RELATIONSHIP PROBABLE)	INCIDENCE LESS THAN 1% (CAUSAL RELATIONSHIP UNKNOWN)
GATSROINTESTINAL Dyspepsia (8.7%), diarrhea (7.2%), abdominal pain (6.3%), nausea (5.8%), constipation	Peptic ulcer disease (see also WARNINGS) gastritis, bloody diarrhea, stomatitis, esophageal disease, hematemesis, hepatitis,	Periodontal abscess, appetite changes, cholecystitis, and dry mouth.

INCIDENCE GREATER THAN 1%	INCIDENCE LESS THAN 1% (CAUSAL RELATIONSHIP PROBABLE)	INCIDENCE LESS THAN 1% (CAUSAL RELATIONSHIP UNKNOWN)
(3.3%), GI bleeding (1.7%), elevated liver enzymes, vomiting (1.6%).	cholestatic and non-cholestatic jaundice*.	
CENTRAL NERVOUS SYSTEM Headache (2.9%), nervousness and other manifestations of CNS "stimulation" (eg. Anxiety, insomnia, reflexes increased, and tremor) (2.0%), and symptoms associated with CNS "inhibition" (eg. Amnesia, asthenia, somnolence, malaise, and depression) (2.4%).	Ataxia, cerebrovascular ischemia, confusion, paresthesia, and twitching.	Convulsion, meningitis, hypertonia, cerebrovascular accident, emotional lability, and subarchnoid hemorrhage.
DERMATOLOGICAL Rash (2.3%)	Angiodema, urticaria, eczema, pruritus, photosensitivity*, toxic epidermal necrolysis*, and exfoliative dermatitis*.	
CARDIOVASCULAR	Heart failure, hypertension, vascular disease and vasodilation.	Arrhythmias, angina pectoris, and myocardial infarction.
SPECIAL SENSES Dizziness (2.1%), tinnitus (1.5%), and changes in vision (1.5%)	Conjunctivitis and parosmia.	Ear disease, corneal opacity, glaucoma, retrobulbar neuritis, changes in taste, transient hearing loss, retinal hemorrhage*.
HEMATOLOGIC	Decrease in hemoglobin and haematocrit, iron deficiency anemia, hemolytic anemia*, aplastic anemia*, leukopenia, eosiniphilia, ecchymosis, thrombocytopenia* (see also PRECAUTIONS, Hematology).	Lymphadenopathy.
GENITOURINARY Sign and symptoms suggesting urinary tract infection (1.6%)	Hematuria and renal failure, interstitial nephritis*.	Menstrual disturbances, vaginal and uterine hemorrhage, vulvovaginitis, and prostate disease.
RESPIRATORY Rhinitis (1.7%).	Aasthma and epistaxis.	Bronchitis, laryngitis, dyspnea, pulmonary embolism, pulmonary infarct, and hyperventilation.
OTHER Edema (2.5%).	Body weight changes, chills and fever, anaphylactic reaction*, hyperuricemia.	Hyperkalemia, myasthenia.

* Adverse reactions reported only in worldwide postmarketing experience or the literature (which presumably indicates that they are rarer).

SYMPTOMS AND TREATMENT OF OVERDOSE

Information on overdosage is available for 13 children and 12 adults. Nine of the 13 children were less than 6 years old. Drowsiness occurred after doses of 150 to 800 mg in 3 of these young children (with dilated pupils in one), and in a 2-year-old who also had semi-consciousness, pinpoint pupils, diminished tone, and elevated liver enzymes. Other children who ingested doses of 200 mg to 2.5 g showed no symptoms.

Among the adults a 70-year-old man with a history of chronic obstructive airway disease died. Toxicological analysis showed acute flurbiprofen overdose and a blood ethanol concentration of 100 mg/dL. In the other cases, symptoms were as follows: coma and respiratory depression after 3-6 g; drowsiness, nausea and epigastric pain after 2.5-5 g; epigastric pain and dizziness after 3 g; headache and nausea after ≤2 g; agitation after 1.5 g; and drowsiness after 1.0 g. One patient, who took 200-400 mg flurbiprofen and 2.4 g fenoprofen, had disorientation and diplopia. Three adults had no symptoms after 3-5 g flurbiprofen.

Treatment of overdose: the stomach should be emptied by vomiting or lavage, though little drug will likely be recovered if more than an hour as elapsed since ingestion. Supportive treatment should be instituted as necessary. Some patients have been given supplemental oral or intravenous fluids and required no other treatment.

DOSAGE AND ADMINISTRATION

Rheumatoid Arthritis, Osteoarthritis, Ankylosing Spondylitis:

The recommended dose is 200 mg per day given in divided doses. Some patients may require up to 300 mg per day. The dose should be adjusted until the minimum effective maintenance dose is established. During the course of treatment, the maximum daily dose of 300 mg should be used only during symptom exacerbations and not for maintenance therapy.

Dysmenorrhea:

The recommended dosage is 50 mg given four times daily.

Mild to Moderately Severe Pain:

The usual recommended dose is 50 mg given every four to six hours as needed.

INFORMATION TO THE PATIENT

WHAT IS FLURBIPROFEN

FLURBIPROFEN is a product name for flurbiprofen, a medicine to relieve pain and reduce inflammation. FLURBIPROFEN which has been prescribed to you by your doctor, is one of a large group of non-steroidol anti-inflammatory drugs (NSAIDs), is not related to cortisone and does not contain acetylsalicylic acid (ASA).

FLURBIPROFEN is used to treat certain types of arthritis (rheumatoid arthritis, osteoarthritis, ankylosing spondylitis); dysmenorrhea (menstrual pain); and mild to moderate pain accompanied by inflammation (bursitis, tendinitis, soft-tissue trauma, pain following dental procedures).

FLURBIPROFEN helps to relieve joint pain, swelling, stiffness and fever by reducing the production of certain substances (prostaglandins) and helping to control inflammation and other body reactions.

WHEN TO TAKE FLURBIPROFEN

You should take FLURBIPROFEN only as directed by your doctor. Do not take more of it, do not take it more often and do not take it for a longer period of time than your doctor ordered. Be sure to take FLURBIPROFEN regularly as prescribed. In some types of arthritis, up to two weeks may pass before you feel the full effects of this medicine. During treatment, your doctor may decide to adjust the dosage according to your response to the medication.

Generally patients are instructed to take FLURBIPROFEN two to four times a day. FLURBIPROFEN will work whether or not you take it with meals. However, if you take three doses, you may wish to take them with meals. First, this spaces the tablet throughout the day and makes it easier for you to remember to take your medication. Second, since some people may experience an upset stomach with products like FLURBIPROFEN, taking the medication with meals can reduce or prevent stomach upset.

If your doctor prescribes four doses, the fourth dose is usually taken at bedtime. If FLURBIPROFEN upsets your stomach, you may wish to take the bedtime dose with a snack.

THE BEST DOSAGE OF FLURBIPROFEN FOR YOU

Arthritis, as you know, is a condition that has its ups and downs, and the amount of pain and inflammation you experience can change from day to day and from week to week. After the initial period of treatment with FLURBIPROFEN, your doctor may want to make adjustments to find the best dosage for you.

By accurately reporting how you feel, you can help your doctor decide whether the initial dosage should be increased or decreased. FLURBIPROFEN comes in two tablet strengths - 50 mg and 100 mg - so your doctor can easily lower or raise the dosage.

INCREASING THE DOSAGE

Sometimes higher doses of FLURBIPROFEN may be needed because of the success of your treatment. The explanation is simple: as your ability to do things improves, you may find yourself automatically increasing your activities. This, in turn, may cause you to feel more pain. If this happens, your dosage of FLURBIPROFEN may need to be increased to control the pain at this increased level of activity. If your symptoms get worse because of flare-up in your arthritis, your doctor may want you to. Increase your dosage of FUJRBIPROFEN until the symptoms are once again under control.

UPPER AND LOWER DOSAGE LIMITS OF FLURBIPROFEN

When FLURBIPROFEN is relieving the symptoms of your arthritis and you are accustomed to the medication, your doctor may set upper and lower dosage limits and tell you to adjust the dose within these limits, according to your pain and inflammation. It is important, however, not to go beyond the upper limits your doctor has set.

SPECIFIC DOSING INSTRUCTIONS

Rheumatoid arthritis - Initially two 100 mg (blue) tablets per day to a maximum of six 50 mg (white) tablets or three 100 mg (blue) tablets per day.

Osteoarthritis - Initially two 100 mg (blue) tablets per day to a maximum of six 50 mg (white) tablets or three 100 mg (blue) tablets per day.

Ankylosing Spondylitis - Initially two 100 mg (blue) tablets per day to a maximum of six 50 mg (white) tablets or three 100 mg (blue) tablets per day.

Dysmenorrhea - One 50 mg (white) tablet four times per day.

Mild to Moderately Severe Pain - One 50 mg (white) tablet every four to six hours when needed for pain.

Do not take ASA (acetylsalicylic acid), ASA containing compounds or other drugs used to relieve symptoms of arthritis while taking FLURBIPROFEN unless directed to do so by your physician.

If you are prescribed this medication for use over a long period of time, your doctor will check your health during regular visits to assess your progress and to ensure that this medication is not causing unwanted effects.

SIDE EFFECTS OF FLURBIPROFEN

Flurbiprofen has been proven to be a relatively safe, trouble free medication without serious side effects in most patients. Any medication, even acetylsalicylic acid {ASA), may sometimes cause side effects, and the same is true of flurbiprofen. If you know about these side effects, you may be able to prevent, reduce, or modify them if they occur. Your doctor may require certain tests to monitor the effectiveness of your treatment program and any possible side effects. Chances are excellent that you will be able to tolerate and experience the benefits of taking FLURBIPROFEN.

The most frequent side effect of most medications, even acetylsalicylic acid (ASA), used to treat arthritis is some type of stomach upset. This side effect for flurbiprofen in clinical studies was much less than reported for acetylsalicylic acid (ASA), and can take the form of nausea, pain in the gut, heartburn, or a sense of fullness or bloating. Very often, as already mentioned, this discomfort can be controlled by taking FLURBIPROFEN with meals or a glass of milk.

Elderly, frail or debilitated patients often seem to experience more frequent or more severe side effects. Although not all of these side effects are common, when they do occur they may require medical attention. Check with your doctor immediately if any of the following are noted:

- bloody or black tarry stools;
- shortness of breath, wheezing, any trouble in breathing or tightness in the chest;
- skin rash, swelling, hives or itching;
- indigestion, nausea, vomiting, stomach pain or diarrhea;
- yellow discolouration of the skin or eyes, with or without fatigue;
- any changes in the amount or colour of your urine (such as dark; red or brown);
- swelling of the feet or lower legs;
- blurred vision or any visual disturbance;
- mental confusion, depression, dizziness, lightheadedness;
- hearing problems.

FACTS TO REMEMBER ABOUT FLURBIPROFEN

Before taking this medication tell your doctor, pharmacist or dentist if you:

- are allergic to FLURBIPROFEN (flurbiprofen) or other related medicines of the NSAID group such as acetylsalicylic acid, diclofenac, diflunisal, fenoprofen, ibuprofen, indomethacin, ketoprofen, mefenamic acid, piroxicam, sulindac, tiaprofenic acid or tolmetin;
- have a history of stomach upset, ulcers, or liver or kidney diseases;
- are pregnant or intend to become pregnant while taking this medication;
- are breast-feeding;
- are taking any other medication (either prescription or non-prescription);
- have any other medical problem(s).

While taking this medication:

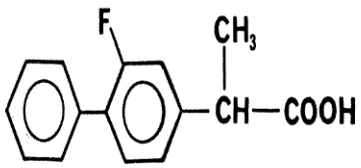
- tell any other doctor, dentist or pharmacist that you consult or see, that you are taking this medication;
- be cautious about driving or participating in activities that require alertness if you are drowsy, dizzy or lightheaded after taking this medication;
- check with your doctor if you are not getting any relief or if any problems develop;
- report any unusual reactions to your doctor. This is very important as it will aid in the early detection and prevention of potential complications;
- your regular medical checkups are essential.

If you require more information on this drug, consult your doctor or pharmacist.

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: flurbiprofen
Chemical Name: 2-(2-fluoro-4-biphenylyl) propionic acid.
Structural Formula:



Molecular Formula: $C_{15}H_{13}FO_2$
Molecular Weight: 244.25 g/mol

Description: Flurbiprofen is a white or almost white crystalline powder with a melting point of 114 to 117°C. It is practically insoluble in water; soluble in 3 parts of ethanol (96%), in 4 parts of chloroform and in 4.5 parts of ether. It dissolves in aqueous solutions of alkali hydroxides and carbonates.

Composition

In addition to the active ingredient flurbiprofen, each tablet contains the non-medicinal ingredients carnauba wax, colloidal silicon dioxide, croscarmellose sodium, hydroxypropyl methylcellulose, lactose, microcrystalline cellulose, polyethylene glycol, stearic acid, and titanium dioxide. Each 100 mg tablet also contains FD&C blue #2.

Stability and Storage Recommendations

Store at controlled room temperature 15° to 30°C.

AVAILABILITY

FLURBIPROFEN 50 mg tablets are white, oval, biconvex, film-coated tablets, engraved "AP0-50" on one side, containing 50 mg of flurbiprofen, available in bottles of 100, 500 and 1000.

FLURBIPROFEN 100 mg tablets are blue, oval, biconvex, film-coated tablets, engraved “AP0-100" on one side, containing 100 mg of flurbiprofen, available in bottles of 100, 500 and 1000.

Flurbiprofen is a Schedule F drug.

PHARMACOLOGY

Flurbiprofen was evaluated in standard animal models. The calculated anti-inflammatory effect in the carrageenan-induced inflammation model for flurbiprofen, expressed as ED_{50}, was 4 mg/kg.

Flurbiprofen suppressed adjuvant induced developing polyarthritis and established arthritis in the rat. The minimum effective dose of flurbiprofen in rats with acute inflammation and developing arthritis was less than 0.1 mg/kg given orally.

In yeast-induced fever in rats, the antipyretic activity of flurbiprofen 0.4 mg/kg given orally was equivalent to ASA 80.0 mg/kg.

The analgesic activity of flurbiprofen was assessed using a model of acetylcholine-induced writhing in the mouse. Flurbiprofen produced a significant inhibition of the writhing response at the extremely low dose of 0.04 mg/kg. Fifty percent inhibition (ID_{50}) of writhing activity was observed with flurbiprofen at a dose less than 0.33 mg/kg.

TOXICOLOGY

Acute Toxicity:

The LD_{50} values for single dose flurbiprofen administration are summarized below:

Species	Route	LD_{50} (mg/kg)
Mouse	Oral	750
Mouse	Intraperitoneal	200
Rat	Oral	160
Rat	Intraperitoneal	400

In mice, primary signs of toxicity were prostration, ataxia, loss of righting reflex, laboured respiration, twitches, convulsions, CNS depression, and splayed hind limbs.

In rats, primary signs of toxicity were tremors, convulsions, labored respiration, and prostration. Signs of toxicity were observed mostly in the intraperitoneal studies •

A series of single dose studies were conducted in mice (given 8-500 mg/kg) and rats (given 50-320 mg/kg), to study the incidence of renal papillary necrosis (RPN) produced by flurbiprofen. The overall incidence in mice was 7.9%, and in the rat 8.2%. RPN was observed at doses ranging from 12.5 to 320 mg/kg in the mouse and at 125 to 320 mg/kg in the rat.

Subacute and Chronic Toxicity:

Flurbiprofen given orally to cats at 0.25, 1.0 and 4.0 mg/kg/day for 30 days produced gastrointestinal ulceration at all dosage levels. In dogs flurbiprofen given orally at 0.04, 0.2 and 1.0 mg/kg/day for 30 days produced evidence of gastrointestinal damage (ulceration, erosions, scars) in all animals at all doses. Severe gastrointestinal damage and enlargement of the spleen were noted at the 1.0 mg/kg/day dose.

In rodents, dose levels of 1, 5 and 25 mg/kg/day were administered orally to mice (3 months) and rats (6 months). All female mice died from intestinal ulceration and peritonitis at the high dose level between 4 and 49 doses. Two of ten males on the same dosage died after 5 and 66 doses respectively. One had hemorrhage in the lower ileum suggesting that cause of death may have been gastrointestinal hemorrhage. Hemoglobin concentration was markedly reduced in males given 25 mg/kg/day and slightly reduced in those given 5 mg/kg/day. In the rats, ulcerative gastrointestinal lesions were noted at the 25 mg/kg/day dose level in 11 out of 12 female animals. Edema of the renal papillae was seen at the 25 mg/kg/day dose level in 8 out of 12 female animals.

Monkeys were administered flurbiprofen 3, 10 and 30 mg/kg/day for 22 months, and no drug related effects were observed at all dose levels.

Other monkey studies at much higher doses (50, 75, 100 and 150 mg/kg/day) showed flurbiprofen to be poorly tolerated at these dose levels.

Gastrointestinal damage was observed at dosages greater than 75 mg/kg/day. Renal papillary necrosis was observed in one monkey dosed at 100 mg/kg/day and one monkey dosed at 50 mg/kg/day.

Flurbiprofen was administered orally to baboons at 1, 5 and 25 mg/kg/day for one month. Toxic effects in the 25 mg/kg/day group manifested as small weight loss and presence of occult blood in the feces.

In another study, flurbiprofen was given orally to baboons at 1, 5 and 25 mg/kg/day for six months. Gastric ulceration was reported in all baboons at the high and middle dose levels.

Reproduction Studies:

Reproduction studies in rats at levels of 0.5, 1.0 and 3.0 mg/kg/day showed no evidence of an adverse effect on mating, fertility or gestation. However, parturition was affected as evidenced by the occurrence of prolonged labour, delivery of stillborn fetuses and presence of retained fetuses at necropsy mainly at the 1.0 and 3.0 mg/kg/day levels. Similar results were obtained when 0.2 to 25 mg/kg/day was administered to rats from day 1 of pregnancy to parturition. In perinatal and postnatal studies in rats, administration, of 0 2 mg/kg/day from day 1 of gestation and throughout lactation was well tolerated and did not impair lactation or suckling. However, when doses of 0.4 to 10 mg/kg/day were administered from day 16 of gestation to parturition, the development of parturition was affected in a dose-related fashion, producing fetal distress which bears a close relation to the increase in the time taken for parturition and for the gestation period as a whole.

Teratology studies have been conducted in mice (up to 12 mg/kg/day), rats (up to 25 mg/kg/day) and rabbits (up to 7.5 mg/kg/day) and flurbiprofen was not teratogenic in these studies.

Carcinogenicity and Mutagenicity:

In a two year oral carcinogenicity study in the rat, flurbiprofen was given 0.5, 2.0 and 4.0 mg/kg/day. Results of this study did not suggest a carcinogenic potential. However, three non-neoplastic, dose-related toxic effects were observed i.e., renal papillary necrosis, ulcerative gastritis (females only) and cholangiofibrosis. These effects occurred in the middle and high dose groups.

Other carcinogenicity studies have been conducted in mice at dose levels of 2, 5 and 12 mg/kg/day for 80 weeks, and in rats at levels of 2, 5 and 12 mg/kg/day (reduced to 5 mg/kg/day in 32nd week of study) for two years. The high dose level was reduced from 12 to 5 mg/kg/day, due to signs of gastrointestinal lesions. Results of these studies did not suggest carcinogenic potential.

The micronucleus test was done in rats using a total dose of 0, 50, 100 and 200 mg/kg i.p. of U-27, 182 (administered in two equal dose at 24 hr intervals). Results showed no increase in chromosomal damage.

In cytogenetic experiments using sister chromatid exchange rates in human lymphocytes *in vivo* to determine possible damage to genetic material, therapeutic application of flurbiprofen for 2 weeks did not produce any genetic effects.

The possible mutagenic effects of flurbiprofen were investigated using the Salmonella mutagenicity (Ames) test. Results of this test do not suggest any potential for mutagenesis.

BIBLIOGRAPHY

1. Aaron CS, Mazurek J, Zimmer DM, Swenson DH. The Salmonella mutagenicity test: evaluation of 29 drug candidates. Mutat Res 1989; 223: 171-182.

2. Brewis IDL. A comparative study of flurbiprofen and indomethacin in rheumatoid arthritis. Curr Med Res Opin 1977; 5: 48-52.

3 Brooks CD, Linet OI, Schellenberg D, et al. Clinical safety of flurbiprofen. J Clin Pharmacal 1990; 30: 342-351.

4. Busson M. A long-term study of flurbiprofen in rheumatological disorders: I. Rheumatoid arthritis. J Int Med Res 1986; 14: 1-6.

5. Caille G, du Souich P, Vezina M, Pollock SR, Stalker DJ. Pharmacokinetic interaction between flurbiprofen and antacids in healthy volunteers. Biopharm & Drug Dispos 1989; 10: 607-615.

6. Cardoe N, de Silva M, Glass RC, Risdall PC. Serum concentrations of flurbiprofen in rheumatoid patients receiving flurbiprofen over long periods of time. Curr Med Res Opin 1977; 5: 21-25.

7. Cox SR, Forbes KK. Excretion of flurbiprofen into breast milk. Pharmacotherapy 1987; 7(6): 211-215.

8. Cremoncini CM, Libroia A, Valente C, Cremoncini A, et al. Flurbiprofen and thyroid function tests. Br J Clin Pract 1984; 38: 399-402.

9. Frank O. A double-blind comparative study of 150 mg flurbiprofen daily and 75 mg indomethacin daily in the treatment of osteoarthrosis of the hip joint. Curr Med Res Opin 1977; 5: 91-98.

10. Glenn EM, Rohloff N, Bowman BJ, Lyster SC. The pharmacology of 2-(2-fluoro-4-biphenylyl)propionic acid (flurbiprofen): a potent non-steroidal anti-inflammatory drug. Agents & Actions 1973; 3: 210-216.

11. Good A, Mena H. Treatment of ankylosing spondylitis with flurbiprofen and indomethacin. Curr Med Res Opin 1977; 5: 117-121.

12. Information Letter, Health Protection Branch. Nonsteroidal Anti-inflammatory Drugs. OD-33; August 21, 1985. Kaiser DG, Brooks CD, Lomen PL. Pharmacokinetics of flurbiprofen. Am J Med 1986; 80 (suppl 3A): 10-15.

13. Kieffer G. Flurbiprofène, un anti-inflammatoire non-stéroidien. Résultats sur 4126 observations en pratique rhumatologique ambulatoire. Rhumatologie 1981; 33: 397-403.

14. Kieffer G. Flurbiprofène: Résultats préliminaires sur 10,077 observations en pratique ambulatoire. Gaz Med Fr 1980; 87: 1630-1632.

15. Kowanko IC, Pownall R, Knapp MS, Swannell AJ, Mahoney PGC. Circadian variations in the signs and symptoms of rheumatoid arthritis and in the therapeutic effectiveness of flurbiprofen at different times of day. Br J Clin Pharmacal 1981; 11: 477-484.

16. Kullich W, Klein G. Investigations of the influence of non-steroidal antirheumatic drugs on the rates of sister-chromatid exchange. Mutat Res 1986; 174(2): 131-134.

17. Lomen PL, Turner LF, Lamborn KR. Safety of flurbiprofen in the treatment of ankylosing spondylitis, osteoarthritis, and rheumatoid arthritis. A summary of liver and kidney assay data. Am J Med 1986; 80 (suppl 3A): 23-30.

18. Lomen PL, Turner LF, Lanborn KR, Brinn EL. Flurbiprofen in the treatment of rheumatoid arthritis: a comparison with aspirin. Am J Med 1986; 80 (suppl 3A): 89-95.

19. Lomen PL, Turner LF, Lamborn KR, Brinn E, Sattler LP. Flurbiprofen in the treatment of ankylosing spondylitis. A comparison with phenylbutazone. Am J Med 1986; 80 (suppl3A): 120-126.

20. Marbet GA, Duckert F, Walter M, Six P, Airenne H. Interaction study between phenprocoumon and flurbiprofen. Curr Med Res Opin 1977; 5: 26-31.

21. Mena HR, Willkens RF. Treatment of ankylosing spondylitis with flurbiprofen or phenylbutazone. Eur J Clin Pharmacal 1977; 11: 263-266.

22. Pitney WR, Nicol M, Dean S, Hickey A. Effect of flurbiprofen on bleeding time and platelet aggregation. Thromb Res 1978; 13: 811-819.

23. Rawles JM. Antagonism between non-steroidal anti-inflammatory drugs and diruetics. Scot Med J 1982; 27: 37-40.

24. Shapiro SS. Flurbiprofen for the treatment of primary dysmenorrhea Am J Med 1986; 80 (suppl 3A): 71-75.

25. Stephens WH, El-Ghobarey AF, Macleod MM, Buchanan WW. A double-blind crossover trial of mefenamic acid, sulindac, and flurbiprofen in rheumatoid arthritis. Curr Med Res Opin 1979; 5: 754-758.

26. Sullivan KM, Small RE, Rock WL, Cox SR, Willis HE. Effects of cimetidine or ranitidine on the pharmacokinetics of flurbiprofen. Clin Pharm 1986; 5: 586-589.

27. United States Food and Drug Administration. Medical Officer Review of NDA 18-766 - Safety. Ansaid (flurbiprofen). December 6, 1988: 1-253, 652-669.

28. United States Food and Drug Administration. Pharmacology and Toxicology Review of NDA 18-766 (Original Summary). Ansaid (flurbiprofen) 08/31/82: 1-23.

29. United States Food and Drug Administration. Pharmacology and Toxicology

Review of NDA 18-766 (Review No. 3). Ansaid (flurbiprofen). August 6, 1985: 1-9.

30. The Upjohn Company. Ansaid (flurbiprofen). Physicians' Desk Reference. Barnhart ER (Publ.). Medical Economics Co. Inc., Oradell, NJ; 1990 (Edition 44): 2209-2211.

31. Webster J, Petrie JC, McLean I, Hawksworth GM. Flurbiprofen interaction with single doses of atenolol and propranolol. Br J Clin Pharmacal 1984; 18: 861-866.

32. Muckle DS. Flurbiprofen for the treatment of soft tissue trauma. Am J Med 1986; 80(suppl 3A): 76-80.

33. Mena HR, Lomen PL. Turner LF. Lamborn KR. Brinn EL. Treatment of acute shoulder syndrome with flurbiprofen. Am J Med 1986; 80(suppl 3A): 141-144.

34. Cooper SA, Mardirossian G. Comparison of flurbiprofen and aspirin in the relief of postsurgical pain using the dental model. Am J Med 1986; 80(suppl 3A): 36-40.

35. Dionne RA. Suppression of dental pain by the preoperative administration of flurbiprofen. Am J Med 1986; 80(suppl 3A): 41-49.