Pfizer

انسيد

Ansaid®

(Flurbiprofen)

NAME OF THE MEDICINAL PRODUCT
Ansaid®

QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 100 mg of flurbiprofen.

PHARMACEUTICAL FORM
Tablets

THERAPEUTIC INDICATIONS
Ansaid® (flurbiprofen) is indicated for the acute or long-term treatment of the signs and symptoms of:

- Rheumatoid arthritis
- Osteoarthritis
- Ankylosing spondylitis
- Acute bursitis/tendonitis
- Acute gout
- Mild to moderately severe pain
- Dysmenorrhea
- Soft-tissue trauma

POSOLOGY AND METHOD OF ADMINISTRATION
Undesirable effects may be minimized by using the minimum effective dose for the shortest duration necessary to control symptoms.

The recommended starting dose of Ansaid® (flurbiprofen) is 100 to 300 mg total daily dose administered in two, or three divided doses (BID, or TID regimen). The largest recommended single dose in a multiple-dose daily regimen is 100 mg. The dose should be tailored to each patient according to the severity of the symptoms and the response to therapy.

Although a few patients have received higher doses, doses above 300 mg per day are not recommended.

CONTRAINDICATIONS
Ansaid® (flurbiprofen) is contraindicated in patients with demonstrated sensitivity to it. The potential exists for cross sensitivity to aspirin and other NSAIDs. It should not be given to patients in whom Ansaid® (flurbiprofen), aspirin, or other nonsteroidal anti-inflammatory drugs induce allergic-type reactions. Ansaid® (flurbiprofen) or other nonsteroidal anti-inflammatory drugs should not be given to patients with the aspirin triad (bronchial asthma, rhinitis, aspirin intolerance). Fatal asthmatic and anaphylactoid reactions have been reported in such patients.

Treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery.
Patients with severe renal failure.
Patients with severe hepatic failure.
Patients with severe heart failure.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE
The use of Ansaid® (flurbiprofen) with concomitant NSAIDs including COX-2 inhibitors should be avoided.

Cardiovascular Effects
NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with known cardiovascular disease may be at greater risk. To minimize the potential risk for an adverse cardiovascular event in patients treated with Ansaid® (flurbiprofen), the lowest effective dose should be used for the shortest duration possible. Physicians and patients should remain alert for the development of such events, even in the absence of previous cardiovascular symptoms. Patients should be informed about the signs and/or symptoms of serious cardiovascular toxicity and the steps to take if they occur.

Hypertension
As with all NSAIDS, Ansaid® (flurbiprofen) can lead to the onset of new hypertension or worsening of pre-existing hypertension, either of which may contribute to the increased incidence of cardiovascular events. NSAIDs, including Ansaid® (flurbiprofen), should be used with caution in patients with hypertension. Blood pressure should be monitored closely during the initiation of therapy with Ansaid® (flurbiprofen) and throughout the course of therapy.

Fluid Retention and Edema
As with other drugs known to inhibit prostaglandin synthesis, fluid retention and edema have been observed in some patients taking NSAIDs, including Ansaid® (flurbiprofen). Therefore, Ansaid® (flurbiprofen) should be used with caution in patients with compromised cardiac function and other conditions predisposing to, or worsened by, fluid retention. Patients with pre-existing congestive heart failure or hypertension should be closely monitored.

Gastrointestinal (GI) Effects
NSAIDs, including Ansaid® (flurbiprofen), can cause serious gastrointestinal (GI) adverse events including inflammation, bleeding, ulceration, and perforation of the stomach, small intestine, or large intestine, which can be fatal. When GI bleeding or ulceration occurs in patients receiving Ansaid® (flurbiprofen), the treatment should be withdrawn. Patients most at risk of developing these types of GI complications with NSAIDs are the elderly, patients with cardiovascular disease, patients using concomitant aspirin, or patients with a prior history of, or active, gastrointestinal disease, such as ulceration, GI bleeding or inflammatory conditions. Therefore, Ansaid® (flurbiprofen) should be used with caution in these patients.

Hepatic Effects
As with other NSAIDs, borderline elevations of one or more liver laboratory tests may occur in up to 15% of patients. 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 reactions while on therapy with flurbiprofen. Severe hepatic reactions, including jaundice and cases of fatal hepatitis, have been reported with flurbiprofen as with other NSAIDs. 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) treatment with flurbiprofen should be discontinued.

Skin Reactions
Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported very rarely in association with the use of NSAIDs, including Ansaid® (flurbiprofen). Patients appear to be at highest risk for these events early in the course of therapy, the onset of the event occurring in the majority of cases within the first month of treatment. Ansaid® (flurbiprofen) should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Renal Effects
In rare cases, NSAIDs, including Ansaid® (flurbiprofen), may cause interstitial nephritis, glomerulitis, papillary necrosis and the nephrotic syndrome. NSAIDs inhibit the synthesis of renal prostaglandin which plays a supportive role in the maintenance of renal perfusion in patients whose renal blood flow and blood volume are decreased. In these patients, administration of an NSAID may precipitate overt renal decompensation, which is typically followed by recovery to pretreatment state upon discontinuation of NSAID therapy. Patients at greatest risk of such a reaction are those with congestive heart failure, liver cirrhosis, nephrotic syndrome and overt renal disease. Such patients should be carefully monitored while receiving NSAID therapy.

Since flurbiprofen is eliminated primarily by the kidney, patients with significantly impaired renal function should be closely monitored and a reduction in dosage should be anticipated to avoid drug accumulation. Those patients at high risk for developing renal dysfunction on chronic therapy with flurbiprofen should have renal function monitored periodically.

Hypersensitivity
Anaphylactoid sensitivity may occur even in patients without prior exposure to Ansaid® (flurbiprofen).

Ophthalmologic Effects
Nonsteroidal anti-inflammatory drugs including Ansaid® (flurbiprofen) may rarely cause serious eye problems. Therefore, patients experiencing blurred or diminished vision during therapy should have prompt ophthalmologic examinations.

General Precautions
Ansaid® (flurbiprofen) inhibits collagen-induced platelet aggregation, and patients who may be adversely affected by prolonged bleeding time should be carefully observed when flurbiprofen is administered.

Nonsteroidal anti-inflammatory drugs, including Ansaid® (flurbiprofen), can increase the risk of bleeding in patients receiving anticoagulants (see section **Interaction with other medicinal products and other forms of interaction**), and should be given with caution.

Nonsteroidal anti-inflammatory drugs including Ansaid® (flurbiprofen) can cause reductions in hemoglobin and should be used with caution in patients who are anemic.

Aspirin Sensitivity and Pre-existing asthma
About 10% of patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin-sensitive asthma has been associated with severe bronchospasm which can be fatal. Since cross-reactivity, including bronchospasm, between aspirin and other nonsteroidal anti-inflammatory drugs has been reported in such aspirin-sensitive patients, Ansaid® (flurbiprofen) should not be administered to patients with this form of aspirin-sensitivity and should be used with caution in all patients with pre-existing asthma (see section **Contraindications**).

Use in Children
Ansaid® (flurbiprofen) safety and effectiveness in children has not been established.

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION
Antacids - In geriatric subjects antacid suspensions caused a reduction in the rate but not the extent of flurbiprofen absorption.

Anticoagulants - Ansaid® (flurbiprofen) affects bleeding parameters and serious clinical bleeding has been reported. Caution is advised.

Anti-hypertensives including diuretics, angiotensin-converting enzyme (ACE) inhibitors and angiotensin II antagonists (AIIA): NSAIDs can reduce the efficacy of diuretics and other antihypertensive drugs.

In patients with impaired renal function (e.g. dehydrated patients or elderly patients with compromised renal function), the co-administration of an ACE inhibitor or an AIIA with a cyclo-oxygenase inhibitor can increase the deterioration of the renal function, including the possibility of acute renal failure, which is usually reversible. The occurrence of these interactions should be considered in patients taking Ansaid® (flurbiprofen) with an ACE inhibitor or an AIIA.

Therefore, the concomitant administration of these drugs should be done with caution, especially in elderly patients. Patients should be adequately hydrated and the need to monitor the renal function should be assessed in the beginning of the concomitant treatment and periodically thereafter.

Aspirin - Concurrent administration of Ansaid® (flurbiprofen) and aspirin is not recommended since it may result in significantly lower serum Ansaid® (flurbiprofen) concentrations.

Beta-adrenergic Blocking Agents - Ansaid® (flurbiprofen) pretreatment attenuated the hypotensive effect of propranolol but did not appear to affect the beta-blocker mediated reduction in heart rate.

Cimetidine, Ranitidine - A small but statistically significant increase in flurbiprofen serum concentration may result with administration of these agents.

Cyclosporine: Because of their effect on renal prostaglandins, cyclooxygenase inhibitors such as Ansaid® (flurbiprofen) can increase the risk of nephrotoxicity with cyclosporine.

Digoxin - Concurrent administration with Ansaid® (flurbiprofen) did not reveal a change in steady state serum levels of either drug.

Diuretics - Patients receiving Ansaid® (flurbiprofen) and furosemide or other diuretics should be observed closely, since flurbiprofen can interfere with the effects of furosemide. Non-steroidal anti-inflammatory drugs have been shown to interfere with the action of thiazide diuretics and potassium-sparing diuretics.

Oral Hypoglycemic Agents - Concomitant administration of Ansaid® (flurbiprofen) and hypoglycemic agents revealed a slight reduction in blood sugar concentrations but no signs or symptoms of hypoglycemia.

Methotrexate: Caution is advised when methotrexate is administered concurrently with NSAIDs, including Ansaid® (flurbiprofen), because NSAID administration may result in increased plasma levels of methotrexate.

Tacrolimus: Possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus.

FERTILITY, PREGNANCY AND LACTATION

Fertility
Based on the mechanism of action, the use of NSAIDs may delay or prevent rupture of ovarian follicles, which has been associated with reversible infertility in some women. In women who have difficulties conceiving or who are undergoing investigation of infertility,withdrawal of NSAIDs, including flurbiprofen should be considered.

Pregnancy
Because of the known effects of nonsteroidal anti-inflammatory drugs on the fetal cardiovascular system (closure of ductus arteriosus), use during late pregnancy should be avoided.
Inhibition of prostaglandin synthesis might adversely affect pregnancy. Data from epidemiological studies suggest an increased risk of spontaneous abortion after use of prostaglandin synthesis inhibitors in early pregnancy. In animals, administration of prostaglandin synthesis inhibitors has been shown to result in increased pre- and post-implantation loss.

Lactation
Ansaid® (flurbiprofen) is poorly excreted into human milk. The nursing infant dose is predicted to be approximately 0.1 mg/day in the established milk of a woman taking flurbiprofen tablets 200 mg/day.

Available data show that levels of Ansaid® (flurbiprofen) are low and therefore unlikely to cause adverse effects in breast-fed infants.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
The effect of Ansaid® (flurbiprofen) on the ability to drive or use machinery has not been studied.

UNDESIRABLE EFFECTS
Adverse reaction information was derived from patients who received flurbiprofen in blinded-controlled and open-label clinical trials. Only events considered probably drug related are listed here.

MedDRA System Organ Class Frequency	**Adverse Drug Reactions** (Within each frequency grouping, ADRs are listed in alphabetical order)
Infections & Infestations	
Common	Rhinitis, signs and symptoms suggesting urinary tract infection
Blood & lymphatic system disorders	
Uncommon	Iron deficiency anemia
Unknown	Platelet aggregation inhibition
Immune System Disorders	
Rare	Anaphylactoid reaction
Metabolism and nutrition disorders	
Common	Body weight changes
Uncommon	Hyperuricemia, fluid retention
Psychiatric disorders	
Common	Anxiety, depression, insomnia, nervousness
Uncommon	Confusion
Nervous system disorders	
Common	Amnesia, dizziness, headache, reflexes increased, somnolence, tremor
Uncommon	Ataxia, cerebrovascular ischemia, paresthesia, parosmia
Eye disorders	
Common	Changes in vision
Uncommon	Conjunctivitis
Ear and labyrinth disorders	
Common	Tinnitus
Cardiac disorders	
Uncommon	Heart failure
Rare	Myocardial infarction
Vascular disorders	
Uncommon	Hypertension, vascular diseases, vasodilatation
Respiratory, thoracic and mediastinal disorders	
Uncommon	Asthma, epistaxis
Gastrointestinal disorders	
Common	Abdominal pain, constipation, diarrhea, dyspepsia, flatulence, GI bleeding, nausea, vomiting
Uncommon	Bloody diarrhea, esophageal disease, gastritis, hematemesis, peptic ulcer disease, stomatitis, Gastrointestinal ulcer
Rare	Gastrointestinal perforation
Hepato-biliary disorders	
Uncommon	Hepatitis
Skin and subcutaneous tissue disorders	
Common	Rash
Uncommon	Angioedema, eczema, pruritus, urticaria,
Musculosketetal connective tissue and bone disorders	
Uncommon	Twitching
Renal and urinary disorders	
Uncommon	Hematuria, renal failure
Rare	Glomerulonephritis95, renal papillary necrosis95, nephrotic syndrome95
General disorders and administration site conditions	
Common	Asthenia, edema, malaise
Uncommon	Chills, fever
Investigations	
Common	Elevated liver enzymes
Uncommon	Decrease in hemoglobin and hematocrit

The following adverse reactions were derived principally from worldwide marketing experience and the literature and accurate incidence rate estimates are generally impossible.

MedDRA System Organ Class	**Adverse Drug Reactions**
Blood and lymphatic system disorders	Aplastic anemia, hemolytic anemia, thrombocytopenia
Immune system disorders	Anaphylaxis
Gastrointestinal disorders	Colitis, exacerbation of inflammatory bowel disease, small intestine inflammation with loss of blood and protein
Hepato-biliary disorders	Cholestatic and non-cholestatic jaundice
Skin and subcutaneous tissue disorders	Exfoliative dermatitis, photosensitivity, Stevens-Johnson syndrome, toxic epidermal necrolysis
Nervous System Disorder	Aspetic meningitis
Renal and urinary disorders	Interstitial nephritis

No drug abuse or drug dependence has been observed with Ansaid® (flurbiprofen).

OVERDOSE
Manifestations of Ansaid® (flurbiprofen) overdose have included decreased mental status, coma, diminished muscle tone, headache, diplopia, elevated liver enzymes, respiratory depression, nausea, and epigastric pain.

PHARMACOLOGICAL PROPERTIES

PHARMACODYNAMIC PROPERTIES
Ansaid® (flurbiprofen) is a nonsteroidal anti-inflammatory drug that exhibits anti-inflammatory, analgesic, and antipyretic activities in animal models. The mechanism of action of flurbiprofen, like that of other nonsteroidal anti-inflammatory drugs, is not completely understood but may be related to prostaglandin synthetase inhibition.

PHARMACOKINETIC PROPERTIES
Ansaid® (flurbiprofen) is rapidly and non-stereoselectively absorbed, with peak plasma concentrations occurring at about 2 hours. Administration of Ansaid® (flurbiprofen) tablets with either food or antacids may alter the rate but not the extent of Ansaid® (flurbiprofen) absorption. Ranitidine has been shown to have no effect on either the rate or extent of flurbiprofen absorption.

Distribution: The apparent volume of distribution (Vz/F) of both R- and S-flurbiprofen is approximately 0.12 L/Kg. Both flurbiprofen enantiomers are more than 99% bound to plasma proteins, primarily albumin. Plasma protein binding is relatively constant for the typical average steady-state concentrations (≤10 µg/mL) achieved with recommended doses.

Metabolism: Several Ansaid® (flurbiprofen) metabolites have been identified in human plasma and urine. These metabolites include 4'-hydroxy-flurbiprofen, 3',4' dihydroxy-flurbiprofen, 3'-hydroxy-4'-methoxy-flurbiprofen, their conjugates, and conjugated flurbiprofen. Unlike other aryl propionic acid derivatives (eg, ibuprofen), metabolism of R-flurbiprofen to S-flurbiprofen is minimal. In vitro studies have demonstrated that cytochrome P450 2C9 plays an important role in the metabolism of flurbiprofen to its major metabolite, 4'-hydroxy-flurbiprofen. The 4'-hydroxy-flurbiprofen metabolite showed little anti-inflammatory activity in animal models of inflammation. Ansaid® (flurbiprofen) does not induce enzymes that alter its metabolism.

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

Flurbiprofen metabolism is predominantly mediated via cytochrome P450 CYP 2C9 in the liver. Patients who are known or suspected to be poor CYP2C9 metabolizers based on previous history/experience with other CYP2C9 substrates should be administered flurbiprofen with caution as they may have abnormally high plasma levels due to reduced metabolic clearance.

Excretion: Following dosing with flurbiprofen tablets, less than 3% of Ansaid® (flurbiprofen) is excreted unchanged in the urine, with about 70% of the dose eliminated in the urine as parent drug and metabolites. Because renal elimination is a significant pathway of elimination of Ansaid® (flurbiprofen) metabolites, dosing adjustment in patients with moderate or severe renal dysfunction may be necessary to avoid accumulation of flurbiprofen metabolites. The mean terminal disposition half-lives (t 1/2) of R- and S-flurbiprofen are similar, about 4.7 and 5.7 hours, respectively. There is little accumulation of flurbiprofen following multiple doses.

PRECLINICAL SAFETY DATA
Carcinogenicity, reproductive and teratology studies were conducted. Ansaid® (flurbiprofen) was not found to be carcinogenic, teratogenic or to have adverse reproductive effects in these studies.

PHARMACEUTICAL PARTICULARS

LIST OF EXCIPIENTS
Microcrystalline Cellulose, Latose Hydrous, Colloidal Silicone Dioxide, Croscarmellose Sodium Magnesium Stearate, Opadry Blue & Carnauba wax.

INCOMPATIBILITIES
Not applicable

SHELF LIFE
36 months.

NATURE AND CONTENTS OF CONTAINER
Ansaid® is available in blister pack of 30's.

INSTRUCTIONS FOR USE AND HANDLING AND DISPOSAL
No special requirement.

DOSAGE
Use as directed by the physician.

INSTRUCTIONS
Avoid exposure to heat & sunlight.
Store below 30°C.
Keep out of the reach of children.

CAUTION
To be sold on the prescription of a registered medical practitioner only.

خوراک:
ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

ہدایات:
دوا کو گرمی اور سورج کی روشنی سے بچائیں۔
دوا کو ۳۰ ڈگری سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔
بچوں کی پہنچ سے دور رکھیں۔

تاکید:
صرف رجسٹرڈ میڈیکل پریکٹشنر کے نسخہ پر فروخت کریں۔

Pfizer

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B-2, S.I.T.E., Karachi, Pakistan.

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