PRODUCT MONOGRAPH

ANSAID*

Flurbiprofen tablets USP
50 mg and 100 mg Tablets

Nonsteroidal anti-inflammatory drug (NSAID)

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flurbiprofen tablets USP

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Tablet / 50 mg, 100 mg	Lactose *For a complete listing see DOSAGE FORMS, COMPOSITION AND PACKAGING section.*

INDICATIONS AND CLINICAL USE

Ansaid (flurbiprofen) is indicated for the following:

- Relief of signs and symptoms of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis.
- Relief of pain associated with dysmenorrhoea.
- Relief of mild to moderate pain accompanied by inflammation. (e.g. bursitis, tendinitis, soft tissue trauma).

For patients with an increased risk of developing CV and/or GI adverse events, other management strategies that do NOT include the use of NSAIDs should be considered first (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS).
Use of Ansaid should be limited to the lowest effective dose for the shortest possible duration of treatment in order to minimize the potential risk for cardiovascular or gastrointestinal adverse events (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS).

Ansaid, as a NSAID, does NOT treat clinical disease or prevent its progression.

Ansaid, as a NSAID, only relieves symptoms and decreases inflammation for as long as the patient continues to take it.

Patient Subsets
Geriatrics (>65 years of age):
Evidence from clinical studies and postmarket experience suggests that use in the geriatric population is associated with differences in safety (see **WARNINGS AND PRECAUTIONS, Special Populations**).

Pediatrics (<18 years of age):
Safety and efficacy have not been established in the pediatric population (see **CONTRAINDICATIONS**).

CONTRAINDICATIONS

Ansaid (flurbiprofen) is contraindicated in:

- The peri-operative setting of coronary artery bypass graft surgery (CABG). Although Ansaid has NOT been studied in this patient population, a selective COX-2 inhibitor NSAID studied in such a setting has led to an increased incidence of cardiovascular/thromboembolic events, deep surgical infections and sternal wound complications.
- The third trimester of pregnancy, because of risk of premature closure of the ductus arteriosus and prolonged parturition
- Women who are breastfeeding, because of the potential for serious adverse reactions in nursing infants
- Severe uncontrolled heart failure
- Known or suspected hypersensitivity to flurbiprofen or to any of the components/excipients, or other nonsteroidal anti-inflammatory drugs (NSAIDs).
- History of asthma, urticaria, or allergic-type reactions after taking ASA or other NSAIDs (i.e. complete or partial syndrome of ASA-intolerance - rhinosinusitis, urticaria/ angioedema, nasal polyps, asthma). Fatal asthmatic and anaphylactoid reactions have occurred in such individuals. As well, individuals with the above medical problems are at risk of a severe reaction even if they have taken NSAIDs in the past without any adverse effects. The potential for cross-reactivity between different NSAIDs must be kept in mind (see **WARNINGS AND PRECAUTIONS - *Hypersensitivity Reactions - Anaphylactoid Reactions***).
- Active gastric / duodenal / peptic ulcer, active GI bleeding, a history of recurrent ulceration or active inflammatory disease of the gastrointestinal system.
- Cerebrovascular bleeding or other bleeding disorders
- Inflammatory bowel disease
- Severe liver impairment or active liver disease
- Severe renal impairment (creatinine clearance <30 mL/min or 0.5 mL/sec) or deteriorating renal disease (individuals with lesser degrees of renal impairment are at risk of deterioration of their renal function when prescribed NSAIDs and must be monitored) (see **WARNINGS AND PRECAUTIONS - *Renal***)
- Known hyperkalemia (see **WARNINGS AND PRECAUTIONS - Renal - Fluid and Electrolyte Balance**)
- Children and adolescents less than 18 years of age.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Risk of Cardiovascular (CV) Adverse Events: Ischemic Heart Disease, Cerebrovascular Disease, Congestive Heart Failure (NYHA II-IV) (see **WARNINGS AND PRECAUTIONS - *Cardiovascular***).

Ansaid is a non-steroidal anti-inflammatory drug (NSAID). Use of some NSAIDs is associated with an increased incidence of cardiovascular adverse events (such as myocardial infarction, stroke or thrombotic events) which can be fatal. The risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk.

Caution should be exercised in prescribing Ansaid to any patient with ischemic heart disease (including but NOT limited to acute myocardial infarction, history of myocardial infarction and/or angina), cerebrovascular disease (including but NOT limited to stroke, cerebrovascular accident, transient ischemic attacks and/or amaurosis fugax) and/or congestive heart failure (NYHA II-IV).

Use of NSAIDs, such as Ansaid, can promote sodium retention in a dose-dependent manner, through a renal mechanism, which can result in increased blood pressure and/or exacerbation of congestive heart failure (see also WARNINGS AND PRECAUTIONS - *Renal - Fluid and Electrolyte Balance*).

Randomized clinical trials with Ansaid have not been designed to detect differences in cardiovascular events in a chronic setting. Therefore, caution should be exercised when prescribing Ansaid.

Risk of Gastrointestinal (GI) Adverse Events (see WARNINGS AND PRECAUTIONS - *Gastrointestinal*).

Use of NSAIDs, such as Ansaid, is associated with an increased incidence of gastrointestinal adverse events (such as peptic/duodenal ulceration, perforation, obstruction and gastrointestinal bleeding).

General:
Frail or debilitated patients may tolerate side effects less well and therefore special care should be taken in treating this population. **To minimize the potential risk for an adverse event, the lowest effective dose should be used for the shortest possible duration**. As with other NSAIDs, caution should be used in the treatment of elderly patients who are more likely to be suffering from impaired renal, hepatic or cardiac function. For high risk patients, alternate therapies that do not involve NSAIDs should be considered.

Ansaid is NOT recommended for use with other NSAIDs, with the exception of low-dose ASA for cardiovascular prophylaxis, because of the absence of any evidence demonstrating synergistic benefits and the potential for additive adverse reactions (see **DRUG INTERACTIONS - *Drug/DRUG INTERACTIONS - Acetylsalicylic acid (ASA) or other NSAIDs***). In common with other anti-inflammatory drugs, Ansaid may mask the usual signs of infection.

Carcinogenesis and Mutagenesis:
(See TOXICOLOGY**)**

Cardiovascular:
Ansaid is a non-steroidal anti-inflammatory drug (NSAID). Use of some NSAIDs is associated with an increased incidence of cardiovascular adverse events (such as myocardial infarction, stroke or thrombotic events) which can be fatal. The risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk.
Caution should be exercised in prescribing Ansaid to patients with risk factors for cardiovascular disease, cerebrovascular disease or renal disease, such as any of the following (NOT an exhaustive list):

- **Hypertension**
- **Dyslipidemia / Hyperlipidemia**
- **Diabetes Mellitus**
- **Congestive Heart Failure (NYHA I)**
- **Coronary Artery Disease (Atherosclerosis)**
- **Peripheral Arterial Disease**
- **Smoking**
- **Creatinine Clearance < 60 mL/min or 1 mL/sec**

For patients with a high risk of developing an adverse CV event, other management strategies that do NOT include the use of NSAIDs should be considered first. **To minimize the potential risk for an adverse CV event, the lowest effective dose should be used for the shortest possible duration**.

Cardiovascular Thrombotic Events
Physicians and patients should remain alert for the development of such events, even in the absence of previous CV symptoms. Patients should be informed about the signs and/or symptoms of serious CV events and the steps to take if they occur.

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

Hypertension

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

Congestive Heart Failure and Edema

Fluid retention and edema have been observed in patients treated with Ansaid. Therefore, as with many other NSAIDs, the possibility of precipitating congestive heart failure in elderly patients or those with compromised cardiac function should be borne in mind. Ansaid should be used with caution in patients with heart failure, hypertension or other conditions predisposing to fluid retention (see **WARNINGS AND PRECAUTIONS - *Renal - Fluid and Electrolyte Balance***).

Endocrine and Metabolism:

With nonsteroidal anti-inflammatory treatment there is a potential risk of hyperkalemia, particularly in patients with conditions such as diabetes mellitus or renal failure; elderly patients; or in patients receiving concomitant therapy with beta-adrenergic blockers, angiotensin converting enzyme inhibitors or some diuretics. Serum electrolytes should be monitored periodically during long-term therapy, especially in those patients who are at risk.

Corticosteroids:

Ansaid (flurbiprofen) is NOT a substitute for corticosteroids. It does NOT treat corticosteroid insufficiency. Abrupt discontinuation of corticosteroids may lead to exacerbation of corticosteroid-responsive illness. Patients on prolonged corticosteroid therapy should have their therapy tapered slowly if a decision is made to discontinue corticosteroids (see **DRUG INTERACTIONS - Drug-DRUG INTERACTIONS - *Glucocorticoids***).

Gastrointestinal (GI):

Serious GI toxicity (sometimes fatal), such as peptic / duodenal ulceration, inflammation, perforation, obstruction and gastrointestinal bleeding, can occur at any time, with or without warning symptoms, in patients treated with NSAIDs, such as Ansaid. Minor upper GI problems, such as dyspepsia, commonly occur at any time. Health care providers should remain alert for ulceration and bleeding in patients treated with Ansaid, even in the absence of previous GI tract symptoms. Most spontaneous reports of fatal GI events are in elderly or debilitated patients and therefore special care should be taken in treating this population. **To minimize the potential risk for an adverse GI event, the lowest effective dose should be used for the shortest possible duration**. For high risk patients, alternate therapies that do not involve NSAIDs should be considered (see **WARNINGS AND PRECAUTIONS - *Special Populations - Geriatrics***). Patients should be informed about the signs and/or symptoms of serious GI toxicity and instructed to discontinue using Ansaid and seek emergency medical attention if they experience any such symptoms. The utility of periodic laboratory monitoring has NOT been demonstrated, nor has it been adequately assessed. Most patients who develop a serious upper GI adverse event on NSAID therapy have no symptoms. Upper GI ulcers, gross bleeding or perforation, caused by

NSAIDs, appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year. These trends continue, thus increasing the likelihood of developing a serious GI event at some time during the course of therapy. Even short-term therapy has its risks.
The incidence of these complications increases with increasing dose.
Caution should be taken if prescribing Ansaid to patients with a prior history of peptic / duodenal ulcer disease or gastrointestinal bleeding as these individuals have a greater than 10-fold higher risk for developing a GI bleed when taking a NSAID than patients with neither of these risk factors. In these cases the physician must weigh the benefits of treatment against the possible hazards. Other risk factors for GI ulceration and bleeding include the following: *Helicobacter* pylori infection, increased age, prolonged use of NSAID therapy, excess alcohol intake, smoking, female gender, poor general health status or concomitant therapy with any of the following:

- Anti-coagulants (e.g. warfarin)
- Anti-platelet agents (e.g. ASA, clopidogrel)
- Oral corticosteroids (e.g. prednisone)
- Selective Serotonin Reuptake Inhibitors (SSRIs) (e.g. citalopram, fluoxetine, paroxetine, sertraline)

Ansaid 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 such as ulcerative colitis and Crohn's disease. In these cases the physician must weigh the benefits of treatment against the possible hazards.

If ulceration is suspected or confirmed, or if GI bleeding occurs, Ansaid should be discontinued immediately, appropriate treatment instituted and the patient monitored closely.
No studies to date have identified any group of patients not at risk of developing ulceration and bleeding. Studies to date show that all NSAIDs can cause GI tract adverse events as existing data do not clearly identify differences in risk between various NSAIDs.

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 the continuation of Ansaid therapy when and if these adverse reactions appear.

Genitourinary:
Some NSAIDs are associated with persistent urinary symptoms (bladder pain, dysuria, urinary frequency), hematuria or cystitis. The onset of these symptoms may occur at any time after the initiation of therapy with an NSAID. Some cases have become severe on continued treatment. Should urinary symptoms occur, in the absence of an alternate explanation, treatment with Ansaid should be stopped to ascertain if symptoms disappear. This should be done before any urological investigations or treatments are carried out.
Hematologic:
NSAIDs inhibiting prostaglandin biosynthesis interfere with platelet function to varying degrees; patients who may be adversely affected by such an action, such as those on anti-coagulants or suffering from haemophilia or platelet disorders, should be carefully observed when Ansaid is administered.

Anti-coagulants:
Numerous studies have shown that the concomitant use of NSAIDs and anti-coagulants increases the risk of bleeding. Concurrent therapy of Ansaid with warfarin requires close monitoring of the international normalized ratio (INR).
Even with therapeutic INR monitoring, increased bleeding may occur.

Anti-platelet Effects:
NSAIDs inhibit platelet aggregation and have been shown to prolong bleeding time in some patients. Unlike acetylsalicylic acid (ASA), their effect on platelet function is quantitatively less, or of shorter duration, and is reversible.
Ansaid and other NSAIDs have no proven efficacy as anti-platelet agents and should NOT be used as a substitute for ASA or other anti-platelet agents for prophylaxis of cardiovascular thromboembolic diseases. Anti-platelet therapies (e.g. ASA) should NOT be discontinued.
There is some evidence that use of NSAIDs with ASA can markedly attenuate the cardioprotective effects of ASA (see **DRUG INTERACTIONS - *Drug-DRUG INTERACTIONS - Acetylsalicylic Acid (ASA) or other NSAIDs***).
Concomitant administration of Ansaid with low dose ASA increases the risk of GI ulceration and associated complications.

Blood Dyscrasias:
Blood dyscrasias (such as neutropenia, leukopenia, thrombocytopenia, aplastic anemia and agranulocytosis) associated with the use of NSAIDs are rare, but could occur with severe consequences.

Anemia is sometimes seen in patients receiving NSAIDs, including Ansaid. This may be due to fluid retention, GI blood loss, or an incompletely described effect upon erythropoiesis. Patients on long-term treatment with NSAIDs, including Ansaid, should have their hemoglobin or hematocrit checked if they exhibit any signs or symptoms of anemia or blood loss.

Hepatic / Biliary / Pancreatic:
As with other NSAIDs, borderline elevations of one or more liver enzyme tests (AST, ALT, alkaline phosphatase) 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 function test has occurred, should be evaluated for evidence of the development of a more severe hepatic reaction while on therapy with Ansaid. The ALT (SGPT) test is probably the most sensitive indicator of liver injury. Meaningful (3 times the upper limit of normal) elevations of ALT or AST (SGOT) have been reported in controlled clinical trials in less than 1% of patients.

Severe hepatic reactions including jaundice and cases of fatal hepatitis, liver necrosis and hepatic failure, some of them with fatal outcomes, have been reported with NSAIDs.
Although such reactions are rare, if abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop (e.g. jaundice), or if systemic manifestations occur (e.g. eosinophilia, rash, etc.), this drug should be discontinued.

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

Hypersensitivity Reactions:

Anaphylactoid Reactions:

As with NSAIDs in general, anaphylactoid reactions have occurred in patients without known prior exposure to Ansaid. In post-marketing experience, rare cases of anaphylactic/ anaphylactoid reactions and angioedema have been reported in patients receiving Ansaid. Ansaid should NOT be given to patients with the ASA-triad. This symptom complex typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking ASA or other NSAIDs (see **CONTRAINDICATIONS**).

ASA-Intolerance:

Ansaid should NOT be given to patients with complete or partial syndrome of ASA-intolerance (rhinosinusitis, urticaria/angioedema, nasal polyps, asthma) in whom asthma, anaphylaxis, urticaria/angioedema, rhinitis or other allergic manifestations are precipitated by ASA or other NSAIDs. Fatal anaphylactoid reactions have occurred in such individuals. As well, individuals with the above medical problems are at risk of a severe reaction even if they have taken NSAIDs in the past without any adverse reaction (see **CONTRAINDICATIONS**).

Cross-sensitivity:

Patients sensitive to one NSAID may be sensitive to any of the other NSAIDs as well.

Serious Skin Reactions:

(See **WARNINGS AND PRECAUTIONS - *Skin***)

Immune:

(see **WARNINGS AND PRECAUTIONS - *Infection- Aseptic Meningitis***).

Infection:

Ansaid, in common with other NSAIDs, may mask signs and symptoms of an underlying infectious disease.

Aseptic Meningitis:

Rarely, with some NSAIDs, the symptoms of aseptic meningitis (stiff neck, severe headaches, nausea and vomiting, fever or clouding of consciousness) have been observed. Patients with autoimmune disorders (systemic lupus erythematosus, mixed connective tissue diseases, etc.) seem to be pre-disposed. Therefore, in such patients, the health care provider must be vigilant to the development of this complication.

Neurologic:

Some patients may experience drowsiness, dizziness, blurred vision, vertigo, tinnitus, hearing loss, insomnia or depression with the use of NSAIDs, such as Ansaid. In clinical trials, 1-3% of patients experienced drowsiness, dizziness, vertigo, insomnia or depression with the use of

Ansaid. If patients experience these side effects, they should exercise caution in carrying out activities that require alertness

Ophthalmologic:
Blurred and/or diminished vision has been reported with the use of NSAIDs, including Ansaid. If such symptoms develop, Ansaid should be discontinued and an ophthalmologic examination performed. Ophthalmologic examination should be carried out at periodic intervals in any patient receiving Ansaid for an extended period of time.

Peri-Operative Considerations:
(See **CONTRAINDICATIONS** - Coronary Artery Bypass Graft Surgery)

Psychiatric:
Some patients may experience depression with the use of Ansaid (see **WARNINGS AND PRECAUTIONS - *Neurologic***).

Renal:
Long-term administration of NSAIDs 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, low-grade proteinuria, and occasionally nephrotic syndrome.

Renal insufficiency due to NSAID use is seen in patients with pre-renal conditions leading to reduction in renal blood flow or blood volume. Under these circumstances, renal prostaglandins have a supportive role in the maintenance of renal perfusion and glomerular filtration rate (GFR). In these patients, administration of a NSAID may cause a dose-dependent reduction in prostaglandin synthesis leading to impaired renal function. Patients at greatest risk of this reaction are those with pre-existing insufficiency (GFR < 60 mL/min or 1 mL/s), dehydrated patients, patients on salt restricted diets, those with congestive heart failure, cirrhosis, liver dysfunction, taking angiotensin-converting enzyme inhibitors, angiotensin-II receptor blockers, cyclosporin, diuretics, and the elderly. Serious or life-threatening renal failure has been reported in patients with normal or impaired renal function after short term therapy with NSAIDs. Even patients at risk who demonstrate the ability to tolerate a NSAID under stable conditions may decompensate during periods of added stress (e.g. dehydration due to gastroenteritis). Discontinuation of NSAIDs is usually followed by recovery to the pre-treatment state.

Caution should be used when initiating treatment with NSAIDs, such as Ansaid, in patients with considerable dehydration. It is advisable to rehydrate patients first prior to initiation of therapy. Caution is also recommended in patients with pre-existing kidney disease. Ansaid 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, utilization of lower doses of Ansaid should be considered and patients carefully monitored.

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

Advanced Renal Disease: (see **CONTRAINDICATIONS**).

Fluid and Electrolyte Balance:
Use of NSAIDs, such as Ansaid, can promote sodium retention in a dose-dependent manner, which can lead to fluid retention and edema, and consequences of increased blood pressure and exacerbation of congestive heart failure. Thus, caution should be exercised in prescribing Ansaid in patients with a history of congestive heart failure, compromised cardiac function, hypertension, increased age or other conditions predisposing to fluid retention (see **WARNINGS AND PRECAUTIONS - *Cardiovascular***).

Use of NSAIDs, such as Ansaid, can increase the risk of hyperkalemia, especially in patients with diabetes mellitus, renal failure, increased age, or those receiving concomitant therapy with adrenergic blockers, angiotensin-converting enzyme inhibitors, angiotensin-II receptor antagonists, cyclosporin, or some diuretics.
Electrolytes should be monitored periodically (see **CONTRAINDICATIONS**).

Respiratory:
ASA-induced asthma is an uncommon but very important indication of ASA and NSAID sensitivity. It occurs more frequently in patients with asthma who have nasal polyps.

Sexual Function / Reproduction:
The use of Ansaid, as with any drug known to inhibit cyclooxygenase/prostaglandin synthesis, may impair fertility and is not recommended in women attempting to conceive. Therefore, in women who have difficulties conceiving, or who are undergoing investigation of infertility, withdrawal of Ansaid should be considered.

Skin:
In rare cases, serious skin reactions such as Stevens-Johnson syndrome, toxic epidermal necrolysis, exfoliative dermatitis and erythema multiforme have been associated with the use of some NSAIDs. Because the rate of these reactions is low, they have usually been noted during post-marketing surveillance in patients taking other medications also associated with the potential development of these serious skin reactions. Thus, causality is NOT clear. These reactions are potentially life threatening but may be reversible if the causative agent is discontinued and appropriate treatment instituted. Patients should be advised that if they experience a skin rash they should discontinue their NSAID and contact their physician for assessment and advice, including which additional therapies to discontinue.

Special Populations:
Pregnant Women:
Ansaid is CONTRAINDICATED for use during the third trimester of pregnancy because of risk of premature closure of the ductus arteriosus and the potential to prolong parturition (see TOXICOLOGY).

Caution should be exercised in prescribing Ansaid during the first and second trimesters of pregnancy (see TOXICOLOGY).

Inhibition of prostaglandin synthesis may adversely affect pregnancy and/or the embryo-foetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation after use of a prostaglandin synthesis inhibitor in early pregnancy.

In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation loss and embryo-foetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period. 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.

Nursing Women:
The safe use of flurbiprofen during lactation has not been established. Flurbiprofen is secreted in breast milk. The use of this drug is not recommended during lactation (see **CONTRAINDICATIONS**).

Pediatrics (<18 years of age):
(see **CONTRAINDICATIONS**)

Geriatrics (>65 years of age):
As with all NSAID's, Ansaid (flurbiprofen) should be used with caution in the elderly, particularly women. (see **ACTION AND CLINICAL PHARMACOLOGY – Pharmacokinetics**).

Patients older than 65 years (referred to in this document as older or elderly) and frail or debilitated patients are more susceptible to a variety of adverse reactions from NSAIDs. The incidence of these adverse reactions increases with dose and duration of treatment. In addition, these patients are less tolerant to ulceration and bleeding. Most reports of fatal GI events are in this population. Older patients are also at risk of lower esophageal ulceration and bleeding. For such patients, consideration should be given to a starting dose lower than the one usually recommended, with individual adjustment when necessary, and under close supervision. See information in this section under Endocrine and Metabolism, and Renal for further advice. See also information under **DRUG INTERACTIONS section under Glucocorticoids.**.

Monitoring and Laboratory Tests:
Cardiovascular***:*** (Hypertension): Blood pressure should be monitored regularly during therapy with Ansaid. (see **WARNINGS AND PRECAUTIONS – *Cardiovascular* –** Hypertension**)**

Renal: Renal function (serum creatinine, and serum urea, etc.) should be monitored in high-risk populations, such as the elderly, patients with advanced renal disease, patients with cardiovascular disease and diabetes mellitus, as well as in the setting of concomitant use of diuretics, ACE inhibitors, and methotrexate (see **CONTRAINDICATIONS; DRUG INTERACTIONS – Antihypertensives and methotrexate, WARNINGS AND PRECAUTIONS – Fluid and Electrolytes Balance**). If abnormal renal tests persist or worsen,

Ansaid should be discontinued.

Patients on long-term treatment with NSAIDs, including Ansaid, should have their electrolytes such as serum potassium checked regularly if they exhibit any signs or symptoms of renal disease (see **WARNINGS AND PRECAUTIONS – Fluid and Electrolytes Balance**).

Hepatic:
Patient with symptoms and/or signs of liver dysfunction, or in whom an abnormal liver function test has occurred, should be monitored carefully for evidence of the development of a more severe hepatic reaction while on therapy with Ansaid. If abnormal liver tests persist or worsen, Ansaid should be discontinued (see **WARNINGS AND PRECAUTIONS - Hepatic / Biliary / Pancreatic*)***.

Hematologic:
Anemia is commonly observed in rheumatoid arthritis and is sometimes aggravated by NSAIDs, which may produce fluid retention or minor gastrointestinal blood loss in some patients. Therefore, patients who have initial hemoglobin values of 10 g/dL or less, and who are to receive long-term therapy, should have hemoglobin values determined periodically. (see **WARNINGS AND PRECAUTIONS – *Hematologic* - Blood Dyscrasias).**

Concurrent therapy of Ansaid with warfarin requires close monitoring of the international normalized ratio (INR), (see **WARNINGS AND PRECAUTIONS – Anticoagulants**).

Plasma Lithium: When lithium and flurbiprofen are concurrently administered, a reduction in lithium dose is recommended and plasma concentrations of lithium should be monitored. Plasma concentrations of lithium should also be monitored when stopping or starting an NSAID (see **DRUG INTERACTIONS – Lithium**).

Vision Changes: Blurred and/or diminished vision has been reported with the use of Ansaid and other NSAIDs. Patients experiencing eye complaints should have ophthalmologic examinations (see **WARNINGS AND PRECAUTIONS – *Ophthalmologic)***.

ADVERSE REACTIONS

Adverse Drug Reaction Overview
The most common adverse reactions encountered with NSAIDs are gastrointestinal, of which peptic ulcer, with or without bleeding, is the most severe. Fatalities have occurred, particularly in the elderly.

Clinical Trial Adverse Drug Reactions
Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

In company-sponsored clinical trials of Ansaid (flurbiprofen) in which a total of 2820 patients were treated, gastrointestinal adverse reactions were those most commonly seen, the most severe of which were gastrointestinal bleeding and ulceration.

Events Occurring in ≥ 1% with Ansaid Patients from Clinical Trials	
Central Nervous System	
Headache	2.6%
asthenia	1.0%
Gastrointestinal	
abdominal pain	6.8%
dyspepsia	6.0%
diarrhea	5.7%
nausea	4.5%
constipation	2.6%
gastrointestinal bleeding	1.7%
flatulence	1.4%
emesis	1.2%
elevated liver enzymes	1.4%
Dermatologic	
rash	1.9%
General Body	
Edema	2.6%
Pain	1.9%
Flu syndrome	2.0%
Hematologic	
decrease in hemoglobin and hematocrit	4.6%
Respiratory	
pharyngitis	6.1%
infection	1.2%
rhinitis	1.3%
sinusitis	1.6%
Special Senses	
dizziness	1.5%
tinnitus	1.2%
Urogenital	
urinary tract infections	1.5%

Less Common Clinical Trial Adverse Drug Reactions (<1%)

Cardiovascular:	Incidence 0.1 to 1.0%: hypertension, arrhythmias, inotropic problems, palpitations, vasodilatation, angina, phlebitis, vascular distress, extrasystoles, right heart failure, myocardial infarction, vasculitis
	Incidence less than 0.1%: tachycardia, syncope
Central Nervous System:	Incidence 0.1% to 1.0%: somnolence, hypertonia, insomnia, nervousness, paresthesia, depression, mood changes, tremors, anxiety, amnesia, migraine, ataxia, cerebrovascular accident, confusion, cerebral ischemia, malaise, increased reflex
	Incidence less than 0.1%: EEG abnormalities, neuralgia, convulsions, meningitis, speech disorder, twitch, euphoria, decreased libido
Dermatologic:	Incidence 0.1 to 1.0%: herpetic infections, alopecia, dry skin, eczema, nail discoloration, pruritus, sweating, skin ulcerations, urticaria
	Incidence less than 0.1%: seborrhea, angioedema, exfoliation
Gastrointestinal:	Incidence 0.1 to 1.0%: increased appetite, stomatitis, gastrointestinal distress, gastritis, gastroenteritis, ulcer (peptic, gastric or duodenal), melena (includes rectal bleed, bloody diarrhea), oral inflammation, eructation, dry mouth, esophagitis, hematemesis, colitis, hepatitis, rectal discomfort, periodontal abscess, gingivitis, glossitis, anorexia, vomiting
	Incidence less than 0.1%: gums bleeding, cholecystitis
General Body:	Incidence 0.1% to 1.0%: fever, abdominal enlargement, chills, infection, allergic reaction, death
	Incidence less than 0.1%: injury
Hematologic:	Incidence 0.1% to 1.0%: iron deficiency anemia, ecchymosis, eosinophilia, leukopenia, lymphadenopathy, neutropenia
	Incidence less than 0.1%: anemia, leukocytosis, petechia, thrombocytopenia, WBC abnormality.
Metabolic:	Incidence 0.1 to 1.0%: weight changes, hyperuricemia
	Incidence less than 0.1%: electrolyte changes (Ca++, K+), increased CPK, thirst
Musculoskeletal:	Incidence 0.1 to 1.0%: arthritis, injury, myalgia
	Incidence less than 0.1%: myasthenia, tenosynovitis, joint disease

Respiratory:	Incidence 0.1 to 1.0%: bronchitis, epistaxis, increase in cough, dyspnea, laryngitis, lung disorder, asthma, voice alterations Incidence less than 0.1%: hyperventilation, pleural distress, pulmonary infarct, pulmonary embolism, pneumonia
Special Senses:	Ear: vertigo 0.6%; pain 0.3%; disorder 0.2% Incidence less than 0.1%: vestibular disturbances Eye: ocular inflammations 0.3%; amblyopia 0.6%; vision disturbances 0.4%; blepharitis 0.1%; conjunctivitis 0.5%; keratoconjunctivitis 0.1%; photophobia 0.1% Incidence less than 0.1%: diplopia, visual field problems, corneal opacity, lacrimal distress, glaucoma, pain, scleritis Others: taste changes 0.2%; parosmia <0.1%
Urogenital:	Incidence 0.1 to 1.0%: urine abnormalities, hematuria, cystitis, frequency, vaginitis, breast pain, kidney function abnormalities Incidence less than 0.1%: dysuria, albuminuria, pyuria, pain, kidney stones, kidney failure, incontinence, ejaculatory abnormality, leukorrhea, urethritis, retention, dysmenorrhea, menstrual distress, impotence

Post-Market Adverse Drug Reactions

Additional reports of serious adverse events temporally associated with Ansaid during worldwide post-marketing experience are included below. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or clearly establish a causal relationship to Ansaid exposure. These include the following: Aseptic meningitis, cholestatic and non-cholestatic jaundice, exacerbation of inflammatory bowel disease, small intestine inflammation with loss of blood and protein, photosensitivity, toxic epidermal necrolysis, interstitial nephritis anaphylaxis, Stevens-Johnson syndrome.

Abnormal Hematologic and Clinical Chemistry Findings

Decrease in hemoglobin and hematocrit was observed in clinical trials at an incidence of 4.6 %. Iron deficiency anemia, ecchymosis, eosinophilia, leukopenia, lymphadenopathy, neutropenia were reported in clinical trials at an incidence of 0.1% to 1.0% (see **ADVERSE REACTIONS – Clinical Trials Adverse Drug Reactions**).

DRUG INTERACTIONS

Overview

Factors such as excess alcohol intake, smoking, age, female gender and concomitant NSAID and oral steroid or anticoagulant use have been associated with increased risk of GI adverse events such as ulceration and bleeding.

Ansaid 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 Ansaid 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.

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.

Drug-Drug Interactions:

Acetylsalicylic Acid (ASA) or other NSAIDs:

The use of Ansaid in addition to any other NSAID, including over-the-counter ones (such as ASA and ibuprofen) for analgesic and/or anti-inflammatory effects is NOT recommended because of the absence of any evidence demonstrating synergistic benefits and the potential for additive adverse reactions.

The exception is the use of low dose ASA for cardiovascular protection, when another NSAID is being used for its analgesic/anti-inflammatory effect, keeping in mind that combination NSAID therapy is associated with additive adverse reactions.
The concurrent administration of Ansaid and ASA may result in significantly lowering flurbiprofen concentrations.
Some NSAIDs (e.g. ibuprofen) may interfere with the anti-platelet effects of low dose ASA, possibly by competing with ASA for access to the active site of cyclooxygenase-1.

Antacids:

In geriatric subjects, antacid suspensions caused a reduction in the rate but not the extent of flurbiprofen absorption.

Anticoagulants:

Numerous studies have shown that the concomitant use of NSAIDs and anticoagulants increases the risk of GI adverse events such as ulceration and bleeding (see **WARNINGS AND PRECAUTIONS - *Hematologic - Anti-coagulants***).

Because prostaglandins play an important role in hemostasis, and NSAIDs affect platelet function, concurrent therapy of Ansaid with warfarin requires close monitoring to be certain that no change in anticoagulant dosage is necessary.

Anti-hypertensives:

NSAIDs may diminish the anti-hypertensive effect of Angiotensin Converting Enzyme (ACE) inhibitors.

Combinations of ACE inhibitors, angiotensin-II antagonists, or diuretics with NSAIDs might have an increased risk for acute renal failure and hyperkalemia. Blood pressure and renal

function (including electrolytes) should be monitored more closely in this situation, as occasionally there can be a substantial increase in blood pressure.

Anti-platelet Agents (including ASA):
There is an increased risk of bleeding, via inhibition of platelet function, when anti-platelet agents are combined with NSAIDs, such as Ansaid (see **WARNINGS AND PRECAUTIONS - *Hematologic - Anti-platelet Effects***).

ß-adrenergic Blocking Agents:
Ansaid pretreatment attenuated the hypotensive effect of propranolol but did not appear to affect the ß-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.

Cyclosporin and Tacrolimus:
Although this interaction has not been studied with flurbiprofen, co-administration of cyclosporin or tacrolimus and any NSAID may increase the nephrotoxic effect of cyclosporin or tacrolimus due to the NSAID's effect on renal prostaglandins. Renal function should be monitored when flurbiprofen and either of these drugs are used in combination.

CYP2C9 Substrates:
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.
Digoxin:
Concurrent administration with flurbiprofen did not reveal a change in steady state serum levels of either drug.

Diuretics:
Clinical studies as well as post-marketing observations have shown that NSAIDs can reduce the effect of diuretics.
Ansaid can interfere with the effects of furosemide. NSAIDs have been shown to interfere with the action of thiazide diuretics and potassium-sparing diuretics.
Glucocorticoids:
Numerous studies have shown that the concomitant use of NSAIDs and oral glucocorticoids increases the risk of GI side effects such as ulceration and bleeding. This is especially the case in older (>65 years of age) individuals.

Lithium:
Combined use of lithium and flurbiprofen resulted in significant elevation of lithium trough plasma concentration and area under the curve. When lithium and flurbiprofen are concurrently administered, a reduction in lithium dose is recommended. Plasma concentrations of lithium

should also be monitored when stopping or starting a NSAID.

Methotrexate:
Although a pharmacokinetic interaction has not been reported between low dose methotrexate and flurbiprofen, in rheumatoid arthritis patients with normal renal function, monitoring of toxic signs and symptoms and renal function is recommended. The dose of methotrexate should be reduced if toxicity or impairment of renal function is observed. The interaction of intermediate and high dose methotrexate and flurbiprofen has not been studied. Since significant toxicity has been reported with coadministration of intermediate or high dose methotrexate and other NSAIDs, the concomitant use of intermediate or high dose methotrexate and flurbiprofen should be avoided.

Oral Contraceptives:
No drug interaction data are available for Ansaid and the co-administration of oral contraceptives.

Oral Hypoglycemics*:*
Concomitant administration of flurbiprofen and hypoglycemic agents revealed a slight reduction in blood sugar concentrations but no signs or symptoms of hypoglycemia.

Selective Serotonin Reuptake Inhibitors (SSRIs):
Concomitant administration of NSAIDs and SSRIs may increase the risk of gastrointestinal ulceration and bleeding (see **WARNINGS AND PRECAUTIONS** - ***Gastrointestinal***).

Drug-Food Interactions
Interactions with food have not been established.

Drug-Herb Interactions
Interactions with herbal products have not been established.

Drug-Laboratory Interactions
Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations
Consideration should be given to reducing the starting dose in elderly patients.

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.

Recommended Dose and Dosage Adjustment

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 (see **ADVERSE REACTIONS**).

Dysmenorrhoea:
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.

Missed Dose
The missed dose should be taken as soon as remembered. If the next dose is due within 2 hours, a single dose should be taken and the next dose skipped.

Administration
Ansaid (flurbiprophen) should be taken immediately after a meal, or with food or milk.

OVERDOSAGE

Information on Ansaid (flurbiprofen) overdosage is available for 13 children and 12 adults; all persons receiving only a flurbiprofen overdose and all but one person exposed to more than one drug recovered. Manifestations of flurbiprofen overdose have included decreased mental status, coma, diminished muscle tone, headache, diplopia, elevated liver enzymes, respiratory depression, nausea, and epigastric pain.

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

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action
The mode of action of flurbiprofen, like that of other NSAID 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.

Pharmacodynamics

Ansaid (flurbiprofen), a phenylalkanoic acid derivative, is a NSAID which also possesses analgesic and antipyretic activities.

Pharmacokinetics

Table 1 Summary of Mean (SD) Flurbiprofen Pharmacokinetic Parameters

	Peak Conc. (µg/mL)	Time of Peak Conc. (h)	Area Under the Curve (AUC* (µg h/mL)	Apparent Volume of Distribution (Vz/F, L)	Terminal Disposition Half-life ($t_{1/2}$, h)
100 mg single-dose Normal Healthy Adults (18 to 40 years) N=15	14 (4)	1.9 (1.5)	83 (20)	14 (3)	7.5 (0.8)
Steady-state (100 mg every 12 hours) Geriatric Arthritis Patients (65 to 83 years) N=13	16 (5)	2.2 (3)	77 (24)	12 (5)	5.8 (1.9)

*AUC from 0 to infinity for single doses and from 0 to the end of the dosing interval for multiple-doses

Absorption:

In bioavailability studies in normal volunteers, Ansaid reached peak blood levels in approximately 2 hours (range of 0.5 to 4 hours). Administration of Ansaid with food does not alter total drug availability but delays absorption.

Distribution:

Ansaid is extensively bound (99%) to human plasma protein such as albumin, but less than 10% of the primary albumin binding sites would be occupied by the drug. Flurbiprofen binds to a different primary site on albumin than do anticoagulants, sulfonamides and phenytoin. Mean peak serum concentrations of flurbiprofen were higher in the elderly female patients.

Metabolism:

Flurbiprofen metabolism is predominantly mediated via cytochrome P450 CYP 2C9 in the liver. Ansaid is rapidly excreted in the urine as free and unaltered intact drug (20%) and hydroxylated metabolites (50%). About 90% of the flurbiprofen in urine is present as conjugates. In animal models of inflammation the metabolites showed little activity.

Excretion:

The elimination half life of flurbiprofen is approximately 7 hours with a range of 3 to 9 hours. Excretion of Ansaid is 88 - 98% complete within 24 hours after the last dose.

Special Populations and Conditions

Geriatrics:

With the exception of elderly females, flurbiprofen pharmacokinetics were similar in geriatric arthritis patients, younger arthritis patients, and young healthy volunteers receiving Ansaid Tablets 100 mg as either single or multiple doses. Mean peak serum concentrations of flurbiprofen were higher in the elderly female patients, therefore dosage adjustment may be necessary.

Poor CYP2C9 metabolizers:

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.

Hepatic Insufficiency:
Hepatic metabolism may account for >90% of flurbiprofen elimination, so patients with hepatic disease may require reduced doses of Ansaid Tablets compared to patients with normal hepatic function. The pharmacokinetics of R- and S-flurbiprofen were similar, however, in alcoholic cirrhosis patients (N=8) and young healthy volunteers (N=8) following administration of a single 200 mg dose of Ansaid tablets. Flurbiprofen plasma protein binding may be decreased in patients with liver disease and serum albumin concentrations below 3.1 g/dL (see **WARNINGS AND PRECAUTIONS**, Hepatic/Biliary/Pancreatic).

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

STORAGE AND STABILITY

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

DOSAGE FORMS, COMPOSITION AND PACKAGING

Ansaid (flurbiprofen) is available as 50 mg (white) and 100 mg (blue) elliptical, film-coated tablets imprinted with Ansaid logo, in bottles of 100.

Non-medicinal ingredients present in Ansaid (both strengths) include carnauba wax, colloidal silicon dioxide, croscarmellose sodium, hypromellose, lactose, magnesium stearate, microcrystalline cellulose, propylene glycol, and titanium dioxide; in addition, the 100 mg tablet contains FD&C Blue No. 2.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

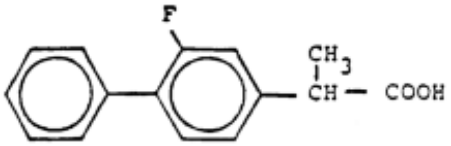
Proper name: Flurbiprofen

Chemical name: (±)-2-(2-fluoro-4-biphenylyl)propionic acid

Molecular formula: $C_{15}H_{13}FO_2$

Molecular weight: 244.26

Structural formula:



Physicochemical properties: A white or slightly yellow crystalline powder with a melting point of 110°C. It is slightly soluble in water at pH 7.0, and readily soluble in most polar solvents.

CLINICAL TRIALS

Randomized clinical trials with Ansaid have NOT been designed to detect differences in cardiovascular adverse events in a chronic setting.

Rheumatoid Arthritis

The safety and efficacy of flurbiprofen *(average daily dose: 50 mg four times daily)* in the treatment of rheumatoid arthritis in adults were demonstrated in eight multicenter, placebo and/or active (ASA – 3600 to 4000 mg daily; ibuprofen – 2400 to 3200 mg daily) controlled clinical studies. These 2 long-term studies (24-weeks and 52 weeks) involved a total of 884 patients of which 445 received flurbiprofen.

Osteoarthritis

The safety and efficacy of flurbiprofen (*average daily dose: 50 mg two or three times daily)* in the treatment of osteoarthritis were demonstrated in 5 short-term and 1 long-term multicenter, placebo or active controlled clinical studies and one long-term open-label study (26 weeks). Overall, data from 496 flurbiprofen-treated patients with osteoarthritis were included in the statistical analyses. The 5 short-term studies compared flurbiprofen with ASA (2000 mg to 4000

mg daily), ibuprofen 1600 mg or placebo. The long-term study (24-week) compared flurbiprofen (n= 22 patients) with ASA (n=23 patients).

Ankylosing Spondylitis
The safety and efficacy of flurbiprofen in the treatment of ankylosing spondylitis were demonstrated in five multicenter, active controlled clinical studies. This included two long-term studies (both 26-week) which compared flurbiprofen with phenylbutazone (200 mg to 500 mg daily) and indomethacin (25 mg tid to 150 mg daily), respectively. Data from 107 flurbiprofen-treated patients were included in the statistical analyses, including 73 patients from the long-term studies. The average daily dose of flurbiprofen during these studies was 50 mg taken three or four times daily.

Dysmenorrhoea
The safety and efficacy of flurbiprofen in treating dysmenorrhoea was demonstrated in three double-blind, crossover, placebo-controlled studies comparing flurbiprofen (50 mg) to ASA (650 mg) and placebo in 3 successive painful menstrual cycles. Data were evaluable from a total of 133 women who completed all three cycles. Endpoints assessed included patient ranking, mean degree of relief, and patients needing additional medication.

Mild to Moderately Severe Pain
The safety and efficacy of flurbiprofen in treating symptoms of acute bursitis/tendinitis were demonstrated in one open-label dose-finding study and one double-blind placebo and active controlled clinical study involving a total of 60 flurbiprofen-treated patients.

The safety and efficacy of flurbiprofen (50 mg or 25 mg) in the treatment of post-extraction dental pain were demonstrated in two single-dose, double blind placebo and active (ASA 650 mg) controlled clinical studies involving a total of 190 flurbiprofen-treated patients.

The safety and efficacy of flurbiprofen (50 mg and 25 mg) in the treatment of post-partum uterine and post-episiotomy pain were demonstrated in 2 single-dose, double-blind placebo and active (aspirin 650 mg, codeine 60 mg and codeine 120 mg) controlled studies involving a total of 289 patients of which 129 received flurbiprofen.

DETAILED PHARMACOLOGY

Ansaid (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 acetic acid-induced writhing in the rat, and compared to other NSAIDs. Fifty percent inhibition (ID_{50}) of writhing activity was observed with flurbiprofen 0.3 mg/kg.

TOXICOLOGY

Single-Dose Toxicity:

Species	Route	LD_{50} (mg/kg)
Mouse	oral	750
Mouse	intraperitoneal	120-332*
Rat	oral	109 (fasted) 600 (non-fasted)
Rat	intraperitoneal	332-400*
Rat	intravenous	150

*These ranges represent LD_{50} values from several studies

Signs of toxicity included the following:
Mice: Convulsions, depression and hypersensitivity to stimuli, ataxia, prostration, labored breathing.
Rat: Gasping respiration, tremor, atonic and distended stomach, intestinal ulceration.
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.

Repeat-Dose 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. Haemoglobin 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 at 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.

Carcinogenicity:
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.

Reproductive and Developmental Toxicity:
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 labor, 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 (2 to 12 mg/kg/day), rats (0.5 to 3.0 mg/kg/day) and rabbits (0.675 to 7.5 mg/kg/day) and flurbiprofen was not teratogenic in these studies.

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PART III: CONSUMER INFORMATION

ANSAID
(flurbiprofen)

Read this information each time you refill your prescription in case new information has been added.

This leaflet is part III of a three-part "Product Monograph" published when Ansaid was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will NOT tell you everything about Ansaid. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
Ansaid, which has been prescribed to you by your doctor, is used to treat the symptoms of 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,).

What it does:
Ansaid (flurbiprofen), as a nonsteroidal anti-inflammatory drug (NSAID), can reduce the chemicals produced by your body which cause pain and swelling. It helps to relieve joint pain, swelling, stiffness and fever by reducing the production of certain substances (prostaglandins) and by helping to control inflammation.

Ansaid, as a nonsteroidal anti-inflammatory drug (NSAID), does NOT cure your illness or prevent it from getting worse. Ansaid can only relieve pain and reduce swelling as long as you continue to take it.

When it should not be used:
DO NOT TAKE Ansaid if you have any of the following medical conditions:

- Heart bypass surgery (planning to have or recently had)
- Severe, uncontrolled heart failure
- Bleeding in the brain or other bleeding disorders
- Current pregnancy (after 28 weeks of pregnancy)
- Currently breastfeeding (or planning to breastfeed)
- , Allergy to other NSAIDs (Nonsteroidal Anti-Inflammatory Drugs) or to ASA (Acetylsalicylic Acid), or to any component of the formulation
- Active peptic ulcers or active intestinal disease
- Bleeding from the stomach or gut (active)
- Inflammatory bowel disease (Crohn's Disease or Ulcerative Colitis)
- Liver disease (active or severe)
- Kidney disease (severe or worsening)
- High potassium in the blood
- If you are already taking another NSAID

Patients who took a drug in the same class as Ansaid after a type of heart surgery (coronary artery bypass grafting (CABG)) were more likely to have heart attacks, strokes, blood clots in the leg(s) or lung(s), and infections or other complications than those who did NOT take that drug.

Ansaid should NOT be used in patients under 18 years of age since the safety and effectiveness have NOT been established.

What the medicinal ingredient is:
Flurbiprofen

What the important nonmedicinal ingredients are:
Non-medicinal ingredients present in Ansaid (both strengths) include carnauba wax, colloidal silicon dioxide, croscarmellose sodium, hypromellose, lactose, magnesium stearate, microcrystalline cellulose, propylene glycol, and titanium dioxide. In addition, the 100 mg tablet contains FD&C Blue No. 2.

What dosage forms it comes in:
Tablet 50 mg, 100 mg

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions
If you have, or previously had, any of the following medical conditions, see your health care provider to discuss treatment options other than Ansaid:

- **Heart Attack or Angina**
- **Stroke or Mini-stroke**
- **Loss of Vision**
- **Current Pregnancy (less than 28 weeks)**
- **Congestive Heart Failure**

BEFORE you use Ansaid talk to your doctor or pharmacist if you have any of the following:

- High blood pressure
- High cholesterol
- Diabetes mellitus or on a low sugar diet
- Atherosclerosis
- Poor circulation to your extremities
- Smoker or ex-smoker
- Kidney disease or urine problems
- Previous ulcer or bleeding from the stomach or gut
- Previous bleeding in the brain
- Bleeding problems
- Family history of allergy to NSAIDs (such as acetylsalicylic acid (ASA), celecoxib, diclofenac, diflunisal, etodolac, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, mefenamic acid, meloxicam, nabumetone, naproxen, oxaprozin, piroxicam, rofecoxib, sulindac, tenoxicam, tiaprofenic acid, tolmetin, or valdecoxib (NOT a complete list)
- Family history of asthma, nasal polyps long-term swelling of the sinus (chronic sinusitis) or chronic urticaria (hives);

- you are on any special diet, such as a low-sodium or low-sugar diet.
- Breast feeding or intend to breast feed while taking this medication;
- Any other medical problem(s) such as alcohol abuse, bleeding problems, etc.

Also, before taking this medication, tell your health care provider if you are planning to get pregnant.

WHILE taking Ansaid:

- Tell any other doctor, dentist or pharmacist or any other health care professional that you see that you are taking this medication, especially if you are planning to have heart surgery;
- Do NOT drink alcoholic beverages while taking this medication because you would be more likely to develop stomach problems;
- Fertility may be decreased. The use of Ansaid is not recommended in women trying to get pregnant. In women who have difficulty conceiving, stopping Ansaid should be considered;
- Some NSAIDs may cause drowsiness or fatigue in some people taking them; 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 of your arthritis or if any problems develop;
- Report any untoward reactions to your doctor; this is very important as it will aid in the early detection and prevention of potential complications;
- See your physician for regular medical checkups as these are essential.

INTERACTIONS WITH THIS MEDICATION

Talk to your health care provider and pharmacist if you are taking any other medication (prescription or non-prescription) such as any of the following (NOT a complete list):

- Acetylsalicylic Acid (ASA) or other NSAIDs (e.g. ASA, celecoxib, diclofenac, ibuprofen, indomethacin, ketorolac, meloxicam, naproxen
- Antacids
- Antidepressants
    - Selective Serotonin Reuptake Inhibitors (SSRIs) (e.g. citalopram, fluoxetine, paroxetine, sertraline)
- Blood pressure medications
    - ACE (angiotensin converting enzyme) inhibitors (e.g. enalapril, lisinopril, perindopril, ramipril)
    - ARBs (angiotensin II receptor blockers) (e.g. candesartan, irbesartan, losartan, valsartan)
- Blood thinners (e.g. warfarin, ASA, clopidogrel)
- Corticosteroids (including glucocorticoids) (e.g. prednisone)
- Cyclosporin
- Digoxin
- Diuretics (e.g. furosemide, hydrochlorothiazide)
- Lithium
- Methotrexate
- Oral contraceptives
- Oral hypoglycemics (diabetes medications)
- Tacrolimus
- Cimetidine/Ranitidine
- Sulfonamides
- Phenytoin

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

Your health care provider may prescribe low dose ASA (acetylsalicylic acid) as a blood thinner to reduce your risk of having a heart attack or stroke while you are taking Ansaid. Take only the amount of ASA prescribed by your health care provider. You are more likely to upset or damage your stomach if you take both Ansaid and ASA than if you took Ansaid alone.

PROPER USE OF THIS MEDICATION

Usual Dose:

Medical Condition	Starting Dose	Maximum Dose (per day)
Rheumatoid arthritis, Osteoarthritis, Ankylosing Spondylitis	100 mg every 12 hours	100 mg every 8 hours
Dysmenorrhoea	50 mg every 6 hours	50 mg every 6 hours
Mild to Moderately Severe Pain	50 mg every 6 hours	50 mg every 4 hours

To lessen stomach upset, take this medicine immediately after a meal or with food or milk. Also, you should remain standing or sitting upright (i.e. do not lie down) for about 15-30 minutes after taking the medicine. This helps to prevent irritation that may lead to trouble swallowing.

Take Ansaid only as directed by your health care provider. **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 health care provider recommended. If possible, you should take the lowest dose of this medication for the shortest time period.** Taking too much Ansaid may increase your chances of unwanted and sometimes dangerous side effects, especially if you are elderly, have other diseases or take other medications.

Be sure to take Ansaid regularly as prescribed. In some types of arthritis, up to two weeks may pass before you feel the full effects of this medicine. If you will be using Ansaid for more than 7 days, see your health care provider regularly to discuss whether this medicine is working for you and if it is causing you any unwanted effects. 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.

This medication has been prescribed specifically for you. Do NOT give it to anyone else. It may harm them, even if their symptoms seem to be similar to yours.

Ansaid is NOT recommended for use in patients under 18 years of age since safety and effectiveness have NOT been established.

Missed Dose:
Take as soon as you remember. If your next dose is due within 2 hours, take a single dose now and skip the next dose.

Overdose:
The symptoms of overdose may include confusion, coma, diminished muscle tone, headache, double vision, slow breathing, nausea, and abdominal pain. Seek immediate medical attention if you think that you or anyone else may have taken too much Ansaid. Do this even if there are no signs of discomfort or poisoning.

If you take more than the prescribed dose, contact your health care provider immediately.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Ansaid may cause some undesirable reactions especially when used for a long time or in large doses. When these side effects occur, you may require medical attention. Report all symptoms or side effects to your health care provider.
Ansaid may cause you to become drowsy or tired. Be careful about driving or participating in activities that require you to be alert. If you become drowsy, dizzy or light-headed after taking Ansaid, do NOT drive or operate machinery.
Ansaid may cause you to become more sensitive to sunlight. Any exposure to sunlight or sunlamps may cause sunburn, skin blisters, skin rash, redness, itching or discolouration, or vision changes. If you have a reaction from the sun, check with your health care provider.

Check with your doctor immediately if you experience unexpected weakness while taking this medication, or if you vomit any blood or have dark or bloody stools;

Check with your health care provider IMMEDIATELY if you develop chills, fever, muscle aches or pains, or other flu-like symptoms, especially if they occur before or together with a skin rash. These symptoms may be the first signs of a SERIOUS ALLERGIC REACTION to this medication.

Elderly, frail, or debilitated patients often seem to experience more frequent or more severe side effects.

SERIOUS SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Symptom	STOP taking Ansaid and get emergency medical attention IMMEDIATELY	STOP taking Ansaid and talk to your physician or pharmacist
Bloody or black tarry stools	✔	
Shortness of breath, wheezing, any trouble breathing or chest tightness	✔	
Skin rash, hives, swelling or itching	✔	
Blurred vision, or any visual disturbance	✔	
Any change in the amount or colour of your urine (red or brown)	✔	
Any pain or difficulty experienced while urinating		✔
Swelling of the feet, lower legs; weight gain		✔
Vomiting or persistent indigestion, nausea, stomach pain or diarrhea		✔
Yellow discolouration of the skin or eyes, with or without itchy skin		✔
Malaise, fatigue, loss of appetite		✔
Headaches, stiff neck		✔
Mental confusion, depression		✔
Dizziness, lightheadedness		✔
Hearing problems		✔

This is NOT a complete list of side effects. If you develop any other symptoms while taking Ansaid, see your health care provider.

HOW TO STORE IT

Store at controlled room temperature (15-30°C).
Do NOT keep outdated medicine or medicine no longer needed. Any outdated or unused medicine should be returned to your pharmacist.
Keep out of the reach of children.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Health Canada by:

toll-free telephone: 866-234-2345
toll-free fax: 866-678-6789
By email: cadrmp@hc-sc.gc.ca

By regular mail:
National AR Centre
Marketed Health Products Safety and Effectiveness Information Division
Marketed Health Products Directorate
Tunney's Pasture, AL 0701C
Ottawa ON K1A 0K9

NOTE: Before contacting Health Canada, you should contact your physician or pharmacist.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals, may be obtained by contacting the sponsor, Pfizer Canada Inc., at:
1-800-463-6001

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