NALFON- fenoprofen calcium tablet, film coated
Xspire Pharma, LLC

NALFON ®(fenoprofen calcium tablets, USP)

Cardiovascular Thrombotic Events

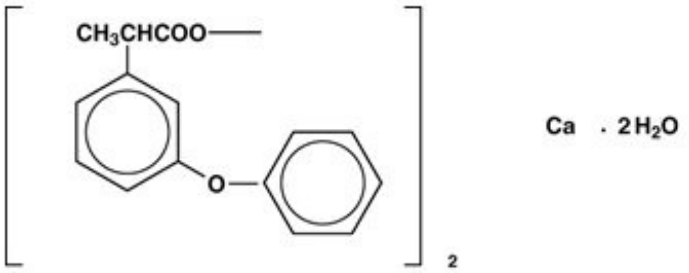
- **Nonsteroidal anti-inflammatory drugs (NSAIDs) cause an increased risk of serious cardiovascular thrombotic events, including myocardial infarction and stroke, which can be fatal. This risk may occur early in treatment and may increase with duration of use (see WARNINGSand PRECAUTIONS).**
- **Fenoprofen calcium tablets are contraindicated in the setting of coronary artery bypass graft (CABG) surgery (see CONTRAINDICATIONSand WARNINGS).**

Gastrointestinal Risk

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

DESCRIPTION

NALFON ®(fenoprofen calcium tablets) USP is a nonsteroidal, anti-inflammatory, antiarthritic drug. Chemically, fenoprofen calcium is an arylacetic acid derivative. The structural formula is as follows:



Benzeneacetic acid, α-methyl-3-phenoxy-, calcium salt (2:1)-(±)-, dihydrate

Fenoprofen calcium, USP is a white crystalline powder, soluble in alcohol (95%) to the extent of approximately 15 mg/mL at 25°C, slightly soluble in water and insoluble in benzene.

The pKa of fenoprofen calcium is 4.5 at 25°C.

Film-coated NALFON tablets for oral administration are available containing fenoprofen calcium as the dihydrate equivalent to 600 mg of fenoprofen and the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, pregelatinized starch, sodium lauryl sulfate, titanium dioxide and FD&C Yellow No. 6 Aluminum Lake.

CLINICAL PHARMACOLOGY

NALFON ®tablets is a nonsteroidal, anti-inflammatory, antiarthritic drug that also possesses analgesic and antipyretic activities. Its exact mode of action is unknown, but it is thought that prostaglandin synthetase inhibition is involved.

Results in humans demonstrate that fenoprofen has both anti-inflammatory and analgesic actions. The emergence and degree of erythemic response were measured in adult male volunteers exposed to ultraviolet irradiation. The effects of fenoprofen, aspirin and indomethacin were each compared with those of a placebo. All three drugs demonstrated antierythemic activity.

In all patients with rheumatoid arthritis, the anti-inflammatory action of NALFON has been evidenced by relief of pain, increase in grip strength and reductions in joint swelling, duration of morning stiffness and disease activity (as assessed by both the investigator and the patient). The anti-inflammatory action of NALFON has also been evidenced by increased mobility (i.e., a decrease in the number of joints having limited motion).

The use of NALFON in combination with gold salts or corticosteroids has been studied in patients with rheumatoid arthritis. The studies, however, were inadequate in demonstrating whether further improvement is obtained by adding NALFON to maintenance therapy with gold salts or steroids. Whether or not NALFON used in conjunction with partially effective doses of a corticosteroid has a “steroid-sparing” effect is unknown.

In patients with osteoarthritis, the anti-inflammatory and analgesic effects of NALFON have been demonstrated by reduction in tenderness as a response to pressure and reductions in night pain, stiffness, swelling and overall disease activity (as assessed by both the patient and the investigator). These effects have also been demonstrated by relief of pain with motion and at rest and increased range of motion in involved joints.

In patients with rheumatoid arthritis and osteoarthritis, clinical studies have shown fenoprofen to be comparable to aspirin in controlling the aforementioned measures of disease activity, but mild gastrointestinal reactions (nausea, dyspepsia) and tinnitus occurred less frequently in patients treated with fenoprofen than in aspirin-treated patients. It is not known whether fenoprofen calcium causes less peptic ulceration than does aspirin.

In patients with pain, the analgesic action of NALFON has produced a reduction in pain intensity, an increase in pain relief, improvement in total analgesia scores and a sustained analgesic effect.

Under fasting conditions, fenoprofen is rapidly absorbed and peak plasma levels of 50 mcg/mL are achieved within 2 hours after oral administration of 600 mg doses. Good dose proportionality was observed between 200 mg and 600 mg doses in fasting male volunteers. The plasma half-life is approximately 3 hours. About 90% of a single oral dose is eliminated within 24 hours as fenoprofen glucuronide and 4’ hydroxy-fenoprofen glucuronide, the major urinary metabolites of fenoprofen. Fenoprofen is highly bound (99%) to albumin.

The concomitant administration of antacid (containing both aluminum and magnesium hydroxide) does not interfere with absorption of NALFON.

There is less suppression of collagen-induced platelet aggregation with single doses of fenoprofen calcium than there is with aspirin.

INDICATIONS AND USAGE

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

NALFON tablets are indicated:

- For relief of mild to moderate pain in adults.
- For relief of the signs and symptoms of rheumatoid arthritis.
- For relief of the signs and symptoms of osteoarthritis.

CONTRAINDICATIONS

NALFON tablets are contraindicated in patients who have shown hypersensitivity to fenoprofen calcium.

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

NALFON is contraindicated in the setting of coronary artery bypass graft (CABG) surgery (see WARNINGS).

NALFON is contraindicated in patients with a history of significantly impaired renal function (see WARNINGS: Advanced Renal Disease).

WARNINGS

Cardiovascular Effects

Cardiovascular Thrombotic Events

Clinical trials of several COX-2 selective and nonselective NSAIDs of up to 3 years duration have shown an increased risk of serious cardiovascular (CV) thrombotic events, including myocardial infarction (MI) and stroke, which can be fatal. Based on available data, it is unclear that the risk for CV thrombotic events is similar for all NSAIDs. The relative increase in serious CV thrombotic events over baseline conferred by NSAID use appears to be similar in those with and without known CV disease or risk factors for CV disease. However, patients with known CV disease or risk factors had a higher absolute incidence of excess serious CV thrombotic events, due to their increased baseline rate. Some observational studies found that this increased risk of serious CV thrombotic events began as early as the first weeks of treatment. The increase in CV thrombotic risk has been observed most consistently at higher doses.

To minimize the potential risk for an adverse CV event in NSAID-treated patients, use the

lowest effective dose for the shortest duration possible. Physicians and patients should remain alert for the development of such events, throughout the entire treatment course, even in the absence of previous CV symptoms. Patients should be informed about the signs and/or symptoms of serious CV events and the steps to take if they occur.

There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious CV thrombotic events associated with NSAID use. The concurrent use of aspirin and an NSAID, such as NALFON, increases the risk of serious gastrointestinal (GI) events (see GI WARNINGS).

Status Post Coronary Artery Bypass Graft (CABG) Surgery

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

Post-MI Patients

Observational studies conducted in the Danish National Registry have demonstrated that patients treated with NSAIDs in the post-MI period were at increased risk of reinfarction, CV-related death, and all-cause mortality beginning in the first week of treatment. In this same cohort, the incidence of death in the first year post MI was 20 per 100 person years in NSAID-treated patients compared to 12 per 100 person years in non-NSAID exposed patients. Although the absolute rate of death declined somewhat after the first year post-MI, the increased relative risk of death in NSAID users persisted over at least the next 4 years of follow-up.

Avoid the use of NALFON tablets in patients with a recent MI unless the benefits are expected to outweigh the risk of recurrent CV thrombotic events. If NALFON tablets are used in patients with a recent MI, monitor patients for signs of cardiac ischemia.

Hypertension

NSAIDs, including NALFON, can lead to onset of new hypertension or worsening of preexisting hypertension, either of which may contribute to the increased incidence of CV events. Patients taking thiazides or loop diuretics may have impaired response to these therapies when taking NSAIDs. NSAIDs, including NALFON, 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.

Heart Failure and Edema

The Coxib and traditional NSAID Trialists' Collaboration meta-analysis of randomized controlled trials demonstrated an approximately 2-fold increase in hospitalizations for heart failure in COX-2 selective-treated patients and nonselective NSAID-treated patients compared to placebo-treated patients. In a Danish National Registry study of patients with heart failure, NSAID use increased the risk of MI, hospitalization for heart failure, and death.

Additionally, fluid retention and edema have been observed in some patients treated with NSAIDs. Use of fenoprofen calcium may blunt the CV effects of several therapeutic

agents used to treat these medical conditions [e.g., diuretics, ACE inhibitors, or angiotensin receptor blockers (ARBs)] (see Drug Interactions).

Avoid the use of NALFON tablets in patients with severe heart failure unless the benefits are expected to outweigh the risk of worsening heart failure. If NALFON tablets are used in patients with severe heart failure, monitor patients for signs of worsening heart failure.

Gastrointestinal Effects

Risk of Ulceration, Bleeding and Perforation

NSAIDs, including NALFON tablets, can cause serious gastrointestinal (GI) adverse events including inflammation, bleeding, ulceration and perforation of the stomach, small intestine or large intestine, which can be fatal. These serious adverse events can occur at any time, with or without warning symptoms, in patients treated with NSAIDs. Only one in five patients, who develop a serious upper GI adverse event on NSAID therapy, is symptomatic. Upper GI ulcers, gross bleeding or perforation caused by NSAIDs occur in approximately 1% of patients treated for 3 to 6 months, and in about 2% to 4% of patients treated for one year. These trends continue with longer duration of use, increasing the likelihood of developing a serious GI event at some time during the course of therapy. However, even short-term therapy is not without risk.

NSAIDs should be prescribed with extreme caution in those with a prior history of ulcer disease or gastrointestinal bleeding. Patients with *a prior history of peptic ulcer disease and/or gastrointestinal bleeding*who use NSAIDs have a greater than 10-fold increased risk for developing a GI bleed compared to patients with neither of these risk factors. Other factors that increase the risk for GI bleeding in patients treated with NSAIDs include concomitant use of oral corticosteroids or anticoagulants, longer duration of NSAID therapy, smoking, use of alcohol, older age and poor general health status. Most spontaneous reports of fatal GI events are in elderly or debilitated patients and therefore, special care should be taken in treating this population.

To minimize the potential risk for an adverse GI event in patients treated with a NSAID, the lowest effective dose should be used for the shortest possible duration. Patients and physicians should remain alert for signs and symptoms of GI ulceration and bleeding during NSAID therapy and promptly initiate additional evaluation and treatment if a serious GI adverse event is suspected. This should include discontinuation of the NSAID until a serious GI adverse event is ruled out. For high risk patients, alternate therapies that do not involve NSAIDs should be considered.

Renal Effects

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

Advanced Renal Disease

No information is available from controlled clinical studies regarding the use of NALFON tablets in patients with advanced renal disease. Therefore, treatment with NALFON tablets is not recommended in patients with advanced renal disease (see CONTRAINDICATIONS).

Anaphylactoid Reactions

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

Skin Reactions

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

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) has been reported in patients taking NSAIDs such as NALFON tablets. Some of these events have been fatal or life-threatening. DRESS typically, although not exclusively, presents with fever, rash, lymphadenopathy, and/or facial swelling. Other clinical manifestations may include hepatitis, nephritis, hematological abnormalities, myocarditis, or myositis. Sometimes symptoms of DRESS may resemble an acute viral infection. Eosinophilia is often present. Because this disorder is variable in its presentation, other organ systems not noted here may be involved. It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, discontinue NALFON tablets and evaluate the patient immediately.

Fetal Toxicity

Premature Closure of Fetal Ductus Arteriosus

Avoid use of NSAIDs, including NALFON tablets, in pregnant women at about 30 weeks gestation and later. NSAIDs including NALFON tablets, increase the risk of premature closure of the fetal ductus arteriosus at approximately this gestational age.

Oligohydramnios/Neonatal Renal Impairment

Use of NSAIDs, including NALFON tablets, at about 20 weeks gestation or later in pregnancy may cause fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. These adverse outcomes are seen, on average, after

days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation. Oligohydramnios is often, but not always, reversible with treatment discontinuation. Complications of prolonged oligohydramnios may, for example, include limb contractures and delayed lung maturation. In some postmarketing cases of impaired neonatal renal function, invasive procedures such as exchange transfusion or dialysis were required.

If NSAID treatment is necessary between about 20 weeks and 30 weeks gestation, limit NALFON tablets use to the lowest effective dose and shortest duration possible. Consider ultrasound monitoring of amniotic fluid if NALFON tablets treatment extends beyond 48 hours. Discontinue Fenoprofen Calcium Tablets if oligohydramnios occurs and follow up according to clinical practice (see PRECAUTIONS; Pregnancy).

Ocular

Studies to date have not shown changes in the eyes attributable to the administration of NALFON tablets. However, adverse ocular effects have been observed with other anti-inflammatory drugs. Eye examinations, therefore, should be performed if visual disturbances occur in patients taking fenoprofen.

Central Nervous System

Caution should be exercised by patients whose activities require alertness if they experience CNS side effects while taking NALFON tablets.

Hearing

Since the safety of NALFON tablets has not been established in patients with impaired hearing, these patients should have periodic tests of auditory function during prolonged therapy with fenoprofen.

PRECAUTIONS

General

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

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

Hepatic Effects

Borderline elevations of one or more liver tests may occur in up to 15% of patients taking NSAIDs including NALFON tablets. These laboratory abnormalities may progress, may remain unchanged or may be transient with continuing therapy. Notable elevations of ALT or AST (approximately three or more times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials with NSAIDs. In addition, rare cases of severe hepatic reactions, including jaundice and fatal fulminant hepatitis, liver

necrosis and hepatic failure, some of them with fatal outcomes have been reported.

A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of a more severe hepatic reaction while on therapy with NALFON tablets. If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), NALFON tablets should be discontinued.

Hematological Effects

Anemia is sometimes seen in patients receiving NSAIDs, including NALFON tablets. This may be due to fluid retention, occult or gross GI blood loss or an incompletely described effect upon erythropoiesis. Patients on long-term treatment with NSAIDs, including NALFON tablets, should have their hemoglobin or hematocrit checked if they exhibit any signs or symptoms of anemia. NSAIDs inhibit platelet aggregation and have been shown to prolong bleeding time in some patients. Unlike aspirin, their effect on platelet function is quantitatively less, of shorter duration, and reversible. Patients receiving NALFON tablets who may be adversely affected by alterations in platelet function, such as those with coagulation disorders or patients receiving anticoagulants, should be carefully monitored.

Preexisting Asthma

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

Information for Patients

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

1. **Cardiovascular Thrombotic Events**: Advise patients to be alert for the symptoms of cardiovascular thrombotic events, including chest pain, shortness of breath, weakness, or slurring of speech, and to report any of these symptoms to their healthcare provider immediately (see WARNINGS).
2. NALFON tablets, like other NSAIDs, can cause GI discomfort and, rarely, serious GI side effects, such as ulcers and bleeding, which may result in hospitalization and even death. Although serious GI tract ulcerations and bleeding can occur without warning symptoms, patients should be alert for the signs and symptoms of ulcerations and bleeding, and should ask for medical advice when observing any indicative sign or symptoms including epigastric pain, dyspepsia, melena and hematemesis. Patients should be apprised of the importance of this follow-up (see WARNINGS: Gastrointestinal Effects: Risk of Ulceration, Bleeding, and Perforation).
3. Serious Skin Reactions, including DRESS Advise patients to stop taking NALFON tablets immediately if they develop any type of rash or fever and to contact their healthcare provider as soon as possible (see WARNINGS).

4. **Heart Failure and Edema**: Advise patients to be alert for the symptoms of congestive heart failure including shortness of breath, unexplained weight gain, or edema and to contact their healthcare provider if such symptoms occur (see WARNINGS).
5. Patients should be informed of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, pruritus, jaundice, right upper quadrant tenderness and "flu- like" symptoms). If these occur, patients should be instructed to stop therapy and seek immediate medical therapy.
6. Patients should be informed of the signs of an anaphylactoid reaction (e.g. difficulty breathing, swelling of the face or throat). If these occur, patients should be instructed to seek immediate emergency help (see WARNINGS).
7. Fetal Toxicity Inform pregnant women to avoid use of NALFON tablets and other NSAIDs starting at 30 weeks gestation because of the risk of the premature closing of the fetal ductus arteriosus. If treatment with NALFON tablets is needed for a pregnant woman between about 20 to 30 weeks gestation, advise her that she may need to be monitored for oligohydramnios, if treatment continues for longer than 48 hours (see WARNINGS; Fetal Toxicity, PRECAUTIONS; Pregnancy).

Laboratory Tests

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

Drug Interactions

ACE Inhibitors

Reports suggest that NSAIDs may diminish the antihypertensive effect of ACE inhibitors. This interaction should be given consideration in patients taking NSAIDs concomitantly with ACE inhibitors.

Aspirin

The coadministration of aspirin decreases the biologic half-life of fenoprofen because of an increase in metabolic clearance that results in a greater amount of hydroxylated fenoprofen in the urine. Although the mechanism of interaction between fenoprofen and aspirin is not totally known, enzyme induction and displacement of fenoprofen from plasma albumin binding sites are possibilities. As with other NSAIDs, concomitant administration of NALFON tablets and aspirin is not generally recommended because of the potential of increased adverse effects.

Diuretics

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

Lithium

NSAIDs have produced an elevation of plasma lithium levels and a reduction in renal lithium clearance. The mean minimum lithium concentration increased 15% and the renal clearance was decreased by approximately 20%. These effects have been attributed to inhibition of renal prostaglandin synthesis by the NSAID. Thus, when NSAIDs and lithium are administered concurrently, subjects should be observed carefully for signs of lithium toxicity.

Methotrexate

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

Warfarin

The effects of warfarin and NSAIDs on GI bleeding are synergistic, such that users of both drugs together have a risk of serious GI bleeding higher than users of either drug alone.

Phenobarbital

Chronic administration of phenobarbital, a known enzyme inducer, may be associated with a decrease in the plasma half-life of fenoprofen. When phenobarbital is added to or withdrawn from treatment, dosage adjustment of NALFON tablets may be required.

Plasma Protein Binding

*In vitro*studies have shown that fenoprofen, because of its affinity for albumin, may displace from their binding sites other drugs that are also albumin bound, and this may lead to drug interactions. Theoretically, fenoprofen could likewise be displaced. Patients receiving hydantoins, sulfonamides or sulfonylureas should be observed for increased activity of these drugs and, therefore, signs of toxicity from these drugs.

Drug/Laboratory Test Interactions

Amerlex-M kit assay values of total and free triiodothyronine in patients receiving fenoprofen have been reported as falsely elevated on the basis of a chemical cross-reaction that directly interferes with the assay. Thyroid-stimulating hormone, total thyroxine and thyrotropin-releasing hormone response are not affected.

Carcinogenesis, Mutagenesis and Impairment of Fertility

Long-term studies in animals have not been conducted to evaluate the carcinogenic potential of NALFON. Studies have not been conducted to determine the effect of NALFON on mutagenicity or fertility.

Pregnancy

Risk Summary

Use of NSAIDs, including NALFON tablets, can cause premature closure of the fetal ductus arteriosus and fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. Because of these risks, limit dose and duration of NALFON tablets use between about 20 and 30 weeks of gestation, and avoid NALFON tablets use at about 30 weeks of gestation and later in pregnancy (see WARNINGS; Fetal Toxicity).

Premature Closure of Fetal Ductus Arteriosus

Use of NSAIDs, including NALFON tablets, at about 30 weeks gestation or later in pregnancy increases the risk of premature closure of the fetal ductus arteriosus.

Oligohydramnios/Neonatal Renal Impairment

Use of NSAIDs at about 20 weeks gestation or later in pregnancy has been associated with cases of fetal renal dysfunction leading to oligohydramnios, and in some cases, neonatal renal impairment.

Data from observational studies regarding other potential embryofetal risks of NSAID use in women in the first or second trimesters of pregnancy are inconclusive.

Reproductive studies conducted in rats and rabbits have not demonstrated evidence of developmental abnormalities when given daily oral doses of 50 or 100 mg/kg fenoprofen calcium, respectively (0.15 and 0.6 times the maximum human daily dose of 3200 mg based on body surface area comparisons). However, animal reproduction studies are not always predictive of human response.

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

Based on animal data, prostaglandins have been shown to have an important role in endometrial vascular permeability, blastocyst implantation, and decidualization. In animal studies, administration of prostaglandin synthesis inhibitors, such as fenoprofen, resulted in increased pre- and post-implantation loss. Prostaglandins also have been shown to have an important role in fetal kidney development. In published animal studies, prostaglandin synthesis inhibitors have been reported to impair kidney development when administered at clinically relevant doses.

The estimated background risk of major birth defects and miscarriage for the indicated population(s) is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Premature Closure of Fetal Ductus Arteriosus:

Avoid use of NSAIDs in women at about 30 weeks gestation and later in pregnancy, because NSAIDs, including NALFON tablets, can cause premature closure of the fetal ductus arteriosus (see WARNINGS; Fetal Toxicity).

Oligohydramnios/Neonatal Renal Impairment:

If an NSAID is necessary at about 20 weeks gestation or later in pregnancy, limit the use to the lowest effective dose and shortest duration possible. If NALFON tablets treatment extends beyond 48 hours, consider monitoring with ultrasound for oligohydramnios. If oligohydramnios occurs, discontinue NALFON tablets and follow up according to clinical practice (see WARNINGS; Fetal Toxicity).

Data

Human Data

There are no adequate and well-controlled studies of in pregnant women.

Premature Closure of Fetal Ductus Arteriosus:

Published literature reports that the use of NSAIDs at about 30 weeks of gestation and later in pregnancy may cause premature closure of the fetal ductus arteriosus.

Oligohydramnios/Neonatal Renal Impairment:

Published studies and postmarketing reports describe maternal NSAID use at about 20 weeks gestation or later in pregnancy associated with fetal renal dysfunction leading to oligohydramnios, and in some cases, neonatal renal impairment. These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation. In many cases, but not all, the decrease in amniotic fluid was transient and reversible with cessation of the drug. There have been a limited number of case reports of maternal NSAID use and neonatal renal dysfunction without oligohydramnios, some of which were irreversible. Some cases of neonatal renal dysfunction required treatment with invasive procedures, such as exchange transfusion or dialysis.

Methodological limitations of these postmarketing studies and reports include lack of a control group; limited information regarding dose, duration, and timing of drug exposure; and concomitant use of other medications. These limitations preclude establishing a reliable estimate of the risk of adverse fetal and neonatal outcomes with maternal NSAID use. Because the published safety data on neonatal outcomes involved mostly preterm infants, the generalizability of certain reported risks to the full-term infant exposed to NSAIDs through maternal use is uncertain.

Labor and Delivery

The effects of NALFON tablets on labor and delivery in pregnant women are unknown. In rat studies, maternal exposure to NSAIDs, as with other drugs known to inhibit prostaglandin synthesis, increased the incidence of dystocia, delayed parturition and decreased pup survival.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from NALFON tablets, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients below the age of 18 have not been established.

Geriatric Use

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

ADVERSE REACTIONS

During clinical studies for rheumatoid arthritis, osteoarthritis or mild to moderate pain and studies of pharmacokinetics, complaints were compiled from a checklist of potential adverse reactions, and the following data emerged. These encompass observations in 6,786 patients, including 188 observed for at least 52 weeks. For comparison, data are also presented from complaints received from the 266 patients who received placebo in these same trials. During short-term studies for analgesia, the incidence of adverse reactions was markedly lower than that seen in longer-term studies.

Adverse Drug Reactions Reported in ≥ 1% of Patients During Clinical Trials

Digestive System: During clinical trials with fenoprofen calcium, the most common adverse reactions were gastrointestinal in nature and occurred in 20.8% of patients receiving fenoprofen as compared to 16.9% of patients receiving placebo. In descending order of frequency, these reactions included dyspepsia (10.3% fenoprofen vs. 2.3% placebo), nausea (7.7% vs. 7.1%), constipation (7% vs. 1.5%), vomiting (2.6% vs. 1.9%), abdominal pain (2% vs. 1.1%) and diarrhea (1.8% vs. 4.1%). The drug was discontinued because of adverse gastrointestinal reactions in less than 2% of patients during premarketing studies.

Nervous System: The most frequent adverse neurologic reactions were headache (8.7% vs. 7.5%) and somnolence (8.5% vs. 6.4%). Dizziness (6.5% vs. 5.6%), tremor (2.2% vs. 0.4%) and confusion (1.4% vs. none) were noted less frequently. Fenoprofen was discontinued in less than 0.5% of patients because of these side effects during premarketing studies.

Skin and Appendages: Increased sweating (4.6% vs. 0.4%), pruritus (4.2% vs. 0.8%) and rash (3.7% vs. 0.4%) were reported. Fenoprofen was discontinued in about 1% of patients because of an adverse effect related to the skin during premarketing studies.

Special Senses: Tinnitus (4.5% vs. 0.4%), blurred vision (2.2% vs. none) and decreased hearing (1.6% vs. none) were reported. Fenoprofen was discontinued in less than 0.5% of patients because of adverse effects related to the special senses during premarketing studies.

Cardiovascular: Palpitations (2.5% vs. 0.4%). Fenoprofen was discontinued in about 0.5% of patients because of adverse cardiovascular reactions during premarketing studies.

Miscellaneous: Nervousness (5.7% vs. 1.5%), asthenia (5.4% vs. 0.4%), peripheral edema (5% vs. 0.4%), dyspnea (2.8% vs. none), fatigue (1.7% vs. 1.5%), upper respiratory infection (1.5% vs. 5.6%) and nasopharyngitis (1.2% vs. none).

Adverse Drug Reactions Reported in < 1% of Patients During Clinical Trials

Digestive System: Gastritis, peptic ulcer with/without perforation, gastrointestinal hemorrhage, anorexia, flatulence, dry mouth and blood in the stool. Increases in alkaline phosphatase, LDH, SGOT, jaundice and cholestatic hepatitis, aphthous ulcerations of the buccal mucosa, metallic taste and pancreatitis (see PRECAUTIONS).

Cardiovascular: Atrial fibrillation, pulmonary edema, electrocardiographic changes and supraventricular tachycardia.

Genitourinary Tract: Renal failure, dysuria, cystitis, hematuria, oliguria, azotemia, anuria, interstitial nephritis, nephrosis and papillary necrosis (see WARNINGS).

Hyper sensitivity: Angioedema (angioneurotic edema).

Hematologic: Purpura, bruising, hemorrhage, thrombocytopenia, hemolytic anemia, aplastic anemia, agranulocytosis and pancytopenia.

Nervous System: Depression, disorientation, seizures and trigeminal neuralgia.

Special Senses: Burning tongue, diplopia and optic neuritis.

Skin and Appendages: Exfoliative dermatitis, toxic epidermal necrolysis, Stevens-Johnson Syndrome and alopecia.

Miscellaneous: Anaphylaxis, urticaria, malaise, insomnia, tachycardia, personality change, lymphadenopathy, mastodynia and fever.

OVERDOSAGE

Signs and Symptoms

Symptoms of overdose appear within several hours and generally involve the gastrointestinal and central nervous systems. They include dyspepsia, nausea, vomiting, abdominal pain, dizziness, headache, ataxia, tinnitus, tremor, drowsiness and confusion. Hyperpyrexia, tachycardia, hypotension and acute renal failure may occur rarely following overdose. Respiratory depression and metabolic acidosis have also been reported following overdose with certain NSAIDs.

Treatment

To obtain up-to-date information about the treatment of overdose, a good resource is your certified Regional Poison Control Center. Telephone numbers of certified poison control centers are listed in the Physicians' Desk Reference (PDR). In managing overdosage, consider the possibility of multiple drug overdoses, interaction among drugs and unusual drug kinetics in your patient.

Protect the patient's airway and support ventilation and perfusion. Meticulously monitor and maintain, within acceptable limits, the patient's vital signs, blood gases, serum electrolytes, etc. Absorption of drugs from the gastrointestinal tract may be decreased by giving activated charcoal, which, in many cases, is more effective than lavage; consider charcoal instead of or in addition to gastric emptying.
Repeated doses of charcoal over time may hasten elimination of some drugs that have been absorbed.Safeguard the patient's airway when employing gastric emptying or

charcoal.

Alkalinization of the urine, forced diuresis, peritoneal dialysis, hemodialysis and charcoal hemoperfusion do not enhance systemic drug elimination.

DOSAGE AND ADMINISTRATION

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

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

Analgesia

For the treatment of mild to moderate pain, the recommended dosage is 200 mg given orally every 4 to 6 hours, as needed.

Rheumatoid Arthritis and Osteoarthritis

For the relief of signs and symptoms of rheumatoid arthritis or osteoarthritis the recommended dose is 400 mg to 600 mg given orally, 3 or 4 times a day. The dose should be tailored to the needs of the patient and may be increased or decreased depending on the severity of the symptoms. Dosage adjustments may be made after initiation of drug therapy or during exacerbations of the disease. Total daily dosage should not exceed 3200 mg.

NALFON tablets may be administered with meals or with milk. Although the total amount absorbed is not affected, peak blood levels are delayed and diminished.

Patients with rheumatoid arthritis generally seem to require larger doses of NALFON tablets than do those with osteoarthritis. The smallest dose that yields acceptable control should be employed.

Although improvement may be seen in a few days in many patients, an additional 2 to 3 weeks may be required to gauge the full benefits of therapy.

HOW SUPPLIED

NALFON (fenoprofen calcium tablets), USP are available containing fenoprofen calcium, USP equivalent to 600 mg fenoprofen.

The 600 mg tablet is an orange film-coated, capsule-shaped tablet debossed with **"600"**on one side of the tablet and scored on the other side.

They are available as follows:

NDC 42195-688-10

bottles of 100 tablets

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

Protect from light.

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

PHARMACIST: Dispense a Medication Guide with each prescription.

Medication Guide for Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

What is the most important information I should know about medicines called Nonsteroidal Anti-inflammatoryDrugs (NSAIDs)?
NSAIDs can cause serious side effects, including:

- **Increased risk of a heart attack or stroke that can lead to death.**This risk may happen early in treatment and may increase:
  - with increasing doses of NSAIDs
  - with longer use of NSAIDs

Do not take NSAIDs right before or after a heart surgery called a “coronary artery bypass graft (CABG)."
Avoid taking NSAIDs after a recent heart attack, unless your healthcare provider tells you to. You may have an increased risk of another heart attack if you take NSAIDs after a recent heart attack .

- **Increased risk of bleeding, ulcers, and tears (perforation) of the esophagus (tube leading from the mouth to the stomach), stomach and intestines:**
  - anytime during use
  - without warning symptoms
  - that may cause death

- **The risk of getting an ulcer or bleeding increases with:**
  - past history of stomach ulcers, or stomach or intestinal bleeding with use of NSAID
  - taking medicines called “corticosteroids”, “anticoagulants”, “SSRIs”, or “SNRIs”
  - increasing doses of NSAIDs
  - older age
  - longer use of NSAIDs
  - poor health
  - smoking
  - advanced liver disease
  - drinking alcohol
  - bleeding problems

- **NSAIDs should only be used:**
  - exactly as prescribed
  - at the lowest dose possible for your treatment
  - for the shortest time needed

What are NSAIDs?
NSAIDs are used to treat pain and redness, swelling, and heat (inflammation) from

medical conditions such as different types of arthritis, menstrual cramps, and other types of short-term pain.

Who should not take NSAIDs?
Do not take NSAIDs:

- if you have had an asthma attack, hives, or other allergic reaction with aspirin or any other NSAIDs.
- right before or after heart bypass surgery.

Before taking NSAIDs, tell your healthcare provider about all of your medical conditions, including if you:

- have liver or kidney problems
- have high blood pressure
- have asthma
- are pregnant or plan to become pregnant. Taking NSAIDs at about 20 weeks of pregnancy or later may harm your unborn baby. If you need to take NSAIDs for more than 2 days when you are between 20 and 30 weeks of pregnancy, your healthcare provider may need to monitor the amount of fluid in your womb around your baby. **You should not take NSAIDs after about 30 weeks of pregnancy.**
- are breastfeeding or plan to breast feed.

Tell your healthcare provider about all of the medicines you take, including prescription or over-the- counter medicines, vitamins or herbal supplements.NSAIDs and some other medicines can interact with each other and cause serious side effects. **Do not start taking any new medicine without talking to your healthcare provider first.**

What are the possible side effects of NSAIDs?
NSAIDs can cause serious side effects, including:
See "What is the most important information I should know about medicines called Nonsteroidal Anti-inflammatory Drugs (NSAIDs)?

- new or worse high blood pressure
- heart failure
- liver problems including liver failure
- kidney problems including kidney failure
- low red blood cells (anemia)
- life-threatening skin reactions
- life threatening allergic reactions
- **Other side effects of NSAIDs include:**stomach pain, constipation, diarrhea, gas, heartburn, nausea, vomiting, and dizziness.

Get emergency help right away if you get any of the following symptoms:

- shortness of breath or trouble breathing
- slurred speech
- chest pain
- swelling of the face or throat
- weakness on one side of your body

Stop taking your NSAID and call your healthcare provider right away if you get any of the following symptoms:

- nausea
- vomit blood
- more tired or weaker than usual
- there is blood in your bowel movement or it is black and sticky like tar
- diarrhea
- itching
- unusual weight gain
- your skin or eyes look yellow
- skin rash or blisters with fever
- indigestion or stomach pain
- swelling of the arms, legs, hands and feet
- flu-like symptoms

If you take too much of your NSAID, call your healthcare provider or get medical help right away.
These are not all the possible side effects of NSAIDs. For more information, ask your healthcare provider or pharmacist about NSAIDs.
Call your doctor for medical advice about side effects . You may report side effects to FDA at 1-800-FDA-1088.

Other information about NSAIDs

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

General information about the safe and effective use of NSAIDs
Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use NSAIDs for a condition for which it was not prescribed. Do not give NSAIDs to other people, even if they have the same symptoms that you have. It may harm them.
If you would like more information about NSAIDs, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about NSAIDs that is written for health professionals.

Manufactured for: Xspire Pharma, LLC, Ridgeland, MS, 39157 U.S.A.
For more information, call Xspire Pharma, LLC at 1-601-990-9497.

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

Xspire Pharma LLC.
Ridgeland, MS 39157 U.S.A.

REVISED APRIL 2021

Rx only

Keep container tightly closed.

Keep this and all medication out of the reach of children.

Protect from light.

Usual Adult Dosage: See accompanying prescribing information.

PACKAGING

Rx only

Keep container tightly closed.

Keep this and all medication out of the reach of children.

Protect from light.

Usual Adult Dosage: See accompanying prescribing information.

NALFON

fenoprofen calcium tablet, film coated

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:42195-688
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
FENOPROFEN CALCIUM (UNII: 0X2CW1QABJ) (FENOPROFEN - UNII:RA33EAC7KY)	FENOPROFEN	600 mg

Inactive Ingredients	
Ingredient Name	**Strength**
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
CROSCARMELLOSE SODIUM (UNII: M28OL1HH48)	
HYPROMELLOSE, UNSPECIFIED (UNII: 3NXW29V3WO)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	

POLYETHYLENE GLYCOL, UNSPECIFIED (UNII: 3WQ0SDW1A)	
POLYSORBATE 80 (UNII: 6OZP39ZG8H)	
STARCH, CORN (UNII: O8232NY3SJ)	
SODIUM LAURYL SULFATE (UNII: 368GB5141J)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
FD&C YELLOW NO. 6 (UNII: H77VEI93A8)	

Product Characteristics

Color	orange (orange)	**Score**	2 pieces
Shape	OVAL (capsule-shaped)	**Size**	20mm
Flavor		**Imprint Code**	600
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:42195-688-10	100 in 1 BOTTLE; Type 0: Not a Combination Product	09/24/2018	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA072267	09/24/2018	

Labeler - Xspire Pharma, LLC (078312042)

Revised: 10/2023 Xspire Pharma, LLC