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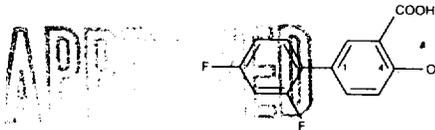
**DRAFT FINAL PRINTED LABELING**

# DIFLUNISAL TABLETS, USP

Revised — May 1995

**DESCRIPTION:**

Diflunisal is 2', 4'- difluoro-4-hydroxy-3-biphenylcarboxylic acid. Its molecular formula is  $C_{17}H_{12}F_2O_3$  and its structural formula is



Diflunisal has a molecular weight of 250.20. It is a stable, white, crystalline compound with a melting point of 211°-213°C. It is practically insoluble in water at neutral or acidic pH. Because it is an organic acid, it dissolves readily in dilute alkali to give a moderately stable solution at room temperature. It is soluble in most organic solvents including ethanol, methanol, and acetone.

Diflunisal is available in 250 and 500 mg tablets for oral administration. Diflunisal tablets contain the following inactive ingredients: FD&C yellow #6 aluminum lake (sunset yellow lake), hydroxypropyl cellulose, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, pregelatinized starch, and titanium dioxide. The 250 mg tablet also contains polyserbate 80.

**CLINICAL PHARMACOLOGY:**

**Action:** Diflunisal is a non-steroidal drug with analgesic, anti-inflammatory and antipyretic properties. It is a peripherally-acting non-narcotic analgesic drug. Habituation, tolerance and addiction have not been reported.

Diflunisal is a difluorophenyl derivative of salicylic acid. Chemically, diflunisal differs from aspirin (acetylsalicylic acid) in two respects. The first of these two is the presence of a difluorophenyl substituent at carbon 1. The second difference is the removal of the O-acetyl group from the carbon 4 position. Diflunisal is not metabolized to salicylic acid, and the fluorine atoms are not displaced from the difluorophenyl ring structure.

The precise mechanism of the analgesic and anti-inflammatory actions of diflunisal is not known. Diflunisal is a prostaglandin synthetase inhibitor. In animals, prostaglandins sensitize afferent nerves and potentiate the action of bradykinin in inducing pain. Since prostaglandins are known to be among the mediators of pain and inflammation, the mode of action of diflunisal may be due to a decrease of prostaglandins in peripheral tissues.

**Pharmacokinetics and Metabolism:** Diflunisal is rapidly and completely absorbed following oral administration with peak plasma concentrations occurring between 2 to 3 hours. The drug is excreted in the urine as two soluble glucuronide conjugates accounting for about 90% of the administered dose. Little or no diflunisal is excreted in the feces. Diflunisal appears in human milk in concentrations of 2-7% of those in plasma. More than 99% of diflunisal in plasma is bound to proteins.

As is the case with salicylic acid, concentration-dependent pharmacokinetics prevail when diflunisal is administered; a doubling of dosage produces a greater than doubling of drug accumulation. The effect becomes more apparent with repetitive doses. In contrast to salicylic acid which has a plasma half-life of 2 1/2 hours, the plasma half-life of diflunisal is 3 to 4 times longer (8 to 12 hours), because of a difluorophenyl substituent at carbon 1. Because of its long half-life and nonlinear pharmacokinetics, several days are required for diflunisal plasma levels to reach steady state following multiple doses. For this reason, an initial loading dose is necessary to shorten the time to reach steady state levels, and 2 to 3 days of observation are necessary for evaluating changes in treatment regimens if a loading dose is not used.

Studies in baboons to determine passage across the blood-brain barrier have shown that only small quantities of diflunisal, under normal or acidic conditions are transported into the cerebrospinal fluid (CSF). The ratio of blood/CSF concentrations after intravenous doses of 50 mg/kg or oral doses of 100 mg/kg of diflunisal was 100:1. In contrast, oral doses of 500 mg/kg of aspirin resulted in a blood/CSF ratio of 5:1.

**Mild to Moderate Pain:** Diflunisal is a peripherally-acting analgesic agent with a long duration of action. Diflunisal produces significant analgesia within 1 hour and maximum analgesia within 2 to 3 hours.

Consistent with its long half-life, clinical effects of diflunisal mirror its pharmacokinetic behavior, which is the basis for recommending a loading dose when instituting therapy. Patients treated with diflunisal, on the first dose, tend to have a slower onset of pain relief when compared with drugs achieving comparable peak effects. However, diflunisal produces longer-lasting responses than the comparative agents.

Comparative single dose clinical studies have established the analgesic efficacy of diflunisal at various dose levels relative to other analgesics. Analgesic effect measurements were derived from hourly evaluations by patients during eight and twelve-hour postdosing observation periods. The following information may serve as a guide for prescribing diflunisal.

Diflunisal 500 mg was comparable in analgesic efficacy to aspirin 650 mg, acetaminophen 600 mg or 650 mg, and acetaminophen 650 mg with propoxyphene napsylate 100 mg. Patients treated with diflunisal had longer lasting responses than the patients treated with the comparative analgesics.

Diflunisal 1000 mg was comparable in analgesic efficacy to acetaminophen 600 mg with codeine 60 mg. Patients treated with diflunisal had longer lasting responses than the patients who received acetaminophen with codeine.

A loading dose of 1000 mg provides faster onset of pain relief, shorter time to peak analgesic effect, and greater peak analgesic effect than an initial 500 mg dose.

In contrast to the comparative analgesics, a significantly greater proportion of patients treated with diflunisal did not re-medicate and continued to have a good analgesic effect eight to twelve hours after dosing. Seventy-five percent (75%) of patients treated with diflunisal continued to have a good analgesic response at four hours. When patients having a good analgesic response at four hours were followed, 78% of these patients continued to have a good analgesic response at eight hours and 64% at twelve hours.

**Chronic Anti-inflammatory Therapy in Osteoarthritis and Rheumatoid Arthritis:** In the controlled, double-blind clinical trials in which diflunisal (500 mg to 1000 mg a day) was compared with anti-inflammatory doses of aspirin (2-4 grams a day), patients treated with diflunisal had a significantly lower incidence of hirsutis and of adverse effects involving the gastrointestinal system than patients treated with aspirin. (See also *Effect on Fecal Blood Loss*).

**Osteoarthritis:** The effectiveness of diflunisal for the treatment of osteoarthritis was studied in patients with osteoarthritis of the hip and/or knee. The activity of diflunisal was demonstrated by clinical improvement in the signs and symptoms of disease activity.

In a double-blind multicenter study of 12 weeks' duration in which dosages were adjusted according to patient response, diflunisal 500 or 750 mg daily, was shown to be comparable in effectiveness to aspirin, 2000 or 3000 mg daily. In open-label extensions of this study to 24 to 48 weeks, diflunisal continued to show similar effectiveness and generally was well tolerated.

**Rheumatoid Arthritis:** In controlled clinical trials, the effectiveness of diflunisal was established for both acute exacerbations and long-term management of rheumatoid arthritis. The activity of diflunisal was demonstrated by clinical improvement in the signs and symptoms of disease activity.

In a double-blind multicenter study of 12 weeks' duration in which dosages were adjusted according to patient response, diflunisal 500 or 750 mg daily was comparable in effectiveness to aspirin 2600 or 3900 mg daily. In open-label extensions of this study to 52 weeks, diflunisal continued to be effective and was generally well tolerated.

Diflunisal 500, 750 or 1000 mg daily was compared with aspirin 2000, 3000, or 4000 mg daily, in a multicenter study of 8 weeks' duration in which dosages were adjusted according to patient response. In this study, diflunisal was comparable in efficacy to aspirin.

In a double-blind multicenter study of 12 weeks' duration in which dosages were adjusted according to patient needs, diflunisal 500 or 750 mg daily and ibuprofen 1600 or 2400 mg daily were comparable in effectiveness and tolerability.

In a double-blind multicenter study of 12 weeks' duration, diflunisal 750 mg daily was comparable in efficacy to naproxen 750 mg daily. The incidence of gastrointestinal adverse effects and tinnitus was comparable for both drugs. This study was extended to 48 weeks on an open-label basis. Diflunisal continued to be effective and generally well tolerated.

In patients with rheumatoid arthritis, diflunisal and gold salts may be used in combination at their usual dosage levels. In clinical studies, diflunisal added to the regimen of gold salts usually resulted in additional symptomatic relief but did not alter the course of the underlying disease.

**Antipyretic Activity:** Diflunisal is not recommended for use as an antipyretic agent. In single 250 mg, 500 mg, or 750 mg doses, diflunisal produced measurable but not clinically useful decreases in temperature in patients with fever; however, the possibility that it may mask fever in some patients, particularly with chronic or high doses, should be considered.

**Uricosuric Effect:** In normal volunteers, an increase in the renal clearance of uric acid and a decrease in serum uric acid was observed when diflunisal was administered at 500 mg or 750 mg daily in divided doses. Patients on long-term therapy taking diflunisal at 500 mg to 1000 mg daily in divided doses showed a prompt and consistent reduction across studies in mean serum uric acid levels, which were lowered as much as 1.4 mg%. It is not known whether diflunisal interferes with the activity of other uricosuric agents.

**Effect on Platelet Function:** As an inhibitor of prostaglandin synthetase, diflunisal has a dose-related effect on platelet function and bleeding time. In normal volunteers, 250 mg b.i.d. for 8 days had no effect on platelet function, and 500 mg b.i.d., the usual recommended dose, had a slight effect. At 1000 mg b.i.d., which exceeds the maximum recommended dosage, however, diflunisal inhibited platelet function. In contrast to aspirin, these effects of diflunisal were reversible, because of the absence of the chemically labile and biologically reactive O-acetyl group at the carbon 4 position. Bleeding time was not altered by dose of 250 mg b.i.d., and was only slightly increased at 500 mg b.i.d. At 1000 mg b.i.d., a greater increase occurred, but was not statistically significantly different from the change in the placebo group.

**Effect of Fecal Blood Loss:** When diflunisal was given to normal volunteers at the usual recommended dose of 500 mg twice daily, fecal blood loss was not significantly different from placebo. Aspirin at 1000 mg four times daily exceeded the expected increase in fecal blood loss. Diflunisal at 1000 mg twice daily (NOTE: exceeds the recommended dosage) caused a statistically significant increase in fecal blood loss, but this increase was only one-half as large as that associated with aspirin 1300 mg twice daily.

**Effect on Blood Glucose:** Diflunisal did not affect fasting blood sugar in diabetic patients who were receiving, tolbutamide or placebo.

#### **INDICATIONS AND USAGE:**

Diflunisal is indicated for acute or long-term use for symptomatic treatment of the following:

1. Mild to moderate pain
2. Osteoarthritis
3. Rheumatoid arthritis

#### **CONTRAINDICATIONS:**

Patients who are hypersensitive to this product.

Patients in whom acute asthmatic attacks, urticaria, or rhinitis are precipitated by aspirin or other non-steroidal, anti-inflammatory drugs.

#### **WARNINGS:**

**Peptic ulceration and gastrointestinal bleeding** have been reported in patients receiving diflunisal. Fatalities have occurred rarely. Gastrointestinal bleeding is associated with higher morbidity and mortality in patients acutely ill with other conditions, the elderly and patients with hemorrhagic disorders. In patients with active gastrointestinal bleeding or an active peptic ulcer, the physician must weigh the benefits of therapy with diflunisal against possible hazards, institute an appropriate ulcer regimen, and carefully monitor the patient's progress. When diflunisal is given to patients with a history of either upper or lower gastrointestinal tract disease, it should be given only after consulting the ADVERSE REACTIONS section and under close supervision.

**Risk of GI Ulcerations, Bleeding and Perforation with NSAID Therapy:** Serious gastrointestinal toxicity such as bleeding, ulceration, and perforation, can occur at any time, with or without warning symptoms, in patients treated chronically with NSAID therapy. Although minor upper gastrointestinal problems, such as dyspepsia, are common, usually developing early in therapy, physicians should remain alert for ulceration and bleeding in patients treated chronically with NSAIDs even in the absence of previous GI tract symptoms. In patients observed in clinical trials of several months to two years duration, symptomatic upper GI ulcers, gross bleeding or perforation appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year. Physicians should inform patients about the signs and/or symptoms of serious GI toxicity and what steps to take if they occur.

Studies to date have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Except for a prior history of serious GI events and other risk factors known to be associated with peptic ulcer disease, such as alcoholism, smoking, etc., no risk factors (e.g., age, sex) have been associated with increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than other individuals and most spontaneous reports of fatal GI events are in this population. Studies to date are inconclusive concerning the relative risk of various NSAIDs in causing such reactions. High doses of any NSAID probably carry a greater risk of these reactions, although controlled clinical trials showing this do not exist in most cases. In considering the use of relatively large doses (within the recommended dosage range), sufficient benefit should be anticipated to offset the potential increased risk of GI toxicity.

#### **PRECAUTIONS:**

##### **General:**

Non-steroidal anti-inflammatory drugs, including diflunisal, may mask the usual signs and symptoms of infection. Therefore, the physician must be continually on the alert for this and should use the drug with extra care in the presence of existing infection.

Although diflunisal has less effect on platelet function and bleeding time than aspirin, at higher doses it is an inhibitor of platelet function, therefore, patients who may be adversely affected should be carefully observed when diflunisal is administered (see CLINICAL PHARMACOLOGY).

Because of reports of adverse eye findings with agents of this class, it is recommended that patients who develop eye complaints during treatment with diflunisal have ophthalmologic studies.

Peripheral edema has been observed in some patients taking diflunisal. Therefore, as with other drugs in this class, diflunisal should be used with caution in patients with compromised cardiac function, hypertension, or other conditions predisposing to fluid retention.

Acetylsalicylic acid has been associated with Reye syndrome. Because diflunisal is a derivative of salicylic acid, the possibility of its association with Reye syndrome cannot be excluded.

**Hypersensitivity Syndrome:** A potentially life-threatening, apparent hypersensitivity syndrome has been reported. This multisystem syndrome includes constitutional symptoms (fever, chills), and cutaneous findings (see ADVERSE REACTIONS, *Dermatologic*). It may also include involvement of major organs (changes in liver function, jaundice, leukopenia, thrombocytopenia, eosinophilia, disseminated intravascular coagulation, renal impairment, including renal failure), and less specific findings (adenitis, arthralgia, myalgia, arthritis, malaise, anorexia, disorientation). If evidence of hypersensitivity occurs, therapy with diflunisal should be discontinued.

**Renal Effects:** As with other non-steroidal anti-inflammatory drugs, long term administration of diflunisal 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 and proteinuria and occasionally nephrotic syndrome.

A second form of renal toxicity has been seen in patients with prerenal and renal conditions leading to a reduction in renal blood flow or blood volume, where the renal prostaglandins have a supportive role in the maintenance of renal perfusion. In these patients administration of an NSAID may cause a dose dependent reduction in prostaglandin formation and may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with conditions such as renal or hepatic dysfunction, diabetes mellitus, advanced age, extracellular volume depletion from any cause, congestive heart failure, septicemia, pyelonephritis, or concomitant use of any nephrotoxic drug. Diflunisal or other NSAIDs should be given with caution and renal function should be monitored in any patient who may have reduced renal reserve. Discontinuation of NSAID therapy is typically followed by recovery to the pretreatment state.

Since diflunisal is eliminated primarily by the kidneys, patients with significantly impaired renal function should be closely monitored; a lower daily dosage should be anticipated to avoid excessive drug accumulation.

##### **Information for Patients:**

Diflunisal, like other drugs of its class, is not free of side effects. The side effects of these drugs can cause discomfort and, rarely, there are more serious side effects such as gastrointestinal bleeding, which may result in hospitalization and even fatal outcomes.

NSAIDs (Non-Steroidal Anti-Inflammatory Drugs) are often essential agents in the management of arthritis and have a major role in the treatment of pain, but they also may be commonly employed for conditions which are less serious.

Physicians may wish to discuss with their patients the potential risks (see **WARNINGS, PRECAUTIONS AND ADVERSE REACTIONS**) and likely benefits of NSAID treatment, particularly when the drugs are used for less serious conditions where treatment without NSAIDs may represent an acceptable alternative to both the patient and physician.

**Laboratory Tests:**

**Liver Function Tests:** As with other non-steroidal anti-inflammatory drugs, borderline elevations of one or more liver tests may occur in up to 15% of patients. These abnormalities may progress, may remain essentially unchanged, or may be transient with continued therapy. The SGPT (ALT) test is probably the most sensitive indicator of liver dysfunction. Meaningful (3 times the upper limit of normal) elevations of SGPT or SGGT (AST) occurred in controlled clinical trials in less than 1% of patients. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of more severe hepatic reactions while on therapy with diflunisal. Severe hepatic reactions, including jaundice, have been reported with diflunisal as well as with other non-steroidal anti-inflammatory drugs. Although such reactions are rare, if abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), diflunisal should be discontinued, since liver reactions can be fatal.

**Gastrointestinal:**

Because serious GI tract ulceration and bleeding can occur without warning symptoms, physicians should follow chronically treated patients for the signs and symptoms of ulceration and bleeding and should inform them of the importance of this follow-up (see **WARNINGS, Risk of GI Ulcerations, Bleeding and Perforation with NSAID Therapy**).

**Drug Interactions:**

Diflunisal prolongs the prothrombin time in patients who are on oral anti-coagulants. Diflunisal has not been shown to interact with tolbutamide. Diflunisal interacts with hydrochlorothiazide, furosemide, acetaminophen, aspirin, indomethacin, sulindac and naproxen (see below).

**Oral Anticoagulants:** In some normal volunteers, the concomitant administration of diflunisal and warfarin, acenocoumarol, or phenprocoumon resulted in prolongation of prothrombin time. This may occur because diflunisal competitively displaces coumarins from protein binding sites. Accordingly, when diflunisal is administered with oral anticoagulants, the prothrombin time should be closely monitored during and for several days after concomitant drug administration. Adjustment of dosage of oral anticoagulants may be required.

**Tolbutamide:** In diabetic patients receiving diflunisal and tolbutamide, no significant effects were seen on tolbutamide plasma levels or fasting blood glucose.

**Hydrochlorothiazide:** In normal volunteers, concomitant administration of diflunisal and hydrochlorothiazide resulted in significantly increased plasma levels of hydrochlorothiazide. Diflunisal decreased the hyperuricemic effect of hydrochlorothiazide.

**Furosemide:** In normal volunteers, the concomitant administration of diflunisal and furosemide had no effect on the diuretic activity of furosemide. Diflunisal decreased the hyperuricemic effect of furosemide.

**Antacids:** Concomitant administration of antacids may reduce plasma levels of diflunisal. This effect is small with occasional doses of antacids, but may be clinically significant when antacids are used on a continuous schedule.

**Acetaminophen:** In normal volunteers, concomitant administration of diflunisal and acetaminophen resulted in an approximate 50% increase in plasma levels of acetaminophen. Acetaminophen had no effect on plasma levels of diflunisal. Since acetaminophen in high doses has been associated with hepatotoxicity, concomitant administration of diflunisal and acetaminophen should be used cautiously, with careful monitoring of patients.

Concomitant administration of diflunisal and acetaminophen in dogs, but not in rats, at approximately 2 times the recommended maximum human therapeutic dose of each (40-52 mg/kg/day of diflunisal/acetaminophen), resulted in greater gastrointestinal toxicity than when either drug was administered alone. The clinical significance of these findings has not been established.

**Methotrexate:** Caution should be used if diflunisal is administered concomitantly with methotrexate. Non-steroidal anti-inflammatory drugs have been reported to decrease the tubular secretion of methotrexate and to potentiate its toxicity.

**Cyclosporine:** Administration of non-steroidal anti-inflammatory drugs concomitantly with cyclosporine has been associated with an increase in cyclosporine-induced toxicity, possibly due to decreased synthesis of renal prostacyclin. NSAIDs should be used with caution in patients taking cyclosporine, and renal function should be carefully monitored.

**Drug Interactions - Non-steroidal Anti-inflammatory Drugs:** The administration of diflunisal to normal volunteers receiving indomethacin decreased the renal clearance and significantly increased the plasma levels of indomethacin. In some patients the combined use of indomethacin and diflunisal has been associated with fatal gastrointestinal hemorrhage. Therefore, indomethacin and diflunisal should not be used concomitantly.

Since no further clinical data are available about the safety and effectiveness of diflunisal when used in combination with other non-steroidal anti-inflammatory drugs, no recommendation for their concomitant use can be made. The following information was obtained from studies in normal volunteers.

**Aspirin:** In normal volunteers, a small decrease in diflunisal levels was observed when multiple doses of diflunisal and aspirin were administered concomitantly.

**Sulindac:** The concomitant administration of diflunisal and sulindac in normal volunteers resulted in lowering of the plasma levels of the active sulindac sulfide metabolite by approximately one third.

**Naproxen:** The concomitant administration of diflunisal and naproxen in normal volunteers had no effect on the plasma levels of naproxen, but significantly decreased the urinary excretion of naproxen and its glucuronide metabolite. Naproxen had no effect on plasma levels of diflunisal.

**Drug/Laboratory Test Interactions:**

**Serum Salicylate Assays:** Caution should be used in interpreting the results of serum salicylate assays when diflunisal is present. Salicylate levels have been found to be falsely elevated with some assay methods.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:**

Diflunisal did not affect the type or incidence of neoplasia in a 105-week study in the rat given doses up to 40 mg/kg/day (equivalent to approximately 1.3 times the maximum recommended human dose), or in long-term carcinogenic studies in mice given diflunisal at doses up to 80 mg/kg/day (equivalent to approximately 2.7 times the maximum recommended human dose). It was concluded that there was no carcinogenic potential for diflunisal.

Diflunisal passes the placental barrier to a minor degree in the rat. Diflunisal has no mutagenic activity after oral administration in the dominant lethal assay, in the Ames microbial mutagen test or in the V-79 Chinese hamster lung cell assay.

No evidence of impaired fertility was found in reproduction studies in rats at doses up to 50 mg/kg/day.

**Pregnancy:**

**Pregnancy Category C.** A dose of 60 mg/kg/day of diflunisal (equivalent to two times the maximum human dose) was maternotoxic, embryotoxic, and teratogenic in rabbits. In three of six studies in rabbits, evidence of teratogenicity was observed at doses ranging from 40 to 50 mg/kg/day. Teratology studies in mice, at doses up to 45 mg/kg/day, and in rats at doses up to 100 mg/kg/day, revealed no harm to the fetus due to diflunisal. Aspirin and other salicylates have been shown to be teratogenic in a wide variety of species, including the rat and rabbit, at doses ranging from 50 to 400 mg/kg/day (approximately one to eight times the human dose). There are no adequate and well controlled studies with diflunisal in pregnant women. Diflunisal should be used during the first two trimesters of pregnancy only if the potential benefit justifies the potential risk to the fetus. Because of the known effect of drugs of this class on the human fetus (closure of the ductus arteriosus, platelet dysfunction with resultant bleeding, renal dysfunction or failure with oligohydramnios, gastrointestinal bleeding or perforation, and myocardial degenerative changes), use during the third trimester of pregnancy is not recommended.

In rats at a dose of one and one-half times the maximum human dose, there was an increase in the average length of gestation. Similar increases in the length of gestation have been observed with aspirin, indomethacin, and phenylbutazone, and may be related to inhibition of prostaglandin synthetase. Drugs of this class may cause dystocia and delayed parturition in pregnant animals.

**Nursing Mothers:**

Diffunisal is excreted in human milk in concentrations of 2-7% of those in plasma. Because of the potential for serious adverse reactions in nursing infants from diffunisal, 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:**

The adverse effects observed following diffunisal administration to neonatal animals appear to be species, age, and dose-dependent. At dose levels approximately 3 times the usual human therapeutic dose, both aspirin (200 to 400 mg/kg/day) and diffunisal (80 mg/kg/day) resulted in death, leukocytosis, weight loss, and bilateral cataracts in neonatal (4 to 5-day-old) beagle puppies after 2 to 10 doses. Administration of an 80 mg/kg/day dose of diffunisal to 25-day-old puppies resulted in lower mortality, and did not produce cataracts. In newborn rats, a 400 mg/kg/day dose of aspirin resulted in increased mortality and some cataracts, whereas the effects of diffunisal administration at doses up to 140 mg/kg/day were limited to a decrease in average body weight gain.

Safety and effectiveness in infants and pediatric patients have not been established, and use of the drug in pediatric patients below the age of 12 years is not recommended.

**ADVERSE REACTIONS:**

The adverse reactions observed in controlled clinical trials encompass observations in 2,427 patients.

Listed below are the adverse reactions reported in the 1,314 of these patients who received treatment in studies of two weeks or longer. Five hundred thirteen patients were treated for at least 24 weeks, 255 patients were treated for at least 48 weeks, and 46 patients were treated for 96 weeks. In general, the adverse reactions listed below were 2 to 14 times less frequent in the 1,113 patients who received short-term treatment for mild to moderate pain.

**Incidence Greater Than 1%**

**Gastrointestinal:** The most frequent types of adverse reactions occurring with diffunisal are gastrointestinal. These include nausea\*, vomiting, dyspepsia\*, gastrointestinal pain\*, diarrhea\*, constipation, and flatulence.

**Psychiatric:** Somnolence, insomnia.

**Central Nervous System:** Dizziness.

**Special Senses:** Tinnitus.

**Dermatologic:** Rash\*.

**Miscellaneous:** Headache\*, fatigue/tiredness.

**Incidence Less Than 1 in 100**

The following adverse reactions, occurring less frequently than 1 in 100, were reported in clinical trials or since the drug was marketed. The probability exists of a causal relationship between diffunisal and these adverse reactions.

**Dermatologic:** Erythema multiforme, exfoliative dermatitis, Stevens Johnson syndrome, toxic epidermal necrolysis, urticaria, pruritus, sweating, dry mucous membranes, stomatitis, photosensitivity.

**Gastrointestinal:** Peptic ulcer, gastrointestinal bleeding, anorexia, eructation, gastrointestinal perforation, gastritis.

**Liver function abnormalities:** jaundice, sometimes with fever, cholestasis, hepatitis.

**Hematologic:** Thrombocytopenia, agranulocytosis, hemolytic anemia.

**Genitourinary:** Dysuria, renal impairment, including renal failure, interstitial nephritis, hematuria, proteinuria.

**Psychiatric:** Nervousness, depression, hallucinations, confusion, disorientation.

**Central Nervous System:** Vertigo, light-headedness, paresthesias.

**Special Senses:** Transient visual disturbances including blurred vision.

**Hypersensitivity Reactions:** Acute anaphylactic reaction with bronchospasm, angioedema, flushing.

**Hypersensitivity vasculitis.**

**Hypersensitivity syndrome (see PRECAUTIONS).**

**Miscellaneous:** Asthenia, edema.

**Causal Relationship Unknown:** Other reactions have been reported in clinical trials or since the drug was marketed, but occurred under circumstances where a causal relationship could not be established. However, in these rarely reported events, that possibility cannot be excluded. Therefore, these observations are listed to serve as alerting information to physicians.

**Respiratory:** Dyspnea.

**Cardiovascular:** Palpitation, syncope.

**Musculoskeletal:** Muscle cramps.

**Genitourinary:** Nephrotic syndrome.

**Miscellaneous:** Chest pain.

A rare occurrence of fulminant necrotizing fasciitis, particularly in association with Group A  $\beta$ -hemolytic streptococcus, has been described in persons treated with non-steroidal anti-inflammatory agents, including diffunisal, sometimes with fatal outcome (see also PRECAUTIONS, General).

**Potential Adverse Effects:** In addition, a variety of adverse effects not observed with diffunisal in clinical trials or in marketing experience, but reported with other non-steroidal analgesic/anti-inflammatory agents, should be considered potential adverse effects of diffunisal.

\*Incidence between 3% and 9%. Those reactions occurring in 1% to 3% are not marked with an asterisk.

**OVERDOSAGE:**

Cases of overdosage have occurred and deaths have been reported. Most patients recovered without evidence of permanent sequelae. The most common signs and symptoms observed with overdosage were drowsiness, vomiting, nausea, diarrhea, hyperventilation, tachycardia, sweating, tinnitus, disorientation, stupor and coma. Diminished urine output and cardiorespiratory arrest have also been reported. The lowest dosage of diffunisal at which a death has been reported was 15 grams without the presence of other drugs. In a mixed drug overdose, ingestion of 7.5 grams of diffunisal resulted in death.

In the event of overdosage, the stomach should be emptied by inducing vomiting or by gastric lavage, and the patient carefully observed and given symptomatic and supportive treatment. Because of the high degree of protein binding, hemodialysis may not be effective.

The oral LD<sub>50</sub> of the drug is 500 mg/kg and 826 mg/kg in female mice and female rats respectively.

**DOSAGE AND ADMINISTRATION:**

Concentration-dependent pharmacokinetics prevail when diffunisal is administered; a doubling of dosage produces a greater than doubling of drug accumulation. The effect becomes more apparent with repetitive doses.

For mild to moderate pain, an initial dose of 1000 mg followed by 500 mg every 12 hours is recommended for most patients. Following the initial dose, some patients may require 500 mg every 8 hours.

A lower dosage may be appropriate depending on such factors as pain severity, patient response, weight, or advanced age; for example, 500 mg initially, followed by 250 mg every 8-12 hours.

For osteoarthritis and rheumatoid arthritis, the suggested dosage range is 500 mg to 1000 mg daily in two divided doses. The dosage of diffunisal may be increased or decreased according to patient response.

Maintenance doses higher than 1500 mg a day are not recommended.

Diffunisal may be administered with water, milk or meals. Tablets should be swallowed whole, not crushed or chewed.

**HOW SUPPLIED:**

250 mg — Each unscored, peach, round, film-coated tablet embossed with # 545 contains 250 mg of diffunisal, USP. Tablets are supplied in bottles of 60 (NDC 0228-2545-06), 100 (NDC 0228-2545-10) and 500 (NDC 0228-2545-50).

500 mg — Each unscored, orange, round, film-coated tablet embossed with # 546 contains 500 mg of diffunisal, USP. Tablets are supplied in bottles of 60 (NDC 0228-2546-06), 100 (NDC 0228-2546-10), 500 (NDC 0228-2546-50) and 1000 (NDC 0228-2546-96).

Dispense in well-closed containers as defined in the USP.

Store at controlled room temperature 15°-30°C (59°-86°F).

**CAUTION:** Federal law prohibits dispensing without prescription.

Manufactured by:  
PUREPAC PHARMACEUTICAL CO.  
Elizabeth, NJ 07207 USA

40-8779

Revised — May 1995

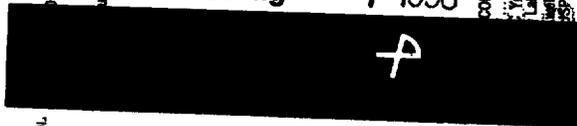
USUAL ADULT DOSAGE:  
See accompanying circular.  
Store at controlled room temperature  
15°-30°C (59°-86°F).  
Manufactured by:  
PUREPAC PHARMACEUTICAL CO.  
Elizabeth, NJ 07207 USA

**PUREPAC** NDC 0228-2545-06

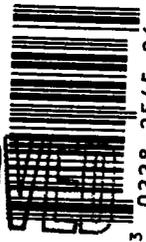
**DIFLUNISAL**  
TABLETS, USP

250 mg <sup>11</sup> 7 1996

CONTAINS:  
250 mg  
Yellow #6 Aluminum Lake  
(Lake) as a color additive.  
light-closed containers as



Lot No. SAMPLE



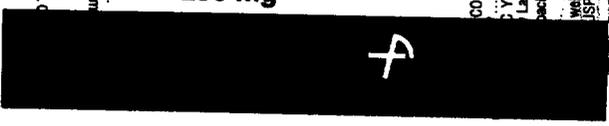
USUAL ADULT DOSAGE:  
See accompanying circular.  
Store at controlled room temperature  
15°-30°C (59°-86°F).  
Manufactured by:  
PUREPAC PHARMACEUTICAL CO.  
Elizabeth, NJ 07207 USA

**PUREPAC** NDC 0228-2545-10

**DIFLUNISAL**  
TABLETS, USP

250 mg

CONTAINS:  
250 mg  
Yellow #6 Aluminum Lake  
(Lake) as a color additive.  
package and not intended for  
well-closed containers as  
USP



Lot No. SAMPLE



USUAL ADULT DOSAGE:  
See accompanying circular.  
Store at controlled room temperature  
15°-30°C (59°-86°F).  
Manufactured by:  
PUREPAC PHARMACEUTICAL CO.  
Elizabeth, NJ 07207 USA

**PUREPAC** NDC 0228-2545-50

**DIFLUNISAL**  
TABLETS, USP

250 mg MAY 7 1996

CONTAINS:  
250 mg  
Yellow #6 Aluminum Lake (Sunset  
color-additive.  
package and not intended for dispensing.  
closed containers as defined in the



Lot No. SAMPLE

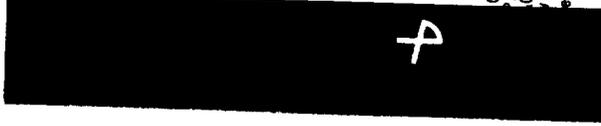


USUAL ADULT DOSAGE: See accompanying literature.  
Store at controlled room temperature 15°-30°C (59°-86°F).  
Manufactured by:  
PUREPAC PHARMACEUTICAL CO.  
Elizabeth, NJ 07207 USA

**PUREPAC** NDC 0228-2546-06  
**DIFLUNISAL**  
TABLETS, USP  
**500 mg**

CONTAINS:  
500 mg  
C Yellow #6 Aluminum Lake  
(Lake) as a color additive.  
Self-closed containers as defined

Lot No. [REDACTED]  
MAY  
SAMPLE



USUAL ADULT DOSAGE: See accompanying literature.  
Store at controlled room temperature 15°-30°C (59°-86°F).  
Manufactured by:  
PUREPAC PHARMACEUTICAL CO.  
Elizabeth, NJ 07207 USA

**PUREPAC** NDC 0228-2546-10  
**DIFLUNISAL**  
TABLETS, USP  
**500 mg**

CONTAINS:  
500 mg  
Yellow #6 Aluminum Lake (Sunset  
color additive.  
Self-closed containers as defined in the

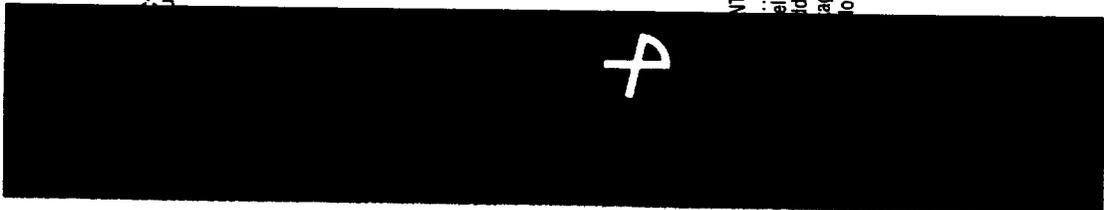
Lot No. [REDACTED]  
MAY  
SAMPLE



USUAL ADULT DOSAGE: See accompanying literature.  
Store at controlled room temperature 15°-30°C (59°-86°F).  
Manufactured by:  
PUREPAC PHARMACEUTICAL CO.  
Elizabeth, NJ 07207 USA

**PUREPAC** NDC 0228-2546-50  
**DIFLUNISAL**  
TABLETS, USP  
**500 mg**

CONTAINS:  
500 mg  
Yellow #6 Aluminum Lake (Sunset Yellow  
color additive.  
Self-closed containers as defined in the USP.



USUAL ADULT DOSAGE: See accompanying literature.  
Store at controlled room temperature 15°-30°C (59°-86°F).  
Manufactured by:  
PUREPAC PHARMACEUTICAL CO.  
Elizabeth, NJ 07207 USA

**PUREPAC** NDC 0228-2546-96  
**DIFLUNISAL**  
TABLETS, USP  
**500 mg**

CONTAINS:  
500 mg  
Yellow #6 Aluminum Lake (Sunset Yellow  
color additive.  
Self-closed containers as defined in the USP.

MAY  
SAMPLE

