PRODUCT MONOGRAPH

NOVO-DIFLUNISAL

(diflunisal)

Film-coated Tablets 250 and 500 mg

THERAPEUTIC CLASSIFICATION

Analgesic, Anti-Inflammatory Agent

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Control # 174380

NAME OF DRUG

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(diflunisal tablets, USP)

250 and 500 mg

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ACTION AND CLINICAL PHARMACOLOGY

Diflunisal is a non-steroidal drug with analgesic, anti- inflammatory and antipyretic properties. The precise mechanism of the analgesic and anti-inflammatory actions of diflunisal is not known, however, it appears to be a peripherally-acting analgesic drug. 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 in part 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. Following single doses, peak plasma concentrations of 41 ± 11 μg/mL (mean ± S.D.) were observed following 250 mg

doses 87 ± 17 µg/mL were observed following 500 mg and 124 ± 11 µg/mL following single 1000 mg doses. However, following administration of 250 mg b.i.d., a mean peak level of 56 ± 14 µg/mL was observed on day 8, while the mean peak level after 500 mg b.i.d. for 11 days was 190 ± 33 µg/mL. The plasma half-life of diflunisal is 8 to 12 hours. 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.

A comparative, multi-dose, bioavailability study was performed on two 500 mg diflunisal tablet products. The pharmacokinetic plasma data calculated for the NOVO-DIFLUNISAL and DOLOBID® tablet formulations is tabulated below.

Phannacokinetic Indices for Diflunisal:

Geometric mean Arithmetic mean (C.V.)			
	NOVO-DIFLUNISAL	**DOLOBID®**	**Percentage of DOLOBID®**
AUC_t (μg•h/mL)	1200 1217 (17)	1200 1220 (17)	100
C_{max} (μg/mL)	134 136 (16)	129 131 (14)	104
T_{max} (h)	3.31 (1.47)	2.92 (1.84)	

* For the T_{max} parameter this is the arithmetic mean (standard deviation).

INDICATIONS AND CLINICAL USE

NOVO-DIFLUNISAL (diflunisal) is indicated for:

- relief of mild to moderate pain accompanied by inflammation in conditions such as musculoskeletal trauma, post-dental extraction or post-episiotomy
- symptomatic relief of osteoarthritis and rheumatoid arthritis.

CONTRAINDICATIONS

Patients who are hypersensitive to any component of this product.

Patients in whom acute asthmatic attacks, urticaria, or rhinitis are precipitated by acetylsalicylic acid or other non-steroidal anti-inflammatory drugs. Fatal anaphylactoid reactions have occurred in such individuals.

Patients with active peptic ulcer or any other active inflammatory disease of the gastrointestinal tract.

WARNINGS

Gastrointestinal System

Peptic ulceration, perforation and gastrointestinal bleeding, sometimes severe and occasionally fatal have been reported during therapy with NSAIDs including diflunisal.

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

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

Elderly, frail and debilitated patients appear to be at higher risk from a variety of adverse reactions from NSAIDs. For such patients, consideration should be given to a starting dose lower than usual, with individual adjustment when necessary and under close supervision. See PRECAUTIONS for further advice.

Pregnancy

The safety of this drug in pregnancy has not been established, and its use during pregnancy is therefore not recommended.

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 50 mg/kg/day, and in rats at doses up to 100 mg/kg/day, revealed no harm to the fetus due to diflunisal. ASA 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).

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 ASA, indomethacin, and phenylbutazone, and may be related to inhibition of prostag1 synthetase. Drugs of this class may cause dystocia and delayed parturition in pregnant animals.

Because of the known effect of drugs of this class on the human fetal cardiovascular system (closure of ductus arteriosus), use during the third trimester of pregnancy is not recommended.

Nursing Mothers

Diflunisal 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 diflunisal, a decision should be made whether to initiate nursing or to administer the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in infants and children have not been established, and use of the drug in children below the age of 12 years is not recommended. (See TOXICOLOGY.)

PRECAUTIONS

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

Gastrointestinal System

If peptic ulceration is suspected or confirmed, or if gastrointestinal bleeding or perforation occurs NOVO-DIFLUNISAL (diflunisal) should be discontinued, an appropriate treatment instituted and patient closely monitored.

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

When diflunisal was given to normal volunteers at 500 mg twice daily, fecal blood loss was not significantly different from placebo. Diflunisal at 1000 mg twice daily caused a statistically significant increase in fecal blood loss.

Renal Function

As with other NSAIDs, 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, 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, the elderly, extracellular volume depletion from any cause, congestive heart failure, sepsis, or concomitant use of diuretics or any nephrotoxic drug. Discontinuation of NSAID therapy is typically followed by recovery to the pretreatment state.

Since diflunisal is eliminated primarily by the kidneys, this drug should be used with great caution in patients with impaired renal function and the elderly; a lower daily dosage should be anticipated to avoid excessive drug accumulation, and patients should be carefully monitored. During long therapy kidney function should be monitored periodically.

Hepatic Function

As with other non-steroidal anti-inflammatory drugs, borderline elevations of one or more liver tests may occur 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 SGOT (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 reaction while on therapy with NOVO-DIFLUNISAL. Severe hepatic reactions, including jaundice and cases of fatal hepatitis, have been reported with 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.), NOVO-DIFLUNISAL should be discontinued since liver reactions can be fatal.

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

Fluid and Electrolyte Balance

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

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

Hematology

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, had a slight effect. At 1000 mg b.i.d., diflunisal inhibited platelet function. In contrast to acetylsalicylic acid these effects of diflunisal were reversible. Bleeding time was not altered by a dose of 250 mg b.i.d., but was 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. Therefore, patients who may be adversely affected should be carefully observed when NOVO-DIFLUNISAL is administered.

Blood dyscrasias associated with the use of NSAIDs are rare, but could have severe consequences.

Infection

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

Ophthalmology

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

Hypersensitivity Reactions

A potentially life-threatening, apparent hypersensitivity syndrome has been reported. This multisystem syndrome includes constitutional symptoms (fever, chills), and cutaneous findings (see 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, arthritis, malaise, anorexia, disorientation).

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 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.

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.

Drug Interactions

Non-steroidal Anti-inflammatory Drugs

Severe adverse reactions involving the gastrointestinal tract have occurred when diflunisal is administered concomitantly with other NSAIDs. The following information was obtained from studies in normal volunteers.

Acetylsalicylic Acid: In normal volunteers, a small decrease in diflunisal levels was observed when multiple doses of diflunisal and acetylsalicylic acid were administered concomitantly.

Indomethacin: The administration of diflunisal to normal volunteers receiving indomethacin decreased the renal clearance and significantly increased the plasma levels of indomethacin. Further, the combined use of indomethacin and diflunisal has been associated with fatal gastrointestinal hemorrhage. Therefore, indomethacin and diflunisal should not be used 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.

Oral Anticoagulants: In some normal volunteers, the concomitant administration of diflunisal and warfarin or acenocoumarol 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.

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.

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

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

Coadministration of aluminium hydroxide suspension significantly decreases absorption of diflunisal by approximately 40%.

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

Lithium: Concurrent use of NSAIDs with lithium has been reported to increase steady-state plasma lithium concentration. It is recommended to monitor lithium plasma concentration during and following concurrent use.

Acetaminophen: Concomitant administration of diflunisal and acetaminophen to normal volunteers resulted in significantly increased (50%) 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 NOVO-DIFLUNISAL and acetaminophen should be used cautiously, with careful monitoring of patients.

ADVERSE REACTIONS

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

The following adverse reactions, listed by body system, have been observed in controlled clinical trials or since the drug was marketed.

3-9%	**1-3%**	**<1%**
Gastrointestinal	vomiting	peptic ulcer
nausea	constipation	gastrointestinal bleeding
dyspepsia	flatulence	anorexia
gastrointestinal pain		gastrointestinal perforation
diarrhea		gastritis
Central Nervous System/Psychiatric	dizziness	vertigo
headache	somnolence	light-headedness
	insomnia	paresthesia
		nervousness
		depression
		hallucination
		confusion
Dermatologic		erythema multiforme
rash		Stevens-Johnson syndrome
		toxic epidermal necrolysis
		exfoliative dermatitis
		pruritus
		sweating
		dry mucous membranes
		stomatitis

3-9%	1-3%	<1%
		photosensitivity uritcaria
Special Senses	tinnitus	transient visual disturbance (including blurred vision)
Hematologic		thrombocytopenia leukopenia pancytopenia agrunalocytosis (rarely) hemolytic anemia
Renal		dysuria renal impairment (including renal failure) interstitial nephritis hematuria proteinuria
Hepatic		jaundice cholestasis live function abnormalities hepatitis
Miscellaneous	fatigue	asthenia edema
Hypersensitivity Reactions		acute anaphylactic reaction with bronchospasm angioedema hypersensitivity vasculitis hypersensitivity syndrome (see PRECAUTIONS)

CAUSAL RELATIONSHIP UNKNOWN

Other reactions have been reported in clinical trials or since the drug was marketed abroad, 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
MISCELLANEOUS:	chest pain, muscle cramps
RENAL:	nephrotic syndrome

SYMPTOMS AND TREATMENT OF 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 diflunisal at which a death has been reported was 15 g without the presence of other drugs. Death has been reported from a mixed drug overdose which included 7.5 g of diflunisal. A dose that is usually fatal has not yet been identified.

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.

DOSAGE AND ADMINISTRATION

NOVO-DIFLUNISAL (diflunisal) has slow onset and long duration of action. NOVO-DIFLUNISAL produces significant analgesia in one hour and maximum analgesia in 2-4 hours. Analgesic effect lasts 8 to 12 hours. These characteristics should be considered when prescribing this drug.

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

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 12 hours.

For osteoarthritis and rheumatoid arthritis, the dosage range is 500 to 1000 mg daily in two divided doses according to patient response.

Maintenance doses higher than 1000 mg a day are not recommended.

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

PHARMACEUTICAL INFORMATION

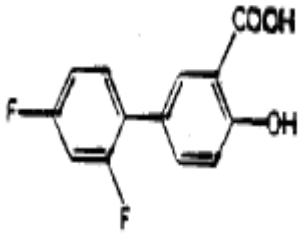
I.

DRUG SUBSTANCE

Proper name: diflunisal

Chemical name: 2' ,4'-difluoro-4-hydroxy-3-biphenylcarboxylic acid

Structural Formula:



Molecular Formula: $C_{13}H_8F_2O_3$

Molecular Weight: 250.20

Description: Diflunisal 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.

COMPOSITION

Each tablet contains either 250 mg or 500 mg of diflunisal and the following non-medicinal ingredients: instant clear gel, avicel PH 102, sodium starch glycolate, sodium lauryl sulfate, starch 1500, collidal silicon dioxide, magnesium stearate, hydroxypropyl-methylcellulose, titanium dioxide, polyethylene glycol, FD & C Yellow #6 aluminum lake, polysorbate 80 and carnauba wax.

STABILITY AND STORAGE RECOMMENDAIJONS

Store at room temperature (15°C - 30°C). Protect from humidity.

AVAILABILITY OF DOSAGE FORMS

NOVO-DIFLUNISAL (diflunisal) is available as peach coloured, capsule-shaped, film-coated tablets, engraved **'N'** on one side and **'250'** on the other side containing 250 mg of diflunisal supplied in bottles of 60, 100 or 500 tablets.

NOVO-DIFLUNISAL is also available as orange coloured, capsule-shaped, film-coated tablets, engraved **'N'** on one side and **'500'** on the other side containing 500 mg of diflunisal supplied in bottles of 60, 100 and 500 and in boxes of 100 as unit dose strips.

INFORMATION TO THE PATIENT

PURPOSE OF THIS MEDICINE

NOVO-DIFLUNISAL (diflunisal) which has been prescribed to you by your physician, is one of a large group of NSAIDs and is used to treat the symptoms of certain types of arthritis, or relief of mild to moderate pain accompanied by inflammation. It helps to relieve joint pain, swelling, stiffness and fever by reducing the production of certain substances (prostaglandins) and helping to control inflammation and other body reactions.

IMPORTANT NOTICE

ADVISE YOUR PHYSICIAN

- If you ever had an allergic reaction (especially difficulty breathing, a runny nose, skin rashes or hives)

- to diflunisal
- to acetylsalicylic acid (ASA)

  (ASA is the active ingredient of many pain and fever preparations that can be sold without prescription).
- to any other anti-inflammatory medication used in the treatment of arthritis such as diclofenac, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, mefenamic acid, piroxicam, sulindac, tiaprofenic acid or tolimetin.

  A previous allergic reaction to one of these could increase the risk of an allergic reaction to NOVO-DIFLUNISAL.

- If you ever had an ulcer with or without bleeding, of the stomach, duodenum, or any part of the digestive tract, liver or kidney diseases or any other medical problems.

- If you are taking other medications (non-prescription or prescription drugs) YOUR PHYSICIAN WILL ADVISE YOU ON THE APPROPRIATE COURSE OF ACTION.

Note also that NOVO-DIFLUNISAL is not recommended for use during pregnancy and that breast-feeding should not be undertaken while on NOVO-DIFLUNISAL.

AVAILABILITY

NOVO-DIFLUNISAL is available for oral administration as tablets containing either 250 mg (peach coloured) or 500 mg (orange coloured) of the active ingredient, diflunisal and the following non-medicinal ingredients: instant clear gel, avicel PH 102, sodium starch glycolate, sodium lauryl sulfate, starch 1500, collidal silicon dioxide, magnesium stearate, hydroxypropylmethylcellulose, titanium dioxide, polyethylene glycol, FD & C Yellow #6 aluminum lake, polysorbate 80 and carnauba wax.

HOW TO USE THIS MEDICINE

- Tablets should be swallowed in whole, not crushed or chewed. To lessen stomach upset, take this medicine immediately after a meal or with food or milk. If stomach upset (indigestion, nausea, vomiting, stomach pain or diarrhea) occurs and continues, contact your physician.
- PLEASE ADHERE TO THE DOSAGE AND ADMINISTRATION INSTRUCTIONS WHICH YOUR PHYSICIAN HAS GIVEN YOU
- 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 physician prescribed.
- If you are taking NOVO-DIFLUNISAL to relieve arthritis, you must take it regularly as prescribed by your physician. In some types of arthritis, up to 2 weeks may pass before you begin to feel better and up to 1 month may pass before you feel the full effects of this medicine. During treatment, your physician may decide to adjust the dosage according to your response to the medication.

IF YOU MISS A DOSE

If you miss a dose of NOVO-DIFLUNISAL and remember within an hour or so, take it right away. Then go back to your regular dosing schedule.

But if you do not remember until later, do not take the missed dose at all and do not double the next one. Instead, go back to your regular dosing schedule.

Do not take ASA, ASA-containing compounds or other drugs used to relieve symptoms of arthritis while taking NOVO-DIFLUNISAL unless directed to do so by your physician.

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

Along with its beneficial effects, NOVO-DIFLUNISAL like other NSAID drugs, may cause some undesirable reactions. Elderly, frail or debilitated patients often seem to experience more frequent or more severe side effects. Although not all of these side effects are common, when they do occur they may require medical attention. Check with your physician immediately if any of the following are noted:

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

While taking this medication

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

KEEP THIS MEDICATION, AND ALL OTHERS, OUT OF THE REACH OF CHILDREN.

PHARMACOLOGY

Diflunisal restores the pain threshold of the rat's foot (inflamed by injection of yeast) to normal at a dose of 4.6 mg/kg orally in comparison with 2.2 mg/kg orally for indomethacin and 87 mg/kg orally for acetylsalicylic acid.

In the standard carrageenan-induced foot inflammation test in rats, diflunisal, 9.8 mg/kg given orally 1 hour prior to injecting the carrageenan, reduced the swelling by 50%. The ED of ASA was 89.2 mg/kg. If the time of testing was delayed so that the drug was given six hours before the carrageenan the ED_{50} for diflunisal was 9.5 mg/kg. This fact indicates a relatively long duration of action.

Metabolism

The absorption, distribution, excretion, and metabolic fate of diflunisal were investigated in the dog and rat.

Absorption

The absorption of orally administered diflunisal is virtually complete in dog and rat. In dogs, maximum plasma concentrations, after an oral dose of 10 mg/kg diflunisal ^{14}COOH, were obtained in 1 hour. Plasma levels of diflunisal at 50 and 100 mg/kg/day averaged 45 and 53 μg/mL. No long-term accumulation of the drug was seen in plasma even with dosages of 100 mg/kg/day.

In rats, peak plasma levels occurred 1 hour after an oral 10 mg/kg dose, with subsequent plasma levels approximating those from an intravenous dose. Plasma levels of radioactivity after 24 hours were barely detectable.

Distribution

Distribution of radioactivity in rats given diflunisal ^{14}COOH generally followed that for body water. After 24 hours, traces (0.6 μg/g or less) of radioactivity were observed in the plasma, red blood cells, kidneys and skeletal muscle. No radioactivity was found in the liver, spleen, heart, mesenteric lymph nodes, adrenals, testes, stomach, large and small intestine, lungs, brain or fat tissue.

Studies with plasma samples from diflunisal-dosed dogs, as well as in vitro studies with human plasma and serum, indicate that diflunisal was highly (>95%) bound to protein.

Studies in baboons to determine passage across the blood brain barrier have shown that only small quantities of diflunisal, under normal or acidotic 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.

Excretion

In the rat and dog, the excretion of radioactivity following an oral dose of diflunisal was similar to that from an intravenous dose, indicating complete oral absorption of the compound. The drug was excreted almost entirely in conjugated form in both the dog and the rat.

TOXICOLOGY

Acute Toxicity

The oral LD_{50} values of diflunisal are summarized below:

Species	**Sex**	**LD_{50} mg/kg**
Mouse-Adult	F	439
Rat-Young Adult	M	710
	F	826
Rat-Weanling	M	470
	F	610
Rat-Infant	M, F	185
Rabbit-Adult	M, F	630

Signs of toxicity in the mouse and rat included ataxia, tremors, clonic convulsions and bradypnea.

The LD_{50} was lower in the infant than in the weanling or young adult rat. No sex differences in toxicity were observed.

In the dog, single, oral doses of diflunisal of 100 to 200 mg/kg caused emesis and diarrhea.

Subacute and Chronic Toxicity

Dogs

13 week study

Diflunisal was given orally to beagle puppies 4 to 5 days old at dosage levels of 10, 20, 40 and 80 mg/kg/day for up to 13 weeks. Four of six puppies given 80 mg/kg/day died after 2 to 10 doses. One of eight puppies given 40 mg/kg/day died after 13 doses. Bilateral cataracts were seen in the two surviving puppies given 80 mg/kg/day after one month of treatment, at which time dosing was discontinued. Twelve days following discontinuation of treatment the size and density of these cataracts began to decrease, and by the 61st day after discontinuation of treatment the cataracts were barely visible. Male pups given 40 mg/kg/day had a 31% decrease in average weight gain compared to male controls. In a similar study, the administration of 80 mg/kg/day of diflunisal to older (25-day old) puppies resulted in lower mortality and did not produce cataracts or other ocular changes.

3 month study

Groups of 2 male and 2 female pure bred beagles approximately 11 months of age were given diflunisal orally at doses of 12.5, 25, 50 or 100 mg/kg/day for 14 weeks. Emesis was seen in the groups receiving 50 and 100 mg/kg/day. Ptyalism occurred frequently in all dogs receiving 100 mg/kg/day. The average decrease in hemoglobin concentration was 2.1 to 2.9 g/100 mL and the average decrease in hematocrit was 3 to 6% in dogs given 100 mg/kg/day of diflunisal in the 4th, 8th and 12th weeks of the study. Decreased serum protein was observed on one or two occasions each in all 4 dogs given diflunisal at 100 mg/kg/day and 2 of 4 dogs given 50 mg/kg/day. Post-mortem findings attributable to the administration of diflunisal were: gastric ulceration in one out of four dogs given 50 mg/kg/day and in two out of four dogs given 100 mg/kg/day, multifocal hemorrhage in the colon of one dog given 12.5 mg/kg/day and one dog given 25 mg/kg/day, renal papillary edema in 2 dogs given 100 mg/kg/day.

27 to 58 week study

Groups of five male and five female purebred beagle dogs 9 to 12 months old were administered diflunisal in doses of 10, 20 or 40 mg/kg/day orally. Two male and two female dogs from each group were sacrificed in the twenty-seventh week while the remaining six dogs were sacrificed in the fifty-eighth week. A gastric ulcer 2 mm in diameter was observed in one of the high dose female dogs sacrificed at twenty-seven weeks. An ulcer 2 mm in diameter with hemorrhage was noted in the fundic mucosa of the stomach of one middle dose female dog sacrificed at fifty-eight weeks.

Rats

30 day study

Diflunisal given to neonatal rats (4 of each sex) at doses of 100 or 140 mg/kg/day orally from day 1 to day 30 postpartum, showed a decrease in average body weight gain of 20% and 22% respectively for females, and 9% and 22% respectively for males.

3 month study

Diflunisal was given orally to groups of 15 male and 15 female rats at doses of 12.5, 25, 50 and 100 mg/kg/day for 14 weeks. One animal died at the highest dose due to ulcerative enteritis, perforations of the small intestine, and peritonitis. There was a slight increase in liver weight in females at 100 mg/kg/day and in males at 25, 50 and 100 mg/kg/day. Renal papillary edema was observed in 1 male and 1 female at 100 mg/kg/day; focal necrosis of the gastric mucosa in 2 males at 100 mg/kg/day; and ulcerative enteritis in 2 males and 2 females at 100 mg/kg/day.

26 to 59 week study

Diflunisal was administered orally to three groups of 35 male and 35 female rats each at doses of 10, 20 or 40 mg/kg/day for up to 59 weeks. After 27 weeks three groups of 10 male and 10 female rats which had received 10, 20 or 40 mg/kg/day were sacrificed. Postmortem examination revealed focal gastritis in one female rat which had received 40mg/kg/day. At the end of 59 weeks of treatment postmortem examination revealed gastrointestinal ulceration in one male and one female given 40 mg/kg/day.

Carcinogenicity

In a two-year study in the mouse, there was an apparent but not statistically significant increase in the incidence of pulmonary adenoma and hepatocellular adenoma.

Diflunisal did not affect the type or incidence of neoplasia in a 105-week study in the rat.

Mutagenecity

Diflunisal had no mutagenic activity in the dominant lethal assay after oral administration at doses of 5, 15 and 45 mg/kg/day to groups of 12 male rats for 70 days prior to repeated mating and at doses of 5 and 45 mg/kg/day to groups of 15 male mice for a period of 5 days prior to repeated mating, or in the Ames microbial mutagen test or in the V-79 Chinese hamster lung cell assay.

Reproductive Studies (See Use in Pregnancy under WARNINGS).

Teratology (See Use in Pregnancy under WARNINGS).

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