

PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

Pr DIFLUNISAL

Diflunisal Tablets

Tablet, 250 mg and 500 mg, Oral

USP

Non-Steroidal Anti-inflammatory Drug (NSAID)

AA PHARMA INC.
1165 Creditstone Road, Unit #1
Vaughan, Ontario
L4K 4N7

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

DIFLUNISAL (Diflunisal Tablets) is indicated for:

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

For patients with an increased risk of developing cardiovascular (CV) and/or gastrointestinal (GI) adverse events, other management strategies that do NOT include the use of non-steroidal anti-inflammatory drugs (NSAIDs) should be considered first (see [2 CONTRAINDICATIONS](#), [7 WARNINGS AND PRECAUTIONS, Cardiovascular](#) and [7 WARNINGS AND PRECAUTIONS, Gastrointestinal](#)).

Use of DIFLUNISAL should be limited to the lowest effective dose for the shortest possible duration of treatment in order to minimize the potential risk for cardiovascular or gastrointestinal adverse events (see [2 CONTRAINDICATIONS](#), [7 WARNINGS AND PRECAUTIONS, Cardiovascular](#) and [7 WARNINGS AND PRECAUTIONS, Gastrointestinal](#)).

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

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

1.1 Pediatrics

Pediatrics (< 12 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of DIFLUNISAL in pediatric patients have not been established; therefore, Health Canada has not authorized an indication for pediatric use (see [2 CONTRAINDICATIONS](#)).

1.2 Geriatrics

Geriatrics (≥ 65 years of age): Evidence from clinical studies and post-market experience suggests that use in the geriatric population is associated with differences in safety (see [4.2 Recommended Dose and Dosage Adjustment](#) and [7.1.4 Geriatrics](#)).

2 CONTRAINDICATIONS

Diflunisal is contraindicated in:

- Patients with a known hypersensitivity to diflunisal or to other NSAIDs, patients who are hypersensitive to diflunisal or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see [6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING](#).
- The peri-operative setting of coronary artery bypass graft surgery (CABG). Although

DIFLUNISAL has NOT been studied in this patient population, a selective COX-2 inhibitor NSAID studied in such a setting has led to an increased incidence of cardiovascular/thromboembolic events, deep surgical infections, and sternal wound complications.

- During the third trimester of pregnancy, because of risk of premature closure of the ductus arteriosus, and prolonged parturition (see [7.1.1 Pregnant women](#)).
- Women who are breastfeeding, because of the potential for serious adverse reactions in nursing infants (see [7.1.2 Breast-feeding](#)).
- Severe uncontrolled heart failure (see [7 WARNINGS AND PRECAUTIONS, Cardiovascular](#)).
- History of asthma, urticaria, or allergic-type reactions after taking acetylsalicylic acid (ASA) or other NSAIDs (i.e. complete or partial syndrome of ASA-intolerance - rhinosinusitis, urticaria/ angioedema, nasal polyps, asthma). Fatal anaphylactoid reactions have occurred in such individuals. Individuals with the above medical problems are at risk of a severe reaction even if they have taken NSAIDs in the past without any adverse reaction. The potential for cross-reactivity between different NSAIDs must be kept in mind (see [7 WARNINGS AND PRECAUTIONS, Immune](#)).
- Active gastric / duodenal / peptic ulcer, active GI bleeding (see [7 WARNINGS AND PRECAUTIONS, Gastrointestinal](#)).
- Cerebrovascular bleeding or other bleeding disorders.
- Inflammatory bowel disease.
- Severe liver impairment or active liver disease (see [7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic](#)).
- Severe renal impairment (creatinine clearance <30mL/min or 0.5mL/sec) or deteriorating renal disease (individuals with lesser degrees of renal impairment are at risk of deterioration of their renal function when prescribed NSAIDs and must be monitored) (see [7 WARNINGS AND PRECAUTIONS, Renal](#)).
- Known hyperkalemia (see [7 WARNINGS AND PRECAUTIONS, Renal, Fluid and Electrolyte Balance](#)).
- Children and adolescents less than 12 years of age.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- **Risk of Cardiovascular (CV) Adverse Events: Ischemic Heart Disease, Cerebrovascular Disease, Congestive Heart Failure (NYHA II-IV)** (see [7 WARNINGS AND PRECAUTIONS, Cardiovascular](#)).

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

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

Use of NSAIDs, such as DIFLUNISAL, can promote sodium retention in a dose-dependent manner, through a renal mechanism, which can result in increased blood pressure and/or exacerbation of congestive heart failure (see [7 WARNINGS AND PRECAUTIONS, Renal, Fluid and Electrolyte Balance](#)).

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

- **Risk of Gastrointestinal (GI) Adverse Events** (see [7 WARNINGS AND PRECAUTIONS, Gastrointestinal](#)).

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

- **Risk in Pregnancy:** Caution should be exercised in prescribing DIFLUNISAL during the first and second trimesters of pregnancy. Use of NSAIDs at approximately 20 weeks of gestation or later may cause fetal renal dysfunction leading to oligohydramnios and neonatal renal impairment or failure (see [7.1.1 Pregnant Women](#)). DIFLUNISAL is contraindicated for use during the third trimester because of risk of premature closure of the ductus arteriosus and uterine inertia (prolonged parturition) (see [2 CONTRAINDICATIONS](#)).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- DIFLUNISAL has a slow onset and a long duration of action.
- DIFLUNISAL produces significant analgesia in one hour and maximum analgesia in 2 to 4 hours. Analgesic effect lasts 8 to 12 hours. These characteristics should be considered when prescribing this drug.
- Use of DIFLUNISAL should be limited to the lowest effective dose for the shortest possible duration of treatment (see [1 INDICATIONS](#)).

4.2 Recommended Dose and Dosage Adjustment

Adults

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.

Osteoarthritis and rheumatoid arthritis

The dosage range is 500 mg to 1000 mg daily in two divided doses according to patient response.

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

Pediatrics (< 12 years of age): Health Canada has not authorized an indication for pediatric patients (see [2 CONTRAINDICATIONS](#)).

Geriatrics (≥ 65 years of age): In the elderly, frail and debilitated, the dosage should be reduced to the lowest level providing control of symptoms, and adjusted when necessary under close supervision (see [7.1.4 Geriatrics](#)).

Renal impairment: A lower dose should be considered in patients with mild or moderate renal impairment (see [7 WARNINGS AND PRECAUTIONS, Renal](#)). DIFLUNISAL is contraindicated in severe renal impairment (creatinine clearance <30 mL/min or 0.5 mL/sec) or deteriorating renal disease (individuals with lesser degrees of renal impairment are at risk of deterioration of their renal function when prescribed NSAIDs and must be monitored) (see [2 CONTRAINDICATIONS](#)).

Hepatic impairment: Patients with impaired hepatic function should be carefully monitored and kept at the minimal effective daily dosage (see [7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic](#)). DIFLUNISAL is contraindicated in severe liver impairment or active liver disease (see [2 CONTRAINDICATIONS](#)).

4.4 Administration

DIFLUNISAL may be administered with water, milk, or meals.

Tablets should be swallowed whole, not crushed or chewed.

4.5 Missed Dose

If the patient misses a dose, instruct the patient to take the dose as soon as they remember. If it is almost time for the next dose, inform the patient to skip the missed dose and continue the regular dosing schedule. The patient should be instructed not to take 2 doses at the same time.

5 OVERDOSAGE

Symptoms

Cases of overdose have occurred and deaths have been reported. Most patients recovered without evidence of permanent sequelae. The most common signs and symptoms observed with overdose 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 dose of DIFLUNISAL at which a death has been reported was 15 grams without the presence of other drugs. Death has been reported from a mixed drug overdose which included 7.5 grams of DIFLUNISAL. A dose that is usually fatal has not yet been identified.

Treatment

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

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Tablet 250 mg, 500 mg	Colloidal silicon dioxide, croscarmellose sodium, FD&C yellow #6, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, starch, and titanium dioxide. Each film-coated 250 mg tablet also contains D&C yellow #10.

Description

DIFLUNISAL Tablets 250 mg: each light-orange, capsule-shaped, film-coated, biconvex tablet engraved “D250” on one side contains 250 mg diflunisal. Available in bottles of 100 and 500 and unit dose packages of 100.

DIFLUNISAL Tablets 500 mg: each orange, capsule-shaped, film-coated, biconvex tablet engraved “D500” on one side contains 500 mg diflunisal. Available in bottles of 100 and 500 and unit dose packages of 100.

7 WARNINGS AND PRECAUTIONS

Please see [3 SERIOUS WARNINGS AND PRECAUTIONS BOX](#).

General

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

DIFLUNISAL is NOT recommended for use with other NSAIDs, with the exception of low-dose ASA for cardiovascular prophylaxis, because of the absence of any evidence demonstrating synergistic benefits and the potential for additive adverse reactions (see [9.4 Drug-Drug Interactions, Acetylsalicylic acid \(ASA\) or other NSAIDs](#)).

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.

Antipyretic Activity: DIFLUNISAL is not recommended for use as an antipyretic agent. In single 250, 500, 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.

Carcinogenesis and Mutagenesis

See [16 NON-CLINICAL TOXICOLOGY](#).

Cardiovascular

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

duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk.

Caution should be exercised in prescribing DIFLUNISAL to patients with risk factors for cardiovascular disease, cerebrovascular disease, or renal disease, such as any of the following (NOT an exhaustive list)

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

Use of NSAIDs, such as DIFLUNISAL, can lead to new hypertension or can worsen pre-existing hypertension, either of which may increase the risk of cardiovascular events as described above. Thus, blood pressure should be monitored regularly. Consideration should be given to discontinuing DIFLUNISAL should hypertension either develop or worsen with its use.

Use of NSAIDs, such as DIFLUNISAL, can induce fluid retention and edema, and may exacerbate congestive heart failure, through a renally-mediated mechanism (see [7 WARNINGS AND PRECAUTIONS, Renal, Fluid and Electrolyte Balance](#)).

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

Driving and Operating Machinery

Some patients may experience visual disturbances, drowsiness, dizziness, vertigo, insomnia, or depression with the use of DIFLUNISAL. Therefore, patients should exercise caution in carrying out potentially hazardous activities that require alertness.

Endocrine and Metabolism

Corticosteroids: DIFLUNISAL is NOT a substitute for corticosteroids. It does NOT treat corticosteroid insufficiency. Abrupt discontinuation of corticosteroids may lead to exacerbation of corticosteroid-responsive illness. Patients on prolonged corticosteroid therapy should have their therapy tapered slowly if a decision is made to discontinue corticosteroids (see [9.4 Drug-Drug Interactions, Glucocorticoids](#))

Gastrointestinal

Serious GI toxicity (sometimes fatal), such as peptic/duodenal ulceration, inflammation, perforation, obstruction, and gastrointestinal bleeding, can occur at any time, with or without warning symptoms, in patients treated with NSAIDs, such as DIFLUNISAL. Minor upper GI problems, such as dyspepsia, commonly occur at any time. Healthcare professionals should remain alert for ulceration and bleeding in patients treated with DIFLUNISAL, even in the absence of previous GI tract symptoms. Most spontaneous reports of fatal GI events are in elderly or debilitated patients and therefore special care should be taken in treating this population. **To minimize the potential risk for an adverse GI event, the lowest effective dose should be used for the shortest possible duration.** For high risk patients, alternate therapies that do not involve NSAIDs should be considered (see [7.1.4 Geriatrics](#)).

Patients should be informed about the signs and/or symptoms of serious GI toxicity and instructed to discontinue using DIFLUNISAL and seek emergency medical attention if they experience any such symptoms. The utility of periodic laboratory monitoring has NOT been demonstrated, nor has it been adequately assessed. Most patients who develop a serious upper GI adverse event on NSAID therapy have no symptoms. Upper GI ulcers, gross bleeding or perforation, caused by NSAIDs, appear to occur in approximately 1% of patients treated for 3 to 6 months, and in about 2 to 4% of patients treated for one year. These trends continue, thus increasing the likelihood of developing a serious GI event at some time during the course of therapy. Even short-term therapy has its risks.

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 DIFLUNISAL 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.

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

Caution should be taken if prescribing DIFLUNISAL to patients with a prior history of peptic/duodenal ulcer disease or gastrointestinal bleeding as these individuals have a greater than 10-fold higher risk for developing a GI bleed when taking a NSAID than patients with neither of these risk factors. Other risk factors for GI ulceration and bleeding include the following: *Helicobacter pylori* infection, increased age, prolonged use of NSAID therapy, excess alcohol intake, smoking, poor general health status, or concomitant therapy with any of the following:

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

There is no definitive evidence that the concomitant administration of histamine H₂-receptor antagonists and/or antacids will either prevent the occurrence of gastrointestinal side effects or allow continuation of 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.

Genitourinary

Some NSAIDs are associated with persistent urinary symptoms (bladder pain, dysuria, urinary frequency), hematuria, or cystitis. The onset of these symptoms may occur at any time after the initiation of therapy with a NSAID. Should urinary symptoms occur, in the absence of an alternate explanation, treatment with DIFLUNISAL should be stopped to ascertain if symptoms disappear. This should be done before urological investigations or treatments are carried out.

Hematologic

NSAIDs inhibiting prostaglandin biosynthesis interfere with platelet function to varying degrees; patients who may be adversely affected by such an action, such as those on anti-coagulants or suffering from haemophilia or platelet disorders, should be carefully observed when DIFLUNISAL is administered.

As an inhibitor of prostaglandin synthetase, DIFLUNISAL has a dose-related effect on platelet function and bleeding time. In normal volunteers, 250 mg twice daily (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 DIFLUNISAL is administered.

Anti-coagulants: Numerous studies have shown that the concomitant use of NSAIDs and anti-coagulants increases the risk of bleeding. Concurrent therapy of DIFLUNISAL with warfarin requires close monitoring of the international normalized ratio (INR). Even with therapeutic INR monitoring, increased bleeding may occur (see [9.4 Drug-Drug Interactions, Oral Anticoagulants](#)).

Anti-platelet Effects: NSAIDs inhibit platelet aggregation and have been shown to prolong bleeding time in some patients. Unlike acetylsalicylic acid (ASA), their effect on platelet function is quantitatively less, or of shorter duration, and is reversible.

DIFLUNISAL and other NSAIDs have no proven efficacy as anti-platelet agents and should NOT be used as a substitute for ASA or other anti-platelet agents for prophylaxis of cardiovascular thromboembolic diseases. Anti-platelet therapies (e.g. ASA) should NOT be discontinued. There is some evidence that use of NSAIDs with ASA can markedly attenuate the cardioprotective effects of ASA (see [9.4 Drug-Drug Interactions, Acetylsalicylic Acid \(ASA\) or other NSAIDs](#)).

Concomitant administration of DIFLUNISAL with low dose ASA increases the risk of GI ulceration and associated complications.

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

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

Hepatic/Biliary/Pancreatic

As with other NSAIDs, borderline elevations of one or more liver enzyme tests (AST, ALT, alkaline phosphatase) may occur in up to 15% of patients. These abnormalities may progress, may remain essentially unchanged, or may be transient with continued therapy. Meaningful (3 times the upper limit of normal) elevations of SGPT (ALT) 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 function test has occurred, should be evaluated for evidence of the development of more severe hepatic reaction while on therapy with DIFLUNISAL. Severe hepatic reactions, including jaundice and cases of fatal hepatitis, liver necrosis, and hepatic failure, some of them with fatal outcomes, have been reported with NSAIDs.

Although such reactions are rare, if abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop (e.g. jaundice), or if systemic manifestations occur (e.g., eosinophilia, associated with rash, etc.), DIFLUNISAL should be discontinued since liver reactions can be fatal.

If there is a need to prescribe DIFLUNISAL in the presence of impaired liver function, it must be done under strict observation (see [Monitoring and Laboratory Tests, Hepatic](#)).

Immune

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

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

Hypersensitivity Reactions: A potentially life-threatening, apparent hypersensitivity syndrome has been reported. This multisystem syndrome includes constitutional symptoms (fever, chills) and cutaneous findings (see [8.3 Less Common Clinical Trial Adverse Reactions, Skin and subcutaneous tissue disorders](#)). 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).

Anaphylactoid Reactions: As with NSAIDs in general, anaphylactoid reactions have occurred in patients without known prior exposure to DIFLUNISAL. In post-marketing experience, rare cases of anaphylactic/ anaphylactoid reactions and angioedema have been reported in patients receiving DIFLUNISAL. DIFLUNISAL should NOT be given to patients with the ASA-triad. This symptom complex typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking ASA or other NSAIDs (see [2 CONTRAINDICATIONS](#)).

ASA-Intolerance: DIFLUNISAL should NOT be given to patients with complete or partial syndrome of ASA-intolerance (rhinosinusitis, urticaria/angioedema, nasal polyps, asthma) in whom asthma, anaphylaxis, urticaria/angioedema, rhinitis or other allergic manifestations are precipitated by ASA or other NSAIDs. Fatal anaphylactoid reactions have occurred in such individuals. As well, individuals with the above medical problems are at risk of a severe reaction even if they have taken NSAIDs in the past without any adverse reaction (see [2 CONTRAINDICATIONS](#)).

Cross-sensitivity: Patients sensitive to one NSAID may be sensitive to any of the other NSAIDs as well.

Monitoring and Laboratory Tests

The following testing or monitoring is recommended for various populations of patients taking DIFLUNISAL. This is not an exhaustive list.

Cardiovascular: Blood pressure should be monitored regularly (see [2 CONTRAINDICATIONS](#), [3 SERIOUS WARNINGS AND PRECAUTIONS BOX](#), [7 WARNINGS AND PRECAUTIONS, Cardiovascular](#) and [9 DRUG INTERACTIONS](#)).

Hematology: Hemoglobin, hematocrit, red blood cells (RBCs), white blood cells (WBCs), and platelets should be checked in patients on long-term treatment with DIFLUNISAL. Concurrent therapy with anticoagulants requires close monitoring of the international normalized ratio (INR) (see [7 WARNINGS AND PRECAUTIONS, Hematologic](#) and [9 DRUG INTERACTIONS](#)).

Lithium plasma concentration (in case of lithium co-prescription) should be monitored (see [9.4 Drug-Drug Interactions, Lithium](#)).

Hepatic: Serum transaminase and bilirubin should be monitored regularly during DIFLUNISAL treatment (see [7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic](#)).

Ophthalmologic: An ophthalmologic examination should be carried out at periodic intervals (see [7 WARNINGS AND PRECAUTIONS, Ophthalmologic](#)).

Pregnancy: If DIFLUNISAL is administered in the middle (approximately 20 weeks) to the end of the second trimester, it is recommended that pregnant women on DIFLUNISAL be closely monitored for amniotic fluid volume since DIFLUNISAL may result in reduction of amniotic fluid volume and even oligohydramnios (see [7.1.1 Pregnant women](#)). DIFLUNISAL is contraindicated for use in the third trimester of pregnancy (see [2 CONTRAINDICATIONS](#), [3 SERIOUS WARNINGS AND PRECAUTIONS BOX, Risk in Pregnancy](#) and [7.1.1 Pregnant women](#)).

Renal: Serum creatinine, creatinine clearance, and serum urea should be monitored in patients during DIFLUNISAL treatment. Electrolytes including serum potassium should be monitored (see [2 CONTRAINDICATIONS](#), [3 SERIOUS WARNINGS AND PRECAUTIONS BOX](#), [7 WARNINGS AND PRECAUTIONS, Renal](#) and [9 DRUG INTERACTIONS](#)).

Neurologic

Some patients may experience drowsiness, dizziness, blurred vision, vertigo, tinnitus, hearing loss, or insomnia with the use of NSAIDs, such as DIFLUNISAL. If patients experience such adverse reaction(s), they should exercise caution in carrying out activities that require alertness.

Ophthalmologic

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

Peri-Operative Considerations

See [2 CONTRAINDICATIONS](#).

Psychiatric

Some patients may experience depression with the use of NSAIDs, such as DIFLUNISAL.

Renal

Long-term administration of NSAIDs, including DIFLUNISAL, to animals has resulted in renal papillary necrosis and other abnormal renal pathology. In humans, there have been reports of acute interstitial nephritis, hematuria, low grade proteinuria, and occasionally nephrotic syndrome.

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

Caution should be used when initiating treatment with NSAIDs, such as DIFLUNISAL, in patients with considerable dehydration. Such patients should be rehydrated prior to initiation of therapy. Caution is also recommended in patients with pre-existing kidney disease.

Diflunisal and its metabolites are eliminated primarily by the kidneys, therefore the drug should be used with great caution in patients with impaired renal function and the elderly. In these cases, lower doses of DIFLUNISAL should be anticipated and patients should be carefully monitored (see [Monitoring and Laboratory Tests, Renal](#)).

During long-term therapy or in patients who may have reduced renal reserve, kidney function should be monitored periodically.

Advanced Renal Disease: See [2 CONTRAINDICATIONS](#).

Fluid and Electrolyte Balance: Use of NSAIDs, such as DIFLUNISAL, can promote sodium retention in a dose-dependent manner, which can lead to fluid retention and edema, and consequences of increased blood pressure and exacerbation of congestive heart failure. Thus, caution should be exercised in prescribing DIFLUNISAL in patients with a history of congestive heart failure, compromised cardiac function, hypertension, increased age or other conditions predisposing to fluid retention (see [7 WARNINGS AND PRECAUTIONS, Cardiovascular](#)).

Use of NSAIDs, such as DIFLUNISAL, can increase the risk of hyperkalemia, especially in patients with diabetes mellitus, renal failure, increased age, or those receiving concomitant therapy with adrenergic blockers, angiotensin-converting enzyme inhibitors, angiotensin-II receptor antagonists, cyclosporin, or some diuretics.

Electrolytes should be monitored periodically (see [2 CONTRAINDICATIONS](#)).

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.

Reproductive Health: Female and Male Potential

- **Fertility**

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

- **Teratogenic Risk**

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 prostaglandin synthetase. Drugs of this class may cause dystocia and delayed parturition in pregnant animals (see [7.1.1 Pregnant women](#)).

Because of the known effect of drugs of this class on the human fetal cardiovascular system (closure of ductus arteriosus), use of DIFLUNISAL during the third trimester of pregnancy is contraindicated (see [2 CONTRAINDICATIONS](#)).

Respiratory

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

Skin

Serious skin reactions: Use of some NSAIDs, such as DIFLUNISAL, has been associated with rare post-market cases of serious, fatal, or otherwise life-threatening skin reactions, including:

- Drug reaction with eosinophilia and systemic symptoms (DRESS),
- Stevens-Johnson syndrome,
- Toxic epidermal necrolysis,
- Exfoliative dermatitis, and
- Erythema multiforme.

Patients appear to be at a higher risk for these events early in the course of therapy, with the onset of cases usually occurring within the first month of treatment. These reactions may be reversible if the causative agent is discontinued and appropriate treatment instituted. Patients should be advised that they should discontinue their NSAID at the first appearance of a skin rash, mucosal lesions, or any other sign of hypersensitivity, and contact their physician immediately for assessment and advice, including which therapies to discontinue.

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, and 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.

7.1 Special Populations

7.1.1 Pregnant Women

DIFLUNISAL is contraindicated for use during the third trimester of pregnancy because of risks of premature closure of the ductus arteriosus and the potential to prolong parturition (see [2 CONTRAINDICATIONS](#) and [16 NON-CLINICAL TOXICOLOGY](#)). Caution is recommended in prescribing DIFLUNISAL during the first and second trimesters of pregnancy, particularly from the middle to end of the second trimester of pregnancy (onset at approximately 20 weeks) due to possible fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment or failure.

Published studies and post-marketing reports describe maternal NSAID use at approximately 20 weeks gestation or later in pregnancy associated with fetal renal dysfunction leading to oligohydramnios, and in some cases, neonatal renal impairment or failure. NSAIDs were shown to cause significant reduction in fetal urine production prior to reduction of amniotic fluid volume. There have also been a limited number of case reports of maternal NSAID use and neonatal renal dysfunction and renal impairment without oligohydramnios, some of which were irreversible, even after treatment discontinuation.

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. Complications of prolonged oligohydramnios may for example, include limb contractures and delayed lung maturation. In some post-marketing cases of impaired neonatal renal function, invasive procedures such as exchange transfusion or dialysis were required.

If after careful consideration of the benefit-risk, NSAID treatment is considered necessary to be administered anywhere from the middle (onset at approximately 20 weeks) to the end of the second trimester of pregnancy, the use should be limited to the lowest effective dose and shortest duration possible. It is also recommended that ultrasound monitoring of amniotic fluid be considered if DIFLUNISAL treatment extends beyond 48 hours and that NSAIDs treatment be discontinued if oligohydramnios occurs, followed by appropriate medical follow up.

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

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

DIFLUNISAL is not recommended in labour and delivery because, through its prostaglandin synthesis inhibitory effect, it may adversely affect fetal circulation and inhibit uterine contractions, thus increasing the risk of uterine hemorrhage (see [2 CONTRAINDICATIONS](#)).

7.1.2 Breast-feeding

DIFLUNISAL is contraindicated in women who are breastfeeding, because of the potential for serious adverse reactions in nursing infants (see [2 CONTRAINDICATIONS](#)).

Diflunisal is excreted in human milk in concentrations of 2% to 7% of those in plasma (see [10.3 Pharmacokinetics, Distribution](#)). Because of the potential for serious adverse reactions in nursing infants from DIFLUNISAL, a decision should be made whether to initiate breastfeeding or to administer the drug, taking into account the importance of the drug to the mother.

7.1.3 Pediatrics

Pediatrics (< 12 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of DIFLUNISAL in pediatric patients below the age of 12 years have not been established; therefore, Health Canada has not authorized an indication for pediatric use (see [2 CONTRAINDICATIONS](#)).

7.1.4 Geriatrics

Geriatrics (> 65 years of age): Patients older than 65 years (referred to in this document as older or elderly) and frail or debilitated patients are more susceptible to a variety of adverse reactions from NSAIDs. The incidence of these adverse reactions increases with dose and duration of treatment. In addition, these patients are less tolerant to ulceration and bleeding. Most reports of fatal GI events are in this population. Older patients are also at risk of lower esophageal injury including ulceration and bleeding. For such patients, consideration should be given to a starting dose lower than the one usually recommended, with individual adjustment when necessary and under close supervision (see [4.2 Recommended Dose and Dosage Adjustment, Geriatrics](#) and [7 WARNINGS AND PRECAUTIONS](#)).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The most common adverse reactions encountered with nonsteroidal 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 (see [7 WARNINGS AND PRECAUTIONS, Gastrointestinal](#)).

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

The following adverse reactions have been observed in controlled clinical trials or since the drug was marketed.

Table 2 - Adverse reactions reported with DIFLUNISAL

	Incidence (3% to 9%)	Incidence (1% to 3%)
Ear and labyrinth disorders		Tinnitus
Gastrointestinal disorders	Nausea Dyspepsia GI pain Diarrhea	Vomiting Constipation Flatulence
General disorders and administration site conditions		Fatigue

	Incidence (3% to 9%)	Incidence (1% to 3%)
Nervous system disorders	Headache	Dizziness Somnolence Insomnia
Skin and subcutaneous tissue disorders	Rash	

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 adverse drug reactions are listed below to alert physicians of their occurrence.

Cardiac disorders: Palpitation, syncope.

General disorders and administration site conditions: Chest pain.

Musculoskeletal and connective tissue disorders: Muscle cramps.

Respiratory, thoracic and mediastinal disorders: Dyspnea.

Renal and urinary disorders: Nephrotic syndrome.

8.3 Less Common Clinical Trial Adverse Reactions

Less Common Adverse Drug Reactions (<1%)

The following adverse reactions have been reported with an incidence of less than 1% in controlled clinical trials or since the drug was marketed.

Blood and lymphatic system disorders: Thrombocytopenia, leukopenia, pancytopenia, agranulocytosis (rarely), hemolytic anemia.

Eye disorders: Transient visual disturbance (including blurred vision).

Gastrointestinal disorders: Peptic ulcer, gastrointestinal bleeding, gastrointestinal perforation, gastritis, stomatitis.

General disorders and administration site conditions: Asthenia, edema, sweating.

Hepatobiliary disorders: Jaundice, cholestasis, liver function abnormalities, hepatitis.

Immune system disorders: Acute anaphylactic reaction with bronchospasm, angioedema, hypersensitivity vasculitis, hypersensitivity syndrome (see [7 WARNINGS AND PRECAUTIONS, Immune](#)).

Metabolism and nutrition disorders: Anorexia.

Nervous system disorders: Vertigo, light-headedness, paresthesia.

Psychiatric disorders: Nervousness, depression, hallucinations, confusion.

Renal and urinary disorders: Dysuria, renal impairment (including renal failure), interstitial nephritis, hematuria, proteinuria.

Skin and subcutaneous tissue disorders: Erythema multiforme, stevens-johnson syndrome, toxic epidermal necrolysis, exfoliative dermatitis, pruritus, dry mucous membranes, photosensitivity, urticaria.

9 DRUG INTERACTIONS

9.3 Drug-Behavioural Interactions

There are no specific studies about the effects on the ability to drive vehicles and to use machinery. Patients who experience visual disturbances or other central nervous system disturbances should refrain from these activities (see [7 WARNINGS AND PRECAUTIONS, Driving and Operating Machinery](#)).

Concurrent use of alcohol with an NSAID may increase the risk of gastrointestinal side effects, including ulceration and hemorrhage (see [7 WARNINGS AND PRECAUTIONS, Gastrointestinal](#)).

9.4 Drug-Drug Interactions

The drugs listed in Table 3 are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 3 - Established or Potential Drug-Drug Interactions

Proper/Common name	Source of Evidence	Effect	Clinical comment
Acetylsalicylic Acid (ASA) or other NSAIDs	CT	<p>Some NSAIDs (e.g. ibuprofen) may interfere with the anti-platelet effects of low dose ASA, possibly by competing with ASA for access to the active site of cyclooxygenase-1.</p> <p>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.</p> <p>In normal volunteers, a small decrease in DIFLUNISAL levels was observed when multiple doses of DIFLUNISAL and acetylsalicylic acid were administered concomitantly.</p>	<p>The use of DIFLUNISAL in addition to any other NSAID, including over-the-counter ones (such as ASA and ibuprofen) for analgesic and/or anti-inflammatory effects is NOT recommended because of the absence of any evidence demonstrating synergistic benefits and the potential for additive adverse reactions.</p> <p>The exception is the use of low dose ASA for cardiovascular protection, when another NSAID is being used for its analgesic/anti-inflammatory effect, keeping in mind that combination NSAID therapy is associated with additive adverse reactions.</p>
Acetaminophen	CT	<p>Concomitant administration of DIFLUNISAL and acetaminophen to normal volunteers resulted in significantly increased plasma levels of acetaminophen. Acetaminophen had no effect on plasma levels of diflunisal.</p>	<p>Acetaminophen in high doses has been associated with hepatotoxicity, concomitant administration of DIFLUNISAL and acetaminophen should be used cautiously, with careful monitoring of patients.</p>

Proper/Common name	Source of Evidence	Effect	Clinical comment
Indomethacin	CT	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.	Indomethacin and DIFLUNISAL should not be used concomitantly.
Naproxen	CT	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.	
Sulindac	CT	The concomitant administration of DIFLUNISAL and sulindac in normal volunteers resulted in lowering of the plasma levels of the active sulindacsulfide metabolite by approximately one - third.	

Proper/Common name	Source of Evidence	Effect	Clinical comment
Antacids	T	<p>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.</p> <p>Coadministration of aluminum hydroxide suspension significantly decreases absorption of diflunisal by approximately 40%.</p>	
Anti-hypertensives e.g., Angiotensin Converting Enzyme (ACE) Inhibitors, Angiotensin Receptor Blockers (ARBs), or Beta-Blockers (including propranolol)	T	<p>NSAIDs may diminish the anti-hypertensive effect of ACE inhibitors, ARBs, or Beta-Blockers.</p> <p>Combinations of ACE inhibitors, angiotensin-II antagonists, or diuretics with NSAIDs might have an increased risk for acute renal failure and hyperkalemia.</p>	<p>Blood pressure and renal function (including electrolytes) should be monitored more closely in this situation, as occasionally there can be a substantial increase in blood pressure (see Z WARNINGS AND PRECAUTIONS, Renal, Fluid and Electrolyte Balance).</p>
Anti-platelet Agents (including ASA)	T	<p>There is an increased risk of bleeding, via inhibition of platelet function, when antiplatelet agents are combined with NSAIDs, such as DIFLUNISAL (see Z WARNINGS AND PRECAUTIONS, Hematologic, Anti-platelet Effects).</p>	<p>Monitor patients for signs of bleeding (see Z WARNINGS AND PRECAUTIONS, Hematologic).</p>

Proper/Common name	Source of Evidence	Effect	Clinical comment
Cyclosporin	T	Increased risk of nephrotoxicity, particularly in elderly subjects.	Monitor for signs of worsening renal function. Monitor for dosage adjustment.
Digoxin	T	NSAIDs may exacerbate cardiac failure, reduce GFR and increase plasma glycoside levels. A pharmacokinetic interaction between DIFLUNISAL and digoxin has not been demonstrated.	Caution is advised, in particular in patients with renal impairment, since NSAIDs may reduce renal function and decrease renal clearance of cardiac glycosides. Monitor serum digoxin levels
Diuretics e.g., Furosemide	CT	Clinical studies as well as post-marketing observations have shown that NSAIDs can reduce the effect of diuretics. 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.	Patients taking diuretics are at greater risk of developing renal failure secondary to a decrease in renal blood flow caused by prostaglandin inhibition (see 7 WARNINGS AND PRECAUTIONS, Renal). Observe patients for signs of worsening renal function, in addition to assuring diuretic efficacy including antihypertensive effects.
Hydrochlorothiazide	CT	In normal volunteers, concomitant administration of DIFLUNISAL and hydrochlorothiazide resulted in significantly increased plasma levels of hydrochlorothiazide. DIFLUNISAL decreased the hyperuricemic effect of hydrochlorothiazide.	

Proper/Common name	Source of Evidence	Effect	Clinical comment
Glucocorticoids	CT	Some studies have shown that the concomitant use of NSAIDs and oral glucocorticoids increases the risk of GI adverse events such as ulceration and bleeding. This is especially the case in older (> 65 years of age) individuals.	Monitor patients, particularly those over 65 years of age, for signs of bleeding (see 7 WARNINGS AND PRECAUTIONS, Gastrointestinal).
Lithium	C, CT	Concurrent use of NSAIDs with lithium has been reported to increase steady-state plasma lithium concentrations. NSAIDs have produced elevations in plasma lithium levels and reductions in renal lithium clearance. The mean minimum lithium concentration increased 15%, and the renal clearance decreased by approximately 20%. This effect has been attributed to inhibition of renal prostaglandin synthesis by NSAIDs.	It is recommended to monitor lithium plasma concentrations when starting the NSAID use, during treatment, and following concurrent use.
Methotrexate	C	NSAIDs have been reported to decrease the tubular secretion of methotrexate and potentiate its toxicity (e.g., neutropenia, thrombocytopenia, renal dysfunction).	Caution should be used if DIFLUNISAL is administered concomitantly with methotrexate. Monitor patients for methotrexate toxicity.

Proper/Common name	Source of Evidence	Effect	Clinical comment
Oral Anticoagulants	CT	<p>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.</p>	<p>Accordingly, when DIFLUNISAL is administered with oral anticoagulants, the prothrombin time should be closely monitored during and for several days after concomitant drug administration.</p> <p>Adjustment of dosage of oral anticoagulants may be required.</p>
Oral hypoglycemics e.g., Tolbutamide	CT	<p>In vitro studies with human plasma and serum indicated that diflunisal was extensively (>95%) bound to protein. Therefore, DIFLUNISAL may compete for binding sites with drugs such as oral hypoglycemic agents.</p> <p>In diabetic patients receiving DIFLUNISAL and tolbutamide, no significant effects were seen on tolbutamide plasma levels or fasting blood glucose.</p>	<p>Patients should be monitored.</p>

Proper/Common name	Source of Evidence	Effect	Clinical comment
Selective Serotonin Reuptake Inhibitors (SSRIs)		<p>Serotonin release by platelets plays an important role in hemostasis.</p> <p>Case-control and cohort epidemiological studies showed that concomitant use of drugs that interfere with serotonin reuptake and an NSAID may potentiate the risk of bleeding more than an NSAID alone.</p> <p>Concomitant administration of NSAIDs and SSRIs may increase the risk of gastrointestinal ulceration and bleeding (see 7 WARNINGS AND PRECAUTIONS, Gastrointestinal).</p>	Monitor for signs of bleeding.
Tacrolimus		Possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus, particularly in elderly subjects.	<p>Monitor for necessary dosage adjustment.</p> <p>Monitor for signs of worsening renal function.</p>
Quinolone antibacterials	C	There have been isolated reports of convulsions which may have been due to concomitant use of quinolones and NSAIDs.	Patients should be observed for adjustment of dose if required.

C = Case Study; CT = Clinical Trial; T = Theoretical

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Diflunisal is a nonsteroidal anti-inflammatory drug (NSAID) 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.

10.2 Pharmacodynamics

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 ED₅₀ 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 ED₅₀ for diflunisal was 9.5 mg/kg. This fact indicates a relatively long duration of action.

10.3 Pharmacokinetics

Pharmacokinetics

As in 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 mcg/mL [mean± standard deviation (S.D.)] were observed following 250 mg doses; 87±17 mcg/mL were observed following 500 mg doses; and 124±11 mcg/mL were observed following single 1000 mg doses. However, following administration of 250 mg b.i. d., a mean peak level of 56±14 mcg/mL was observed on day 8, while the mean peak level after 500 mg b.i.d. for 11 days was 190±33 mcg/mL. The plasma half-life of diflunisal is 8 to 12 hours. Because of its long half-life and non-linear 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.

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 ¹⁴COOH, were obtained in 1 hour. Plasma levels of diflunisal at 50 and 100 mg/kg/day averaged 45 and 53 mcg/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.

Diflunisal is rapidly and completely absorbed following oral administration with peak plasma concentrations occurring between 2 to 3 hours.

Distribution

Distribution of radioactivity in rats given diflunisal ¹⁴COOH generally followed that for body water. After 24 hours, traces (0.6 mcg/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.

Diflunisal appears in human milk in concentrations of 2% to 7% of those in plasma (see [7.1.2 Breast-feeding](#)). More than 99% of diflunisal in plasma is bound to proteins.

Metabolism

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

Elimination

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.

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.

Special Populations and Conditions

Pregnancy and Breast-feeding: Diflunisal appears in human milk in concentrations of 2% to 7% of those in plasma.

11 STORAGE, STABILITY AND DISPOSAL

Store at room temperature 15°C to 30°C. Protect from light and moisture.

Keep out of reach and sight of children.

12 SPECIAL HANDLING INSTRUCTIONS

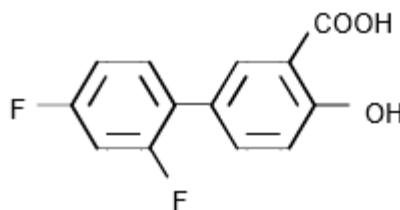
None.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	Diflunisal
Chemical name:	2',4'-difluoro-4-hydroxy-3-biphenylcarboxylic acid
Molecular formula and molecular mass:	C ₁₃ H ₈ F ₂ O ₃ and 250.20
Structural formula:	



Physicochemical properties:	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.
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14 CLINICAL TRIALS

14.2 Comparative Bioavailability Studies

A bioavailability study was performed using healthy human volunteers. The rate and extent of absorption of diflunisal after a single 500 mg oral dose of DIFLUNISAL and DOLOBID (diflunisal) 500 mg tablets was measured and compared. The results of this bioavailability study are summarized in Table 4.

Table 4: Results of a Bioavailability Study Comparing DIFLUNISAL to DOLOBID

Parameter	Geometric Mean Arithmetic Mean (C.V.)		
	Diflunisal	Dolobid (diflunisal)	Ratio of Means %
AUC _T (mcg•hr/mL)	885 910 (25)	900 922 (24)	98.3
AUC _I (mcg•hr/mL)	907 933 (25)	923 945 (24)	98.3
C _{max} (mcg/mL)	63.5 64.5 (18)	69.9 71.0 (19)	90.8
T _{max} * (h)	2.95 (1.15)	2.82 (1.14)	Not applicable
T _½ * (h)	9.94 (1.75)	10.07 (1.48)	Not applicable

*For the T_{max} and t_½ parameters, these are the arithmetic means (standard deviations).

C.V. = coefficient of variation, AUC_T = area under the curve to the last quantifiable concentration, AUC_I = area under the curve to infinity, C_{max} = maximum plasma concentration, T_{max} = time to peak plasma concentration, T_½ = drug half-life

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology

Acute Toxicity

LD ₅₀ (and 95% probability level inclusive - sexes combined only - of the 20% confidence limits) mg/kg.		
SPECIES	SEX	Oral
Mice*	F	412 (319-532)
	M	423 (289-619)
	Combined	412 (344-494)
Rat*	F	425 (289-626)
	M	605 (474-772)
	Combined	485 (406-579)

* 6 groups, each with 5 animals/sex were treated with the test article (diflunisal) at logarithmically spaced doses.

F = Female, M = Male

Mortality generally occurred over a 24 hour period post-dosing in mice, and a 4-hour period in rats.

Signs of systemic toxicity included piloerection, and/or paleness, lethargy, reduced motor activity, hunched back, ptosis, and/or coma.

Necropsy of these animals generally demonstrated paleness of kidneys, liver, and/or spleen, reddening of the stomach and/or small intestine, and/or dark (or pale) red mucoid material in the small intestine, petechiae throughout the liver, reddening of the lungs, enlargement of the folds or dark foci on the mucosa of the glandular portion of the stomach.

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 day 61 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 purebred 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, and 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 2mm 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 post-partum, 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. Post-mortem examination revealed focal gastritis in one female rat which had received 40 mg/kg/day. At the end of 59 weeks of treatment, post-mortem 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.

Genotoxicity

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 and Developmental Toxicology

No evidence of impaired fertility was found in reproduction studies in rats at doses up to 100 mg/kg/day (see [7.1.1 Pregnant Women](#) and [7 WARNINGS AND PRECAUTIONS, Reproductive Health: Female and Male Potential, Teratogenic Risk](#)).

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrDIFLUNISAL

Diflunisal Tablets

Read this carefully before you start taking **DIFLUNISAL** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **DIFLUNISAL**.

Serious Warnings and Precautions

Heart and blood vessel problems:

- DIFLUNISAL can cause heart and blood vessel problems like heart attacks, stroke, blood clots, high blood pressure and heart failure. These can lead to death.
- The risk of having heart problems is higher if you take DIFLUNISAL for long periods of time and/or at higher doses and/or in people who have heart disease.
- Tell your healthcare professional if you have or had heart attacks problems, high blood pressure or diabetes.

Stomach and intestine (gastrointestinal) problems:

- DIFLUNISAL can cause stomach and intestine problems like ulcers, inflammation, bleeding, holes/perforation, blockage or pain.

Talk to your healthcare professional about any medical conditions you have and drugs you are taking.

Pregnancy:

- **DO NOT** take DIFLUNISAL if you are pregnant and in a later stage of pregnancy (28 weeks or later).
- If you are pregnant and in an earlier stage of pregnancy (less than 28 weeks) **only** take DIFLUNISAL if you are told to do so by your healthcare professional.
- Medicines like DIFLUNISAL may cause harm to you and your baby. Your healthcare professional will need to closely monitor your health and that of your baby (including your amniotic fluid levels) if they prescribe DIFLUNISAL during this time.
- Tell your healthcare professional right away if you become pregnant, think you may be pregnant or want to get pregnant during your treatment with DIFLUNISAL.

What is DIFLUNISAL used for?

DIFLUNISAL is used in adults and children 12 years of age and older to:

- Treat the signs and symptoms of arthritis disorders such as:
 - Osteoarthritis
 - Rheumatoid arthritis
- Help relieve mild to moderate pain with inflammation:
 - in muscle and bone injuries (sprains and strains)
 - after surgery (including dental surgery)
 - after giving birth (postpartum pain)

How does DIFLUNISAL work?

DIFLUNISAL belongs to a group of medicines called nonsteroidal anti-inflammatory drugs (NSAIDs). It can reduce the chemicals produced by your body which cause pain and swelling.

DIFLUNISAL does NOT cure your illness or prevent it from getting worse. It can only treat the symptoms and relieves pain and inflammation as long as you take it.

What are the ingredients in DIFLUNISAL?

Medicinal ingredients: Diflunisal

Non-medicinal ingredients: Colloidal silicon dioxide, croscarmellose sodium, D&C yellow #10 (250 mg tablet only), FD&C yellow #6, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, starch and titanium dioxide.

DIFLUNISAL comes in the following dosage forms:

Tablets: 250 mg and 500 mg

Do not use DIFLUNISAL if you:

- have heart bypass surgery (planning to have or recently had).
- have severe, uncontrolled heart failure.
- have bleeding in the brain or other bleeding disorders.
- are pregnant and in a later stage of pregnancy (28 weeks or later).
- are currently breastfeeding (or planning to breastfeed).
- are allergic to diflunisal or any other ingredients in this medicine or the container.
- have a history of asthma, hives, growths in your nose, sinus swelling or symptoms of an allergic reaction after taking acetylsalicylic acid (ASA) or other NSAIDs.
- have active stomach or intestine ulcers.
- have active bleeding from the stomach or gut.

- have inflammatory bowel disease (Crohn’s Disease or Ulcerative Colitis).
- have liver disease (active or severe).
- have kidney disease (severe or worsening).
- have high potassium in the blood.
- are under 12 years old.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take DIFLUNISAL. Talk about any health conditions or problems you may have, including if you:

- have high blood pressure, high cholesterol or diabetes
- have or had heart attacks, chest pain, heart disease, stroke or heart failure
- have poor blood flow to your extremities (like hands and feet)
- smoke or used to smoke
- drink a lot of alcohol
- have a stomach infection
- have liver or kidney problems, urine problems or are dehydrated
- have a history of ulcer or bleeding from the stomach or gut (small or large intestine)
- have other bleeding or blood problems
- have asthma
- have immune system problems

Other warnings you should know about:

Serious Side Effects: DIFLUNISAL may cause serious side effects, including:

- **Allergic Reactions:** In rare cases, serious or life-threatening allergic reactions have been reported with some NSAIDs, such as DIFLUNISAL. See the Serious Side Effects section below for more information on the symptoms.
- **Reye’s Syndrome (disorder of swelling in the brain and liver):** Reye’s syndrome has been associated with the use of Acetylsalicylic acid (ASA). Since DIFLUNISAL is a byproduct of ASA, its use may also be associated with Reye’s syndrome.
- The use of DIFLUNISAL may hide symptoms of a **fever**.
- **Blood and bleeding problems:**
 - DIFLUNISAL can cause blood problems, bleeding and prolonged bleeding.
 - Taking DIFLUNISAL with the following medicines can increase the risk of bleeding:
 - anticoagulants (prevents blood clots), corticosteroids (anti-inflammatory), or antidepressants like selective serotonin reuptake inhibitors (SSRIs).

- **Serious Skin Reactions:** In rare cases, serious or life-threatening skin reactions (see the [Serious side effects and what to do about them table](#) below) have been reported with some NSAIDs, such as DIFLUNISAL. These skin problems most often happen during the first month of treatment. Tell your healthcare professional immediately if you notice any changes in your skin both during and after treatment.

DIFLUNISAL might cause you to become more sensitive to sunlight. Sunlight or sunlamps may cause sunburn, skin blisters, skin rash, redness, itching or discolouration, or vision changes. If you have a reaction from the sun, talk to your healthcare professional.

Check-ups and testing: You will have regular visits with your healthcare professional during treatment with DIFLUNISAL to monitor your health. They will:

- Check your blood pressure.
- Check your eyes. DIFLUNISAL can cause blurred or reduced vision.
- Do blood and urine tests to check your liver, kidney and blood health.

Surgery: Tell any doctor, dentist, pharmacist or healthcare professional that you see, that you are taking this medicine. This is especially important if you are planning to have heart surgery.

Driving and using machinery: DIFLUNISAL may cause eye or nervous system problems. This includes tiredness, trouble sleeping, blurred vision, spinning or dizziness (vertigo), hearing problems or depression. Be careful about driving or participating in activities that require you to be alert. If you become drowsy, dizzy or light-headed after taking DIFLUNISAL, do NOT drive or operate machinery.

Fertility in Women: DIFLUNISAL may affect your fertility. This means that it may be difficult for you to have a child. If you have trouble having a child, you might need to stop taking DIFLUNISAL. Talk to your healthcare professional if you have questions about this.

Adults (65 years or older): Side effects like gastrointestinal problems may happen more often. Your healthcare professional might have you start with a lower dose of DIFLUNISAL. They will monitor your health during and after treatment.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with DIFLUNISAL:

- Acetylsalicylic Acid (ASA) or other NSAIDs, used to treat pain, fever, or inflammation, like:
 - celecoxib, diclofenac, ibuprofen, indomethacin, ketorolac, meloxicam, naproxen, sulindac, acetaminophen
- Antacids, used to treat ulcers

- Medicines used to treat depression (antidepressants) like citalopram, fluoxetine, paroxetine, sertraline, and lithium
- Medicines used to treat high blood pressure, like enalapril, ramipril, candesartan, irbesartan, propranolol
- Medicines used as blood thinners or to prevent blood clots, like warfarin, ASA, clopidogrel
- Medicines used to lower extra fluid levels (diuretics), like furosemide, hydrochlorothiazide
- Corticosteroids (including glucocorticoids), used to treat inflammation, like prednisone
- Medicines used to treat diabetes like oral sulphonylurea hypoglycemics (e.g., tolbutamide), or other oral hypoglycemics
- Medicines used to treat bacteria infections (antibiotics) like quinolone or sulphonamide
- Medicines used to lower the risk of organ transplant rejection, like cyclosporine and tacrolimus
- Digoxin, used to treat heart disorders
- Medicines used to treat different cancers, like methotrexate
- Alcohol

How to take DIFLUNISAL:

- Take exactly as your healthcare professional has told you. They should recommend the lowest dose possible for your treatment for the shortest time needed.
- If you will be taking this medicine for more than 7 days, see your healthcare professional regularly. They will check if it is working for you and if it is causing you any side effects.
- **This medication has been prescribed specifically for you. Do NOT give it to anyone else. It may harm them, even if their symptoms seem to be similar to yours.**
- Take right after a meal or with food to avoid an upset stomach.
- Swallow your tablets whole. Do NOT break, crush, or chew them.

Usual dose:

Adults and Children 12 years and older:

- Your healthcare professional will decide on the best dosage for you based on your condition.
- Your healthcare professional may change your dose, stop your treatment for a period of time or recommend that you stop treatment completely. This may happen if you:
 - experience serious side effects, or
 - your disease gets worse.

Overdose:

If you think you, or a person you are caring for, have taken too much DIFLUNISAL, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

- If you miss a dose, take the dose as soon as possible. Take your next dose at the usual time.
- If it is close to the time of your next dose, skip the missed dose. Take your next dose at the usual time.
- Do not take two doses at the same time to make up for a forgotten dose.

What are possible side effects from using DIFLUNISAL?

These are not all the possible side effects you may have when taking DIFLUNISAL. If you experience any side effects not listed here, tell your healthcare professional .

- Nausea, vomiting, diarrhea, constipation, stomach upset/abdominal pain, heartburn, indigestion, feeling gassy
- Lack of energy, tired
- Headache, dizziness, light-headedness
- Feeling of burning/prickliness/numbing
- Confusion, hard to concentrate or think, nervousness, hallucinations
- Bruises, skin rash, swelling, hives or itching
- Taste disorder, thirst, dry mouth
- Muscle pain
- Mouth sores/swelling
- Hair loss
- Increased sweating
- Eating disorder, anorexia
- Temporary vision problems, blurred vision

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
COMMON			
Gastrointestinal (GI) problems (bleeding, blockage, holes, ulcers or inflammation in your GI tract): blood in vomit, black tarry or bloody stool, dizziness, stomach pain, bloating, loss of appetite, weight loss, nausea, vomiting, constipation or diarrhea, chills or fever		✓	
Hypertension (high blood pressure): fatigue, dizziness or fainting, chest pain	✓		
UNCOMMON			
Anaphylaxis/hypersensitivity (severe allergic reactions): sudden wheeziness and chest pain or tightness; or swelling of eyelids, face, lips, tongue or throat, fever, chills, swelling or anaphylactic reaction/shock			✓
Aseptic meningitis (inflammation of the protective lining of the brain that is not caused by infection): Headaches, stiff neck, nausea and vomiting, fever or clouding of consciousness			✓
Blood problems (breakdown of red blood cells, low white and/or red blood cell or platelet count): feeling tired or weak, pale skin, dizziness, fainting, thirst, rapid breathing, bruising or bleeding for longer than usual if you hurt yourself, fever, chills,		✓	
Congestive heart failure (heart does not pump blood as well as it should): shortness of breath, fatigue and weakness, swelling in ankles, legs and feet, cough, fluid retention, lack of appetite, nausea, rapid or irregular heartbeat, reduced ability to exercise			✓
Cystitis (bladder infection): increased need to urinate, pain in the pelvis or lower back, frequent urination during the night, cloudy urine that may contain blood, burning or		✓	

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
pain urinating			
Depression (sad mood that will not go away): difficulty sleeping or sleeping too much, changes in appetite or weight, reduced sex drive and thoughts of death or suicide.		✓	
Kidney disorder/problems (including kidney failure): nausea, vomiting, fever, swelling of extremities, fatigue, thirst, dry skin, irritability, dark urine, increased or decreased urine output, blood in the urine, rash, weight gain (from retaining fluid), loss of appetite, mental status changes (drowsiness, confusion, coma)		✓	
Liver problems (including hepatitis, liver failure, cholestasis): yellowing of your skin and eyes (jaundice), right upper stomach area pain or swelling, nausea or vomiting, unusual dark urine, unusual tiredness		✓	
Lung problems, asthma: increased shortness of breath, wheezing, difficulty breathing, cough and chest tightness, irregular heartbeat			✓
Myocardial infarction (heart attack): pressure or squeezing pain between the shoulder blades, in the chest, jaw, left arm or upper abdomen, shortness of breath, dizziness, fatigue, light-headedness, clammy skin, sweating, indigestion, anxiety, feeling faint and possible irregular heartbeat.			✓
Stroke (bleeding or blood clot in the brain): sudden numbness, weakness or tingling of the face, arm, or leg, particularly on one side of the body, sudden headache, blurry vision, difficulty swallowing or speaking, or lethargy, dizziness, fainting, vomiting, trouble understanding, trouble with walking			✓

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
and loss of balance			
Tinnitus (hearing problems): includes ringing, buzzing, clicking or hissing in ears, loss of hearing		✓	
Vertigo (a sense of severe spinning dizziness, lightheadedness)		✓	
RARE			
Serious Skin Reactions: fever, severe rash, swollen lymph glands, flu-like feeling, blisters and peeling skin that may start in and around the mouth, nose, eyes and genitals and spread to other areas of the body, swelling of face and/or legs, yellow skin or eyes, shortness of breath, dry cough, chest pain or discomfort, feeling thirsty, urinating less often, less urine or dark urine, hives, red or dry itchy skin, purple or red spots on skin			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html>) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store at room temperature 15°C to 30°C.

Protect from light and moisture.

Keep out of reach and sight of children.

If you want more information about DIFLUNISAL:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html>). Find the Patient Medication Information on the manufacturer's website (<https://www.aapharma.ca/en/>), or by calling 1-877-998-9097.

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