# THERAPEUTICS

**Brands**
- Dolobid

**Generic?**
Yes

**Class**
- Nonsteroidal anti-inflammatory (NSAID)

**Commonly Prescribed For**
(FDA approved in bold)
- Mild-to-moderate pain
- Arthritis
- Management of postoperative dental pain
- Headaches, arthritis, painful inflammatory disorders
- Musculoskeletal pain

## How the Drug Works
- Diflunisal is a nonacetylated salicylate. Like other NSAIDs, inhibits cyclo-oxygenase thus inhibiting synthesis of prostaglandins, a mediator of inflammation

## How Long until It Works
- Less than 4 hours

## If It Works
- Continue to use

## If It Doesn’t Work
- Some patients only have a partial response where some symptoms are improved but others persist or continue to wax and wane without stabilization of pain
- Other patients may be nonresponders, sometimes called treatment-resistant or treatment-refractory
- Consider increasing dose, switching to another agent or route, or adding an appropriate augmenting agent or utilizing an entirely different nonpharmacologic approach (e.g. neuromodulation)
- Consider biofeedback or hypnosis for pain
- Consider physical medicine approaches to pain relief
- Consider the presence of noncompliance and counsel patient
- Switch to another agent with fewer AEs

## Best Augmenting Combos for Partial Response or Treatment-Resistance
- Consider adding an opioid

## Tests
- None for healthy individuals
- Blood urea nitrogen (BUN)/creatinine – if suspected renal issues
- Consider checking liver function tests for long-term use

## ADVERSE EFFECTS (AEs)

### How Drug Causes AEs
- Effects on prostaglandins likely cause most GI and renal AEs

### Notable AEs
- Inhibition of platelet aggregation is usually mild
- Elevation in hepatic transaminases (usually borderline)
- Headache, dizziness, insomnia, somnolence, fatigue
- Rash
- Nausea, dyspepsia, GI pain, diarrhea, constipation, flatulence, vomiting, GI ulceration
- Tinnitus (1% to 3%)

### Life-Threatening or Dangerous AEs
- GI ulcers and bleeding, increasing with duration of therapy
- May worsen congestive heart failure
- May increase risk of fluid retention and edema, cardiovascular events, including myocardial infarction and stroke
- Renal insufficiency, proteinuria, and hyperkalemia
- Thrombocytopenia
- Hypersensitivity reactions – most common in patients with asthma, anaphylactoid reaction, Stevens–Johnson syndrome, toxic epidermal necrolysis

### Weight Gain
- Unusual
Sedation
- Not unusual

What to Do about AEs
- For significant GI or intracranial bleeding, stop drug. Some AEs respond to lowering dose
- Administer tablet with food or milk to decrease GI distress
- For GI irritation, consider sucralfate, H₂-receptor antagonist, proton pump inhibitors, or prostaglandin analog

Best Augmenting Agents for AEs
- Proton pump inhibitors may reduce risk of GI ulcers
- Many AEs cannot be improved with an augmenting agent

DOSING AND USE

Usual Dosage Range
- 500–1500 mg/day

Dosage Forms
- Tablets: 500 mg

How to Dose
- Pain management: can give initial loading dose 500 mg, 1000 mg followed by 250–500 mg every 8–12 hours

Dosing Tips
- Taking with food decreases absorption and reduces GI AEs

Overdose
- GI distress or bleed, drowsiness, paresthesias, and numbness are most common. Severe overdose may cause hypertension, metabolic acidosis, hepatic or renal failure, and cardiac arrest. Consider multiple doses of activated charcoal or hemodialysis for severe cases

Long-Term Use
- Safe for long-term use

Habit Forming
- No

How to Stop
- No need to taper

Pharmacokinetics
- Half-life is 8–12 hours, dose peak at 2–3 hours. Extensive hepatic metabolism; metabolic pathways are saturable. Renal excretion, urine (~3% unchanged drug, 90% as glucuronide conjugates) within 72–96 hours. Greater than 99% protein bound

Drug Interactions
- Use with alcohol, bisphosphonates, corticosteroids, anticoagulants, and other NSAIDs increases GI bleeding risk
- Cyclosporine and other NSAIDs increase risk of nephrotoxicity
- Cholestyramine may decrease absorption
- Aspirin use may decrease NSAID serum levels and increases risk of GI AEs
- May blunt effectiveness of beta-blockers and angiotensin-converting enzyme inhibitors
- May decrease effect of loop diuretics and spironolactone
- May increase drug levels and effects of digoxin, aminoglycosides, methotrexate, lithium, and phenytoin

Other Warnings/Precautions
- Risk factors for GI bleeding include smoking, alcoholism, older age, poor health status, and treatment with anticoagulants or corticosteroids
- May cause photosensitivity

Do Not Use
- Hypersensitivity to any NSAID, treatment with anticoagulants, renal or hepatic disease, age under 12, rectal bleeding or proctitis (suppositories)

SPECIAL POPULATIONS

Renal Impairment
- Use with caution in chronic renal insufficiency as may worsen renal function. Use low dose and monitor frequently

Hepatic Impairment
- Use with caution in patients with significant disease. May have increased risk of GI bleeding and toxicity
Cardiac Impairment
- May cause fluid retention and decompensation in patients with cardiac failure. May cause hypertension or lower effectiveness of antihypertensives

Elderly
- More likely to experience GI bleeding or CNS AEs

Pregnancy
- Category C, except category D in 3rd trimester. May prolong pregnancy and increase risk of septal heart defects, incidence of dystocias, and delivery time. May cause premature closure of ductus arteriosus and pulmonary hypertension. Do not use, especially in 3rd trimester

Breast-Feeding
- Most NSAIDs are excreted in breast milk. Do not breast-feed due to effects on infant cardiovascular system

Potential Advantages
- Less apt to result in excessive bleeding/GI bleeding

Potential Disadvantages
- Usual NSAID drawbacks

Primary Target Symptoms
- Pain
- Inflammation

Pearls
- Nonacetylated salicylates like diflunisal have fewer effects on platelet function and less GI mucosal insult than traditional nonselective NSAIDs

Suggested Reading


