DICLOFENAC

**Therapeutics**

**Brands**
- Cambria, Vataflam, Voltaren-XR, Zipsor, Arthrotec® (in combination with misoprostol)

**Generic?**
Yes

**Class**
- Nonsteroidal anti-inflammatory (NSAID); a phenylacetic acid derivative

**Commonly Prescribed For**
(FDA approved in bold)
- Relief of mild-to-moderate acute pain
- Relief of mild-to-moderate pain; primary dysmenorrhea
- Acute and chronic treatment of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis
- Treatment of acute migraine with or without aura
- Arthrotec® (in combination with misoprostol): rheumatoid arthritis, osteoarthritis
- Postoperative pain/posttraumatic pain (particularly in orthopedics)

**How the Drug Works**
- Inhibits cyclo-oxygenase thus inhibiting synthesis of prostaglandins, a mediator of inflammation
- It is conceivable that diclofenac may inhibit the thromboxane–prostanoid receptor, affect arachidonic acid release and uptake, inhibit lipoxigenase enzymes, and activate the nitric oxide–cGMP antinociceptive pathway. Other novel mechanisms of action may include the inhibition of substrate P, inhibition of peroxisome proliferator activated receptor gamma (PPAR-gamma), blockage of acid-sensing ion channels, alteration of interleukin-6 production, and inhibition of N-methyl-D-aspartate (NMDA) receptor hyperalgesia
- It is conceivable that it may also act as a potassium channel opener.

**How Long until It Works**
- Less than 2 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
- Consider evaluation for another diagnosis or for a comorbid condition (e.g. medical illness, substance abuse, etc.)

**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)
- Edema
- Dizziness, headache
- Pruritus, rash
- Fluid retention
- Abdominal distension, abdominal pain, constipation, diarrhea, dyspepsia, flatulence, GI perforation, heartburn, nausea, peptic ulcer/GI bleed, vomiting
- Anemia, bleeding time increased
- Liver enzyme abnormalities (>3 × ULN; ≤4%)
- Tinnitus
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

- 1000–2000 mg/day

Dosage Forms

- Suppository: not available in U.S.
- Arthrotec 50®, 50 mg Diclofenac + Misoprostol 200 µg
- Arthrotec 75®, 75 mg Diclofenac + Misoprostol 200 µg
- Capsule, liquid filled, oral, as potassium: Zipsor™: 25 mg (contains gelatin)
- Powder for solution, oral, as potassium: Cambia™: 50 mg/packet (1s) (contains phenylalanine 25 mg/packet; anise-mint flavor)
- Tablet, oral, as potassium: 50 mg
- Cataflam®: 50 mg
- Tablet, delayed release, enteric coated, oral, as sodium: 25 mg, 50 mg, 75 mg
- Tablet, extended release, oral, as sodium: 100 mg
- Voltaren®-XR: 100 mg

How to Dose

- Analgesia: oral:
  - Immediate release tablet: starting dose 50 mg 3 times/day (maximum dose 150 mg/day); may administer 100 mg loading dose, followed by 50 mg every 8 hours (maximum dose day 1: 200 mg/day; maximum dose day 2 and thereafter: 150 mg/day)
  - Immediate release capsule: 25 mg 4 times/day
- Primary dysmenorrhea: oral:
  - Immediate release tablet: starting dose 50 mg 3 times/day (maximum dose 150 mg/day); may administer 100 mg loading dose, followed by 50 mg every 8 hours
- Rheumatoid arthritis:
  - Oral: immediate release tablet: 150–200 mg/day in 3–4 divided doses; delayed release tablet: 150–200 mg/day in 2–4 divided doses; extended release tablet: 100 mg/day (may increase dose to 200 mg/day in 2 divided doses)
  - Rectal suppository (not available in U.S.): Canadian labeling: insert 50 mg or 100 mg rectally as single dose to substitute for final (3rd) oral daily dose (maximum combined dose [rectal and oral]: 150 mg/day)
- Osteoarthritis:
  - Oral: immediate release tablet: 150–200 mg/day in 3–4 divided doses; delayed release tablet: 150–200 mg/day in 2–4 divided doses; extended release tablet: 100 mg/day; may increase dose to 200 mg/day in 2 divided doses
  - Arthrotec® – Arthrotec 50® 3 times/day
  - For patients that experience intolerance:
    - Arthrotec 75® – 2 times/day or Arthrotec 50® 2 times/day
  - Ankylosing spondylitis:
    - Oral: delayed release tablet: 100–125 mg/day in 4–5 divided doses
DICLOFENAC (continued)

- **Migraine:**
  - Oral solution: 50 mg (one packet) as a single dose at the time of migraine onset; safety and efficacy of a second dose have not been established

**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**
- **Onset of action:**
  - Cataflam® (potassium salt) is more rapid than the sodium salt because it dissolves in the stomach instead of the duodenum
- **Distribution:** ~1.4 L/kg
- **Protein binding:** >99%, primarily to albumin
- **Metabolism:** hepatic; undergoes first-pass metabolism; forms several metabolites (1 with weak activity)
  - Bioavailability: 55%
  - Half-life elimination: ~2 hours
  - Time to peak, serum: Cambia™ ~0.25 hours; Cataflam® ~1 hour; Voltaren® XR ~5 hours; Zipsor™ ~0.5 hour
  - Excretion: urine ~65%; feces ~35%

**Metabolism**
- Substrate (minor) of CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A4; inhibits CYP1A2 (moderate), 2C9 (weak), 2E1 (weak), 3A4 (weak)

**Drug Interactions**
- Use with alcohol, bisphosphonates, corticosteroids, anticoagulants, and other NSAIDs increases GI bleeding risk

- **Cyclosporine and 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 celecoxib or any other NSAIDs, aspirin, sulfonamides, renal or hepatic disease, pain in the setting of coronary artery bypass graft (CABG) surgery

**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

TOPICAL DICLOFENAC

DOSING AND USE

Osteoarthritis
- Topical gel (Voltaren®): Note: Maximum total body dose of 1% gel should not exceed 32 g/day
- Lower extremities: apply 4 g of 1% gel to affected area 4 times daily (maximum 16 g per joint per day)
- Upper extremities: apply 2 g of 1% gel to affected area 4 times daily (maximum 8 g per joint per day)
- Topical solution (Pennsaid®): apply 40 drops to each affected area 4 times daily
- Count 10 drops into the hand and apply to each side of the knee (anterior, posterior, lateral, medial) then wash hands completely. One bottle of diclofenac sodium topical solution 1.5% w/w is a 30-day supply for one knee

Actinic keratosis (AK)
- Topical (Solaraze® Gel): apply 3% gel to lesion area twice daily for 60–90 days

Acute pain (strains, sprains, contusions):
- Patch: apply 1 patch twice daily to most painful area of skin (diclofenac epolamine topical patch) 1.3%. Flector® Patch (10 × 14 cm containing 180 mg diclofenac epolamine)
- Gel (Voltaren® Emulgel™ [CAN; not available in U.S.]): apply to affected area(s) of skin 3 or 4 times daily for up to 7 days

Labeled Indications
- Topical gel 1%: relief of osteoarthritis pain in joints amenable to topical therapy (e.g. ankle, elbow, foot, hand, knee, wrist)
- Topical gel 3%: actinic keratosis (AK) in conjunction with sun avoidance
- Topical patch: acute pain due to minor strains, sprains, and contusions
- Topical solution: relief of osteoarthritis pain of the knee

Administration
- Topical gel: do not cover with occlusive dressings or apply sunscreens, cosmetics, lotions, moisturizers, insect repellents or other topical medications to treated area. Do not wash area for 1 hour following application. Wash hands immediately after application (unless hands are treated joint). Avoid sunlight exposure to treated areas
  - 1% formulation: apply gel to affected area or joint and rub into skin gently, making sure to apply to entire affected area or joint
  - 3% formulation: apply to lesion with gel and smooth into skin gently
- Topical solution: apply to clean, dry, intact skin; do not apply to eyes, mucous membranes, or open wounds. Wash hands before and after use. Apply 10 drops at a time directly onto knee or into hand then onto knee (helps avoid spillage). Spread evenly around knee (front, back, sides). Allow knee to dry before applying clothing. Do not shower or bathe for at least 30 minutes after applying. Do not apply heat or occlusive dressing to treated knee; protect treated knee from sunlight. Cosmetics, insect repellent, lotion, moisturizer, sunscreens, or other topical medication may be applied to treated knee once solution has dried
- Transdermal patch: apply to intact, nondamaged skin. Remove transparent liner prior to applying to skin. Wash hands after applying as well as after removal of patch. May tape down edges of patch, if peeling occurs. Should not be worn while bathing or showering. Fold used patches so the adhesive side sticks to itself; dispose of used patches out of reach of children and pets

Dosage forms: Excipient information presented when available (limited, particularly for generics); consult specific product labeling
- Gel, topical, as sodium
  - Solaraze®: 3% (100 g) (contains benzyl alcohol)
  - Voltaren® Gel: 1% (100 g) (contains isopropyl alcohol)
- Patch, transdermal, as epolamine
  - Flector®: 1.3% (30 g) (contains metal; 180 mg)
- Solution, topical, as sodium
  - Pennsaid®: 1.5% (150 mL)

Pharmacodynamics/Kinetics
- Absorption: topical gel: 6% to 10%; topical solution: ~2% to 3%
- Half-life elimination: patch: ~12 hours
- Time to peak, serum: Flector®: 10–20 hours; Pennsaid®: 5–17 hours; Solaraze® Gel: ~5 hours; Voltaren® Gel: 10–14 hours

Advantages of topical administration
- Less drug available systemically, thus, fewer AEs
THE ART OF PAIN PHARMACOLOGY

Potential Advantages
- Once-daily dosing

Potential Disadvantages
- Usual NSAID drawbacks

Primary Target Symptoms
- Pain
- Inflammation

Pearls
- Diclofenac inhibits COX-2 preferentially more than COX-1

- Available in the U.S. in multiple topical formulations
- Intravenous/injectable formulations are not yet available in the U.S. (Voltarol®, Dyloject®)
- Use cautiously in patients with significant cardiovascular disease
- Diclofenac coupled to an H(2)S-releasing moiety is not yet available but may result in less GI and CV insult than diclofenac
- Can potentially utilize topical Voltaren 1% gel (2 g) off-label onto hands/wrists 4 times daily for significantly painful arthritis

Suggested Reading

