**TIZANIDINE**

**Therapeutics**

**Brands**
- Zanaflex, Sirdalud

**Generic?**
No

**Class**
- Skeletal muscle relaxant, centrally acting; alpha-2 agonist

**Commonly Prescribed for**
(FDA approved in bold)
- Acute and intermittent management of increased muscle tone related to spasticity
- Spasticity can result from neurological conditions, such as multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), primary lateral sclerosis, and spinal cord injury
- Migraine prophylaxis
- Neck pain/lower back pain
- Myofascial pain

**How the Drug Works**
- Alpha-2 adrenergic agonist (mostly at alpha-2A receptors) which also acts at imidazoline receptors. Reduces spasticity by increasing presynaptic inhibition of motor neurons

**How Long Until It Works**
- Pain – hours-weeks

**If It Works**
- Slowly titrate to most effective tolerated dose

**If It Doesn’t Work**
- Increase to highest tolerated dose. If ineffective, gradually reduce dose and consider alternative medications

**Best Augmenting Combos for Partial Response or Treatment-Resistance**
- Botulinum toxin is effective, especially as an adjunct for focal spasticity, i.e., post-stroke or head injury affecting the upper limbs. For conditions with multiple areas of spasticity, i.e., cerebral palsy, this combination can be very useful
- May be used carefully in combination with baclofen, although additive sedation can be problematic

**Use other centrally acting muscle relaxants with caution due to potential additive CNS depressant effect**

**Tests**
- Monitor liver and renal function at baseline and at 1, 2, and 3 months. Monitor hepatic enzymes at 6 months and periodically after that

**Adverse Effects (AEs)**

**How Drug Causes AEs**
- Related to alpha-2 adrenergic agonist effect causing hypotension. Increased sedation may be due to actions at the imidazoline receptors

**Notable AEs**
- Dry mouth, weakness, and somnolence are most common. Dizziness, hypotension, and elevation of hepatic transaminases
- Hallucinations (usually visual) occur in about 3% of patients

**Life-Threatening or Dangerous AEs**
- Bradycardia and prolongation of QTc interval with higher doses. Tizanidine withdrawal can cause rebound hypertension

**Weight Gain**
- Not unusual

**Sedation**
- Common

**What to Do About AEs**
- Lower the dose and titrate more slowly

**Best Augmenting Agents for AEs**
- Most AEs cannot be improved by an augmenting agent. MS-related fatigue can respond to CNS stimulants such as modafinil but it is easier to temporarily lower the dose until tolerance develops
TIZANIDINE (continued)

**DOSING AND USE**

**Usual Dosage Range**
- 6–24 mg/day in 3–4 divided doses, maximum 32 mg/day

**Dosage Forms**
- Tablets: 2, 4 mg
- Capsules: 2, 4, 6 mg

**How to Dose**
- Start with one 2 or 4 mg tablet daily. Increase by 2–4 mg every 3 days as tolerated to a goal of 24 mg/daily – either 8 mg 3 times a day or 6 mg 4 times a day – or until desired clinical effect is met. Some patients may increase to 32 mg/day if no AEs

**Dosing Tips**
- Sedation peaks the first week. Slower titration may reduce AEs

**Overdose**
- One case of profound respiratory depression reported. Ensure adequate airway protection and intubate if needed. Gastric lavage and forced diuresis with furosemide and mannitol may be helpful

**Long-Term Use**
- Not well studied

**Habit Forming**
- No

**How to Stop**
- Taper slowly to avoid rebound tachycardia and hypertension (although much less problematic than clonidine)

**Pharmacokinetics**
- Bioavailability is 40%, with hepatic metabolism into inactive metabolites. 30% protein bound. Half-life is 2–2.5 hours and peak effect at 1–1.5 hours. The duration of effect is 3–6 hours. Food delays peak effect and half-life

**Drug Interactions**
- Oral contraceptives decrease tizanidine clearance by about 50%
- Alcohol impairs tizanidine clearance and adds to depressant effect
- Tizanidine delays the effect of acetaminophen
- Use with other CNS depressants increases sedation

**Other Warnings/Precautions**
- Decreased spasticity can be problematic for some patients who require tone to maintain upright posture, balance, and ambulation
- In animal studies, dose-related corneal opacities and retinal degeneration occurred

**Do Not Use**
- Known hypersensitivity

**SPECIAL POPULATIONS**

**Renal Impairment**
- Clearance is reduced in patients with creatinine clearance less than 25 mL/min. Reduce dose

**Hepatic Impairment**
- Due to potential for elevation of hepatic transaminases, use with caution in any patient with significant hepatic disease

**Cardiac Impairment**
- No known effects

**Elderly**
- Drug metabolism is slower in elderly patients. Use with caution

**Children and Adolescents**
- Not studied in children

**Pregnancy**
- Category C. Use only if there is a clear need

**Breast Feeding**
- Unknown if excreted in breast milk but likely due to lipid solubility. Do not use
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Potential Advantages

- Effective treatment for spasticity with relatively benign AE profile. Effectiveness is similar to diazepam and oral baclofen with fewer AEs and less severe withdrawal.

Potential Disadvantages

- Hypotension can be problematic in some and rebound hypertension from discontinuation may be confused for autonomic dysreflexia. Sedation often limits use.

Primary Target Symptoms

- Spasticity, pain

Pearls

- Generally well-tolerated alternative to other muscle relaxants, such as oral baclofen, dantrolene, and diazepam.
- Chemically similar to another alpha-2 adrenergic agonist, clonidine, but has only a fraction (1/10 to 1/50th) of the blood pressure lowering effect.
- In migraine prophylaxis, may be helpful for some patients either as an acute pain medication or as a “bridge” treatment for daily pain. Some studies suggest usefulness as a longer-term prophylactic agent but AEs often outweigh benefit.
- Effective for some patients with acute myofascial pain, back pain and neck pain.

Suggested Reading

Freitag FG. Preventative treatment for migraine and tension-type headaches: do drugs having effects on muscle spasm and tone have a role? CNS Drugs 2003;17(6):373–81.


