### TIMOLOL

#### THERAPEUTICS

**Brands**
- Blocadren (oral), Betimol, Betim, Timoptic, Istalol (ocular solution)

**Generic?**
- Yes

**Class**
- Antihypertensive, beta-blocker (non-selective)

**Commonly Prescribed for**
*(FDA approved in bold)*
- Migraine prophylaxis
- Hypertension
- Myocardial infarction
- Chronic open angle glaucoma or ocular hypertension (ocular solution)
- Congestive heart failure (stable)
- Angina pectoris due to coronary atherosclerosis
- Prevention of variceal bleeding

#### How the Drug Works
- Migraine: Proposed mechanisms include inhibition of adrenergic pathway, interaction with serotonin system and receptors, inhibition of nitric oxide production, and normalization of contingent negative variation. Prevention of cortical spreading depression may be the mechanism of action for all migraine preventives.

#### How Long Until It Works
- Migraines – within 2 weeks, but can take up to 3 months on a stable dose to see full effect

#### If It Works
- In migraine, the goal is a 50% or greater decrease in migraine frequency or severity. Consider tapering or stopping if headaches remit for more than 6 months or if considering pregnancy

#### If It Doesn’t Work
- Increase to highest tolerated dose
- Migraine: address other issues, such as medication-overuse, other coexisting medical disorders, such as anxiety, and consider changing to another drug or adding a second drug

### Best Augmenting Combos for Partial Response or Treatment-Resistance
- Migraine: For some patients, low-dose polytherapy with 2 or more drugs may be better tolerated and more effective than high-dose monotherapy. May use in combination with AEDs, antidepressants, natural products, and non-pharmacologic treatments, such as biofeedback, to improve headache control

#### Tests
- None required

### ADVERSE EFFECTS (AEs)

**How Drug Causes AEs**
- Antagonism of beta receptors

**Notable AEs**
- Bradycardia, hypotension, hyper- or hypoglycemia, weight gain
- Bronchospasm, cold/flu symptoms, sinusitis, pneumonias
- Dizziness, vertigo, fatigue/tiredness, depression, sleep disturbances
- Sexual dysfunction, decreased libido, dysuria, urinary retention, joint pain
- Exacerbation of symptoms in peripheral vascular disease and Raynaud’s syndrome

#### Life-Threatening or Dangerous AEs
- In acute CHF, may further depress myocardial contractility
- Can blunt premonitory symptoms of hypoglycemia in diabetes and mask clinical signs of hyperthyroidism
- Non-selective beta-blockers, such as timolol, can inhibit bronchodilation, making them contraindicated in asthma, severe COPD
- Risk of excessive myocardial depression in general anesthesia

#### Weight Gain
- Not unusual

#### Sedation
- Common
TIMOLOL (continued)

What to Do About AEs
- Lower dose, take higher dose in the evening or switch to another drug

Best Augmenting Agents for AEs
- When patients have significant benefit from beta-blocker therapy but hypotension limits treatment, consider alpha-agonists (midodrine) or volume expanders (fludrocortisones) for symptomatic relief

Pharmacokinetics
- Half-life 4 hours. Bioavailability is 75%. Hepatic metabolism. Metabolites are excreted by kidney. <10% protein binding. Lower lipid solubility than propranolol

Drug Interactions
- Oral contraceptives, ciprofloxacin, and hydroxychloroquine can increase levels and/or effects of timolol and other beta-blockers
- Use with calcium channel blockers can be synergistic or additive, use with caution
- Barbiturates, penicillins, rifampin, calcium and aluminum salts, thyroid hormones, and cholestyramine can decrease effects of beta-blockers
- NSAIDs, sulfipyrazone and salicylates inhibit prostaglandin synthesis and may inhibit the antihypertensive activity of beta-blockers
- Timolol can increase levels of lidocaine, resulting in toxicity
- Increased postural hypotension with prazosin and peripheral ischemia with ergot alkaloids
- Sudden discontinuation of clonidine while on beta-blockers or when stopping together can cause life-threatening increases in blood pressure

Other Warnings/Precautions
- Slight increases in blood urea, serum potassium, and uric acid, with decrease of HDL cholesterol and hematocrit. These alterations are not progressive or clinically significant
- Rare development of antinuclear antibodies (ANA)
- May worsen muscle weakness in myasthenia gravis

Do Not Use
- Sinus bradycardia, greater than 1st degree heart block, cardiogenic shock
- Bronchial asthma, severe COPD
- Proven hypersensitivity to beta-blockers

DOSING AND USE

Usual Dosage Range
- 10–60 mg/day

Dosage Forms
- Tablets: 5, 10, 20 mg
- Ocular solution: 0.25 or 0.5%

How to Dose
- Migraine: Initial dose 10 mg twice daily in migraine. Can gradually increase weekly to usual effective dose: 20–60 mg/day

Dosing Tips
- Patients on a stable dose of 20 mg/day can take the entire dose once daily, usually in the evening

Overdose
- Bradycardia, hypotension, low-output heart failure, shock, seizures, coma, hypoglycemia, apnea, cyanosis, respiratory depression, and bronchospasm. Epinephrine and dopamine are used to treat toxicity

Long-Term Use
- Safe for long-term use

Habit Forming
- No

How to Stop
- Do not abruptly discontinue. Gradually reduce dosage over 1–2 weeks. Stopping may exacerbate angina, and there are reports of tachyarrhythmias or myocardial infarction with rapid discontinuation in patients with cardiac disease

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SPECIAL POPULATIONS

Renal Impairment
- No significant changes in half-life or concentration with moderate failure, but marked hypotensive episodes have occurred in patients undergoing dialysis. Use with caution

Hepatic Impairment
- May need to reduce dose with significant hepatic disease

Cardiac Impairment
- Do not use in acute shock, MI, hypotension, and greater than 1st degree heart block, but indicated in clinically stable patients post-MI to reduce risk of reinfarction. Metoprolol, another beta-blocker, is commonly used to reduce mortality and hospitalization for patients with stable CHF, in patients already receiving ACE inhibitors and diuretics

Elderly
- Use with caution. May increase risk of stroke

Children and Adolescents
- Not studied in children. The pediatric dose is unknown

Pregnancy
- Category C. Embryotoxic in animal studies only at doses much higher than maximum recommended human doses. May reduce perfusion of the placenta. Use if potential benefit outweighs risk to the fetus. Most beta-blockers are class C, except atenolol, which is D and acebutolol, pindolol and sotalol, which are B

Breast Feeding
- Not recommended. Timolol is found in breast milk

THE ART OF NEUROPHARMACOLOGY

Potential Advantages
- Proven effectiveness in migraine and fewer drug interactions than propranolol. Perhaps fewer CNS side effects

Potential Disadvantages
- Multiple potential AEs including bradycardia, hypotension, and fatigue. Less known efficacy for treating coexisting conditions, such as anxiety and tremor, compared with propranolol

Primary Target Symptoms
- Migraine frequency and severity

Pearls
- Alternative beta-blockers for migraine: metoprolol 100–200 mg/day, propranolol 40–400 mg/day (FDA approved), atenolol 50–200 mg/day, nadolol 20–160 mg/day
- Beta-blockers that are partial agonists, with intrinsic sympathomimetic activity, are not effective in migraine prophylaxis. These include acebutolol, alprenolol, and pindolol
- Often used in combination with other drugs in migraine
- Not effective for cluster headache
- Beta-1 selective antagonists, such as metoprolol, may be an option for patients with asthma or severe COPD
- Recent studies have downgraded beta-blockers as a first-line treatment for hypertension compared with other classes due to lack of effectiveness, increased rate of stroke in elderly, and risk of provoking type II diabetes
- Often used in combination with other agents for hypertension, especially thiazide diuretics
**Suggested Reading**


