IOPIDINE® 1% IOPIDINE® 0.5%
Alcon
Apraclonidine HCl
Controls Postsurgical Intraocular Pressure
Glaucoma Therapy

Action And Clinical Pharmacology: Apraclonidine is a relatively selective alpha adrenergic agonist and does not have significant membrane stabilizing (local anesthetic) activity. When instilled into the eye, apraclonidine has the action of reducing intraocular pressure. The precise mechanism of the ocular hypotensive action of apraclonidine is not completely established at this time. Aqueous fluorophotometry studies in man suggest that apraclonidine's predominant action may be related to a reduction of aqueous formation.

Apraclonidine is a partial agonist for alpha 1 and alpha 2 adrenergic receptors. The affinity of apraclonidine for alpha 2 receptors, as measured by competitive radioligand binding studies, is higher than its affinity towards alpha 1 receptors.

The onset of action with apraclonidine can usually be noted within 1 hour and the maximum intraocular pressure reduction usually occurs 3 to 5 hours after application of a single dose.

Indications And Clinical Uses: 1%: To control or prevent postsurgical elevations in intraocular pressure that occur in patients after anterior segment laser ophthalmic surgery including argon laser trabeculoplasty, argon laser iridotomy and neodymium:yttrium aluminum garnet (Nd:YAG) laser posterior capsulotomy.

0.5%: For adjunctive use in lowering intraocular pressure and may be used as a short-term therapy in glaucoma patients on maximally tolerated medical therapy who require an additional IOP reduction.

The largest body of clinical data regarding the efficacy of apraclonidine as an adjunctive drug has been obtained in patients using timolol as the primary therapy. However, apraclonidine has also been found effective in combination with topical betaxolol, carbachol, dipivefrin, echothiophate, epinephrine, levobunolol and pilocarpine and systemic acetazolamide and methazolamide.

The addition of apraclonidine 0.5% to patients already using 2
aqueous suppressing drugs (i.e., beta-blocker plus carbonic anhydrase inhibitor) as part of their maximally tolerated medical therapy may not provide much additional benefit. Since apraclonidine 0.5% is an aqueous suppressing drug, the addition of a third aqueous suppressant may not significantly reduce IOP.

**Contra-Indications:** Hypersensitivity to any component of this medication or to clonidine. Also contraindicated in patients receiving MAO inhibitors.

**Manufacturers’ Warnings In Clinical States:** Since apraclonidine is a potent depressor of intraocular pressure, patients who develop exaggerated reductions in intraocular pressure should be closely monitored.

Although the acute administration of 2 drops of apraclonidine 1% has minimal effect on heart rate or blood pressure in clinical studies evaluating patients undergoing anterior segment laser surgery, the preclinical pharmacologic profile of this drug suggests that caution should be observed in treating patients with severe cardiovascular disease including hypertension.

The possibility of a vasovagal attack occurring during laser surgery should be considered and caution used in patients with history of such episodes.

Use of apraclonidine 0.5% can lead to an allergic-like reaction characterized wholly or in part by the symptoms of hyperemia, pruritus, discomfort, tearing, foreign body sensation and edema of the lids and conjunctiva. If ocular allergic-like symptoms occur, apraclonidine 0.5% therapy should be discontinued. The allergic-like reaction associated with apraclonidine use may be masked by seasonal allergic conjunctivitis.

Not for injection. Topical ophthalmic use only.

**Precautions:** General: (Glaucoma Therapy): Although the topical use of apraclonidine 0.5% has not been studied in renal failure patients, structurally related clonidine undergoes a significant increase in half-life in patients with severe renal impairment. Close monitoring of patients with impaired renal function is advised if they are candidates for topical apraclonidine 0.5% solution therapy. Close monitoring of patients with impaired liver function is also advised as the systemic dosage form of clonidine is partly metabolized in the liver.
Apraclonidine 0.5% should be used with caution in patients with coronary insufficiency, recent myocardial infarction, cerebrovascular disease, chronic renal failure, Raynaud's disease, or thromboangiitis obliterans. Caution and monitoring of depressed patients are advised since apraclonidine has been rarely associated with depression.

Occupational Hazards: Apraclonidine 0.5% can cause dizziness and somnolence. Patients who engage in hazardous activities requiring mental alertness should be warned of the potential for a decrease in mental alertness while using apraclonidine 0.5% solution.

**Drug Interactions:** No specific drug interactions with topical glaucoma drugs (betaxolol, carbachol, dipivefrin, echothiophate, epinephrine, levobunolol, pilocarpine, timolol) or systemic medications (acetazolamide, methazolamide) were identified in clinical studies of apraclonidine 0.5%. The possibility of an additive or potentiating effect with CNS depressants (alcohol, barbiturates, opiates, sedatives, anesthetics) should be borne in mind. Tricyclic antidepressants have been reported to blunt the hypotensive effect of systemic clonidine. It is not known whether the concurrent use of these agents with apraclonidine can lead to a reduction in IOP lowering effect. No data on the level of circulating catecholamines after apraclonidine withdrawal are available. Caution, however, is advised in patients taking tricyclic antidepressants which can affect the metabolism and uptake of circulating amines.

Since apraclonidine may reduce pulse and blood pressure, caution in using drugs such as beta-blockers (ophthalmic and systemic), antihypertensives, and cardiac glycosides is advised. Patients using cardiovascular drugs concurrently with Apraclonidine should have their pulse and blood pressure frequently monitored. Caution should be exercised with simultaneous use of clonidine and other similar pharmacologic agents.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a series of 5 in vitro cell assays and 1 in vivo, apraclonidine was nonmutagenic. There was no significant increase in tumor incidence or type following 2 years of oral administration of apraclonidine to rats at dose levels 20 times the maximum recommended human dose or in mice at dose levels 12 times the maximum recommended human dose. Reproduction and fertility studies in rats showed no adverse effect on male or female fertility at doses 5 to 10 times the maximum recommended human dose.
Pregnancy: There are no adequate and well-controlled studies in pregnant women. Apraclonidine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Teratogenicity studies with apraclonidine in rabbits and rats at doses up to 3 mg/kg/day in rabbits (60 times the maximum recommended human dose) and 0.3 mg/kg/day in rats (6 times the maximum recommended human dose) showed no evidence of fetal malformations, although embryotoxicity was evident at the high dose level in the rabbit study. Dose-related maternal toxicity was evident in both the rat and rabbit studies.

Lactation: It is not known if topically applied apraclonidine is excreted in human milk. However, systemic clonidine can be found in mother's milk, and a decision should be made whether to discontinue apraclonidine 0.5% use in nursing women or continue therapy, taking into account the importance of the drug to the mother. For surgical use, a decision should be considered to discontinue nursing temporarily for the 1 day apraclonidine 1% solution is used.

Children: Safety and effectiveness in children have not been established.

**Adverse Reactions:** Surgical Use: The following adverse events were reported in association with the use of apraclonidine 1% in laser surgery: upper lid elevation (1.3%), conjunctival blanching (0.4%), and mydriasis (0.4%).

Glaucoma Therapy: Use of apraclonidine 0.5% can lead to an allergic-like reaction characterized wholly or in part by the symptoms of hyperemia, pruritus, discomfort, tearing, foreign body sensation, and edema of the lids and conjunctiva. If ocular allergic-like symptoms occur, therapy should be discontinued.

The overall discontinuation rate in clinical studies with apraclonidine 0.5% was 16%. The most commonly reported events leading to discontinuation included (in decreasing order of frequency) hyperemia, pruritus, discomfort, tearing, dry mouth, lid edema, and foreign body sensation.

The following adverse reactions (incidence) were reported in clinical studies of apraclonidine 0.5% as being related to therapy:
Ocular: hyperemia (11.9%), pruritus (11.3%), discomfort (7.2%), tearing (4.8%), foreign body sensation (2.7%), lid edema (2.4%), dry eye (2.1%), blurred vision (1.8%), blanching (1.5%), conjunctivitis (1.5%), lid margin crusting (1.2%), conjunctival edema (0.9%), discharge (0.9%), abnormal vision (0.9%), pain (0.6%), lid disorder (0.6%), edema (0.6%), lid erythema (0.6%), irritation (0.3%), keratitis (0.3%), blepharitis (0.3%), blepharoconjunctivitis (0.3%), photophobia (0.3%), conjunctival follicles (0.3%), scleritis (0.3%), keratopathy (0.3%), lid scales (0.3%), corneal infiltrate (0.3%), corneal staining (0.3%).

Body as a Whole: headache (2.7%), asthenia (2.1%), chest pain (0.6%), abnormal coordination (0.3%), malaise (0.3%).

Cardiovascular: peripheral edema (0.3%), arrhythmia (0.3%). Although no reports of bradycardia related to apraclonidine 0.5% were available from clinical studies, the possibility of its occurrence based on apraclonidine's alpha 2 agonist effect should be considered.

CNS: somnolence (1.2%), dizziness (1.2%), depression (0.6%), nervousness (0.6%), insomnia (0.3%), paresthesia (0.3%).

Digestive System: dry mouth (12.8%), constipation (1.5%), nausea (0.6%).

Musculoskeletal: myalgia (0.3%).

Respiratory System: dry nose (3.3%), rhinitis (1.2%), dyspnea (0.3%), pharyngitis (0.3%).

Skin: contact dermatitis (0.3%), dermatitis (0.3%).

Special Senses: taste perversion (3.6%), parosmia (0.3%).

This listing is presented in Table I and lists treatment-related adverse reactions which occurred at an incidence rate of 2% or more during placebo-controlled clinical studies of apraclonidine 0.5%.

**Symptoms And Treatment Of Overdose:** Symptoms and Treatment: Overdose is unlikely with topical ocular instillation, as the volume of exposure is limited by the capacity of the cul-de-sac. The small volume packaging and unique design of the Drop-Tainer limit the potential for accidental overdosage by ingestion. Signs of toxicity of apraclonidine in animals include lethargy, decreased activity, loss of appetite, hypothermia, decreased GI motility and constipation.
Following oral administration of apraclonidine to monkeys, plasma levels 100 times greater than those seen in human plasma level studies were associated with moderate signs of toxicity, including lethargy, hypoactivity, and loss of appetite; no significant target organ toxicities were found. Acute oral toxicity studies in rats and mice resulted in LD50 values of 64 and 5 mg/kg, respectively. While higher doses usually caused deaths within 24 hours, lower doses often resulted in delayed deaths.

While no instances of human ingestion of apraclonidine are known, overdose with the oral form of clonidine has been reported to cause hypotension, transient hypertension, asthenia, vomiting, irritability, diminished or absent reflexes, lethargy, somnolence, sedation or coma, pallor, hypothermia, bradycardia, conduction defects, arrhythmias, dryness of the mouth, miosis, apnea, respiratory depression, hypoventilation, and seizure.

Treatment of an oral overdose includes supportive and symptomatic therapy; a patent airway should be maintained. Gastric lavage i.v. fluids, atropine, dopamine, tolazoline, furosemide and diazoxide have been reported to be useful in treating the systemic symptoms associated with oral clonidine overdose. Hemodialysis is of limited value, since a maximum of 5% of circulating drug is removed.

**Dosage And Administration:** 1%: 1 drop of apraclonidine 1% should be instilled in the scheduled operative eye 1 hour before initiating anterior segment laser surgery and a second drop should be instilled in the same eye immediately upon completion of the laser surgical procedure. Use a separate container for each single-drop dose and discard each container after use.

0.5%: 1 to 2 drops of apraclonidine 0.5% should be instilled in the affected eye(s) 2 or 3 times daily. Since apraclonidine 0.5% will be used with other ocular glaucoma therapies, an approximate 5-minute interval between instillation of each medication should be practiced to prevent washout of the previous dose. Not for injection into the eye. Not for oral ingestion.

**Availability And Storage:** 1%: Each mL of sterile, isotonic, aqueous solution contains: apraclonidine HCl USP 1.15% equivalent to apraclonidine base 1% with benzalkonium chloride 0.01% as preservative. Nonmedicinal ingredients: hydrochloric acid, purified water, sodium acetate, sodium chloride and sodium hydroxide. Plastic ophthalmic dispensers of 0.1 mL. Pouches of 2. These dispensers are enclosed in a foil overwrap as an added barrier to evaporation.
0.5%: Each mL of sterile, isotonic, aqueous solution contains: apraclonidine HCl USP 0.575% equivalent to apraclonidine base 0.5% with benzalkonium chloride 0.01% as preservative. Nonmedicinal ingredients: hydrochloric acid, purified water, sodium acetate, sodium chloride and sodium hydroxide. Plastic Drop-Tainer dispensers of 5 and 10 mL.

Store between 2 and 30°C. Do not freeze. Protect from light.