

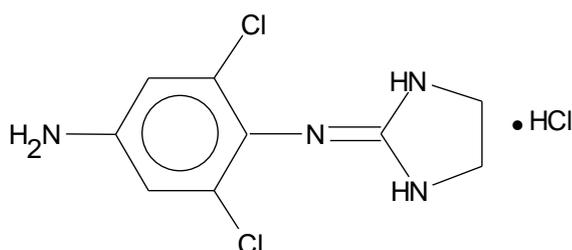
PRODUCT INFORMATION

IOPIDINE® (apraclonidine hydrochloride) Eye Drops 0.5%

NAME OF THE MEDICINE

IOPIDINE Eye Drops 0.5% contains apraclonidine hydrochloride, an alpha-adrenergic agonist, in a sterile isotonic solution for topical application to the eye. Apraclonidine hydrochloride is a white to off-white crystalline powder sparingly soluble in water (29.1 mg/mL) with a molecular weight of 281.6. The pKa₁ value is 1.16; pKa₂ value is 9.22.

Structural formula:



Empirical formula: C₉H₁₀Cl₂N₄.HCl

Chemical name: 2[(4-amino-2,6-dichlorophenyl)imino]imidazolidine hydrochloride.

DESCRIPTION

IOPIDINE Eye Drops 0.5% contains 5.75 mg/mL apraclonidine hydrochloride equivalent to 5.0 mg of apraclonidine in a sterile isotonic base comprising benzalkonium chloride 0.1 mg/mL as preservative, sodium acetate, sodium chloride and purified water.

PHARMACOLOGY

Animal Pharmacology

Pharmacodynamics:

Apraclonidine is an alpha-adrenergic agonist with higher potency and affinity for α₂-compared to α₁-adrenoceptors. It has been shown to produce a lowering of intraocular pressure (IOP) in rabbits and monkeys with elevated IOP and in cats with normal IOP. The physicochemical properties of apraclonidine limit its rate of passage across the blood-brain barrier to access the central nervous system. It produced a decrease in blood pressure in rats when given intracerebroventricularly but not intravenously. Topical ocular administration to dogs did not change cardiovascular parameters, but intravenous administration to rats and dogs produced a transient elevation of blood pressure and a slight decrease in heart rate.

Administration of apraclonidine intravenously to cats and via the topical ocular route to monkeys resulted in a reduced anterior segment blood flow, whereas flow to the posterior segment, i.e. retina, choroid or optic nerve head, was not affected. Chronic treatment of primates with apraclonidine 1.5% ocularly three times a day for one year did not result in morphologic effects which would be indicative of vasoconstriction of the anterior or posterior segments of the eye. Although ocular blood flow studies have not been conducted in humans, the animal studies provide a basis for the safe use of this drug in the treatment of ocular hypertension and open angle glaucoma.

Pharmacokinetics:

Following topical ocular administration to New Zealand white rabbits, apraclonidine reached peak concentrations after two hours in the aqueous humour, iris, ciliary body and lens. The cornea exhibited the greatest concentration and peaked at the earliest time point (20 minutes). The tissue distribution of apraclonidine from the highest to lowest concentration in microgram equivalents of tissue was cornea, iris-ciliary body, aqueous humour, lens and vitreous humour. The elimination half-life of apraclonidine from the aqueous humour was determined to be approximately two hours.

Following IV administration, the plasma half-life of parent apraclonidine was 9 hours in cynomolgus monkeys and 3 hours in rat. In both species the half-life of the radioactivity from ³H-apraclonidine was longer than that of the parent drug and urinary excretion was the primary route of elimination (65-75% of dose) with the balance excreted in the faeces.

Clinical Pharmacology

Pharmacodynamics:

Optic nerve head damage and visual field loss are the result of sustained elevated intraocular pressure and poor ocular perfusion. When instilled in the eye, IOPIDINE Eye Drops 0.5% have the action of reducing elevated, as well as normal IOP, whether or not accompanied by glaucoma. The onset of the ocular hypotensive action of apraclonidine usually occurs within one hour and the peak pressure reduction can usually be seen three to five hours after administration of a single dose. Repeated dose-response and comparative studies (0.125% -1% apraclonidine) demonstrate that 0.5% apraclonidine is at the top of the dose/response IOP reduction curve.

Aqueous fluorophotometry studies demonstrate that apraclonidine's predominant mechanism of action is reduction of aqueous flow via stimulation of the α -adrenergic system.

Unlike beta-blockers and adrenaline, apraclonidine reduces aqueous flow during the day and also at night during sleep. Apraclonidine's mechanism of action may account for the additional IOP reductions observed after instillation of apraclonidine in patients receiving maximally tolerated medical therapy.

The clinical utility of IOPIDINE 0.5% is most apparent for those glaucoma patients on maximally tolerated medical therapy who require additional short-term IOP reduction. Clinical studies have shown that IOPIDINE 0.5% is effective in combination with topical beta blockers, sympathomimetics, parasympathomimetics and oral carbonic anhydrase inhibitors. However, the IOP-lowering efficacy of IOPIDINE 0.5% diminishes over time in some patients. This loss of effect appears to be an individual

occurrence with a variable time of onset and should be closely monitored (see INDICATIONS).

Ophthalmic apraclonidine has minimal effect on cardiovascular parameters.

Pharmacokinetics:

Studies of IOPIDINE 0.5% dosed one drop three times a day for both eyes for 10 days in 12 normal volunteers yielded a peak plasma concentration of less than 1.0 ng/mL (range 0.6 - 0.9 ng/mL) with a trough concentration of 0.5 ng/mL. The plasma half-life was estimated to be 8 hours with an elimination rate constant of 0.083 +/- 0.048 hours⁻¹.

INDICATIONS

IOPIDINE 0.5% is indicated to control intraocular pressure in glaucoma patients on maximally tolerated glaucoma therapy for a period of 3 months.

In clinical studies the drop in intraocular pressure appeared to decrease after Day 60 which may be associated with a progression of the disease or loss of effect of the drug. This phenomenon appears to be an individual occurrence with variable time of onset.

As with any patient on maximally tolerated therapy (see DOSAGE AND ADMINISTRATION), patients using IOPIDINE 0.5% to delay surgery should have frequent follow-up examinations and treatment with IOPIDINE 0.5% should be discontinued if IOP rises significantly.

In patients who have maintained a response to IOPIDINE 0.5% for 3 months and a decision is made to continue treatment, safety aspects, including any evidence of corneal changes (see PRECAUTIONS), and IOP control should be closely monitored.

CONTRAINDICATIONS

IOPIDINE 0.5% is contraindicated in patients with hypersensitivity to any component of the formulation or to systemic clonidine and in patients receiving monoamine oxidase inhibitors, systemic sympathomimetics or tricyclic antidepressants.

PRECAUTIONS

Not for injection or oral ingestion. Since apraclonidine is a potent depressor of intraocular pressure, patients who develop an exaggerated reduction in IOP should be closely monitored.

IOPIDINE 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.

While the topical administration of IOPIDINE 0.5% had minimal effect on heart rate or blood pressure in clinical studies evaluating glaucoma patients, the preclinical pharmacological profile of this drug suggests that caution should be observed in treating patients with severe, uncontrolled cardiovascular disease, including hypertension. The possibility of a vasovagal attack should be considered and caution should be exercised in patients with a history of such episodes.

Although the topical use of IOPIDINE 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. Caution is advised in patients with renal failure. Close monitoring of cardiovascular parameters in patients with impaired renal function is advised if they are candidates for topical therapy with IOPIDINE 0.5%. Close monitoring of cardiovascular parameters in patients with impaired hepatic function is also advised as the systemic dosage form of clonidine is partly metabolised in the liver.

Caution and monitoring of depressed patients are advised since apraclonidine has been infrequently associated with depression (see INTERACTIONS WITH OTHER MEDICINES).

Topical apraclonidine can lead to an allergic-like reaction requiring discontinuation of therapy with IOPIDINE 0.5% (see ADVERSE EFFECTS); the overall discontinuation rate in clinical studies was 15%.

Apraclonidine can cause dizziness or somnolence. Patients should be warned of the potential for decreased mental alertness while using IOPIDINE 0.5% and advised not to drive or operate machinery.

Where the decision is made to continue treatment with IOPIDINE 0.5% beyond three months patients should be closely monitored for any evidence of corneal changes. No adverse ocular effects were observed in cynomolgus monkeys treated with apraclonidine 1.5%, 2 drops three times daily for 15 months. Repeated ocular dosing to rabbit eyes of apraclonidine 0.5%, 2 drops three times daily for one month showed minimal to moderate congestion and discharge of the conjunctiva, minimal corneal cloudiness, and impaired pupillary response although there were no accompanying histological changes. Following oral administration to rats and mice for 2 years corneal lesions (inflammation, vascularisation and mineralisation) were reported. These changes appear to be species related and were not observed in systemic or topical studies in primates or reported clinically. Adequate data on the efficacy and safety of the use of apraclonidine beyond 3 months have not been presented.

In patients with angle-closure glaucoma the immediate treatment objective is to re-open the angle by constriction of the pupil with a miotic agent. IOPIDINE 0.5% has not been demonstrated to be effective in cases of angle closure glaucoma.

IOPIDINE 0.5% eye drops contain benzalkonium chloride which may cause eye irritation and is known to discolour soft contact lenses. Avoid contact with soft contact lenses. Patients must be instructed to remove contact lenses prior to the application of IOPIDINE 0.5% eye drops and wait at least 15 minute before reinsertion.

Effects on Fertility

Studies have not been performed to evaluate the effect of topical ocular administration of Iopidine 0.5% on human fertility. The fertility of male and female rats was not affected by the apraclonidine administered at oral doses up to 0.5 mg/kg/day.

Use in Pregnancy

CATEGORY B3

There are no well controlled studies of IOPIDINE 0.5% in pregnant women.

IOPIDINE 0.5% is not recommended during pregnancy.

IOPIDINE 0.5% should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

Apraclonidine was not teratogenic in rats or rabbits when given orally during the period of organogenesis at doses of up to 0.3 and 3.0 mg/kg/day, respectively but was embryotoxic in rabbits at a dose of 3.0 mg/kg/day. Dose-related maternal toxicity was evident in both the rat and the rabbit studies.

Use in Lactation

It is not known if topically applied apraclonidine is excreted in human milk. A risk to the suckling child cannot be excluded. Breast-feeding should be discontinued during treatment with IOPIDINE 0.5%.

Paediatric Use

IOPIDINE 0.5% is not recommended for use in children; especially in infants under the age of 1 year due to the risk of serious systemic adverse reactions that could occur even with a single dose (see ADVERSE EFFECTS and OVERDOSAGE).

Carcinogenicity and Mutagenicity

Apraclonidine was not genotoxic in a series of assays for gene mutations and chromosomal damage. Apraclonidine showed no evidence of carcinogenicity when administered orally to rats and mice at doses up to 1 and 0.6 mg/kg/day, respectively.

INTERACTIONS WITH OTHER MEDICINES

IOPIDINE 0.5% should not be used in patients receiving MAO inhibitors (see CONTRAINDICATIONS).

No specific drug interactions with topical glaucoma products (betaxolol, carbachol, dipivefrin, ecothiopate, adrenaline, levobunolol, pilocarpine, timolol) or systemic medication (acetazolamide, methazolamide) were identified in the clinical studies with IOPIDINE 0.5%.

However, since apraclonidine may reduce pulse and blood pressure, caution in concomitant use of drugs such as β -blockers (ophthalmic and systemic), anti-hypertensives and cardiac glycosides is advised. Patients using cardiovascular drugs concurrent with apraclonidine should have their pulse and blood pressure monitored frequently. Caution should be exercised with simultaneous use of clonidine and other similar pharmacologic agents.

The possibility exists for an additive or potentiating effect with CNS depressants (alcohol, barbiturates, opiates, sedatives, anaesthetics). 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 IOPIDINE 0.5% can lead to a

reduction in the IOP-lowering effect. No data on the level of circulating catecholamines after apraclonidine withdrawal are available. Caution is advised, however, in patients taking tricyclic antidepressants which can affect the metabolism and uptake of circulating amines (see CONTRAINDICATIONS).

ADVERSE EFFECTS

IOPIDINE 0.5% is generally well tolerated at the recommended dosage for up to 3 months (see INDICATIONS) for control of IOP in glaucoma patients. The most frequently observed effects were ocular.

Use of IOPIDINE 0.5% can lead to an allergic-like reaction characterised wholly or in part by the symptoms of hyperaemia, pruritus, discomfort, tearing, foreign-body sensation, oedema of the lids and conjunctiva. If allergic-like symptoms occur therapy with IOPIDINE 0.5% should be discontinued.

In clinical studies (n = 458 patients) the overall discontinuation rate related to IOPIDINE 0.5% was 15%. The most commonly reported events leading to discontinuation were hyperaemia, pruritus, tearing, discomfort, lid oedema, dry mouth, and foreign body sensation. Other adverse reactions related to apraclonidine were generally mild to moderate, non-serious and did not result in sequelae.

The following adverse reactions (incidence) were reported in clinical studies with IOPIDINE 0.5% as being related to therapy:

Ocular

Hyperaemia (13%), pruritus (10%), discomfort (6%), tearing (4%).

<3% of patients: lid oedema, blurred vision, foreign body sensation, dry eye, conjunctivitis, discharge, blanching.

<1% of patients: lid margin crusting, conjunctival follicles, conjunctival oedema, oedema, abnormal vision, lid disorder, keratitis, blepharitis, photophobia, corneal staining, lid erythema, blepharoconjunctivitis, irritation, corneal erosion, corneal infiltrate, keratopathy, lid scales, lid retraction.

Systemic

Body as a whole: <3% of patients: headache, asthenia, chest pain, abnormal coordination, malaise.

Cardiovascular: <1% of patients: peripheral oedema, arrhythmia.

CNS: <1% of patients: somnolence, dizziness, nervousness, depression, insomnia, paraesthesia.

Digestive system: dry mouth (10.3%). <1% of patients: constipation, nausea.

Musculoskeletal: <1% of patients: myalgia.

Respiratory system: dry nose (2%). <1% of patients: rhinitis, dyspnoea, pharyngitis, asthma.

Dermatologic: <1% of patients: contact dermatitis, dermatitis.

Special senses: Taste perversion (3%), parosmia (<1%).

Post Marketing Events

The following adverse reactions are classified according to the following convention: very common ($\geq 1/10$), common ($\geq 1/100$ to $<1/10$), uncommon ($\geq 1/1,000$ to $<1/100$), rare ($\geq 1/10,000$ to $<1/1,000$), very rare ($<1/10,000$), or not known (cannot be estimated from the available data) according to system organ classes. Within each frequency-grouping, adverse reactions are presented in order of decreasing seriousness. The adverse reactions have been observed during clinical trials and post-marketing experience with IOPIDINE 0.5%.

Eye disorders

Very Common ($\geq 10\%$): conjunctivitis, eye pruritus, ocular hyperaemia.

Common ($\geq 1\%$ to $< 10\%$): eyelid oedema, dry eye, conjunctival follicles, foreign body sensation in eyes, eyelid margin crusting, lacrimation increased, ocular discomfort.

Uncommon ($\geq 0.1\%$ to $< 1\%$): mydriasis, keratitis, keratopathy, visual impairment, visual acuity reduced, photophobia, vision blurred, corneal infiltrates, blepharospasm, blepharitis, eyelid ptosis, erythema of eyelid, eyelid disorders, eye pain, eye oedema, conjunctival vascular disorders, conjunctival oedema, eye discharge, eye irritation.

Infections and Infestations

Common ($\geq 1\%$ to $< 10\%$): rhinitis.

Psychiatric disorders

Uncommon ($\geq 0.1\%$ to $< 1\%$): depression, nervousness.

Nervous System disorders

Common ($\geq 1\%$ to $< 10\%$): headache, dysgeusia.

Uncommon ($\geq 0.1\%$ to $< 1\%$): dizziness, coordination abnormal, somnolence.

Vascular disorders

Uncommon ($\geq 0.1\%$ to $< 1\%$): vasodilation.

Respiratory, thoracic and mediastinal disorders

Common ($\geq 1\%$ to $< 10\%$): nasal dryness.

Uncommon ($\geq 0.1\%$ to $< 1\%$): dyspnoea, rhinorrhoea, throat irritation.

Gastrointestinal disorders

Common ($\geq 1\%$ to $< 10\%$): dry mouth.

Uncommon ($\geq 0.1\%$ to $< 1\%$): nausea, constipation.

Skin and subcutaneous tissue disorders

Common ($\geq 1\%$ to $< 10\%$): dermatitis.

Uncommon ($\geq 0.1\%$ to $< 1\%$): dermatitis contact.

General disorders and administration site conditions

Common ($\geq 1\%$ to $< 10\%$): asthenia.

Uncommon ($\geq 0.1\%$ to $< 1\%$): chest pain, malaise, fatigue, irritability.

Additional adverse reactions identified from post-marketing surveillance include the following. Frequencies cannot be estimated from the available data.

System Organ Classification	MedDRA Preferred Term (v.19.0)
Immune System Disorders	Hypersensitivity
Nervous system disorders	Syncope
Cardiac disorders	Bradycardia
Vascular disorders	hypertension, hypotension

Paediatric Population

IOPIDINE 0.5% is not recommended for use in children. Reactions including lethargy, bradycardia and decreased oxygen saturation have been reported in neonates and infants under 1 year of age even when a single dose of apraclonidine was administered.

DOSAGE AND ADMINISTRATION

One drop of IOPIDINE 0.5% should be instilled into the affected eye(s) three times per day. Since IOPIDINE 0.5% will be used with other ocular glaucoma therapies, an approximate five minute interval between instillation of each medication should be observed to prevent washout of the previous dose (see INDICATIONS).

Clinical studies to establish safety and efficacy in children have not been conducted and, therefore, IOPIDINE 0.5% is not recommended for use in children.

There are no special precautions for administration to the elderly.

Patients with impaired renal and/or hepatic function should be carefully monitored (see PRECAUTIONS).

In order to minimise systemic absorption, apply pressure to the tear duct for two minutes immediately after administration.

OVERDOSAGE

No information on overdosage with IOPIDINE 0.5% is available in humans. Based on information with clonidine, signs of a topical or oral overdose with apraclonidine may include hypotension, lethargy, somnolence, bradycardia, hypoventilation, and seizure, particularly in children. A topical overdose of IOPIDINE 0.5% may be flushed from the eyes with warm tap water. Following accidental overdosage *per ora*, treatment should include drug removal by emesis or activated charcoal as well as symptomatic treatment.

Contact Poisons Information Centre on 13 11 26 (Australia) for advice on management.

PRESENTATION AND STORAGE CONDITIONS

Store below 25°C. Protect from light.

IOPIDINE® Eye Drops 0.5% 5 mL and 10 mL DROP-TAINER™ dispenser

(AUST R 51190)

Consumer Product Information is supplied with this product.

NAME AND ADDRESS OF THE SPONSOR

Novartis Pharmaceuticals Pty Limited

ABN 18 004 244 160

54 Waterloo Road

Macquarie Park NSW 2113.

POISON SCHEDULE OF THE MEDICINE

Prescription only Medicine (Schedule 4)

DATE OF FIRST INCLUSION IN THE ARTG

29 June 1992

DATE OF MOST RECENT AMENDMENT

5 July 2017

Internal document code

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