NEW ZEALAND DATA SHEET

1. IOPIDINE 0.5% EYE DROPS

IOPIDINE® (apraclonidine hydrochloride) Eye Drops 0.5%.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of Iopidine Eye Drops 0.5% contains apraclonidine hydrochloride 5.75 mg, equivalent to apraclonidine base 5 mg.

Excipient with known effect

Benzalkonium chloride 0.1 mg per 1 mL as a preservative.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Eye drops, solution, sterile, isotonic.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Iopidine Eye Drops 0.5% are indicated for short-term adjunctive therapy in patients on maximally tolerated medical therapy who require additional IOP reduction.

Patients on maximally tolerated medical therapy who are treated with Iopidine Eye Drops 0.5% to delay surgery should have frequent follow up examinations and treatment should be discontinued if the intraocular pressure rises significantly.

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

The IOP-lowering efficacy of Iopidine Eye Drops 0.5% diminishes over time in some patients. This loss of effect, or tachyphylaxis, appears to be an individual occurrence with a variable time of onset and should be closely monitored. The benefit for most patients is less than one month.

4.2 Dosage and method of administration

Dose

One drop of Iopidine Eye Drops 0.5% should be instilled into the affected eye(s) three times per day.

Since Iopidine Eye Drops 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.

Paediatric Population

Clinical studies to establish safety and efficacy in children have not been conducted and, therefore, Iopidine Eye Drops 0.5% are not recommended for use in children.

Renal insufficiency

Patients with impaired renal function should be carefully monitored

Hepatic insufficiency

Patients with impaired hepatic function should be carefully monitored.

Elderly

There are no special precautions for administration to the elderly.

Method of Administration

Iopidine Eye Drops 0.5% is for topical use.

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

Patient Information

Do not touch dropper tip to any surface as this may contaminate the contents.

Iopidine Eye Drops 0.5% contain benzalkonium chloride which may cause eye irritation and is known to discolour soft contact lenses. Avoid contact with soft contact lenses. If patients continue to wear soft (hydrophilic) contact lenses while under treatment with Iopidine Eye Drops 0.5%, they should remove their lens (es) prior to instilling the drops in the affected eye(s). Lens(es) should not be inserted into the eye(s) until 15 minutes after instillation of the drops.

4.3 Contraindications

Iopidine Eye Drops 0.5% are contraindicated in patients with hypersensitivity to apraclonidine hydrochloride or to any component of the formulation listed in Section 6.1.

It is also contraindicated with systemic clonidine and in patients receiving monoamine oxidase inhibitors, systemic sympathomimetics or tricyclic antidepressants.

Iopidine Eye Drops 0.5% is contraindicated in patients with hypersensitivity to pilocarpine.

4.4 Special warnings and precautions for use

Not for injection or oral ingestion. Topical ophthalmic use only.

Coronary insufficiency

While the topical administration of Iopidine Eye Drops 0.5% had minimal effect on heart rate or blood pressure in clinical studies evaluating glaucoma patients, the preclinical pharmacology 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.

Renal insufficiency

Although the topical use of Iopidine Eye Drops 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 apraclonidine therapy.

Hepatic insufficiency

Close monitoring of cardiovascular parameters in patients with impaired liver function is also advised as the systemic dosage form of clonidine is partly metabolised in the liver.

Paediatric population

Iopidine Eye Drops 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.

Other

In most patients, a loss of effect occurs over time. This appears to be an individual occurrence with a variable time of onset and should be closely monitored.

Since apraclonidine is a potent depressor of intraocular pressure, patients who develop an exaggerated reduction in IOP should be closely monitored.

Iopidine Eye Drops 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 infrequently associated with depression.

Apraclonidine 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 and advised not to drive or operate machinery.

Glaucoma patients on maximally tolerated medical therapy who are treated with Iopidine Eye Drops 0.5% to delay surgery should have their visual fields monitored periodically.

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

Topical ocular administration of two drops of 0.5, 1.0 and 1.5% apraclonidine eye drops to New Zealand albino rabbits three times daily for one month resulted in sporadic and transient instances of minimal corneal oedema in the 1.5% group only; no histopathological changes were noted in those eyes.

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 Eye Drops 0.5% have not been demonstrated to be effective in cases of angle-closure glaucoma.

4.5 Interactions with other medicines and other forms of interaction

Apraclonidine should not be used in patients receiving MAO inhibitors.

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

However, since apraclonidine may reduce pulse and blood pressure, caution in concomitant use of drugs such as ß-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 Eye Drops 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.

An additive hypotensive effect has been reported with the combination of systemic clonidine and neuroleptic therapy. Systemic clonidine may inhibit the production of catecholamines in response to insulin-induced hypoglycaemia and mask the signs and symptoms of hypoglycaemia.

4.6 Fertility, pregnancy and lactation

Pregnancy

Pregnancy Category 3.

There are no adequate and well controlled studies in pregnant women. Iopidine Eye Drops 0.5% is not recommended during pregnancy. Iopidine Eye Drops 0.5% should be used in pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

For preclinical studied in pregnancy see 5.3. Pregnancy safety data, Pregnancy.

Breast-feeding

It is not known whether this drug is excreted in human milk. A risk to the suckling child cannot be excluded. Breast-feeding should be discontinued during treatment with Iopidine Eye Drops 0.5%.

Fertility

Studies have not been performed to evaluate the effect of topical ocular administration of Iopidine Eye Drops 0.5% on human fertility.

For preclinical studied in fertility see 5.3. Pregnancy safety data, Fertility.

4.7 Effects on ability to drive and use machines

Apraclonidine 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 and advised not to drive or operate machinery.

4.8 Undesirable effects

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

In clinical studies (n=458) the overall discontinuation rate related to Iopidine Eye Drops 0.5% was 15%. The most commonly reported events leading to discontinuation included (in decreasing order of frequency) hyperemia, pruritus, tearing, discomfort, lid oedema, dry mouth, and foreign body sensation.

The following adverse reactions (incidence) were reported in clinical studies of Iopidine Eye Drops 0.5% as being possibly, probably, or definitely related to therapy:

Ocular

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

The following adverse reactions were reported in less than 3% of the patients: lid oedema, blurred vision, foreign body sensation, dry eye, conjunctivitis, discharge, blanching.

The following adverse reactions were reported in less than 1% of the patients: lid margin crusting, conjunctival follicles, conjunctival oedema, oedema, abnormal vision, pain, lid disorder, keratitis, blepharitis, photophobia, corneal staining, lid erythema, blepharoconjunctivitis, irritation, corneal erosion, corneal infiltrate, keratopathy, lid scales, lid retraction.

Nonocular

Body as a Whole	< 3% of patients: headache, asthenia. <1% of patients: chest pain, abnormal coordination, malaise, facial oedema.
Cardiovascular	< 1% of patients: peripheral oedema, arrhythmia. Although no reports of bradycardia related to Iopidine Eye Drops 0.5% were available from clinical studies, the possibility of its occurrence based on apraclonidine's alpha-2-agonist effect should be considered.
CNS	<1% of patients: somnolence, dizziness, nervousness, depression, insomnia, paresthesia.
Digestive System	10% of patients: dry mouth. < 1% of the 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 Experience

The following adverse reactions are classified according to the following convention: very common (≥ 1/10), common (≥ 1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥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 Eye Drops 0.5%.

<u>Eye disorders</u>

Very Common (≥ 10%): conjunctivitis, eye pruritus, ocular hyperaemia.

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

Uncommon (≥ 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.

<u>Infections and Infestations</u>

Common (≥ 1% to < 10%): rhinitis.

<u>Psychiatric disorders</u>

Uncommon (≥ 0.1% to < 1%): depression, nervousness.

<u>Nervous System disorders</u>

Common (≥ 1% to < 10%): headache, dysgeusia.

Uncommon (≥ 0.1% to < 1%): dizziness, coordination abnormal, somnolence.

Vascular disorders

Uncommon (≥ 0.1% to < 1%): vasodilation.

Respiratory, thoracic and mediastinal disorders

Common (≥ 1% to < 10%): nasal dryness.

Uncommon (≥ 0.1% to < 1%): dyspnoea, rhinorrhoea, throat irritation.

Gastrointestinal disorders

Common (≥ 1% to < 10%): dry mouth.

Uncommon (≥ 0.1% to < 1%): nausea, constipation.

Skin and subcutaneous tissue disorders

Common (≥ 1% to < 10%): dermatitis.

Uncommon (≥ 0.1% to < 1%): dermatitis contact.

General disorders and administration site conditions

Common (≥ 1% to < 10%): asthenia.

Uncommon (≥ 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 Eye Drops 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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

While no instances of human ingestion of Iopidine Eye Drops 0.5% 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, apnoea, respiratory depression, hypoventilation, and seizure particularly in children. Treatment of an oral overdose includes supportive and

symptomatic therapy: a patent airway should be maintained. Haemodialysis of limited value, since a maximum of 5% of circulating drug is removed. An ocular overdose of Iopidine Eye Drops 0.5% can be flushed from the eye(s) with lukewarm water.

For advice on the management of overdose contact the National Poisons Centre on 0800 POISON or 0800 764 766.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Ophthalmologicals: Antiglaucoma Preparation and Miotics.

ATC Code: SO1E A03.

Mechanism of action

Optic nerve head damage and visual field loss are the result of sustained elevated intraocular pressure (IOP) 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. Ophthalmic apraclonidine has minimal effect on cardiovascular parameters.

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

An unpredictable decrease of IOP control in some patients and incidence of ocular allergic responses and systemic side effects may limit the utility of Iopidine Eye Drops 0.5%. However, patients on maximally tolerated medical therapy may still benefit from the additional IOP reduction provided by the short-term use of Iopidine Eye Drops 0.5%.

Pharmacodynamic effects

Iopidine Eye Drops 0.5%, because of its alpha-adrenergic activity, act as a vaso-constrictor. Single-dose ocular blood-flow studies in monkeys, using the microsphere technique, demonstrated a reduced blood flow for the anterior segment; however, no reduction in blood flow was observed in the posterior segment of the eye after a topical dose of Iopidine Eye Drops 0.5%. Ocular blood flow studies have not been conducted in humans.

Clinical efficacy and safety

Patients on maximally tolerated medical therapy with uncontrolled IOP and scheduled to undergo laser trabeculoplasty or trabeculectomy surgery were enrolled into a double-masked, placebo-controlled, multi-centre clinical trial to determine if Iopidine Eye Drops 0.5%, dosed three times daily, could delay the need for surgery for up to three months.

All patients enrolled into this trial had advanced glaucoma and were undergoing maximally tolerated medical therapy, i.e. patients were using combinations of a topical beta-blocker, sympathomimetics, parasympathomimetics and oral carbonic anhydrase inhibitors. Patients were considered to be treatment failures in this study if, in the opinion of the investigators, their IOP was uncontrolled by the masked study medication or there was evidence of further optic nerve damage or visual field loss, and surgery was indicated. Of 171 patients receiving masked medication, 84 were treated with Iopidine Eye Drops 0.5% and 87 were treated with placebo (Iopidine vehicle).

Apraclonidine treatment resulted in a significantly greater percentage of treatment successes compared to patients treated with placebo. In this placebo-controlled maximum therapy trial, 14.3% of patients treated with Iopidine Eye Drops 0.5% were discontinued due to adverse events, which primarily comprised allergic-like reactions (12.9%).

5.2 Pharmacokinetic properties

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 $hours^{-1}$.

5.3 Preclinical safety data

Pregnancy

Apraclonidine hydrochloride has been shown to have an embryocidal effect in rabbits when given in an oral dose of 3.0 mg/kg (60 times the maximum recommended human dose). Dose-related maternal toxicity was observed in pregnant rats at 0.3 mg/kg (6 times the maximum recommended human dose).

Fertility

Reproduction and fertility studies in rats showed no adverse effect on male or female fertility at a dose of 0.5 mg/kg (5 to 10 times the maximum recommended human dose).

Carcinogenicity

No significant change in tumour incidence or type was observed following two years of oral administration of apraclonidine hydrochloride to rats and mice at dosages of 1.0 and 0.6 mg/kg, up to 20 and 12 times, respectively, the maximum dose recommended for human topical ocular use.

Mutagenicity

Apraclonidine hydrochloride was not mutagenic in a series of *in vitro* mutagenicity tests, including the Ames test, a mouse lymphoma forward mutation assay, a chromosome aberration assay in cultured Chinese hamster ovary (CHO) cells, a sister chromatid exchange assay in CHO cells, and a cell transformation assay. An *in vivo* mouse micronucleus assay conducted with apraclonidine hydrochloride also provided no evidence of mutagenicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzalkonium chloride

Sodium chloride

Sodium acetate

Sodium hydroxide and/or hydrochloric acid to adjust pH

Purified water.

6.2 Incompatibilities

Not known

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store below 25° C. Protect from light.

Discard container 28 days after opening.

6.5 Nature and contents of container

Bottle plastic, 5 mL or 10 mL

6.6 Special precautions for disposal and other handling

No special requirements for disposal

7. MEDICINE SCHEDULE

Prescription Only Medicine.

8. SPONSOR

Clinect NZ Pty Limited
C/- Ebos Group Limited
108 Wrights Road
Christchurch 8024
New Zealand
Free Call New Zealand: 0800 138 803

9. DATE OF FIRST APPROVAL

8 September 1994

10. DATE OF REVISION OF THE TEXT

16 November 2022

Summary Table of Changes

Section Changed	Summary of New Information
All	Style and Editorial changes
6.5	Update to container description to remove trademark
8	Updated sponsor details with new sponsor