1. NAME OF THE MEDICINAL PRODUCT

IOPIDINE 0.5%

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of solution contains apraclonidine 5 mg (as hydrochloride).

Excipients with known effect:

1 ml of solution contains 0.1 mg benzalkonium chloride.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Ophthalmic, solution.
A colourless to pale yellow solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

IOPIDINE 0.5% is indicated for short term adjunctive therapy of chronic glaucoma in patients on maximally tolerated medical therapy who require additional intraocular pressure (IOP) reduction to delay laser treatment or glaucoma surgery.

The IOP lowering efficacy of IOPIDINE 0.5% diminishes over time in most patients. Although some patients have received successful treatment with IOPIDINE 0.5% for longer periods, the benefit for most patients is less than one month.

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

4.2 Posology and method of administration

Posology
One drop of IOPIDINE 0.5% should be instilled into the affected eye(s) three times per day (t.i.d.). 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. Eye ointments should be administered last. If, for any reason, the drop of IOPIDINE 0.5% does not remain in the eye, then the patient should repeat the dose by placing another drop in the eye. The maximum recommended duration of therapy is one month due to loss of effect over time (tachyphylaxis). However, some patients may benefit from treatment with IOPIDINE 0.5% for longer periods.

There are no special precautions for administration to the elderly.

Paediatric Population
IOPIDINE 0.5% is not indicated for children and adolescents under 18 years old.
The safety and efficacy of IOPIDINE 0.5% in children has not been established. No data are available.

Method of administration
For ocular use only.
After cap is removed, if tamper evident snap collar is loose, remove before using product.

Nasolacrimal occlusion or gently closing the eyelid after instillation is recommended. This may reduce the systemic absorption of medications administered via the ocular route and result in a decrease in systemic side effects.

4.3 Contraindications

IOPIDINE 0.5% is contraindicated in patients with a history of severe or unstable and uncontrolled cardiovascular disease, including severe uncontrolled arterial hypertension.
IOPIDINE 0.5% is contraindicated in children.
IOPIDINE 0.5% is contraindicated in patients with hypersensitivity to the active substance or to any of the excipients listed in section 6.1 or to systemic clonidine and in patients receiving monoamine oxidase inhibitors, systemic sympathomimetics or tricyclic antidepressants.

4.4 Special warnings and precautions for use

While the topical administration of IOPIDINE 0.5% had minimal effect on heart rate or blood pressure in clinical studies evaluating glaucoma patients including those with cardiovascular disease, the possibility of a vasovagal attack should be considered and caution should be exercised in patients with a history of such episodes.

IOPIDINE 0.5% should be used with caution in patients with a history of angina, severe coronary insufficiency, recent myocardial infarction, overt cardiac failure, hypertension, cardiovascular disease, including apoplexy, cerebrovascular disease, Parkinson's syndrome, chronic renal failure, Raynaud's disease or thromboangiitis obliterans.

Caution in and monitoring of depressed patients are advised since apraclonidine has been rarely associated with depression.

In end-stage glaucoma, if reduction in vision occurs immediately following IOPIDINE 0.5% therapy, treatment should be suspended.

As with all glaucoma patients on maximally tolerated medical therapy, those who are treated with IOPIDINE 0.5% to delay surgery should have frequent follow-up examinations and treatment should be discontinued if the intraocular pressure rises significantly. The loss of effect which occurs over time in most patients appears to be an individual occurrence with a variable time of onset and should be closely monitored. Furthermore, these patients should have their visual fields evaluated periodically.

No data are available on the topical use of apraclonidine in patients with renal or hepatic failure. Systemic absorption of apraclonidine following topical administration is low, resulting in plasma levels less than 1.0 ng/ml. Nonetheless, monitoring of patients with impaired renal or hepatic function is advised. 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.

Use of IOPIDINE 0.5% can result in an ocular intolerance reaction characterized wholly or in part by the symptoms of ocular hyperaemia, eye pruritus, ocular discomfort, lacrimation increased, abnormal sensation and oedema of the lids and conjunctival oedema (see section 4.8). If such ocular symptoms occur, IOPIDINE 0.5% therapy should be discontinued. Also, preclinical data suggest that there may be patients who develop a contact sensitization response with repeated use of the drug. Ocular intolerance responses are more common in patients treated for more than one month.

Discontinuation of therapy in the event of rising intraocular pressure should coincide with the initiation of alternative therapy, or pressure-relieving surgery.

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

IOPIDINE 0.5% contains benzalkonium chloride

This medicine contains 0.5 mg benzalkonium chloride in 5mL of the product, which is equivalent to a concentration of 0.1 mg/ml.

IOPIDINE 0.5% contains benzalkonium chloride which may cause eye irritation and is known to discolour soft contact lenses. Contact with soft contact lenses should be avoided. Patients must be instructed to remove contact lenses prior to the application of IOPIDINE 0.5% and wait 15 minutes after instillation of the dose before reinsertion.

Benzalkonium chloride has been reported to cause eye irritation, symptoms of dry eyes and may affect the tear film and corneal surface. Should be used with caution in dry eye patients and in patients where the cornea may be compromised. Patients should be monitored in case of prolonged use.

4.5 Interaction with other medicinal products and other forms of interaction

IOPIDINE 0.5% is contraindicated in patients receiving monoamine oxidase inhibitors, systemic sympathomimetics or tricyclic antidepressants (see section 4.3).

The risk of clinically relevant interactions appears low, considering the plasma levels of apraclonidine given by the ocular route. No drug interactions were reported in those patients who were receiving concomitant medication for glaucoma or for other ocular disorders or for any systemic disease present during clinical studies. Although no specific drug interactions with topical glaucoma drugs or systemic medicaments were identified in clinical studies of IOPIDINE, the possibility of an additive or potentiating effect with CNS depressants (alcohol, barbiturates, opiates, sedatives, anaesthetics) should be considered. There is a theoretical possibility that use of IOPIDINE 0.5% in conjunction with topical sympathomimetics may give rise to a systemic pressor response and blood pressure should be checked initially in patients receiving these drug combinations.

Caution is advised 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 catecholamine in response to insulin-induced hypoglycaemia and mask the signs and symptoms of hypoglycaemia.

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 IOPIDINE 0.5% should have pulse and blood pressure frequently monitored. Caution should be exercised with simultaneous use of clonidine and other similar pharmacologic agents.

If more than one topical ophthalmic medicinal product is being used, the medicines must be administered at least 5 minutes apart. Eye ointments should be administered last.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited studies of IOPIDINE in pregnant women. IOPIDINE 0.5% is not recommended during pregnancy.
Animal studies have been conducted which have demonstrated an absence of teratogenic effects in rats and rabbits. Embryotoxicity has been observed when pregnant rabbits were dosed orally with doses of apraclonidine (doses >1.25 mg/kg/day) that were maternally toxic, and administered over the entire period of organogenesis at exposure levels of (mg/kg/day) of >60 times the recommended dosage regimen for IOPIDINE 0.5% Eye Drops based on a 50 kg person.

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

Fertility
Studies have not been performed to evaluate the effect of topical ocular administration of IOPIDINE 0.5% on male or female fertility. No effect on fertility was observed in rats after oral administration of apraclonidine.

4.7 Effects on ability to drive and use machines

IOPIDINE 0.5% has a moderate influence on the ability to drive and use machines.

Since clonidine-like drugs may cause dizziness or somnolence, patients so affected are advised not to drive or operate machinery. The attention of drivers and machinery operators should be drawn to the risks related to the use of this drug.

4.8 Undesirable effects

Summary of the safety profile

In clinical trials using IOPIDINE the most common adverse reactions were ocular hyperaemia, eye pruritus, and conjunctivitis, occurring in approximately 12% to 23% of patients.

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). Within each frequency-grouping, adverse reactions are presented in order of decreasing seriousness.

System Organ Classification	**MedDRA Preferred Term (v. 19.0)**
Infections and infestations	*Common:* rhinitis
Immune system disorders	*Not known:* hypersensitivity

Psychiatric disorders	*Uncommon:* depression, nervousness, insomnia
Nervous system disorders	*Common:* headache, dysgeusia *Uncommon:* dizziness, abnormal coordination, somnolence, paraesthesia
Eye disorders	*Very common:* conjunctivitis, eye pruritus, ocular hyperaemia *Common:* eyelid oedema, dry eye, conjunctival follicles, foreign body sensation in eyes, eyelid margin crusting, lacrimation increased, ocular discomfort *Uncommon:* mydriasis, keratitis, keratopathy, visual acuity reduced, visual impairment, photophobia, vision blurred, corneal erosion, corneal infiltrates, blepharospasm, blepharitis, eyelid ptosis, erythema of eyelid, eye pain, eye oedema, eyelid disorder, eyelid scales, eyelid retraction, conjunctival vascular disorders, conjunctival oedema, eye discharge, eye irritation
Cardiac disorders	*Uncommon:* chest pain, oedema peripheral, arrhythmia
Vascular disorders	*Uncommon:* vasodilation
Respiratory, thoracic and mediastinal disorders	*Common:* nasal dryness *Uncommon:* asthma, dyspnoea, rhinorrhoea, parosmia, throat irritation
Gastrointestinal disorders	*Common:* dry mouth *Uncommon:* nausea, constipation
Skin and subcutaneous tissue disorders	*Common:* dermatitis *Uncommon:* dermatitis contact, face oedema
Muscoskeletal and connective tissue disorders	*Uncommon:* myalgia
General disorders and administration site conditions	*Common :* asthenia *Uncommon:* malaise, fatigue, irritability
Investigations	*Uncommon:* corneal staining

Description of selected adverse reactions

Use of IOPIDINE 0.5% can lead to an ocular intolerance reaction (see section 4.4). The mean onset time of these reactions was 44 days (range 1-127 days).

In clinical studies, the overall discontinuation rate related to IOPIDINE was 15%. The most commonly reported events leading to discontinuation included (in decreasing order of frequency) ocular hyperaemia, eye pruritus, lacrimation increased, ocular discomfort, eyelid oedema, dry mouth, and abnormal sensation in eye.

The possibility of bradycardia based on apraclonidine's alpha-2-adrenergic agonist effect should be considered. Although there were no reports of bradycardia related to IOPIDINE 0.5% Eye Drops from clinical studies, occasional reports have been received through post-marketing surveillance.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il

4.9 Overdose

IOPIDINE 0.5% may be flushed from the eyes with lukewarm water or sterile saline solution.

Accidental or intentional ingestion of oral 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. Treatment of an oral overdose includes supportive and symptomatic therapy; a patent airway should be maintained. Haemodialysis is of limited value, since a maximum of 5% of circulating drug is removed.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Ophthalmologicals; Antiglaucoma Preparation and Miotics.
ATC code: SO1E A03.

Apraclonidine is a relatively selective alpha-2-adrenergic agonist which does not possess significant membrane stabilising (local anaesthetic) activity. When instilled into the eye, apraclonidine has the action of reducing intraocular pressure.
Ophthalmic apraclonidine has minimal effect on cardiovascular parameters.
Aqueous fluorophotometry studies in man suggest that the mechanism of the ocular hypotensive action of apraclonidine is related to a reduction in aqueous formation.
The onset of action of IOPIDINE 0.5% Eye Drops can usually be noted within one hour and the maximum intraocular pressure reduction usually occurs three to five hours after application of a single dose.

5.2 Pharmacokinetic properties

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 highest to lowest concentration in microgram equivalents per gram 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.

Plasma concentration of apraclonidine following three times daily, bilateral, topical ocular dosing of IOPIDINE to normal human volunteers was less than 1.0 ng/ml. A steady state level was attained after five days of dosing. The half-life of the drug was calculated to be eight hours.

5.3 Preclinical safety data

Administration of apraclonidine intravenously and via the topical ocular route to both cats and 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 hydrochloride 15 mg/ml 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 chronic glaucoma.

Acute Toxicity
The oral LD_{50} ranged from 5 mg/kg (mice) to 64 mg/kg (rats); no lethalities were observed in primates at 55 mg/kg.

Subchronic and Chronic Toxicity

Oral administration
Rats and mice received daily oral doses of up to 1.2 mg/kg and 2 mg/kg, respectively, over a period of 13 weeks. Mortalities occurred from 1.2 mg/kg/day to 1.6 mg/kg/day. Disturbed defaecation, distended abdomen and corneal cloudiness have been observed.

Local administration
The topical ocular administration of apraclonidine hydrochloride solutions (2 drops instilled at 30 minute intervals into one eye for 6 hours) led to dose-dependent conjunctival and corneal irritation in the rabbit from 5 mg/ml.

Rabbits tolerated a solution of 15 mg/ml (2 drops t.i.d.) over a period of one month without signs of systemic toxicity. Nevertheless, conjunctival irritation and sporadic minimal corneal cloudiness have been observed.

No drug-related ophthalmic or systemic findings were observed when monkeys received apraclonidine hydrochloride solutions of 5, 10 and 15 mg/ml by topical ocular administration t.i.d. for one year.

Local tolerance
Assessment of the sensitisation potential in the guinea pig proved apraclonidine hydrochloride to be moderately sensitising.

Mutagenic and Tumorigenic Potential
Mutagenicity testing of apraclonidine hydrochloride using different standard systems all produced negative results. Nevertheless, ocular (keratitis) and renal effects have been reported during these tumorigenic studies.

Reproduction toxicity
Although studies performed in rats and rabbits did not suggest any teratogenic action, slight foetal toxicity was observed at 60 times the therapeutic dosage.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Sodium acetate (trihydrate)
Benzalkonium chloride
Hydrochloric acid and/or Sodium hydroxide (for pH adjustment)
Purified water.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.
May be used for 28 days after the bottle is first opened.

6.4 Special precautions for storage

Do not store above 25°C.
Do not refrigerate or freeze.
Keep the container in the outer carton.

6.5 Nature and contents of container

5 ml white LDPE bottle with a natural LDPE dispensing plug and white polypropylene closure.

6.6 Special precautions for disposal

No special requirements.

7. Manufacturer

Essential Pharma Switzerland GmbH,
Landis + Gyr-Strasse 1 c/o LacMont AG,
6300 Zug, Switzerland

8. REGISTRATION HOLDER

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9. REGISTRATION NUMBER

068-60-28209

Revised in July 2025