

# SUMMARY OF PRODUCT CHARACTERISTICS

## 1 NAME OF THE MEDICINAL PRODUCT

IOPIDINE 5 mg/ml Eye Drops

Apraclonidine 0.5% w/v Eye Drops, Solution

## 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

Eye drops, solution.

A colourless to pale yellow solution

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Apraclonidine 0.5% w/v Eye Drops, Solution 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 Apraclonidine 0.5% w/v Eye Drops, Solution diminishes over time in most patients. Although some patients have received successful treatment with Apraclonidine 0.5% w/v Eye Drops, Solution for longer periods, the benefit for most patients is less than one month.

The addition of Apraclonidine 0.5% w/v Eye Drops, Solution 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 Apraclonidine 0.5% w/v Eye Drops, Solution 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 Apraclonidine 0.5% w/v Eye Drops, Solution should be instilled into the affected eye(s) three times per day (t.i.d.). Since Apraclonidine 0.5% w/v Eye Drops, Solution 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 Apraclonidine 0.5% w/v Eye Drops, Solution 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 praclonidine 0.5% w/v Eye Drops, Solution for longer periods.

There are no special precautions for administration to the elderly.

### *Paediatric Population*

The safety and efficacy of Apraclonidine 0.5% w/v Eye Drops, Solution 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**

Apraclonidine 0.5% w/v Eye Drops, Solution is contraindicated in patients with a history of severe or unstable and uncontrolled cardiovascular disease including severe uncontrolled arterial hypertension. Apraclonidine 0.5% w/v Eye Drops, Solution is contraindicated in children.

Apraclonidine 0.5% w/v Eye Drops, Solution 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.

#### **4.4 Special warnings and precautions for use**

While the topical administration of Apraclonidine 0.5% w/v Eye Drops, Solution 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.

Apraclonidine 0.5% w/v Eye Drops, Solution 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 Apraclonidine 0.5% w/v Eye Drops, Solution therapy, treatment should be suspended.

As with all glaucoma patients on maximally tolerated medical therapy, those who are treated with Apraclonidine 0.5% w/v Eye Drops, Solution 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 Apraclonidine 0.5% w/v Eye Drops, Solution can result in an ocular intolerance reaction characterised 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, Apraclonidine 0.5% w/v Eye Drops, Solution 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.

Apraclonidine 0.5% w/v Eye Drops, Solution contains benzalkonium chloride

This medicine contains 0.5 mg, 1mg benzalkonium chloride in 5mL, 10mL of the product respectively, which is equivalent to a concentration of 0.1 mg/ml.

Apraclonidine 0.5% w/v Eye Drops, Solution 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 Apraclonidine 0.5% w/v Eye Drops, Solution 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**

Apraclonidine 0.5% w/v Eye Drops, Solution 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 Apraclonidine 0.5% w/v Eye Drops, Solution, 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 Apraclonidine 0.5% w/v Eye Drops, Solution 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 Apraclonidine 0.5% w/v Eye Drops, Solution 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 Apraclonidine 0.5% w/v Eye Drops, Solution in pregnant women. Apraclonidine 0.5% w/v Eye Drops, Solution 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 Apraclonidine 0.5% w/v Eye Drops, Solution based on a 50kg 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 Apraclonidine 0.5% w/v Eye Drops, Solution.

### Fertility

Studies have not been performed to evaluate the effect of topical ocular administration of Apraclonidine 0.5% w/v Eye Drops, Solution 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**

Apraclonidine 0.5% w/v Eye Drops, Solution 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 Apraclonidine 0.5% w/v Eye Drops, Solution 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 ( $\geq 1/10$ ), 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). Within each frequency-grouping, adverse reactions are presented in order of decreasing seriousness.

<b>System Organ Classification</b>	<b>MedDRA Preferred Term (v. 19.0)</b>
Infections and infestations	<i>Common:</i> rhinitis
Immune system disorders	<i>Not known:</i> hypersensitivity
Psychiatric disorders	<i>Uncommon:</i> depression, nervousness, insomnia
Nervous system disorders	<i>Common:</i> headache, dysgeusia <i>Uncommon:</i> dizziness, abnormal coordination, somnolence, paraesthesia
Eye disorders	<i>Very common:</i> conjunctivitis, eye pruritus, ocular hyperaemia <i>Common:</i> eyelid oedema, dry eye, conjunctival follicles, foreign body sensation in eyes, eyelid margin crusting, lacrimation increased, ocular discomfort <i>Uncommon:</i> 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, eye lid retraction, conjunctival vascular disorders, conjunctival oedema, eye discharge, eye irritation
Cardiac disorders	<i>Uncommon:</i> chest pain, oedema peripheral, arrhythmia
Vascular disorders	<i>Uncommon:</i> vasodilation
Respiratory, thoracic and mediastinal disorders	<i>Common:</i> nasal dryness <i>Uncommon:</i> asthma, dyspnoea, rhinorrhoea, parosmia, throat irritation
Gastrointestinal disorders	<i>Common:</i> dry mouth <i>Uncommon:</i> nausea, constipation
Skin and subcutaneous tissue disorders	<i>Common:</i> dermatitis <i>Uncommon:</i> dermatitis contact, face oedema
Musculoskeletal and connective tissue disorders	<i>Uncommon:</i> myalgia
General disorders and administration site conditions	<i>Common:</i> asthenia <i>Uncommon:</i> malaise, fatigue, irritability
Investigations	<i>Uncommon:</i> corneal staining

### Description of selected adverse reactions

Use of Apraclonidine 0.5% w/v Eye Drops, Solution

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 Apraclonidine 0.5% w/v Eye Drops, Solution 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 Apraclonidine 0.5% w/v Eye Drops, Solution Eye Drops from clinical studies, occasional reports have been received through postmarketing 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. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: [www.mhra.gov.uk/yellowcard](http://www.mhra.gov.uk/yellowcard).

## **4.9 Overdose**

Apraclonidine 0.5% w/v Eye Drops, Solution 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: S01E 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 Apraclonidine 0.5% w/v Eye Drops, Solution 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 Apraclonidine 0.5% w/v Eye Drops, Solution 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 15mg/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<sub>50</sub> ranged from 5mg/kg (mice) to 64 mg/kg (rats); no lethality was 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 5mg/ml.

Rabbits tolerated a solution of 15mg/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 15mg/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**

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

### **6.2 Incompatibilities**

Not applicable

**6.3 Shelf life**

3 years.

4 weeks after first opening

**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 and/or 10 ml white LDPE DROP-TAINER dispensers with a natural LDPE dispensing plug and white polypropylene closure.

Not all pack sizes may be marketed.

**6.6 Special precautions for disposal**

No special requirements.

**7 MARKETING AUTHORISATION HOLDER**

Essential Pharma Limited,  
Vision Exchange Building  
Triq it-Territorjals, Zone 1,  
Central Business District,  
Birkirkara, CBD 1070,  
Malta

**8 MARKETING AUTHORISATION NUMBER(S)**

PL 50301/0006

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29 December 1994 / 02 December 2009

**10 DATE OF REVISION OF THE TEXT**

11/08/2025