Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

IOPIDINE 1%w/v Eye Drops, Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Apraclonidine 1% w/v (10mg/ml)
(as hydrochloride).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Eye drops, solution
IOPIDINE 1% is a pale yellow solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

IOPIDINE 1% is indicated to control or prevent post surgical elevations in intraocular pressure that occur in patients after anterior segment laser surgery. (Clinical trials have been conducted in trabeculoplasty, iridotomy and capsulotomy).

4.2 Posology and method of administration

For topical ophthalmic use only.

Adults (including the elderly):
One drop of IOPIDINE 1% should be instilled into the eye scheduled for operation one hour before initiating anterior segment laser surgery. A second drop should be instilled into the same eye immediately upon completion of the laser surgical procedure.

If for any reason, the drop of IOPIDINE 1% does not remain in the eye, repeat the dose by placing another drop in the eye.

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.

There are no special precautions for administration to the elderly.

Paediatric population
Safety and effectiveness of IOPIDINE in children have not been established and therefore IOPIDINE 1% is not recommended for use in children.

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

4.3 Contraindications

In patients with a history of severe or unstable and uncontrolled cardiovascular disease.

For use in children.

In patients receiving monoamine oxidase inhibitor therapy, systemic sympathomimetic agents, tricyclic antidepressants.

In patients with hypersensitivity to the active substances (clonidine or apraclonidine) or to any of the excipients.

4.4 Special warnings and precautions for use

Warnings:
While the topical administration of two drops of IOPIDINE 1% had minimal effect on heart rate or blood pressure in clinical studies evaluating patients undergoing anterior segment laser surgery, 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 1% should be used with caution in patients with a history of angina, severe coronary insufficiency, recent myocardial infarction, overt cardiac failure, cerebrovascular disease, 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.

Precautions:
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.

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

4.5 Interaction with other medicinal products and other forms of interaction

The risk of clinically relevant interactions appears low considering the plasma levels of apraclonidine given by the ocular route.

Iopidine 1% is contraindicated in patients receiving monoamine oxidase inhibitors (see section 4.3).

Although no specific drug interactions with topical glaucoma drugs or systemic medicaments were identified in clinical studies of IOPIDINE 1%, 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 1% 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 1% should have pulse and blood pressure frequently monitored. Caution should be exercised with simultaneous use of clonidine and other similar pharmacologic agents.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data from the use of Iopidine 1% in pregnant women. Preclinical studies with apraclonidine have shown embryotoxicity (see section 5.3). The potential risk for humans is unknown. Iopidine 1% is therefore not recommended for use during pregnancy.

Breast-feeding
It is not known if topically applied apraclonidine is excreted in human milk. A risk to the new borns/infants cannot be excluded. Breast-feeding should be discontinued during treatment with IOPIDINE 1% is administered to nursing women.

Fertility
Studies have not been performed to evaluate the effect of topical ocular administration of Iopidine 1% eye drops 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 1% may cause dizziness and drowsiness; patients if so affected should not drive or operate machinery.

4.8 Undesirable effects

Summary of safety profile
In clinical trials, the most common adverse drug reaction was dry mouth which occurred in 5.6% of patients. Other common adverse drug reactions included eyelid retraction and mydriasis, occurring in approximately 3% to 4% of patients. All other drug reactions occurred in less than 2% of patients.

The following adverse reactions have been reported from clinical studies and post marketing surveillance and are classified according to the subsequent 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) and very rare (<1/10,000) or not known (frequency cannot be estimated from available data. Within each frequency-grouping, adverse reactions are presented in order of decreasing seriousness.

Systen Organ Classification	**MedDRA Preferred Term (v.19.0)**
Immune systems disorders	*Not known:* Hypersensitivity
Nervous System Disorders	*Common:* Dysgeusia. Uncommon (> 1/1000 to ≤ 1/100): Syncope vasovagal, paraesthesia, libido decreased, irritability, dizziness postural, headache. Rare (> 1/10,000 to ≤ 1/1000): Hypoaesthesia,
Eye Disorders	*Common:* Ocular hyperaemia, mydriasis, dry eye, abnormal sensation in eye, eyelid retraction, eye disorder (conjunctival blanching) *Uncommon:* Conjunctival haemorrhage, eye inflammation, eyelid disorder (upper lid elevation), hypotony of eye, visual acuity reduced (dim vision), vision blurred, eye allergy, eyelid disorder (upper lid elevation), eye pruritus, dry eye, eye irritation, ocular discomfort, punctate keratitis
Cardiac Disorders	*Uncommon:* Heart rate irregular, bradycardia, Palpitations
Psychiatric Disorders	*Uncommon:* Insomnia, abnormal dreams
Respiratory, Thoracic and Mediastinal Disorders	*Common*: Nasal dryness *Rare:* Dyspnoea, increased upper airway secretion, nasal discomfort,
Vascular Disorders	*Uncommon*: Orthostatic hypotension, Not known: hypotension, Hypertension
Gastrointestinal Disorders	*Common*: Dry mouth *Uncommon*: Diarrhoea, vomiting, abdominal pain, stomach discomfort nausea
Skin and Subcutaneous Tissue Disorders	*Rare:* Hyperhidrosis, pruritus
Musculoskeletal, Connective Tissue and Bone Disorders	*Rare:* Pain in extremity
General Disorders and Administration Site Conditions	*Common:* Fatigue Rare: Chest pain, feeling hot, feeling hot and cold

Paediatric population
Iopidine 1% is contraindicated 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 (See sections 4.3 and 4.9).

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie. By reporting side effects you can help provide more information on the safety of this medicine.

4.9 Overdose

In the case of accidental overdose, Iopidine 1% can be removed by rinsing the eye with water or sterile saline solution.

A 2 month old female child received IOPIDINE 1% 1 drop in each eye. Two to three hours later, the infant presented with extreme pallor, hypothermia and miosis. She became comatose and was treated with glucose perfusion. The infant became responsive, but lethargic and heart rate was noted to be slow but regular. The infant made a full recovery with no sequelae.

A 23 month old male child ingested orally an unknown amount of IOPIDINE 5 mg/ml. The child was admitted to the hospital with hypothermia, bradycardia and drowsiness. Blood analysis revealed an apraclonidine serum level of 2.9 ng/ml. The child was warmed and treated with atropine and dopamine with resolution of hypothermia and bradycardia within 4 hours. The child remained somnolent for 24 hours and was discharged 48 hours after admission with no reported sequelae.

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. 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

Ophthalmologicals; Antiglaucoma Preparation and Miotics.
ATC Code: SO1E A03

5.1 Pharmacodynamic properties

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 1% 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 albino rabbits, apraclonidine reached peak concentrations after two hours in the aqueous humor, 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 humor, lens and vitreous humor. The elimination half-life of apraclonidine from the aqueous humor was determined to be approximately two hours.

Plasma concentration of apraclonidine following three times daily, bilateral, topical ocular dosing of 0.5% apraclonidine ophthalmic solution to normal human volunteers was less than 1.0 ng/ml. A steady state level was attained after five days of dosing. The systemic elimination half-life of apraclonidine was approximately 8 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 1.5% ocularly three times a day for one year did not result in morphological effects.

Acute Toxicity
Acute toxicity was evaluated intravenously and orally in rats and mice and orally in primates. The approximate oral LD_{50} ranged from 5.04 mg/kg (mice) to 63.9 mg/kg (rats); no lethalities were observed in primates at 55 mg/kg. In rodents toxic signs included lethargy, hypothermia, cornea cloudiness, and haemorrhagic areas as well as distension of the gastrointestinal tract. Pronounced inhibition of gastrointestinal motility is considered the cause of mortality in mice. The reduced intestinal motility was observed in mice after intravenous administration of 0.1 mg/kg. Lethargy and disturbed defecation were found in monkeys after oral administration of 55 mg/kg. The normal human dose from ophthalmic use is approximately 0.01 mg/kg/d.

Subchronic and Chronic Toxicity
Rabbits tolerated apraclonidine hydrochloride solutions of 0.5%, 1% or 1.5% (2 drops t.i.d.) over a period of one month without signs of systemic toxicity. Minimal corneal cloudiness was observed sporadically in some eyes receiving the 1.5% apraclonidine hydrochloride solution.

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 in rats at 1.2 mg/kg/d and in mice at 1.6 mg/kg/d. Pharmacotoxic reactions included disturbed defecation and distended abdomen plus corneal cloudiness predominantly in female mice of the high-dose group. Rats in the high-dose group that died before the end of the study showed lymphocytic effects in the spleen and thymus, but these effects were not seen in animals which survived to the end of the study. No drug-related toxic or ophthalmic findings were observed when monkeys received apraclonidine hydrochloride solutions of 0.5%, 1% and 1.5% by topical ocular administration t.i.d. for one year.

Local Tolerance
The topical ocular administration of apraclonidine hydrochloride solutions of 0.5%, 1% and 1.5% (2 drops instilled at 30 min intervals into one eye for 6 h) led to dose-dependent conjunctival and corneal irritation in the rabbit.

Assessment of the sensitization potential in the guinea pig proved apraclonidine hydrochloride to be moderately sensitizing.

Mutagenic and Tumorigenic Potential
Mutagenicity testing of apraclonidine hydrochloride using different standard systems all produced negative results.

Two-year long-term studies evaluating the carcinogenic potential in rats (at doses of 0.1, 0.3 and 1.0 mg/kg/d) and mice (at doses of 0.1, 0.3 and 0.6 mg/kg/d) revealed no signs of a carcinogenic potential of apraclonidine hydrochloride.

Both species showed an increased incidence of ocular changes (mineralization and neo-vascularization of the cornea, and keratitis), which are considered related to the pharmacological effect of the drug in reducing the tear film. In addition, renal changes (mineralisation) were found in rats from 0.3 mg/kg/d onward.

Reproduction Toxicity
Studies performed in rats and rabbits did not suggest any teratogenic effects of apraclonidine. 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 > 100 times the recommended daily dosage regimen for IOPIDINE 1.0% based on a 50 kg person.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium acetate
Sodium chloride
Hydrochloric acid and/or sodium hydroxide (to adjust pH) and purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Unopened: 2 years.
Use immediately after first opening the container.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

Two sealed LDPE form/fill/seal single-dose containers each containing 0.25 mL and wrapped in a foil pouch.

The following pack sizes are available:
1 box containing 1 pouch of 2 single dose containers.
1 box containing 5 pouches of 2 single dose containers.
1 box containing 6 pouches of 2 single dose containers.
1 box containing 10 pouches of 2 single dose containers.
1 box containing 12 foil pouches of 2 single dose containers.
1 box containing 15 pouches of 2 single dose containers.
1 box containing 20 pouches of 2 single dose containers.
1 box containing 25 pouches of 2 single dose containers.

Not all the pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

For single use only.
Discard any unused contents immediately after use.

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

PA22587/002/002

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