1 NAME OF THE MEDICINAL PRODUCT

MYDFRIN™ OPHTHALMIC SOLUTION 2.5%

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredients: 25 mg of Phenylephrine Hydrochloride in one mL solution (2.5%)

Preservative: Benzalkonium Chloride 0.01%

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Eye Drops, solution

Colorless to light yellow solution

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

MYDFRIN™ Ophthalmic Solution 2.5% is indicated

- As a vasoconstrictor, decongestant, and mydriatic in a variety of ophthalmic conditions and procedures.
- For pupillary dilation in uveitis (to prevent or aid in the disruption of posterior synechia formation).
- For many ophthalmic surgical procedures.
- For refraction without cycloplegia.
- For funduscopy and other diagnostic procedures.

4.2 Posology and Method of Administration

Posology

Vasoconstriction and Pupil Dilation:

- A drop of a suitable topical anesthetic may be applied, followed in a few minutes by 1 drop of MYDFRIN™ Ophthalmic Solution 2.5% on the upper limbus.
- Repeat the instillation as necessary after 1 hour, preceded by the use of the topical anesthetic.

Uveitis:

- For recently formed posterior synechiae, 1 drop of MYDFRIN™ Ophthalmic Solution 2.5% may be applied to the upper surface of the cornea and repeated as necessary, not to exceed 3 times.

- Treatment may be continued the following day, if necessary, not to exceed 3 times.

Glaucoma:

- MYDFRIN™ Ophthalmic Solution 2.5% may be used with miotics in patients with open angle glaucoma to reduce the difficulties experienced because of the small field produced by miosis, and still permit and support the effect of the miotic in lowering the intraocular pressure in open angle glaucoma. Marked improvement in visual acuity may occur after using MYDFRIN™ Ophthalmic Solution 2.5% in conjunction with miotic drugs.

Surgery:

- When a short-acting mydriatic is needed for wide dilation of the pupil before intraocular surgery, MYDFRIN™ Ophthalmic Solution 2.5% may be applied topically 30 to 60 minutes before the operation.

Refraction:

- MYDFRIN™ Ophthalmic Solution 2.5% may be used effectively to increase mydriasis with homatropine hydrobromide, cyclopentolate hydrochloride, tropicamide hydrochloride and atropine sulfate.

FOR ADULTS

- One drop of the preferred cycloplegic is placed in each eye, followed in 5 minutes by one drop of MYDFRIN™ Ophthalmic Solution 2.5%. Since adequate cycloplegia is achieved at different time intervals after the instillation of the necessary number of drops, different cycloplegics will require different waiting periods to achieve adequate cycloplegia.

Paediatric population

- For a "one application method": MYDFRIN™ Ophthalmic Solution 2.5% may be combined with one of the preferred rapid acting cycloplegics to produce adequate cycloplegia.

- For Ophthalmoscopic Examination: One drop of MYDFRIN™ Ophthalmic Solution 2.5% is placed in each eye. Sufficient mydriasis to permit examination is produced in 15 to 30 minutes. Dilation lasts from one to three hours.

- For Diagnostic Procedures: Provocative Test for Angle Closure Glaucoma: MYDFRIN™ Ophthalmic Solution 2.5% may be used cautiously as a provocative test when interval narrow angle closure glaucoma is suspected. Intraocular tension and gonioscopy are performed prior to

and after dilation of the pupil with phenylephrine HCl. A “significant” intraocular pressure (IOP) rise combined with gonioscopic evidence of angle closure indicates an anterior segment anatomy capable of angle closure. A negative test does not rule this out. This pharmacologically induced angle closure glaucoma may not simulate real life conditions and other causes for transient elevations of IOP should be excluded.

- Retinoscopy (Shadow Test): When dilation of the pupil without cycloplegic action is desired for retinoscopy, MYDFRIN™ Ophthalmic Solution 2.5% may be used.

NOTE: Heavily pigmented irides may require larger doses in all of the above procedures.

- Blanching Test: One or two drops of MYDFRIN™ Ophthalmic Solution 2.5% should be applied to the injected eye. After five minutes, examine for perilimbal blanching. If blanching occurs, the congestion is superficial and probably does not indicate iridocyclitis.

Method of administration

- For ocular use only.
- To prevent contamination of the dropper tip and solution, care must be taken not to touch the eyelids, surrounding areas or other surfaces with the dropper tip. Keep the bottle tightly closed when not in use.
- If you are using other eye drop or eye ointment medicines, leave at least 5 minutes between each medicine. Eye ointments should be administered last.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients.
- **MYDFRIN™ Ophthalmic Solution 2.5%** are contraindicated in patients with anatomically narrow angles or narrow angle glaucoma.
- **MYDFRIN™ Ophthalmic Solution 2.5%** are contraindicated in newborns and infants with cardiovascular or cerebrovascular disease and in some elderly adults with severe arteriosclerotic, cardiovascular or cerebrovascular disease.

4.4 Special Warnings and Precautions for Use

- Nasolacrimal occlusion or gently closing the eyelid after administration is recommended. This may reduce the systemic absorption of medicinal products administered via the ocular route and result in a decrease in systemic adverse reactions.
- The use in preterm and newborn infants is not recommended unless clearly necessary. The lowest possible dose should be used. Instillation of more than one drop per eye must be avoided (see section 4.4).
- Use with caution in children and elderly or in patients with sympathetic denervation (e.g. patients with insulin dependent diabetes, orthostatic hypotension, hypertension, hyperthyroidism).
- Use with caution, if at all, in patients taking monoamine oxidase inhibitors, tricyclic antidepressants, certain antihypertensive agents, or atropine (see Section 4.5).
- Systemic absorption may be enhanced when applying MYDFRIN™ Ophthalmic Solution 2.5% to an instrumented, traumatised, diseased or postsurgical eye or adnexa, or to patients with suppressed lacrimation, as during anesthesia.
- Rebound miosis has been reported in older persons one day after receiving phenylephrine eye drops, and reinstillation of the drug may produce a reduction in mydriasis. This may be of clinical importance in dilating the pupils of older subjects prior to retinal detachment or cataract surgery.
- Due to a strong action of the drug on the dilator muscle, the use of phenylephrine in the eye may liberate pigment granules from the iris, especially when given in high doses to elderly patients.

<u>Paediatric population</u>

- Full-term, but especially low birth weight and premature infants may be at an increased risk for systemic adverse reactions including transient increases in blood pressure. The infant should be monitored after instillation and routines to adequately deal with emergency situations should be in place.
- The lowest dose necessary to produce the desired effect should always be used.
- Parents should be warned not to get this preparation in their children's mouth or cheeks and to wash their hands and the child's hands or cheeks following administration.
- **MYDFRIN™ Ophthalmic Solution 2.5%** 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 application of MYDFRIN™ Ophthalmic Solution 2.5% and wait at least 15 minutes before reinsertion.

4.5 Interaction with Other Medicinal Products and Other Forms of Interaction

- When administered simultaneously with, or up to 21 days after, administration of monoamine oxidase (MAO) inhibitors, careful supervision and adjustment of dosages are required since exaggerated adrenergic effects may result (see Section 4.4).
- Use with caution, if at all, in patients taking tricyclic antidepressants and certain antihypertensive agents (guanethidine, reserpine, and non-selective beta blockers such as propranolol) as the pressor response is potentiated (see Section 4.4).
- Concomitant use of phenylephrine and atropine may enhance the pressor effects and induce tachycardia in some patients, especially infants (see Section 4.4).
- Phenylephrine may potentiate the cardiovascular depressant effects of potent inhalation anesthetic agents.

4.6 Pregnancy and Lactation

Fertility

- Studies have not been performed to evaluate the effect of ocular administration of MYDFRIN™ Ophthalmic Solution 2.5% on fertility.

Pregnancy

- There are no or limited amount of data from the use of MYDFRIN™ Ophthalmic Solution 2.5% in pregnant women. However, the available data with systemic use of phenylephrine suggest some risk during pregnancy.

Breast-feeding

- It is not known whether phenylephrine/metabolites are excreted into human milk after ocular administration. A risk to the suckling child cannot be excluded.

4.7 Effects on Ability to Drive and Use Machines

Temporary blurred vision or other visual disturbances may affect the ability to drive or use machines. If blurred vision occurs after instillation, the patient must wait until the vision clears before driving or using machinery.

4.8 Undesirable Effects

The following adverse reactions have been identified from post-marketing surveillance following administration of MYDFRIN™ Ophthalmic Solution 2.5%. Frequency cannot be estimated from the available data.

System Organ Classification	MedDRA Preferred Term (v. 15.1)
Immune system disorders	hypersensitivity
Nervous system disorders	dizziness
Eye disorders	eye pain, eye irritation, ocular hyperaemia, conjunctivitis
Cardiac disorders	blood pressure increased, tachycardia
Respiratory, thoracic and mediastinal disorders	pulmonary oedema
Skin and subcutaneous tissue disorders	dermatitis contact

Description of selected adverse reactions

Systemic toxicity can result from topical application of sympathomimetic drugs: headache, blood pressure elevation, extrasystoles, tachycardia, faintness and cerebrovascular accidents have been reported.

4.9 Overdose

In case of accidental ingestion, phenylephrine may cause hypertension, headache, seizures, cerebral haemorrhage, palpitation, paresthesia, or vomiting. Pulmonary oedema or cardiac arrest may occur. Phenylephrine has a rapid onset and short duration of action, thus, treatment of toxicity is supportive. The use of beta blockers and calcium channel blockers for the treatment of acute hypertension secondary to vasoconstriction should be avoided.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: Sympathomimetics excl. antiglaucoma preparations

ATC code: S01FB01

Mechanism of action

Phenylephrine hydrochloride is a sympathomimetic agent that acts directly on α-adrenergic blocking receptors. Following topical application, phenylephrine contracts the iris dilator muscle and smooth

muscle of the conjunctival arterioles, causing pupillary dilation and blanching of the conjunctiva, respectively. Mueller's muscle of the upper lid is stimulated, which widens the palpebral fissure.

Pharmacodynamic effects

Pharmacodynamic effects of PhE involve a 1-adrenergic stimulation: The subsequent hypertension is due to the increase in peripheral vascular resistances and increased filling pressures of the left ventricle. Afterload impedance on left ventricular ejection, and telediastolic volume and pressures, may in turn cause intense tachycardia or reflex bradycardia.

Clinical efficacy and safety

Pupillary dilation following topical administration of phenylephrine hydrochloride ophthalmic solution has been demonstrated in controlled clinical studies in adults and pediatric patients with different levels of iris pigmentation. Pupil movement is generally seen within 15 minutes, maximal mydriasis between 20 to 90 minutes and recovery after 3 to 8 hours. Darker irides tend to dilate slower than lighter irides. Clinical efficacy and safety is supported by published literature. See Section 4.8 for additional information.

Paediatric population

Systemic absorption of sufficient quantities of phenylephrine may lead to systemic α-adrenergic effects, such as rise in blood pressure which may be accompanied by a reflex atropine-sensitive bradycardia. For information concerning posology, precautions, and warnings for pediatric subjects see Section 4.2 and 4.4, respectively.

5.2 Pharmacokinetic Properties

Absorption

Phenylephrine crosses the cornea and into the aqueous humor after topical ocular administration to rabbits. T_{max} in aqueous humor was reported as 1 hour with a C_{max} of 20.2 µM after three drops of 2.5% dosing solution. C_{max} dramatically increased after the removal of cornea's epithelium layer by17-fold, with a decrease in T_{max}. Plasma concentrations in man after topical dosing with phenylephrine 25 mg/ml eye drops, solution was approximately 3 ng/mL, and approximately 10 ng/mL after topical ocular dosing with the phenylephrine 100 mg/ml eye drops, solution.

After oral administration, absorption is complete but oral bioavailability is highly variable with reported value of 38% because of metabolism in the GI tract. However recently, that value has been challenged suggesting that bioavailability is considerable lower then was reported from radiolabel studies. The reported T_{max} range in plasma after oral administration is 0.75 to 2 hours.

Distribution

In rabbits, phenylephrine distributes to the iris-ciliary body after topical ocular administration with a T_{max} of 1 hour. Cornea and iris-cillary body exposure was greater than those found in the aqueous humor.

The volume of distribution (V_d) after IV administration has been reported in normal adult subjects as 340 ± 174 L with a reported V_d range of 184-543 L. Plasma protein binding of phenylephrine is 95%.

Biotransformation

Phenylephrine metabolism occurs in the corneal epithelium in the rabbit after topical ocular administration. Monoamine oxidase activity has also been found in iris-ciliary body and in retina and choroid.
Systemic metabolism in man involves deamination of phenylephrine by monoamine oxidase which produces an aldehyde which is subsequently metabolized to m-hydroxymandelic acid by aldehyde dehydrogenase. Additional conversion of the acid by catechol-O-methyl transferase does occur. Conjugations of the parent drug or metabolite by sulfotransferases and glucuronyltransferases are also important metabolic pathways for phenylephrine. The metabolites, sulfate conjugate of phenylephrine (47% of dose after PO administration), m-hydroxymandelic acid (30% of the dose after PO administration), glucuronide conjugate of phenylephrine (12%); along with other minor metabolites have been identified in human urine. Conjugates of phenylephrine are also major species in plasma after PO administration with plasma parent drug concentrations below the limit of quantitation. Phenylephrine after systemic dosing has demonstrated drug-drug interaction with known monoamine oxidase inhibitors.

Elimination

In rabbit, the half-life for phenylephrine in the aqueous humor was reported to be approximately 1 - 1.5 hours after topical ocular administration of phenylephrine 100 mg/ml eye drops, solution.

After oral administration, phenylephrine undergoes extensive pre-systemic metabolism in the GI tract after oral administration. After IV and PO administration, unchanged phenylephrine in urine accounted for only 16% and 2.6% of the dose, respectively. Elimination half-life after PO and IV administration averaged 2-3 hours. The systemic clearance for phenylephrine after IV administration has been reported to be 2095 mL/min.

Linearity/non-linearity

Linear pharmacokinetics after topical ocular administration of phenylephrine 25 mg/ml and 100 mg/ml eye drops, solution is suggested from the systemic exposure (AUC) in man.

Pharmacokinetic/pharmacodynamic relationship(s)

After topical ocular administration, a clockwise hysteresis was observed when effect (mydriasis) was plotted against aqueous humor concentrations in rabbit. K_m and time plots indicated that K_m increased after 90 min with the higher phenylephrine 100 mg/ml eye drops, solution. This observed tolerance has multiple possible mechanisms; but most likely results in a decrease in receptor activity.

Pharmacokinetics in Special Populations

There are no reports of clinical pharmacokinetics in pediatrics, the elderly, or in hepatic or renal compromised patients.

5.3 Preclinical Safety Data

Non-clinical data reveal no special hazard of phenylephrine 25 mg/ml eye drops, solution for humans, when used as recommended, based on conventional studies of general toxicity, genotoxicity, carcinogenicity and toxicity to reproduction.

6 PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Sodium Bisulfite

Boric Acid

Edetate Disodium (Dihydrate)

Sodium Hydroxide and/or Hydrochloric Acid

Purified Water

6.2 Incompatibilities

None known.

6.3 Shelf Life

24 months

6.4 Special Precautions for Storage

Store below 30°C. Protect from light and excessive heat.

6.5 Nature and Contents of Container

5 ml in plastic DROP-TAINER™ Dispenser.

6.6 Instructions for Use and Disposal

No special requirements.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

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ALCON RESEARCH LLC

Fort Worth, Texas 76134, USA