1 NAME OF THE MEDICINAL PRODUCT

CYCLOMYDRIL* Ophthalmic Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

The active ingredients are cyclopentolate hydrochloride 0.2% and phenylephrine hydrochloride 1.0%.

For excipients, see section 6.1.

3 PHARMACEUTICAL FORM

A colorless to pale yellow sterile solution; eye drops.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

For the production of mydriasis.

4.2 Posology and Method of Administration

Adults, Children (>1 month of age) and Elderly

For fundoscopy: Instill 1 drop in each eye every 5 to 10 minutes (see Section 4.4).

Observe infants closely for at least 30 minutes.

Hepatic and renal impairment

No formal studies have been conducted with CYCLOMYDRIL* Ophthalmic Solution in patients with renal or hepatic impairment (See section 4.4).

Method of Administration

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.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients.

Patients with narrow-angle glaucoma or with anatomically narrow angles.

4.4 Special Warnings and Precautions for Use

The use of this combination may have an adverse effect on individuals suffering from cardiovascular disease, hypertension, and hyperthyroidism; and it may cause central nervous system disturbances.

Mydriatics may produce a transient elevation of intraocular pressure. Determine the intraocular pressure and an estimation of the depth of the angle of the anterior chamber prior to initiation of therapy to avoid glaucoma attacks.

Caution should be observed when considering use of this medication in the presence of Down's syndrome.

Because of risk of provoking hyperthermia, use with caution in patients, especially children, who may be exposed to elevated environmental temperatures or who are febrile.

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.

Patients may experience sensitivity to light and should protect eye in bright illumination during dilation.

CYCLOMYDRIL* Ophthalmic Solution contains benzalkonium chloride which may cause eye irritation and is known to discolor soft contact lenses. Avoid contact with soft contact lenses. Patients must be instructed to remove contact lenses prior to application of CYCLOMYDRIL* Ophthalmic Solution and wait at least 15 minutes before reinsertion

Paediatric population

Newborns and infants (especially premature and low birth weight infants) are especially prone to central nervous system, cardiopulmonary and gastrointestinal side effects from cyclopentolate and to experience transient increases in blood pressure due to the phenylephrine component. The lowest dose necessary to produce the desired effect should always be used.

The infant should be monitored for at least 30 minutes after instillation and routines to adequately deal with emergency situations should be in place.

Use of cyclopentolate has been associated with psychotic reactions and behavioral disturbances, especially in pediatric patients. Increased susceptibility to cyclopentolate has been reported in infants, young children, and in children with spastic paralysis or brain damage.

Seizures and acute psychosis induced by cyclopentolate are especially prominent in children. CYCLOMYDRIL* Ophthalmic Solution should be used with caution in children with known epilepsy.

Feeding intolerance may follow ophthalmic use of this product in infants. It is recommended that feeding be withheld for 4 hours after examination.

Parents should be warned not to get this preparation in their child's mouth and to wash their own and the child's hands following administration.

4.5 Interaction with other Medicinal Products and Other Forms of Interaction

Use with caution, if at all, in patients taking monoamine oxidase inhibitors, tricyclic antidepressants, certain antihypertensive agents, or if atropine has to be administered.

4.6 Pregnancy and Lactation

Fertility

Studies have not been performed to evaluate the effect of topical ocular administration of cyclopentolate hydrochloride and/or phenylepherine hydrochloride on fertility (See Section 5.3).

Pregnancy

There are no studies on the ophthalmic use of cyclopentolate hydrochloride and/or phenylepherine hydrochloride CYCLOMYDRIL* Ophthalmic Solution in pregnant women. Studies in animals have demonstrated teratogenicity following subcutaneous administration of phenylephrine (See Section 5.3). CYCLOMYDRIL* Ophthalmic Solution should be administered to a pregnant woman only if the benefits outweigh the potential risks.

Lactation

It is unknown whether cyclopentolate and/or phenylepherine are excreted in human milk and there is no information on the safety of cyclopentolate and/or phenylepherine in ophthalmic formulations used during breast feeding. However, a risk to the suckling child cannot be excluded. Caution should be exercised when CYCLOMYDRIL* Ophthalmic Solution is administered to a nursing woman.

4.7 Effects on Ability to Drive and Use Machines

Patients should be advised not to drive or engage in hazardous activities while pupils are dilated.

4.8 Undesirable Effects

Tabulated list of adverse reactions [Clinical Studies]

Not applicable. No adverse drug reactions were reported in a clinical study involving CYCLOMYDRIL* Ophthalmic Solution.

Tabulated list of adverse reactions [Post-marketing surveillance]

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

System Organ Classification	MedDRA Term
Nervous system disorders	convulsion
Cardiac disorders	bradycardia
Respiratory, thoracic and mediastinal disorders	apnoea
Gastrointestinal disorders	necrotising colitis, abdominal distension

The ADRs listed above have been reported in newborns and infants (especially in premature infants) with the use of the CYCLOMYDRIL* Ophthalmic Solution.

Description of selected adverse reactions

Cyclopentolate produces reactions similar to those of other anticholinergic drugs. The central nervous system manifestations such as ataxia, incoherent speech, restlessness, hallucinations, hyperactivity, seizures, disorientation as to time and place, and failure to recognize people are possible. Other toxic manifestations of anticholinergic drugs are skin rash, abdominal distention in infants, unusual drowsiness, tachycardia, hyperpyrexia, vasodilation, urinary retention, diminished gastrointestinal motility, and decreased secretion in salivary and sweat glands, pharynx, bronchi and nasal passages.

Severe reactions are manifested by hypotension with rapid progressive respiratory depression.

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

CYCLOMYDRIL* Ophthalmic Solution may increase intraocular pressure and provoke glaucoma attacks in patients predisposed to acute angle closure.

Paediatric population

Use of cyclopentolate has been associated with psychotic reactions and behavioral disturbances in pediatric patients. Increased susceptibility to cyclopentolate has been reported in infants, young children, and in children with spastic paralysis or brain damage (See Section 4.4). These disturbances include ataxia, incoherent speech, restlessness, hallucinations, hyperactivity, seizures, disorientation as to time and place, and failure to recognize people.

Infants may be at an increased risk for systemic adverse reactions from phenylephrine, including transient increases in blood pressure.

Feeding intolerance may follow ophthalmic use of this product in infants.

4.9 Overdose

[Symptoms]

Excessive dosage may produce behavioral disturbances, tachycardia, hyperpyrexia, hypertension, vasodilation, urinary retention, diminished gastrointestinal motility and decreased secretion in salivary and sweat glands, pharynx, bronchi and nasal passages. Severe intoxication is characterized by central nervous system depression, coma, circulatory and respiratory failure, and death.

Pulmonary oedema or cardiac arrest may occur due to phenyleprine toxicity.

[Management]

Patients exhibiting signs of overdosage should receive supportive care and monitoring.

The use of beta blockers and calcium channel blockers for the treatment of acute hypertension in cases of overdose should be avoided.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Cyclopentolate: Ophthalmicologicals, mydriatics and cycloplegics, anticholinergic agents

Cyclopentolate is an anticholinergic drug and phenylephrine is an adrenergic drug. This combination induces mydriasis that is greater than that of either drug alone at its respective concentrations. The concentrations of cyclopentolate hydrochloride and phenylephrine hydrochloride have been selected to induce mydriasis with little accompanying cycloplegia. Heavily pigmented irides may require more doses than lightly pigmented irides.

5.2 Pharmacokinetic Properties

Absorption

Following topical ocular administration, cyclopentolate is absorbed into the eye as well as the systemic circulation. Following topical administration of 2 drops of 1% cyclopentolate to the eye of patients undergoing cataract surgery, aqueous humor drug concentrations during surgery (55 to 125 minutes

postdose) ranged from 1410 to 25,361 nM. The corresponding plasma drug concentrations over this same interval ranged from 1.03 to 7.55 nM. In healthy female volunteers administered 1 drop of 1% cyclopentolate to each eye, a mean maximum plasma drug concentration of 2.06 ± 0.86 nM was achieved within 1 hour. In another study, plasma cyclopentolate concentrations were determined following two 30-microliter unilateral doses of 1% cyclopentolate administered 5 minutes apart. Peak plasma drug concentrations ranged from 3.3 to 15.5 ng/mL (mean: 8.3 ± 4.1 ng/mL) and were achieved within 5 to 15 minutes following the second dose.

Following topical ocular administration, phenylephrine is absorbed into the eye as well as the systemic circulation. Following an i.v. dose, a biphasic elimination profile is observed. The serum elimination half-life is approximately 2 to 3 hours and total clearance is 2 L/minute.

Distribution

Aside from the aqueous humor data reported above for cataract patients, the ocular and systemic distribution of cyclopentolate has not been reported.

Following a single topical dose of 1 mg phenylephrine to albino rabbits, mean maximum drug concentrations were approximately 3 and 35 µg/g in aqueous humor and cornea, respectively, and were achieved within 1 hour. Drug concentrations in both matrices declined in a parallel fashion and were eliminated within 6 hours.

Biotransformation

The metabolic pathways of cyclopentolate have not been reported in the literature.

Phenylephrine is primarily metabolized by conjugation, primarily as the sulfate with smaller amounts of glucuronide also formed. Oral doses exhibit a high degree of first-pass metabolism. Doses administered i.v. undergo extensive deamination to *m*-hydroxymandelic acid.

Elimination

The elimination mechanisms of cyclopentolate have not been reported in the literature.

Phenylephrine is primarily eliminated in the urine, primarily as the sulfate conjugate with smaller amounts of the glucuronide. Virtually no free parent drug is found in urine. Following oral administration, 75-80% of the dose is recovered in urine within 24 hours.

Linearity/non-linearity

The dose proportionality of cyclopentolate and phenylephrine have not been reported in the literature.

Pharmacokinetic/pharmacodynamic relationship(s)

The maximum pupillary dilation in female volunteers administered 1% cyclopentolate bilaterally occurred at 30 minutes post-dose, when plasma concentrations were approaching their maximum values.

In patients undergoing cataract surgery, mydriasis was more pronounced with a viscous 10% phenylephrine solution compared to a non-viscous 2.5% solution. The difference was more pronounced in patients dark iris pigmentation (dark brown) compared to those with light (blue, gray) or moderate (hazel, green, tan) pigmentation.

5.3 Preclinical Safety Data

Nonclinical data with cyclopentolate and/or phenylepherine reveal no special hazard for humans based on conventional studies of repeated dose toxicity, genotoxicity, or carcinogenic potential.

Effects in non-clinical reproductive toxicity studies with phenylepherine were observed only after systemic administration and are considered to have limited applicability due to the topical ocular administration, low dose, and infrequent use of Cyclomydril.

Nonclinical reproduction studies have been conducted with phenylepherine in the rabbit and rat. In the rabbit, subcutaneous administration during various periods during gestation resulted in two abnormal litters, but in rats no malformations were observed at higher parenteral doses.

6 PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Benzalkonium chloride

Boric acid

Edetate disodium

Sodium carbonate and/or hydrochloric acid (to adjust pH)

Purified water

6.2 Incompatibilities

None specified.

6.3 Shelf Life

24 months

6.4 Special Precautions for Storage

Do not store above 25°C.

6.5 Nature and Contents of Container

5 mL in plastic DROPTAINER™ dispensers.

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