Summary of Product Characteristics

1. Name of the medicinal product
MYDRIA MAC

2. Qualitative and quantitative composition

Each 1 bottle (5 mL) contains:

Tropicamide	0.8% w/v
Phenylephrine Hydrochloride	5% w/v
Chlorbutol (as preservative)	0.5% w/v

For the full list of excipients, see section 6.1

3. Pharmaceutical form
eye drops, solution.
A Clear, colourless, sterile solution

4. Clinical particulars
4.1 Therapeutic indications
Mydria mac is indicated:

- to obtain pre-operative mydriasis,
- or for diagnostic purposes when monotherapy is known to be insufficient.

4.2 Posology and method of administration

Restricted use to health-care professionals.

Posology
One or two drops instilled into the eyes 15-30 minutes before the procedure or surgery.

Paediatric population
There are no data in children. Mydria mac is not recommended in these patients (see section 4.4).

Method of administration

- Ophthalmic use only, contact lenses should be removed before instillation and put on no earlier than 15 minutes after it.
- 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.
- If more than one topical ophthalmic product is being used, the products must be administered at least 5 minutes apart. Eye ointments should be administered last.
- Do not use Mydria mac if it is discolored or contains a precipitate.

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
- Patients with cardiac disease, hypertension, aneurysms, thyrotoxicosis, long-standing insulin dependent diabetes mellitus and tachycardia.
- Risk of angle-closure glaucoma: Patients with closed angle glaucoma (unless previously treated with iridectomy) and patients with narrow angle prone to glaucoma precipitated by mydriatics.
- Patients on monoamine oxidase inhibitors, tricyclic anti-depressants and anti-hypertensive agents (including beta-blockers).
- Children because of the increased risk of systemic toxicity.

4.4 Special warnings and precautions for use

- Use with caution in the presence of diabetes, cerebral arteriosclerosis or long standing bronchial asthma.
- To reduce the risk of precipitating an attack of narrow angle glaucoma evaluate the anterior chamber angle before use.
- Ocular hyperaemia can increase the absorption of these drugs given topically.
- Systemic absorption may be minimised by compressing the lacrimal sac at the medial canthus for one minute during and after the instillation of the drops. This blocks the passage of the drops via the naso-lacrimal duct to the wide absorptive area of the nasal and pharyngeal mucosa.
- Tropicamide may cause increased intraocular pressure. The possibility of undiagnosed glaucoma should be considered in some patients, such as elderly patients. Determine the intraocular pressure and an estimation of the depth of the angle of the anterior chamber prior to initiation of therapy.
- Tropicamide-induced psychotic reactions and behavioral disturbances may occur in patients with increased susceptibility to anticholinergic drugs (See Section 4.8 Undesirable effects).
- Use with caution in an inflamed eye as the hyperaemia greatly increases the rate of systemic absorption through the conjunctiva. To reduce systemic absorption the lacrimal sac should be compressed at the medial can thus by digital pressure for at least two minutes after instillation of the drops.
- Extreme caution is advised for susceptible use belladonna alkaloids because of the increased risk of systemic toxicity.

4.5 Interaction with other medicinal products and other forms of interaction

Anti-hypertensive Agents: Topical phenylephrine should not be used as it may reverse the action of many anti-hypertensive agents with possibly fatal consequences.

Monoamine Oxidase Inhibitors: There is an increased risk of adrenergic reactions when used simultaneously with, or up to three weeks after, the administration of MAOIs.

Tricyclic Anti-depressants: The pressor response to adrenergic agents and the risk of cardiac arrhythmia may be potentiated in patients receiving tricyclic anti-depressants (or within several days of their discontinuation).

The effect of anti-muscarinic agents may be enhanced by the concomitant administration of other drugs with anti-muscarinic properties such as amantadine, some anti-histamines, antipsychotics, and phenothiazines.

Halothane: Because of the increased risk of ventricular fibrillation, phenylephrine should be used with caution during general anaesthesia with anaesthetic agents which sensitise the myocardium to sympathomimetics.

Cardiac Glycosides or Quinidine: There is an increased risk of arrhythmias.

4.6 Fertility, pregnancy and lactation

Fertility

There is no adequate information on whether this drug may affect fertility in human males or females.

Pregnancy

There is insufficient evidence as to drug safety in pregnancy and lactation. This product should be used during pregnancy only when it is considered essential by a physician.

Lactation
It is unknown whether Mydria mac/metabolites are excreted in human milk. A risk to the suckling child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Mydria mac therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

4.7 Effects on ability to drive and use machines
Mydria mac may cause stinging and temporarily blurred vision. Warn patients not to drive or operate hazardous machinery until vision is clear.
Tropicamide may cause drowsiness and affect ability to drive and use machines.

4.8 Undesirable effects
The following transient effects have been reported during clinical studies. The frequency of the undesirable effects are not known :

Cardiac disorders:

Palpitations, tachycardia, extrasystoles, arrhythmias.

Arteriospasm coronary, ventricular arrhythmia and myocardial infarction. These sometimes fatal reactions have usually occurred in patients with pre-existing cardiovascular disease

Eye disorders:

Eye pain, stinging, blurred vision, visual discomfort, tearing, irritation, disabling mydriasis because of prolonged pupil dilation, photophobia, superficial punctuate keratitis, blepharitis, allergic conjunctivitis, risk of angle-closure glaucoma, intraocular hypertension, ocular hyperaemia.

Gastrointestinal disorders:

nausea

General disorders and administration site conditions:

drug effect prolonged (mydriasis)

Immune System Disorders:

Hypersensitivity

Nervous system disorders:

dizziness, headache

<u>Paediatric population</u>:

Respiratory, thoracic and mediastinal disorders

Vascular disorders:

Hypertension, syncope

Pulmonary oedema

Psychotic reactions, behavioural disturbances and cardio respiratory collapse have been reported with this class of drug. which may be dangerous in infants and children. An increased risk for systemic toxicity has been observed in infants, small or premature children, or children with Down syndrome, spastic paralysis or brain damage with cycloplegic drugs. (See section 4.4 Special warnings and precautions for use).

Other toxic manifestations of anticholinergic drugs include flushing of the skin, dryness of the mouth, dryness of mucous membranes, dryness of the skin, bradycardia followed by tachycardia with palpitations and arrhythmias, decrease secretion in sweat glands and dryness of the mouth, diminished gastrointestinal motility and constipation, urinary urgency, difficulty and retention and decreased nasal, bronchial and lachrymal secretions.

Local: increased intraocular pressure, transient stinging and sensitivity to light secondary to pupillary dilation. Prolonged administration may lead to local irritation, hyperaemia, oedema and conjunctivitis.

Vomiting, giddiness and staggering may occur, a rash may be present in children and abdominal distention in infants.

4.9 Overdose

Because a severe toxic reaction to phenylephrine is of rapid onset and short duration, treatment is primarily supportive. Prompt injection of a rapidly acting alpha-adrenergic blocking agent such as phentolamine (dose 2 to 5mg iv) has been recommended.

Systemic toxicity tropicamide may occur following topical use, particularly in children, it is manifested by flushing and dryness of the skin, (a rash may be present in children), blurred vision, a rapid and irregular pulse, fever abdominal distention in infants, convulsions and hallucinations and the loss of neuro-muscular co-ordination. Treatment is symptomatic and supportive, (there is no evidence that physostigmine is superior to supportive management). In infants and small children the body surface must be kept moist. If accidentally ingested, induce emesis or perform gastric lavage.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: MYDRIATICS AND CYCLOPLEGICS
ATC code: S01FA56

Mechanism of action

Mydria mac is an ophthalmic solution which combines two synthetic mydriatic agents (phenylephrine, alpha sympathomimetic, and tropicamide, anticholinergic).

Phenylephrine is a direct acting sympathomimetic agent. It causes mydriasis via the stimulation of alpha receptors. There is almost no cycloplegic effect.

Tropicamide is an anticholinergic which blocks the responses of the sphincter muscle of the iris and the ciliary muscle to cholinergic stimulation thus dilating the pupil (mydriasis). At higher concentrations (1%), tropicamide also paralyses accommodation. This preparation acts rapidly and has a relatively short duration of action.

Pharmacodynamic effects

Maximal mydriasis occurs in 60- 90 minutes with recovery after 5 - 7 hours. The mydriatic effects of phenylephrine can be reversed with thymoxamine.

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5.2 Pharmacokinetic properties
Absorption

Phenylephrine is a weak base at physiological pH. The extent of ocular penetration is determined by the condition of the cornea. A healthy cornea presents a physical barrier, in addition to which, some metabolic activity may occur. Where the corneal epithelium is damaged, the effect of the barrier and the extent of metabolism are reduced, leading to greater absorption

Tropicamide administered topically to the human eye does not bind to tissues as firmly as does atropine. The wash out time for half recovery of carbachol responsiveness was shown to be less than 15 minutes for non-pigmented iris and 30 minutes for pigmented iris.

5.3 Preclinical safety data
Safety pharmacology, genotoxicity and conventional reproductive studies have not been conducted with phenylephrine, tropicamide or the fixed combination.

In rats, administration of phenylephrine (12.5 mg/kg, s.c.) resulted in reduced uterine blood flow (86.8% reduction in about 15 minutes), thereby exhibiting foetotoxic and co-teratogenic properties.

A 14-day local tolerance study was conducted in the rabbit, with insertion during 6 hours daily. This study demonstrated a mild irritating effect of the conjunctiva at the site of application.

6. Pharmaceutical particulars
6.1 List of excipients
Chlorbutol
Sodium Nitrate (EMSURE)
Sodium Metabisulphite
Disodium Edetate
Dioctyl Sodium Sulphosuccinate
Glycerin
Hydroxypropyl methylcellulose (HPMC) (Pyrogen free material)
Polyvinyl Pyrolidone (K30)
Polysorbate 80 (Tween-80)
Nitric Acid
Sodium Hydroxide
Water for Injection

6.2 Incompatibilities
Not applicable

6.3 Shelf life
24 months (unopened). 4 weeks (after first opening).

6.4 Special precautions for storage
Keep below 30°C. Protect from light.

6.5 Nature and contents of container
5 ml sterile vials with caramel pink colored HIPS cap with spike in one printed mono carton

6.6 Special precautions for disposal and other handling
No Special requirements.

7. Marketing authorisation holder

Maxim Inter Corporation Co.,Ltd
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Tel. +66 2656 6670-4

8. Marketing authorisation number(s)

2C xxxxx/xx

9. Date of first authorisation/renewal of the authorisation

10. Date of revision of the text

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