1 NAME OF THE MEDICINAL PRODUCT
NAPHCON-A™ Ophthalmic Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Active: Pheniramine maleate 0.3% (3.0 mg / mL) and Naphazoline hydrochloride 0.025% (0.25mg / mL)
Preservative: Benzalkonium chloride 0.01% (0.1 mg / mL)
Excipients: See section 6.1

3 PHARMACEUTICAL FORM
Eye Drops, Solution
Practically clear, colorless to slightly yellow liquid.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications
For relief of ocular irritation and/or congestion or for the treatment of allergic or inflammatory ocular conditions.

4.2 Posology and Method of Administration
Posology
Instill 1 to 2 drops in the affected eye(s) every 3 to 4 hours up to four times daily.

Elderly Population
No dosage adjustment is required in elderly patients, but caution is advised (See Section 4.4).

Pediatric population
The safety and efficacy of Naphcon-A™ in children have not been established. Use with caution in this population. Use in infants and children is not recommended (see sections 4.4 and 4.8).

Method of administration
- For ocular use.
- 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.
- Nasolacrimal occlusion of 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 substance(s) or to any of the excipients.
- Patients with narrow angle glaucoma.

4.4 Special Warnings and Precautions for Use
- Patients being treated with monoamine oxidase inhibitors (MAOIs) may experience a severe hypertensive crisis if administered a sympathomimetic drug (See Section 4.5).
- Use with caution in children, elderly, in patients with cardiovascular disease or in patients with sympathetic denervation (e.g. patients with insulin dependent diabetes, orthostatic hypotension, hypertension, hyperthyroidism) due to the risk for possible systemic effects.
- Prolonged and/or excessive use may lead to rebound ocular vasodilatation or congestion.
- NAPHCON-A™ 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 NAPHCON-A™ Ophthalmic Solution and wait at least 15 minutes before reinsertion.
- Stop use and ask a doctor if symptoms persist or condition worsens or lasts for more than 72 hours.

4.5 Interaction with other Medicinal Products and Other Forms of Interaction
Patients being treated with monoamine oxidase inhibitors (MAOIs) may experience a severe hypertensive reaction if administered with a sympathomimetic drug. Although this reaction has not specifically been reported with NAPHCON-A™ Ophthalmic Solution the possibility of such an interaction should be considered (See Section 4.4).

4.6 Pregnancy and Lactation
Fertility
Studies have not been performed to evaluate the effect of topical ocular administration of NAPHCON-A™ Ophthalmic Solution on human fertility.

Pregnancy
There are no data or there is a limited amount of data on the use of topical ophthalmic naphazoline or pheniramine in pregnant women. Animal studies are insufficient with respect to reproductive toxicity.

Breastfeeding
It is unknown whether topical naphazoline-pheniramine/metabolites are excreted in human milk. However, a risk to the suckling child cannot be excluded.

4.7 Effects on Ability to Drive and Use Machines
NAPHCON-A™ Ophthalmic Solution may cause transient mydriasis, temporary blurred vision or other visual disturbances that may affect the ability to drive or use machines. If there is mydriasis or 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 reported during clinical trials with NAPHCON-A™ Ophthalmic Solution 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). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

System Organ Classification	**MedDRA Preferred Term (v. 26.0)**
Eye disorders	*Common:* Ocular discomfort *Uncommon:* Keratitis, Eye pain, Eye oedema, Ocular hyperaemia

Additional adverse reactions identified from post-marketing surveillance include the following. Frequencies cannot be estimated from the available data.

System Organ Classification	**MedDRA Preferred Term (v. 26.0)**
Eye disorders	*Mydriasis, Eye irritation, Vision blurred*

Pediatric population
Excessive use of naphazoline-pheniramine in infants and young children may cause depression of the central nervous system and significant reduction in body temperature (see Section 4.9).

4.9 Overdose
Postmarketing data has shown that excessive systemic exposure, for example due to intentional or accidental overdose of naphazoline (including inadvertent oral ingestion), may lead to severe cardiovascular and/or cerebrovascular adverse reactions.

In case of overdosage or accidental ingestion, naphazoline-pheniramine can cause the following, particularly in children: depression of the central nervous system with a clear fall in body temperature and symptoms of bradycardia, excessive sweating, drowsiness and coma; hypertension followed by hypotension. Treatment of an oral overdose is symptomatic and supportive.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties
Pharmacotherapeutic group: Sympathomimetics used as decongestants
ATC code: S01GA51

Mechanism of action
Combines the effects of an antihistamine pheniramine maleate and vasoconstrictor naphazoline hydrochloride.

Through its local adrenergic activity NAPHCON-A™ Ophthalmic Solution has a vasoconstrictive effect on the blood vessels, thereby causing a decongestion of the conjunctiva. Pheniramine is a H-receptor antagonist which blocks the effects of histamine in the eye.

Pharmacodynamic effects
Naphazoline is a sympathicomimetic with substantial alpha-adrenergic activity. It is a vasoconstrictor with a fast and long-lasting activity reducing edema and congestion when applied on the mucosa. Pheniramine is a H-receptor antagonist, which does not prevent histamine release, but reduces or eliminates effects on smooth muscle.

Clinical efficacy and safety
No recent clinical trials have been conducted with NAPHCON-A™ Ophthalmic Solution.

Pediatric population
The safety and efficacy of NAPHCON-A™ Ophthalmic Solution in children has not been established (See Section 4.4).

5.2 Pharmacokinetic Properties
Absorption
Pheniramine
The amount of pheniramine absorbed into ocular tissues or systemically is not known after topical ocular administration. Serum exposure of pheniramine as measured by AUC was similar between intravenous and oral dosing, suggesting high bioavailability.

Naphazoline
Amount of naphazoline absorbed into ocular tissues or systemically is not known after topical ocular administration. However, the vasoconstriction of conjunctiva occurs within 10 minutes and persists for 2-6 hours, and systemic effects have been occasionally observed after topical administration.

Distribution
Pheniramine
The volume of distribution (Vss) after intravenous administration ranged from 133 – 142 L.

Naphazoline
No information on the distribution of naphazoline is available.

Biotransformation
Pheniramine
Pheniramine metabolizes to two major metabolites that were identified in urine, N-desmethyl pheniramine and N-didesmethyl-pheniramine. Only the N-desmethyl-pheniramine metabolite was detected in serum after systemic dosing.

Naphazoline
No information on the biotransformation of naphazoline is available.

Elimination
Pheniramine
The major elimination pathway for pheniramine and its major metabolites is urinary secretion. The terminal half-life of pheniramine after oral administration ranged from 16-20 h whether calculated from serum or urine. After intravenous administration, the terminal half-life estimates ranged from 8-18 h.

Naphazoline
No information on the elimination of naphazoline is available.

Linearity/nonlinearity
No information on pharmacokinetic linearity with naphazoline or pheniramine is available.

Pharmacokinetic/pharmacodynamic relationship(s)
No information on pharmacokinetic/pharmacodynamics relationship for naphazoline or pheniramine is available.

5.3 Preclinical Safety Data
Nonclinical data reveal no special hazard for humans based on conventional repeated dose toxicity studies conducted with naphazoline and/or pheniramine.

6 PHARMACEUTICAL PARTICULARS

6.1 List of Excipients
Boric acid
Edetate disodium
Purified water
Sodium borate
Sodium chloride
Sodium hydroxide and/or Hydrochloric acid (to adjust pH)

6.2 Incompatibilities
N/A

6.3 Shelf Life
24 months.

6.4 Special Precautions for Storage
Do not store above 25°C. Protect from light.

6.5 Nature and Contents of Container
Low density polyethylene (LDPE) bottle containing 15 mL of sterile eye drops.

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