SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

DEPORES X 0.1% Eye drops, Emulsion
Sterile

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Per 1 mL
Active substance:
Cyclosporine ..... 1 mg (0.1%)
Excipient(s):
Castor oil ..... 6.25 mg

For list of excipients see 6.1.

3. PHARMACEUTICAL FORM

Ophthalmic emulsion
White, homogeneous emulsion

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Indicated for increasing tear production in patients with ocular inflammation associated with keratoconjunctivitis sicca where tear production is presumed to be suppressed, and for the treatment of vernal keratoconjunctivitis (VKC) and atopic keratoconjunctivitis (AKC).

4.2 Posology and method of administration

Dosage/Frequency and duration of administration:
In patients where tear production is anticipated to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca, the recommended dose is 1 drop in the affected eye(s) twice daily, 12 hours apart.

For patients with vernal keratoconjunctivitis (VKC) and atopic keratoconjunctivitis (AKC), the recommended dose is 1 drop in the affected eye(s) four times daily.

Administration:
Administer by instilling into the eye.

Before use, the bottle should be inverted several times to obtain a homogeneous, white, opaque emulsion. DEPORES X can be used in combination with artificial tears; there should be a 15-minute interval between the instillation of the preparations.

Hands must be thoroughly washed with soap and water before administering the medication. To prevent the tip of the bottle from touching the eye or eyelashes, the lower eyelid is pulled down, and the medication is administered. After administration, apply light pressure to the inner corner of the eye with the tip of the bottle and keep the eyes closed for 1–5 minutes. Excess liquid should be wiped away with a clean cloth. Discard the bottle after use.

Additional information on specific populations:
Renal/Hepatic impairment:
There are no reports regarding topical ophthalmic use in this population.

Pediatric population:
There is no information available regarding the efficacy and safety of DEPORES X.

Geriatric population:
The efficacy and safety of DEPORES X do not differ between younger and older patients.

4.3 Contraindications

Contraindicated in

- Patients with active or suspected ocular or periocular infections
- Patients with known or suspected hypersensitivity to any of the components
- Cases of ocular or periocular malignancies or premalignant conditions.

4.4 Special warnings and precautions for use

DEPORES X is for ophthalmic use only. The emulsion contained in the single-use vials must be used immediately after opening for one or both eyes, and any remaining emulsion in the vial must be discarded immediately after application.

To prevent contamination of the emulsion, the tip of the vial must not come into contact with the eye or any surface.

To prevent eye injury, the tip of the vial must not come into contact with the eye.

Experience with DEPORES X in the treatment of patients with glaucoma is limited.

Caution is advised when DEPORES X is used in combination with beta-blockers, which are known to reduce tear secretion.

When used in combination with corticosteroid-containing eye drops, the effect of DEPORES X on the immune system may be potentiated. Therefore, caution is advised when corticosteroids are administered concurrently with DEPORES X (see Section 4.5).

DEPORES X has not been studied in patients with a history of ocular herpes and should therefore be used with caution in these patients.

DEPORES X should not be administered while a contact lens is in the eye. Patients with typically reduced tear production should not wear contact lenses. If a contact lens is present in the eye, it must be removed before applying the emulsion. Contact lenses may be reinserted 15 minutes after administration of DEPORES X. It has not been studied in patients who wear contact lenses. Close monitoring is recommended for patients with severe keratitis.

The efficacy and safety of DEPORES X have not been studied in children under 16 years of age.

The efficacy and safety of DEPORES X do not differ between younger and older patients.

No increase in ocular bacterial or fungal infections has been reported following DEPORES X administration.

Effects on the immune system: Ophthalmic medications that affect the immune system, including cyclosporine, may impair patients' resistance to ocular infections and malignancies. Therefore, regular eye examinations are recommended (e.g., at least every 6 months in cases where DEPORES X has been used for many years).

DEPORES X contains castor oil as an excipient. It may cause skin reactions.

4.5 Interactions with other medicinal products and other forms of interaction

DEPORES X can be used in combination with artificial tears; there should be a 15-minute interval between the instillation of the preparations. The concurrent use of DEPORES X with corticosteroid-containing eye medications may enhance the immunosuppressive effect of cyclosporine (see Section 4.4).

Additional information on specific populations:
No interaction studies have been conducted.

Pediatric population:
No interaction studies have been conducted.

4.6 Pregnancy and lactation

General recommendation
Pregnancy category: C.

Women of childbearing potential/Birth control (Contraception)
The use of DEPORES X is not recommended in women of childbearing potential who are not using an effective method of birth control.

Pregnancy
There are no adequate and well-controlled studies on the use of cyclosporine in pregnant women.

Following topical ocular application of cyclosporine ophthalmic emulsion 0.05% in humans, systemic concentrations of cyclosporine are below the detectable limit (see Section 5.2), and maternal use is not expected to result in fetal exposure to the drug.

Studies in animals are insufficient regarding effects on pregnancy and/or embryonic/fetal development and/or labor and/or postnatal development (see Section 5.3). The potential risk to humans is unknown.

DEPORES X should not be used during pregnancy unless necessary.

In a study conducted on rats using the oral formulation, teratogenic effects, as well as dystocia and perinatal mortality, were reported.

Lactation
Cyclosporine passes into breast milk following oral administration. There is insufficient information regarding the effects of cyclosporine on newborns/infants. However, at therapeutic doses of cyclosporine-containing eye drops, it is unlikely that sufficient amounts would be present in breast milk. A decision regarding whether to discontinue breastfeeding or DEPORES X treatment should be made by weighing the benefits of breastfeeding for the child against the benefits of treatment for the mother.

Reproductive ability/Fertility
No effects on human reproductive ability/fertility have been reported with topical ophthalmic use.

Studies conducted in male and female rats have shown that oral administration of cyclosporine at a dose of 15 mg/kg/day (approximately 2,000 times the human daily dose of 0.001 mg/kg/day adjusted for body surface area) for 9 weeks (male) and 2 weeks (female) before mating did not impair fertility.

4.7 Effects on the ability to drive and use machinery
DEPORES X has a moderate effect on the ability to drive and use machinery. This medicinal product may cause temporary blurred vision or other visual disturbances that could impair the

ability to drive or use machinery (see Section 4.8). Patients should be advised not to drive or operate machinery until their vision has returned to normal.

4.8 Adverse effects

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); very rare (<1/10,000), unknown (cannot be estimated from available data).

The most common adverse effect was eye burning, with an incidence of 16%. Other side effects (in 1–5% of patients) include ocular itching/irritation, tearing, foreign body sensation, itching, conjunctival hyperemia, photophobia, blurred vision, headache, eyelid edema, conjunctival edema, and eye pain. Headache and urinary tract infection have also been reported.

Neurological disorders:

Common : Headache

Eye disorders

Very common : Eye burning

Common :Ocular itching/irritation, tearing, epiphora (watery eyes), foreign body sensation, itching, eye irritation, conjunctival hyperemia, photophobia, visual disturbances (often blurred vision), eyelid edema, conjunctival edema, eye pain, corneal erosion/ulcer (including corneal epithelial defects, corneal lesions, corneal abnormalities, keratitis, punctate keratitis, ulcerative keratitis, etc.)

Uncommon : Erythema of the eyelids, Herpes simplex keratitis, dry eye, corneal edema, anterior chamber inflammation, blepharitis, stye, bacterial conjunctivitis, bacterial corneal ulcer

Kidney and urinary tract diseases:

Common : Urinary tract infection

Investigations

Uncommon : Elevated ALT, elevated LDH, elevated BUN, elevated creatine kinase, ketones in urine, elevated Mg

Other adverse effects observed with other cyclosporine-containing ophthalmic emulsions:

The most common adverse effects are generally transient and occur during instillation, including eye pain (19%), eye irritation (17.5%), ocular hyperemia (5.5%), increased lacrimation (4.9%), and eyelid erythema (1.7%). These adverse effects are consistent with those reported during postmarketing experience.

Table 1. Adverse effects observed with other cyclosporine-containing ophthalmic emulsions

System Organ Class	Frequency	Adverse Effects
Infections and infestations	Uncommon	Bacterial keratitis Herpes zoster ophthalmicus
Nervous system disorders	Uncommon	Headache
Eye diseases	Very common	Eye pain Eye irritation
	Common	Erythema of the eyelids Increased lacrimation Ocular hyperemia Blurred vision Eyelid edema Conjunctival hyperemia Eye itching
	Uncommon	Conjunctival edema Lacrimal dysfunction Eye discharge Conjunctival irritation Conjunctivitis Foreign body sensation in the eye Deposits in the eye Keratitis Blepharitis Chalazion Corneal infiltrates Corneal scar Itching of the eyelid Iridocyclitis Feeling of discomfort in the eye
General disorders and conditions related to the application site	Uncommon	Reaction at the instillation site

Post-marketing experience

The following adverse effects have been identified for the 0.05% cyclosporine eye drops during the post-marketing period. Since these reactions were voluntarily reported by a population of unknown size, it is not always possible to determine their frequency or establish a causal relationship with drug exposure.

Reported reactions include hypersensitivity (swelling of the eye, hives, rarely severe angioedema, swelling of the face, swelling of the tongue, pharyngeal edema, and dyspnea) and superficial eye injury (resulting from the tip of the vial touching the eye during application).
With oral use, the incidence of hypertrichosis in children (10–18%) tends to be higher than in adults (2–6%).
In the geriatric population, physiological functions are generally reduced.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

4.9 Overdose and Treatment
No cases of overdose have been reported in humans following the ophthalmic use of DEPORES X. In cases where an overdose is suspected, general symptomatic and supportive treatment may be administered.

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic Properties
Pharmacotherapeutic Group: Ophthalmic drugs, other ophthalmologics
ATC Code: S01XA18

Mechanism of action
Cyclosporine inhibits the dephosphorylation of NFAT (a transcription factor) by binding to cyclophilin in T cells, thereby suppressing the production of cytokines such as IL-2.

Inhibitory effect on cytokine production
Cyclosporine suppresses cytokine production (IL-2, IL-4, IL-5, IFN-γ) from mononuclear cells derived from human peripheral blood (IC50 values: 0.021 to 0.173 μM) (in vitro).

Effect on experimental allergic conjunctivitis models
- In an acute allergic conjunctivitis guinea pig model, instillation of cyclosporine at concentrations of 0.1% or higher inhibited histamine release from conjunctival tissue.
- In a guinea pig model of delayed-type allergic conjunctivitis, instillation of cyclosporine at concentrations of 0.05% or higher inhibited neutrophil infiltration into the conjunctival tissue.

Pharmacological effect
Cyclosporine is a potent and selective immunomodulatory agent that exerts its activity by inhibiting the activation of NF-κB, a nuclear factor involved in the regulation of genes related to immune and pro-inflammatory cytokine responses, such as TNF, IL-1, IL-2, and IL-8.

As an anti-inflammatory agent, the 0.1% cyclosporine eye drops act on T helper cells, which are identified in ocular surface tissues and lacrimal glands and play a significant role not only in the immune response but also in the inflammatory response via cytokine synthesis.
Suppression of the immune response occurs in ocular surface tissues because these specific pro-inflammatory cytokines are required to activate T helper cells, which cannot be synthesized or released as they normally would.

Cyclosporine (also known as cyclosporine A) is a cyclic polypeptide immunomodulator with immunosuppressive properties. It has been shown to significantly prolong allogeneic transplant survival in animals and graft survival in all types of solid organ transplantation in humans.

Cyclosporine has also been shown to have anti-inflammatory effects. Animal studies indicate that cyclosporine inhibits the development of cell-mediated reactions. Cyclosporine has been shown to inhibit the production and/or release of pro-inflammatory cytokines, including interleukin 2 (IL-2) and T-cell growth factor (TCGF). It is also known to regulate the release of anti-inflammatory cytokines by increasing their secretion. Cyclosporine appears to block lymphocytes that are in the G_0 or G_1 phase of the cell cycle. All available data indicate that cyclosporine exerts a specific and reversible effect on lymphocytes and does not suppress hematopoiesis or have any effect on the function of phagocytic cells.

In patients with dry eye, following ocular administration, cyclosporine is passively absorbed into T-lymphocyte infiltrates in the cornea and conjunctiva—a process that may be considered an inflammatory immunological mechanism—and inactivates calcineurin phosphatase. Calcineurin inactivation induced by cyclosporine inhibits the dephosphorylation of the transcription factor NF-AT and prevents its translocation into the nucleus, thereby blocking the release of pro-inflammatory cytokines such as IL-2.

Clinical Findings
Efficacy and safety studies
Phase II/III study
In a randomized, double-blind, comparative study involving 54 patients with hay fever who had an inadequate response to antiallergic eye drops (38 patients in the efficacy analysis), the study drug or placebo eye drops were instilled three times daily for 8 weeks, while antiallergic eye drops were also used. The study drug group showed a significant improvement in the conjunctival papilla score of the eyelid compared to the control drug.
Adverse reactions were observed in 6 of the 27 patients (22.2%) in the study group. These

included ocular irritation (14.8%, 4/27 patients) and ocular pruritus (7.4%, 2/27 patients).

5.2 Pharmacokinetic properties

General properties

Absorption:

Following topical application of cyclosporine to the eye, cyclosporine A concentrations in the blood were measured using a specific high-performance liquid chromatography-mass spectrometry assay. In humans, following topical application of cyclosporine twice daily for 12 months, cyclosporine blood concentrations were found to be below the detection limit of 0.1 ng/mL. No drug accumulation in the blood was detected during the 12-month treatment with cyclosporine ophthalmic emulsion.

Distribution:

In white rabbits, when a single dose of 0.05% ^{3}H-cyclosporine eye drops was instilled, it was found to distribute extensively in the external eye tissues such as the cornea and conjunctiva, while penetration into the internal eye tissues such as the anterior chamber fluid, iris-ciliary body, lens, and vitreous was limited. When 0.05% ^{3}H-cyclosporine eye drops were repeated three times daily for 7 days to white rabbits, the concentration in the ocular tissues reached a steady state after approximately 10 applications.

Metabolism:

This preparation is primarily metabolized via the cytochrome P450 3A (CYP3A) enzyme system.

Therefore, when used in combination with other drugs metabolized by the same enzyme system, there is a possibility of increased blood levels of this preparation.

Elimination:

When a single dose of 0.1% ^{3}H-cyclosporine eye drops was administered to rats, 3.1% of the administered dose was excreted in urine and 92.1% in feces within 96 hours following administration.

Additionally, when 0.1% ^{3}H-cyclosporine eye drops were administered to rats with bile duct cannulation, 11.7% of the administered dose was excreted in bile, 3.3% in urine, and 74.9% (including intestinal contents) in feces within 72 hours after administration.

5.3 Preclinical safety data

Teratogenicity:

Cyclosporine oral solution (USP) is teratogenic at maternally toxic doses (30 mg/kg/day in rats and 100 mg/kg/day in rabbits), as evidenced by increased pre- and postnatal mortality, reduced fetal weight, and skeletal abnormalities. These doses are, respectively, 5,000 and 32,000 times the recommended daily human dose (0.001 mg/kg/day) of cyclosporine 0.05% ophthalmic emulsion—administered as one drop (approximately 28 mcL) in each eye twice daily for a 60-

kg human— assuming complete absorption (adjusted for body surface area). No evidence of embryofetal toxicity was observed in rats or rabbits administered cyclosporine at oral doses of up to 17 mg/kg/day or 30 mg/kg/day, respectively, during the organogenesis period. These doses in rats and rabbits are 3,000- and 10,000-fold, respectively, the recommended daily human dose (adjusted for body surface area).

In a single oral dose of 45 mg/kg/day of cyclosporine administered to rats from day 15 of pregnancy through day 21 postpartum, maternal toxicity and an increase in postnatal mortality in the offspring were observed. This dose is 7,000 times the recommended daily human dose adjusted for body surface area (assuming complete absorption of the dose, adjusted for body surface area). No adverse effects were observed in females or offspring at oral doses up to 15 mg/kg/day (2,000 times the recommended daily human dose).

Carcinogenesis:
Systemic carcinogenicity studies were conducted in male and female mice and rats. In a 78-week oral (dietary) mouse study, at doses of 1, 4, and 16 mg/kg/day, there was evidence of a statistically significant trend toward lymphocytic lymphoma in females, and the incidence of hepatocellular carcinomas in mid-dose males was significantly higher than the control value.

In a 24-month oral (dietary) rat study conducted at doses of 0.5, 2, and 8 mg/kg/day, pancreatic islet cell adenomas were found to be significantly more frequent at the low-dose level compared to the control rate. Hepatocellular carcinomas and pancreatic islet cell adenomas were not found to be dose-related. The low doses in mice and rats are approximately 80 times the recommended daily human dose (0.001 mg/kg/day) of 0.05% cyclosporine administered as one drop in each eye twice daily (approximately 28 mcL) to a 60-kg individual, assuming complete absorption (adjusted for body surface area).

Mutagenicity:
Cyclosporine was not found to be mutagenic/genotoxic in the Ames Test, the V79-HGPRT Test, the micronucleus test in mice and Chinese hamsters, the chromosome aberration test in Chinese hamster bone marrow, the mouse dominant lethal assay, or the DNA repair test in the sperm of treated mice. A study using human lymphocytes *in vitro* to analyze cyclosporine-induced sister chromatid exchange (SCE) indicated a positive effect (i.e., SCE induction).

Impaired fertility:
Studies in male and female rats have shown that oral administration of cyclosporine at a dose of 15 mg/kg/day (approximately 2,000 times the human daily dose of 0.001 mg/kg/day adjusted for body surface area) for 9 weeks (male) and 2 weeks (female) before mating did not impair fertility.

Teratogenic effects:
No evidence of teratogenic effects was observed in rats and rabbits administered cyclosporine orally at doses up to 300 mg/kg/day during organogenesis. These doses administered to rats and rabbits are approximately 300,000 times higher than the daily human dose of cyclosporine (0.001 mg/kg/day) administered as a single drop in each eye of a 60-kg individual, assuming complete absorption of the entire dose.

Non-teratogenic effects:
Adverse effects were evaluated in reproductive studies conducted in rats and rabbits using only toxic dose levels. Cyclosporine oral solution is toxic to embryos and fetuses at toxic doses (30 mg/kg/day in rats and 100 mg/kg/day in rabbits); this is evidenced by increased pre- and postnatal mortality, reduced fetal weight, and associated delayed skeletal development. These doses are 30,000 and 100,000 times higher, respectively, than the daily human dose. No evidence of toxicity was observed in the embryos or fetuses of rats and rabbits administered oral cyclosporine doses of up to 17 mg/kg/day or 30 mg/kg/day, respectively, during organogenesis. These doses administered to rats and rabbits are approximately 17,000 and 30,000 times higher, respectively, than the daily human dose. No adverse events were observed at oral doses up to 15 mg/kg/day (15,000 times the human dose).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Castor oil
Polysorbate 80
Carbomer 934
Glycerol
Sodium hydroxide
Water for injection

6.2 Incompatibilities

There are no known incompatibilities.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Do not freeze.

Store at room temperature below 25°C, protected from light.

Once the sachets are opened, the vials inside must be used within 28 days.
The vials are for single use only; any unused portion must be discarded.

6.5 Nature and contents of container
DEPORES X is available as a 0.4 mL emulsion in single-use vials. Each box contains a total of 30 or 50 single-use vials, with 10 vials in each of the 3 or 5 peelable sachets.

6.6 Special precautions for disposal and other handling
Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER
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