# SUMMARY OF PRODUCT CHARACTERISTICS

## 1 NAME OF THE MEDICINAL PRODUCT

Verkazia 1 mg/mL eye drops, emulsion.

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One mL of emulsion contains 1 mg of ciclosporin.

Excipient with known effect

One mL of emulsion contains 0.05 mg cetalkonium chloride.

For the full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Eye drops, emulsion.

Milky white emulsion.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Treatment of severe vernal keratoconjunctivitis (VKC) in children from 4 years of age and adolescents.

### 4.2 Posology and method of administration

Verkazia treatment should only be initiated by an ophthalmologist or a healthcare professional qualified in ophthalmology.

Posology

*Children from 4 years of age and adolescents*

The recommended dose is one drop of Verkazia 4 times a day (morning, noon, afternoon and evening) to be applied to each affected eye during the VKC season. If signs and symptoms of VKC persist after the end of the season, the treatment can be

maintained at the recommended dose or decreased to one drop twice daily once adequate control of signs and symptoms is achieved. Treatment should be discontinued after signs and symptoms are resolved, and reinitiated upon their recurrence.

*Missed dose*

If a dose is missed, treatment should be continued on the next instillation as normal. Patients should be advised not to instill more than one drop for each instillation in the affected eye(s).

*Paediatric population*

There is no relevant use of Verkazia in children below 4 years in the treatment of severe vernal keratoconjunctivitis.

*Patients with renal or hepatic impairment*

The effect of Verkazia has not been studied in patients with renal or hepatic impairment. However, no special dose adjustment is needed in these populations.

Method of administration

Ocular use

*Precautions to be taken before administering the medicinal product*

Patients should be instructed to first wash their hands.

Prior to administration, the single-dose container should be gently shaken.

For single use only. Each single-dose container is sufficient to treat both eyes.

Patients should be instructed to use nasolacrimal occlusion and to close the eyelids for 2 minutes after instillation, to reduce the systemic absorption. This may result in a decrease in systemic undesirable effects and an increase in local activity (see section 4.4).

If more than one topical ophthalmic medicinal product is being used, the medicinal products must be administered at least 15 minutes apart. Verkazia should be administered last (see section 4.4).

## 4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Ocular or peri-ocular malignancies or premalignant conditions.

Active or suspected ocular or peri-ocular infection.

## 4.4 Special warnings and precautions for use

Contact lenses

Patients wearing contact lenses have not been studied. Therefore, the use of Verkazia with contact lenses is not recommended.

Concomitant therapy

Co-administration of Verkazia with eye drops containing corticosteroids may potentiate the effects of Verkazia on the immune system. However, in clinical studies, 18 patients received Verkazia (4 times daily) in co-administration with eye drops containing corticosteroids and no increase in the risk of adverse reactions related to the immune system was identified. Therefore, caution should be exercised when corticosteroids are administered concomitantly with Verkazia (see section 4.5).

Effects on the immune system

Ophthalmic medicinal products, which affect the immune system, including ciclosporin, may affect host defences against local infections and malignancies. Therefore, regular examination of the eye(s) is recommended, e.g. every 3 to 6 months, when Verkazia is used for more than 12 months.

Verkazia has not been studied in patients with an active orofacial herpes simplex infection, a history of ocular herpes, varicella-zoster, or vaccinia virus infection and should therefore be used with caution in such patients.

Excipient

Verkazia contains cetalkonium chloride which may cause eye irritation.

## 4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed with Verkazia.

## 4.6 Fertility, pregnancy and lactation

Women of childbearing potential/contraception in females

Verkazia is not recommended in women of childbearing potential not using effective contraception.

Pregnancy

There are no data from the use of Verkazia in pregnant women.

Studies in animals have shown reproductive toxicity following systemic administration of ciclosporin at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to the clinical use of Verkazia.

Verkazia is not recommended during pregnancy unless the potential benefit to the mother outweighs the potential risk to the foetus.

Breast-feeding

Following systemic absorption ciclosporin is excreted in breast milk. There is insufficient information on the effects of ciclosporin in newborns/infants. However, at therapeutic doses of ciclosporin in eye drops, it is unlikely that sufficient amounts would be present in breast milk. A decision must be made whether to discontinue

breast-feeding or to discontinue/abstain from Verkazia therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

There are no data on the effects of Verkazia on human fertility.

## 4.7 Effects on ability to drive and use machines

Verkazia has moderate influence on the ability to drive and use machines.

This medicinal product may induce temporary blurred vision or other visual disturbances which may affect the ability to drive or use machines (see section 4.8). Patients should be advised not to drive or use machines until their vision has cleared.

## 4.8 Undesirable effects

Summary of the safety profile

The most common adverse reactions with Verkazia are eye pain (11%) and eye pruritus (9%) which are usually transitory and occurred during instillation.

Tabulated list of adverse reactions

The following adverse reactions listed below were observed in clinical studies. They are ranked according to system organ class and classified according to the following 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), very rare (<1/10 000), or not known (cannot be estimated from the available data).

| **MedDRA system organ class** | **MedDRA frequency** | **Adverse reaction** |
|---|---|---|
| Infections and infestations | Common | Upper respiratory tract infection. |
| | Uncommon | Keratitis bacterial, herpes zoster ophthalmic. |
| Nervous system disorders | Common | Headache. |
| Eye disorders | Very common | Eye pain. |
| | Common | Eye pruritus, ocular hyperaemia, eye irritation, ocular discomfort, foreign body sensation in eyes, lacrimation increased, vision blurred, erythema of eyelid, eyelid oedema. |
| | Uncommon | Blepharitis, conjunctival oedema. |
| Respiratory, thoracic and mediastinal disorders | Common | Cough. |

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 Yellow Card Scheme at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

### 4.9 Overdose

Systemic exposure to Verkazia following topical ocular administration has been shown to be negligible. If overdose with Verkazia occurs, it may be flushed from the eye(s) with water and treatment should be symptomatic and supportive.

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Ophthalmologicals, other ophthalmologicals, ATC code: S01XA18.

Mechanism of action and pharmacodynamic effects

Following ocular administration, ciclosporin is passively absorbed by T-lymphocytes where its binding to cyclophilin A inactivates calcineurin, and prevents nuclear factor of activated T cells (NF-AT) translocation into the nucleus, thus blocking the release of pro-inflammatory cytokines such as IL-2 and hence T-lymphocyte activation. Blocking NF-AT also interferes in the allergy process. Ciclosporin inhibits histamine release from mast cells and basophils through a reduction in IL-5 production, and may reduce eosinophil recruitment and effects on the conjunctiva and cornea. Ciclosporin is also known to up-regulate the release of anti-inflammatory cytokines. All available evidence suggests that ciclosporin acts specifically and reversibly on lymphocytes and does not depress haematopoiesis or have any effect on the function of phagocytic cells.

Clinical efficacy

In a 12 month double-masked, vehicle controlled, pivotal clinical trial (VEKTIS study), 169 patients with severe VKC and severe keratitis (grade 4 or 5 on the modified Oxford scale) were randomised to 4 drops of Verkazia (high dose) or 2 drops of Verkazia (low dose) and 2 drops of vehicle or 4 drops of vehicle for the first 4 months (Period 1). Patients randomised to the vehicle group were switched to Verkazia (four times or twice daily) from Month 4 to Month 12 (Period 2).

168 patients [127 children (75.6%) and 41 adolescents (24.4%)] were included in the efficacy analyses. Mean age was 9.2 years (SD: 3.3, age range: 4-17 years). There were more male [n=132 (78.6%)] than female patients [n=36 (21.4%)].

The primary efficacy endpoint which was the average penalties adjusted change of the Corneal Fluorescein Staining (CFS) score from baseline and over Period 1, considered all patients (n=168). Efficacy was assessed every month during the 4

month treatment period and compared with baseline using a composite criterion based on keratitis assessed by the modified Oxford scale, the need for rescue medicinal product (use of topical steroids) and the occurrence of corneal ulceration.

The difference in the Least Square (LS) mean vs. vehicle was 0.76 (95% CI: 0.26, 1.27) for the high dose group and 0.67 (95% CI: 0.16, 1.18) for the low dose group. Both differences were statistically significant with p=0.007 for the high dose and p=0.010 for the low dose group.

Clinical relevance of the primary efficacy endpoint was however difficult to address. In that context, responder rate's results were considered as more reliable endpoint. A responder was defined as a patient 1) with a mean CFS score over the 4 months of treatment ≤ 50% of baseline, 2) who did not withdraw from the study for a reason possibly due to treatment, 3) with no experience of corneal ulceration and 4) no use of rescue medicinal product in the last 4 months of treatment. There was a significantly higher number of CFS responders in both active groups as compared to vehicle (p=0.005 for the high dose group, and p=0.010 for the low dose group) with 55.4%, 50.0% and 27.6% of responders in the high dose, low dose and vehicle groups respectively. The excess rate with respect to vehicle was 27.8% for the high dose regimen and 22.4% for the low dose one.

Rescue medicinal product (topical steroids) was used more often in the vehicle than in the high dose regimen: 32.1% in the high dose group and 31.5% in the low dose group received at least one course of rescue medicinal product while they were 53.4% in the vehicle group.

All four symptoms (photophobia, tearing, itching and mucous discharge) improved over time and the difference from baseline at Month 4 for each symptom largely exceeded 10 mm.

For the average of VKC symptoms, the difference in the LS mean vs. vehicle in the high dose group was statistically significant at all time points compared to vehicle: -19.4 mm ($p<0.05$).

Patient quality of life (Quick questionnaire) improved significantly better in the high dose group compared to vehicle. The improvement was clinically relevant as illustrated by the effect size over 4 months (symptoms domain: 0.67 and daily activities domain: 0.44).

In Period 2, analyses demonstrated stability of improvements achieved during Period 1 for both doses regimen.

## 5.2 Pharmacokinetic properties

Formal pharmacokinetic studies have not been conducted in humans with Verkazia.

Blood concentrations of Verkazia were measured using a specific high-pressure liquid chromatography-mass spectrometry assay. In 166 patients at baseline from one efficacy study (55 patients in the high dose group, 53 in the low dose group and 58 in the vehicle group), plasma concentrations of ciclosporin were measured before administration and after 2, 4 and 12 months of treatment.

In the high dose group after 4 months of ocular instillation of Verkazia 4 times daily, the maximum quantifiable value detected in the 14 patients who had quantifiable levels of cyclosporine was 0.670 ng/mL which is considered to be a negligible value. At Month 12, the maximum quantifiable value detected in the 12 patients who had

quantifiable levels of cyclosporine was 0.291 ng/mL which is considered to be a negligible value.

In the low dose group, after 4 months of ocular instillation of Verkazia 2 times daily, the maximum quantifiable value detected in the 5 patients who had quantifiable levels of cyclosporine was 0.336 ng/mL which is considered to be a negligible value. At Month 12, the maximum quantifiable value detected in the 5 patients who had quantifiable levels of cyclosporine was 0.300 ng/mL which is considered to be a negligible value.

### 5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, phototoxicity and photoallergy, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Medium-chain triglycerides

Cetalkonium chloride

Glycerol

Tyloxapol

Poloxamer 188

Sodium hydroxide (to adjust pH)

Water for injections

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

3 years.

### 6.4 Special precautions for storage

Do not freeze.

Store below 25 °C.

Keep single-dose containers in the pouch in order to protect from light and avoid evaporation.

Discard the opened single-dose container immediately after use.

### 6.5 Nature and contents of container

0.3 mL single-dose, low-density polyethylene (LDPE) containers in a sealed laminate aluminium pouch.

One pouch contains 5 single-dose containers.

Pack sizes of 30, 60, 90 or 120 single-dose containers.

Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal

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

## 7 MARKETING AUTHORISATION HOLDER

Santen Oy
Niittyhaankatu 20
33720 Tampere
Finland

## 8 MARKETING AUTHORISATION NUMBER(S)

PLGB 16058/0028

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

16/12/2024

## 10 DATE OF REVISION OF THE TEXT

16/12/2024