ANNEX I

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 indication

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 national reporting system listed in Appendix V.

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 NUMBERS

EU/1/17/1219/001
EU/1/17/1219/002
EU/1/17/1219/003
EU/1/17/1219/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 6 July 2018

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

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 indication

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 bottle should be gently shaken.

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.

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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.

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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 national reporting system listed in Appendix V.

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
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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).

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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.

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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).

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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

2 years
After first opening of the bottle: 4 weeks.

6.4 Special precautions for storage

Do not freeze.
Store below 25 °C.

6.5 Nature and contents of container

Verkazia is supplied sterile in a white low density polyethylene bottle (9 mL fill in a 11 mL container) and white nozzle with tamper evident system.

Carton containing 1 bottle.

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 NUMBERS

EU/1/17/1219/005

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 6 July 2018

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release
EXCELVISION
27 rue de la Lombardière
ZI la Lombardière
07100 Annonay
France

Santen Oy
Kelloportinkatu 1
33100 Tampere
Finland

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON CONTAINING SINGLE-DOSE CONTAINERS

1. NAME OF THE MEDICINAL PRODUCT

Verkazia, 1 mg/mL eye drops, emulsion
ciclosporin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

A single-dose container of 0.3 mL eye drops emulsion contains 0.3 mg of ciclosporin.

3. LIST OF EXCIPIENTS

Excipients: medium-chain triglycerides, cetalkonium chloride, glycerol, tyloxapol, poloxamer 188, sodium hydroxide and water for injections.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Eye drops, emulsion

30 single-dose containers
60 single-dose containers
90 single-dose containers
120 single-dose containers

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Single use only.
Read the package leaflet before use.
Ocular use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
Discard the opened single-dose container immediately after use.

9. SPECIAL STORAGE CONDITIONS

Do not freeze.
Store below 25 °C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Santen Oy
Niittyhaankatu 20
33720 Tampere
Finland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1219/001
EU/1/17/1219/002
EU/1/17/1219/003
EU/1/17/1219/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

verkazia

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

POUCH LABEL FOR SINGLE-DOSE CONTAINERS

1. NAME OF THE MEDICINAL PRODUCT

Verkazia 1 mg/mL eye drops, emulsion
ciclosporin

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Santen Oy

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Ocular use.
5 single-dose containers.
Single use only.
Do not freeze.
See leaflet for further information.
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.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SINGLE-DOSE CONTAINER LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Verkazia 1 mg/mL eye drops, emulsion
ciclosporin
Ocular use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

0.3 mL

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON CONTAINING ONE BOTTLE

1. NAME OF THE MEDICINAL PRODUCT

Verkazia, 1 mg/mL eye drops, emulsion
ciclosporin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 mL of emulsion contains 1 mg of ciclosporin.

3. LIST OF EXCIPIENTS

Excipients: medium-chain triglycerides, cetalkonium chloride, glycerol, tyloxapol, poloxamer 188, sodium hydroxide and water for injections.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Eye drops, emulsion

1 x 9 mL

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Ocular use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
Discard 4 weeks after first opening.
Open date:

9. SPECIAL STORAGE CONDITIONS

Do not freeze.
Store below 25 °C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Santen Oy
Niittyhaankatu 20
33720 Tampere
Finland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1219/005

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

verkazia

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Verkazia 1 mg/mL eye drops, emulsion
ciclosporin
Ocular use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

9 mL

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Verkazia 1 mg/mL eye drops, emulsion
ciclosporin

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Verkazia is and what it is used for

Verkazia contains the active ingredient, ciclosporin. Ciclosporin reduces the activity of the body's immune (defence) system and in this way it reduces inflammation (body response to harmful stimuli).

Verkazia is used to treat children and adolescents aged 4 to 18 years with severe vernal keratoconjunctivitis (an allergic condition of the eye that occurs more frequently in spring and affects the transparent layer in the front part of the eye and the thin membrane covering the front part of the eye).

2. What you need to know before you use Verkazia

Do not use Verkazia
- if you are allergic to ciclosporin or to any of the other ingredients of this medicine (listed in section 6).
- if you have had or have a cancer in or around your eye.
- if you have an eye infection.

Warnings and precautions
Only use Verkazia in your eye as described under section 3. Do not exceed the treatment period prescribed by your doctor.

Talk to your doctor or pharmacist before using Verkazia:
- if you have had an eye infection or if you suspect you have an eye infection.
- if you have any other kind of eye disease.
- if you wear contact lenses (the use of Verkazia is not recommended with contact lenses).

Children and adolescents
Do not use Verkazia in children under the age of 4 years.

Other medicines and Verkazia
Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines.

Talk to your doctor if you are using eye drops containing steroids administered in association with Verkazia as this association may increase the risk of local infections.

If you are using Verkazia for more than 12 months, you should visit your doctor regularly, e.g. every 3 to 6 months.

If you are using other eye drops, use Verkazia **at least 15 minutes** after using the other eye drops.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before using this medicine.

Verkazia should not be used if you are pregnant. If you could become pregnant you must use contraception while using this medicine.

Verkazia is likely to be present in breast milk in very small amounts. If you are breast feeding talk to your doctor before using this medicine.

Driving and using machines
Your vision may be temporarily blurred after using Verkazia eye drops or you may get other disturbances with your vision. If this happens, wait until your vision clears before you drive or use machines.

Verkazia contains cetalkonium chloride
Cetalkonium chloride may cause eye irritation.

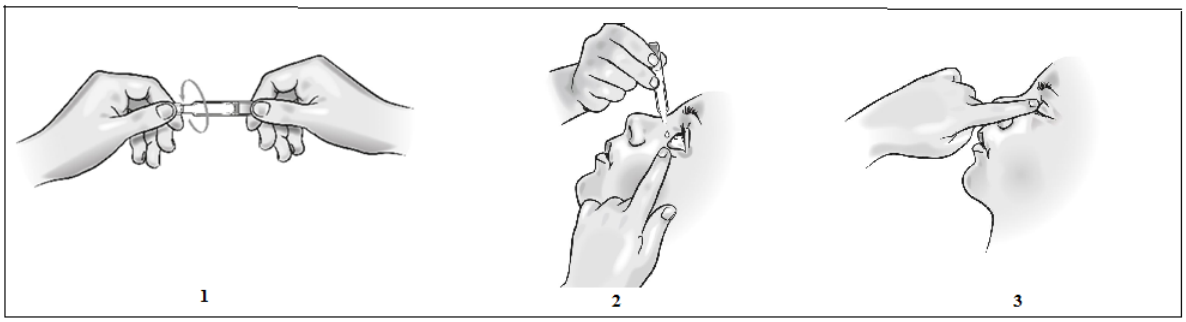
3. How to use Verkazia

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

A caregiver should help a child starting Verkazia treatment, particularly if the child is aged under 10 years, and should continue to supervise the child until the child is able to use Verkazia properly without help.

The recommended dose is 1 drop of Verkazia in each affected eye 4 times a day (morning, mid-day, afternoon and evening). You should continue Verkazia as prescribed by your doctor.

Instructions for use
Follow these instructions carefully and ask your doctor or pharmacist if there is anything you do not understand.



1. Wash your hands.
2. Open the aluminium pouch, which contains 5 single-dose containers.
3. Take one single-dose container from the aluminium pouch, leaving the remaining containers in the pouch.
4. Gently shake the single-dose container.
5. Twist off the cap **(picture 1).**
6. Pull down your lower eyelid **(picture 2).**
7. Tilt your head back and look up at the ceiling.
8. Gently squeeze one drop of the medicine onto your eye. Make sure that the tip of the single-dose container does not touch your eye.
9. Blink a few times so that the medicine spreads across your eye.
10. After using Verkazia, press a finger lightly on the inner corner of your eyelid, next to your nose for 2 minutes **(picture 3).** A small duct that drains tears away from your eye and into your nose is located here. By pressing at this point, you close down the opening of this drainage duct. This helps to stop Verkazia getting into the rest of the body.
11. If you use drops in both eyes, repeat the steps 6 to 9 for your other eye.
12. Discard the single-dose container as soon as you have used it, even if there is still some medicine left in it.

If a drop misses your eye, try again.

If you put in more Verkazia than you should, rinse your eye with water. Do not put in any more drops until it is time for your next regular dose.

If you forget to use Verkazia, continue with the next dose as planned. Do not take a double dose to make up for the forgotten dose. Do not use more than 1 drop 4 times a day in the affected eye(s).

If you stop using Verkazia without speaking to your doctor, your eye allergy will not be controlled and could lead to long-term problems with your sight.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The following side effects have been reported for Verkazia:
The most common side effects are in and around the eyes.

Very common side effects (may affect more than 1 in 10 people)
Pain when the drops are put into the eye.

Common side effects (may affect up to 1 in 10 people)
Common side effects related to the eye:
Itching, redness, irritation and discomfort in or around the eye including a feeling that there is something in the eye. Increased watering of the eye and blurred vision when the drops are put into the eye. Swelling and redness of eyelid.

Common side effects which are not related to the eye:
Upper respiratory tract infection, cough, headache.

Uncommon side effects (may affect up to 1 in 100 people)
Swelling of the eyelid and of the conjunctiva (thin membrane covering the front part of the eye). Bacterial infection of the cornea (transparent front part of the eye). Eye infection caused by herpes zoster virus.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Verkazia

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton, aluminium pouch label, and single-dose container label after EXP. The expiry date refers to the last day of that month.

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.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Verkazia contains
- The active substance is ciclosporin. One mL of Verkazia contains 1 mg of ciclosporin.
- The other ingredients are medium-chain triglycerides, cetalkonium chloride, glycerol, tyloxapol, poloxamer 188, sodium hydroxide (to adjust pH) and water for injections.

What Verkazia looks like and contents of the pack
Verkazia is a milky white eye drops emulsion.

It is supplied in single-dose containers made of a low-density polyethylene (LDPE).

Each single-dose container contains 0.3 mL eye drops emulsion**.**

The single-dose containers are wrapped in a sealed aluminium pouch.

Pack sizes: 30, 60, 90 and 120 single-dose containers.
Not all pack sizes may be marketed.

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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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(UK Tel: +44 (0) 345 075 4863)

This leaflet was last revised in month YYYY.

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

Package leaflet: Information for the patient

Verkazia 1 mg/mL eye drops, emulsion
ciclosporin

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Verkazia is and what it is used for

Verkazia contains the active ingredient, ciclosporin. Ciclosporin reduces the activity of the body's immune (defence) system and in this way it reduces inflammation (body response to harmful stimuli).

Verkazia is used to treat children and adolescents aged 4 to 18 years with severe vernal keratoconjunctivitis (an allergic condition of the eye that occurs more frequently in spring and affects the transparent layer in the front part of the eye and the thin membrane covering the front part of the eye).

2. What you need to know before you use Verkazia

Do not use Verkazia
- if you are allergic to ciclosporin or to any of the other ingredients of this medicine (listed in section 6).
- if you have had or have a cancer in or around your eye.
- if you have an eye infection.

Warnings and precautions
Only use Verkazia in your eye as described under section 3. Do not exceed the treatment period prescribed by your doctor.

Talk to your doctor or pharmacist before using Verkazia:
- if you have had an eye infection or if you suspect you have an eye infection.
- if you have any other kind of eye disease.
- if you wear contact lenses (the use of Verkazia is not recommended with contact lenses).

Children and adolescents
Do not use Verkazia in children under the age of 4 years.

Other medicines and Verkazia
Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines.

Talk to your doctor if you are using eye drops containing steroids administered in association with Verkazia as this association may increase the risk of local infections.

If you are using Verkazia for more than 12 months, you should visit your doctor regularly, e.g. every 3 to 6 months.

If you are using other eye drops, use Verkazia **at least 15 minutes** after using the other eye drops.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before using this medicine.

Verkazia should not be used if you are pregnant. If you could become pregnant you must use contraception while using this medicine.

Verkazia is likely to be present in breast milk in very small amounts. If you are breast feeding talk to your doctor before using this medicine.

Driving and using machines
Your vision may be temporarily blurred after using Verkazia eye drops or you may get other disturbances with your vision. If this happens, wait until your vision clears before you drive or use machines.

Verkazia contains cetalkonium chloride
Cetalkonium chloride may cause eye irritation.

3. How to use Verkazia

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

A caregiver should help a child starting Verkazia treatment, particularly if the child is aged under 10 years, and should continue to supervise the child until the child is able to use Verkazia properly without help.

The recommended dose is 1 drop of Verkazia in each affected eye 4 times a day (morning, mid-day, afternoon and evening). You should continue Verkazia as prescribed by your doctor.

Instructions for use
Follow these instructions carefully and ask your doctor or pharmacist if there is anything you do not understand.

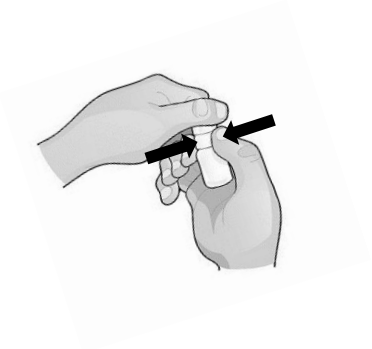
Before administration of the eye drops:

- Wash your hands before opening the bottle.
- Do not use this medicine if you notice that the tamper-proof seal on the bottle neck is broken before you first use it.
- When using the bottle for the very first time, before delivering a drop to the eye, you should practise using the bottle by squeezing it slowly to deliver one drop away from the eye.

- When you are confident that you can deliver one drop at a time, choose the position that you find most comfortable for the instillation of the drops (you can sit down, lie on your back, or stand in front of a mirror).
- Every time when opening a new bottle, place one drop in the waste to activate the bottle.

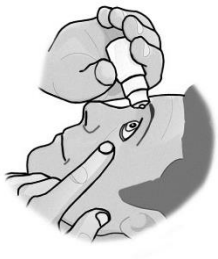
Administration:

1. Gently shake the bottle. Hold the bottle directly below the cap and turn the cap to open the bottle. Do not touch anything with the tip of the bottle to avoid contamination.



2. Tilt your head backwards and hold the bottle above your eye.

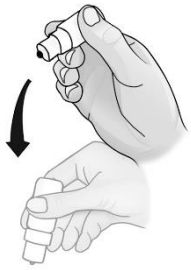
3. Pull the lower eyelid down and look up. Squeeze the bottle gently in the middle and let a drop fall into your eye. Please note that there might be a few seconds delay between squeezing and the drop coming out. Do not squeeze too hard.



4. Close your eye and **press the inner corner of the eye** with your finger for about two minutes. This helps to **stop the medicine from getting into the rest of the body**.

5. Repeat instructions 2 – 4 to deliver a drop into the other eye, if your doctor has instructed you to do this. Sometimes only one eye needs to be treated and your doctor will advise if this applies to you and which eye needs treatment.

6. After each use and prior to recapping, the bottle should be shaken once in a downwards direction, without touching the dropper tip, in order to remove any residual emulsion from the tip. This is necessary to ensure good delivery of the next drop.



7. Wipe off any excess emulsion from the skin around the eye.

At the end of the 4 weeks in-use shelf life of the medicine, there will be some emulsion left in the bottle. Do not attempt to use the excess medicine remaining in the bottle after you have completed the course of treatment. Do not use the eye drops for longer than 4 weeks after first opening the bottle.

If a drop misses your eye, try again.

If you put in more Verkazia than you should, rinse your eye with water. Do not put in any more drops until it is time for your next regular dose.

If you forget to use Verkazia, continue with the next dose as planned. Do not take a double dose to make up for the forgotten dose. Do not use more than 1 drop 4 times a day in the affected eye(s).

If you stop using Verkazia without speaking to your doctor, your eye allergy will not be controlled and could lead to long-term problems with your sight.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The following side effects have been reported for Verkazia:
The most common side effects are in and around the eyes.

Very common side effects (may affect more than 1 in 10 people)
Pain when the drops are put into the eye.

Common side effects (may affect up to 1 in 10 people)
Common side effects related to the eye:
Itching, redness, irritation and discomfort in or around the eye including a feeling that there is something in the eye. Increased watering of the eye and blurred vision when the drops are put into the eye. Swelling and redness of eyelid.

Common side effects which are not related to the eye:
Upper respiratory tract infection, cough, headache.

Uncommon side effects (may affect up to 1 in 100 people)
Swelling of the eyelid and of the conjunctiva (thin membrane covering the front part of the eye). Bacterial infection of the cornea (transparent front part of the eye). Eye infection caused by herpes zoster virus.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Verkazia

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and bottle label after EXP. The expiry date refers to the last day of that month.

Do not freeze.

Store below 25 °C.

After first opening the bottle, the emulsion can be used for **4 weeks.** The bottle must be kept tightly closed.

Do not use this medicine if you notice that the seal is broken the first time you use the container.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Verkazia contains
- The active substance is ciclosporin. One mL of Verkazia contains 1 mg of ciclosporin.
- The other ingredients are medium-chain triglycerides, cetalkonium chloride, glycerol, tyloxapol, poloxamer 188, sodium hydroxide (to adjust pH) and water for injections.

What Verkazia looks like and contents of the pack
Verkazia is a milky white eye drops emulsion.

It is supplied in a white plastic bottle with a white dropper applicator and a white plastic screw cap. Each bottle contains 9 mL of the medicine and each pack contains one bottle.

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Niittyhaankatu 20
33720 Tampere
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27 rue de la Lombardière
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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in month YYYY.

Detailed information on this medicine is available on the European Medicines Agency web site:http://www.ema.europa.eu.