ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

IKERVIS 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 (see section 4.4).

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 keratitis in adult patients with dry eye disease, which has not improved despite treatment with tear substitutes (see section 5.1).

4.2 Posology and method of administration

Treatment must be initiated by an ophthalmologist or a healthcare professional qualified in ophthalmology.

Posology

The recommended dose is one drop once daily to be applied to the affected eye(s) at bedtime. Response to treatment should be reassessed at least every 6 months.

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

Special populations

Elderly patients
The elderly population has been studied in clinical studies. No dose adjustment is required.

Patients with renal or hepatic impairment
The effect of ciclosporin has not been studied in patients with hepatic or renal impairment. However, no special considerations are needed in these populations.

Paediatric population
There is no relevant use of ciclosporin in children and adolescents aged below 18 in the treatment of severe keratitis in patients with dry eye disease, which has not improved despite treatment with tear substitutes.

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. Any unused emulsion should be discarded immediately.

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.

If more than one topical ophthalmic medicinal product is being used, the medicinal products must be administered at least 15 minutes apart. IKERVIS 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

IKERVIS has not been studied in patients with a history of ocular herpes and should therefore be used with caution in such patients.

Contact lenses
Patients wearing contact lenses have not been studied. Careful monitoring of patients with severe keratitis is recommended. Contact lenses should be removed before instillation of the eye drops at bedtime and may be reinserted at wake-up time.

Concomitant therapy
There is limited experience with ciclosporin in the treatment of patients with glaucoma. Regular clinical monitoring should be exercised when treating these patients concomitantly with IKERVIS, especially with beta-blockers which are known to decrease tear secretion.

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. at least every 6 months, when IKERVIS is used for years.

Cetalkonium chloride content
IKERVIS contains cetalkonium chloride. Contact lenses should be removed prior to application and may be reinserted at wake-up time. Cetalkonium chloride may cause eye irritation. Patients should be monitored in case of prolonged use.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed with IKERVIS.

Combination with other medicinal products that affect the immune system

Co-administration of IKERVIS with eye drops containing corticosteroids could potentiate the effects of ciclosporin on the immune system (see section 4.4).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/contraception in females

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

Pregnancy

There is no data from the use of IKERVIS in pregnant women.

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

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

Breast-feeding

Following oral administration, 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 IKERVIS therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

There is no data on the effects of IKERVIS on human fertility.
No impairment of fertility has been reported in animals receiving intravenous ciclosporin (see section 5.3).

4.7 Effects on ability to drive and use machines

IKERVIS 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 are eye pain (19.0%), eye irritation (17.5%), ocular hyperaemia (5.5%), lacrimation increased (4.9%) and eyelid erythema (1.7%) which are usually transitory and occurred during instillation.These adverse reactions are consistent with those that have been reported during post-marketing experience.

Tabulated list of adverse reactions

The following adverse reactions listed below were observed in clinical studies or during post-marketing experience. 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).

System Organ Class	Frequency	Adverse reactions
Infections and infestations	Uncommon	Keratitis bacterial, Herpes zoster ophthalmic.
Eye disorders	Very common	Eye pain, Eye irritation
	Common	Erythema of eyelid, Lacrimation increased, Ocular hyperaemia, Vision blurred, Eyelid oedema, Conjunctival hyperaemia, Eye pruritus
	Uncommon	Conjunctival oedema, Lacrimal disorder, Eye discharge, Conjunctival irritation, Conjunctivitis, Foreign body sensation in eyes, Deposit eye, Keratitis, Blepharitis, Chalazion, Corneal infiltrates, Corneal scar, Eyelid pruritus, Iridocyclitis. Ocular discomfort
General disorders and administration site conditions	Uncommon	Instillation site reaction
Nervous system disorders	Uncommon	Headache

Description of selected adverse reactions

Eye pain
A frequently reported local adverse reaction associated with the use of IKERVIS during clinical trials. It is likely to be attributable to ciclosporin.

Generalised and localised infections
Patients receiving immunosuppressive therapies, including ciclosporin, are at increased risk of infections. Both generalised and localised infections can occur. Pre-existing infections may also be aggravated (see section 4.3). Cases of infections have been reported uncommonly in association with the use of IKERVIS.
As precautionary measure, action should be taken to reduce the systemic absorption (see section 4.2).

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

A topical overdose is not likely to occur after ocular administration. If overdose with IKERVIS occurs, 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

Ciclosporin (also known as ciclosporin A) is a cyclic polypeptide immunomodulator with immunosuppressant properties. It has been shown to prolong survival of allogeneic transplants in animals and significantly improved graft survival in all types of solid organ transplantation in man. Ciclosporin has also been shown to have an anti-inflammatory effect. Studies in animals suggest that ciclosporin inhibits the development of cell-mediated reactions. Ciclosporin has been shown to inhibit the production and/or release of pro-inflammatory cytokines, including interleukin 2 (IL-2) or T-cell growth factor (TCGF). It is also known to up-regulate the release of anti-inflammatory cytokines. Ciclosporin appears to block the resting lymphocytes in the G0 or G1 phase of the cell cycle. All available evidence suggests that ciclosporin acts specifically and reversibly on lymphocytes and does not depress haematopoiesis or has any effect on the function of phagocytic cells.
In patients with dry eye disease, a condition that may be considered to have an inflammatory immunological mechanism, following ocular administration, ciclosporin is passively absorbed into T-lymphocyte infiltrates in the cornea and conjunctiva and inactivates calcineurin phosphatase. Ciclosporin-induced inactivation of calcineurin inhibits the dephosphorylation of the transcription factor NF-AT and prevents NF-AT translocation into the nucleus, thus blocking the release of pro-inflammatory cytokines such as IL-2.

Clinical efficacy and safety

The efficacy and safety of IKERVIS were evaluated in two randomised, double-masked, vehicle-controlled clinical studies in adult patients with dry eye disease (keratoconjunctivitis sicca) who met the International Dry Eye Workshop (DEWS) criteria.

In the 12 month, double-masked, vehicle controlled, pivotal clinical trial (SANSIKA study), 246 Dry Eye Disease (DED) patients with **severe** keratitis (defined as a corneal fluorescein staining (CFS) score of 4 on the modified Oxford scale) were randomised to one drop of IKERVIS or vehicle daily at bedtime for 6 months. Patients randomised to the vehicle group were switched to IKERVIS after 6 months. The primary endpoint was the proportion of patients achieving by month 6 at least a two-grade improvement in keratitis (CFS) and a 30% improvement in symptoms, measured with the Ocular Surface Disease Index (OSDI). The proportion of responders in the IKERVIS group was 28.6%, compared to 23.1% in the vehicle group. The difference was not statistically significant (p=0.326).
The severity of keratitis, assessed using CFS, improved significantly from baseline at month 6 with IKERVIS compared to vehicle (mean change from baseline was -1.764 with IKERVIS *vs.* -1.418 with vehicle, p=0.037). The proportion of IKERVIS-treated patients with a 3-grade improvement in CFS score at month 6 (from 4 to 1) was 28.8%, compared to 9.6% of vehicle-treated subjects, but this was a post-hoc analysis, which limits the robustness of this outcome. The beneficial effect on keratitis was maintained in the open phase of the study, from month 6 and up to month 12.
The mean change from baseline in the 100-point OSDI score was -13.6 with IKERVIS and -14.1 with vehicle at month 6 (p=0.858). In addition, no improvement was observed for IKERVIS compared to vehicle at month 6 for other secondary endpoints, including ocular discomfort score, Schirmer test, use of concomitant artificial tears, investigator's global evaluation of efficacy, tear break-up time, lissamine green staining, quality of life score, and tear osmolarity.
A reduction in the ocular surface inflammation assessed with Human Leukocyte Antigen-DR (HLA-DR) expression (an exploratory endpoint), was observed at month 6 in favour of IKERVIS (p=0.021).

In the 6 month, double-masked, vehicle controlled, supportive clinical trial (SICCANOVE study), 492 DED patients with **moderate to severe** keratitis (defined as a CFS score of 2 to 4) were also randomised to IKERVIS or vehicle daily at bedtime for 6 months. The co-primary endpoints were the change in CFS score, and the change in global score of ocular discomfort unrelated to study medication instillation, both measured at month 6. A small but statistically significant difference in CFS improvement was observed between the treatment groups at month 6 in favour of IKERVIS (mean change from baseline in CFS -1.05 with IKERVIS and -0.82 with vehicle, p=0.009).
The mean change from baseline in ocular discomfort score (assessed using a Visual Analogic Scale) was -12.82 with IKERVIS and -11.21 with vehicle (p=0.808).

In both studies, no significant improvement of symptoms was observed for IKERVIS compared to vehicle after 6 months of treatment, whether using a visual analogue scale or the OSDI.

In both studies one third of the patients in average had Sjögren's syndrome; as for the overall population, a statistically significant improvement in CFS in favour of IKERVIS was observed in this subgroup of patients.

At completion of the SANSIKA study (12 month study), patients were asked to enter the Post SANSIKA study. This study was an open-label, non-randomised, one-arm, 24-month study extension of the Sansika Study. In Post SANSIKA study patients alternatively received IKERVIS treatment or no treatment depending on CFS score (patients received IKERVIS when there was a worsening of keratitis).
This study was designed to monitor the long-term efficacy and relapse rates in patients who have previously received IKERVIS.

The primary objective of the study was to assess the duration of the improvement following IKERVIS treatment discontinuation once the patient was improved with respect to the baseline of the SANSIKA study (i.e. at least 2 grade improvement on the modified Oxford scale).
67 patients were enrolled (37.9% of the 177 patients having ended Sansika). After the 24-month period, 61.3% of 62 patients included in the primary efficacy population did not experience a relapse based on CFS scores. Percentage of patients who experienced a severe keratitis recurrence was 35% and 48% in patients treated 12 months and 6 months with IKERVIS respectively in the SANSIKA study.
Based on the first quartile (the median could not be estimated due to the small number of relapses), time to relapse (back to CFS grade 4) was ≤224 days and ≤175 days in patients previously treated 12 months and 6 months with IKERVIS, respectively. Patients spent more time on CFS grade 2 (Median 12.7 weeks/year) and grade 1 (Median 6.6 weeks/year) than CFS grade 3 (Median 2.4 weeks/year), CFS grades 4 and 5 (Median time 0 week/year).
Assessment of DED symptoms by VAS showed a worsening of patient's discomfort from the time treatment was first stopped to the time it was restarted except pain which remained relatively low and stable. The median global VAS score increased from the time treatment was first stopped (23.3%) to the time treatment was restarted (45.1%).
No significant changes have been observed in the other secondary endpoints (TBUT, lissamine green staining and Schirmer test, NEI-VFQ and EQ-5D) over the course of the extension study.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with IKERVIS in all subsets of the paediatric population in dry eye disease (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

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

Blood concentrations of IKERVIS were measured using a specific high-pressure liquid chromatography-mass spectrometry assay. In 374 patients from the two efficacy studies, plasma concentrations of ciclosporin were measured before administration and after 6 months (SICCANOVE study and SANSIKA study) and 12 months of treatment (SANSIKA study). After 6 months of ocular instillation of IKERVIS once per day, 327 patients had values below the lower limit of detection (0.050 ng/mL) and 35 patients were below the lower limit of quantification (0.100 ng/mL). Measurable values not exceeding 0.206 ng/mL were measured in eight patients, values considered to be negligible. Three patients had values above the upper limit of quantification (5 ng/mL) however they were already taking oral ciclosporin at a stable dose, which was allowed by the studies' protocol. After 12 months of treatment, values were below the low limit of detection for 56 patients and below the low limit of quantification in 19 patients. Seven patients had measurable values (from 0.105 to 1.27 ng/mL), all considered to be negligible values. Two patients had values above the upper limit of quantification, however they were also on oral ciclosporin at a stable dose since their inclusion in the study.

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.

Effects in non-clinical studies were observed only with systemic administration or at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Medium-chain triglycerides
Cetalkonium chloride
Glycerol
Tyloxapol
Poloxamer 188
Sodium hydroxide (for pH adjustment)
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.
After opening of the aluminium pouches, the single-dose containers should be kept in the pouches in order to protect from light and avoid evaporation.
Any opened individual single-dose container with any remaining emulsion should be discarded immediately after use.

6.5 Nature and contents of container

IKERVIS is supplied in 0.3 mL single-dose, low-density polyethylene (LDPE) containers presented in a sealed laminate aluminium pouch.
One pouch contains five single-dose containers.

Pack sizes: 30 and 90 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/1/15/990/001
EU/1/15/990/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19 March 2015
Date of latest renewal: 09 March 2020

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

IKERVIS 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 (see section 4.4).

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 keratitis in adult patients with dry eye disease, which has not improved despite treatment with tear substitutes (see section 5.1).

4.2 Posology and method of administration

Treatment must be initiated by an ophthalmologist or a healthcare professional qualified in ophthalmology.

Posology

The recommended dose is one drop once daily to be applied to the affected eye(s) at bedtime. Response to treatment should be reassessed at least every 6 months.

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

Special populations

Elderly patients
The elderly population has been studied in clinical studies. No dose adjustment is required.

Patients with renal or hepatic impairment
The effect of ciclosporin has not been studied in patients with hepatic or renal impairment. However, no special considerations are needed in these populations.

Paediatric population
There is no relevant use of ciclosporin in children and adolescents aged below 18 in the treatment of severe keratitis in patients with dry eye disease, which has not improved despite treatment with tear substitutes.

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.

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

Patients should be informed of the correct handling of the multidose container. For instructions for use, see section 6.6.

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

IKERVIS has not been studied in patients with a history of ocular herpes and should therefore be used with caution in such patients.

Contact lenses
Patients wearing contact lenses have not been studied. Careful monitoring of patients with severe keratitis is recommended. Contact lenses should be removed before instillation of the eye drops at bedtime and may be reinserted at wake-up time.

Concomitant therapy
There is limited experience with ciclosporin in the treatment of patients with glaucoma. Regular clinical monitoring should be exercised when treating these patients concomitantly with IKERVIS, especially with beta-blockers which are known to decrease tear secretion.

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. at least every 6 months, when IKERVIS is used for years.

Cetalkonium chloride content
IKERVIS contains cetalkonium chloride. Contact lenses should be removed prior to application and may be reinserted at wake-up time. Cetalkonium chloride may cause eye irritation. Patients should be monitored in case of prolonged use.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed with IKERVIS.

Combination with other medicinal products that affect the immune system

Co-administration of IKERVIS with eye drops containing corticosteroids could potentiate the effects of ciclosporin on the immune system (see section 4.4).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/contraception in females

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

Pregnancy

There is no data from the use of IKERVIS in pregnant women.

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

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

Breast-feeding

Following oral administration, 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 IKERVIS therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

There is no data on the effects of IKERVIS on human fertility.
No impairment of fertility has been reported in animals receiving intravenous ciclosporin (see section 5.3).

4.7 Effects on ability to drive and use machines

IKERVIS 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 are eye pain (19.0%), eye irritation (17.5%), ocular hyperaemia (5.5%), lacrimation increased (4.9%) and eyelid erythema (1.7%) which are usually transitory and occurred during instillation.These adverse reactions are consistent with those that have been reported during post-marketing experience.

Tabulated list of adverse reactions

The following adverse reactions listed below were observed in clinical studies or during post-marketing experience. 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).

System Organ Class	Frequency	Adverse reactions
Infections and infestations	Uncommon	Keratitis bacterial, Herpes zoster ophthalmic.
Eye disorders	Very common	Eye pain, Eye irritation
	Common	Erythema of eyelid, Lacrimation increased, Ocular hyperaemia, Vision blurred, Eyelid oedema, Conjunctival hyperaemia, Eye pruritus
	Uncommon	Conjunctival oedema, Lacrimal disorder, Eye discharge, Conjunctival irritation, Conjunctivitis, Foreign body sensation in eyes, Deposit eye, Keratitis, Blepharitis, Chalazion, Corneal infiltrates, Corneal scar, Eyelid pruritus, Iridocyclitis. Ocular discomfort
General disorders and administration site conditions	Uncommon	Instillation site reaction
Nervous system disorders	Uncommon	Headache

Description of selected adverse reactions

Eye pain
A frequently reported local adverse reaction associated with the use of IKERVIS during clinical trials. It is likely to be attributable to ciclosporin.

Generalised and localised infections
Patients receiving immunosuppressive therapies, including ciclosporin, are at increased risk of infections. Both generalised and localised infections can occur. Pre-existing infections may also be aggravated (see section 4.3). Cases of infections have been reported uncommonly in association with the use of IKERVIS.
As precautionary measure, action should be taken to reduce the systemic absorption (see section 4.2).

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

A topical overdose is not likely to occur after ocular administration. If overdose with IKERVIS occurs, 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

Ciclosporin (also known as ciclosporin A) is a cyclic polypeptide immunomodulator with immunosuppressant properties. It has been shown to prolong survival of allogeneic transplants in animals and significantly improved graft survival in all types of solid organ transplantation in man. Ciclosporin has also been shown to have an anti-inflammatory effect. Studies in animals suggest that ciclosporin inhibits the development of cell-mediated reactions. Ciclosporin has been shown to inhibit the production and/or release of pro-inflammatory cytokines, including interleukin 2 (IL-2) or T-cell growth factor (TCGF). It is also known to up-regulate the release of anti-inflammatory cytokines. Ciclosporin appears to block the resting lymphocytes in the G0 or G1 phase of the cell cycle. All available evidence suggests that ciclosporin acts specifically and reversibly on lymphocytes and does not depress haematopoiesis or has any effect on the function of phagocytic cells.
In patients with dry eye disease, a condition that may be considered to have an inflammatory immunological mechanism, following ocular administration, ciclosporin is passively absorbed into T-lymphocyte infiltrates in the cornea and conjunctiva and inactivates calcineurin phosphatase. Ciclosporin-induced inactivation of calcineurin inhibits the dephosphorylation of the transcription factor NF-AT and prevents NF-AT translocation into the nucleus, thus blocking the release of pro-inflammatory cytokines such as IL-2.

Clinical efficacy and safety

The efficacy and safety of IKERVIS were evaluated in two randomised, double-masked, vehicle-controlled clinical studies in adult patients with dry eye disease (keratoconjunctivitis sicca) who met the International Dry Eye Workshop (DEWS) criteria.

In the 12 month, double-masked, vehicle controlled, pivotal clinical trial (SANSIKA study), 246 Dry Eye Disease (DED) patients with **severe** keratitis (defined as a corneal fluorescein staining (CFS) score of 4 on the modified Oxford scale) were randomised to one drop of IKERVIS or vehicle daily at bedtime for 6 months. Patients randomised to the vehicle group were switched to IKERVIS after 6 months. The primary endpoint was the proportion of patients achieving by month 6 at least a two-grade improvement in keratitis (CFS) and a 30% improvement in symptoms, measured with the Ocular Surface Disease Index (OSDI). The proportion of responders in the IKERVIS group was 28.6%, compared to 23.1% in the vehicle group. The difference was not statistically significant (p=0.326).
The severity of keratitis, assessed using CFS, improved significantly from baseline at month 6 with IKERVIS compared to vehicle (mean change from baseline was -1.764 with IKERVIS *vs.* -1.418 with vehicle, p=0.037). The proportion of IKERVIS-treated patients with a 3-grade improvement in CFS score at month 6 (from 4 to 1) was 28.8%, compared to 9.6% of vehicle-treated subjects, but this was a post-hoc analysis, which limits the robustness of this outcome. The beneficial effect on keratitis was maintained in the open phase of the study, from month 6 and up to month 12.
The mean change from baseline in the 100-point OSDI score was -13.6 with IKERVIS and -14.1 with vehicle at month 6 (p=0.858). In addition, no improvement was observed for IKERVIS compared to vehicle at month 6 for other secondary endpoints, including ocular discomfort score, Schirmer test, use of concomitant artificial tears, investigator's global evaluation of efficacy, tear break-up time, lissamine green staining, quality of life score, and tear osmolarity.
A reduction in the ocular surface inflammation assessed with Human Leukocyte Antigen-DR (HLA-DR) expression (an exploratory endpoint), was observed at month 6 in favour of IKERVIS (p=0.021).

In the 6 month, double-masked, vehicle controlled, supportive clinical trial (SICCANOVE study), 492 DED patients with **moderate to severe** keratitis (defined as a CFS score of 2 to 4) were also randomised to IKERVIS or vehicle daily at bedtime for 6 months. The co-primary endpoints were the change in CFS score, and the change in global score of ocular discomfort unrelated to study medication instillation, both measured at month 6. A small but statistically significant difference in CFS improvement was observed between the treatment groups at month 6 in favour of IKERVIS (mean change from baseline in CFS -1.05 with IKERVIS and -0.82 with vehicle, p=0.009).
The mean change from baseline in ocular discomfort score (assessed using a Visual Analogic Scale) was -12.82 with IKERVIS and -11.21 with vehicle (p=0.808).

In both studies, no significant improvement of symptoms was observed for IKERVIS compared to vehicle after 6 months of treatment, whether using a visual analogue scale or the OSDI.

In both studies one third of the patients in average had Sjögren's syndrome; as for the overall population, a statistically significant improvement in CFS in favour of IKERVIS was observed in this subgroup of patients.

At completion of the SANSIKA study (12 month study), patients were asked to enter the Post SANSIKA study. This study was an open-label, non-randomised, one-arm, 24-month study extension of the Sansika Study. In Post SANSIKA study patients alternatively received IKERVIS treatment or no treatment depending on CFS score (patients received IKERVIS when there was a worsening of keratitis).
This study was designed to monitor the long-term efficacy and relapse rates in patients who have previously received IKERVIS.

The primary objective of the study was to assess the duration of the improvement following IKERVIS treatment discontinuation once the patient was improved with respect to the baseline of the SANSIKA study (i.e. at least 2 grade improvement on the modified Oxford scale).
67 patients were enrolled (37.9% of the 177 patients having ended Sansika). After the 24-month period, 61.3% of 62 patients included in the primary efficacy population did not experience a relapse based on CFS scores. Percentage of patients who experienced a severe keratitis recurrence was 35% and 48% in patients treated 12 months and 6 months with IKERVIS respectively in the SANSIKA study.
Based on the first quartile (the median could not be estimated due to the small number of relapses), time to relapse (back to CFS grade 4) was ≤224 days and ≤175 days in patients previously treated 12 months and 6 months with IKERVIS, respectively. Patients spent more time on CFS grade 2 (Median 12.7 weeks/year) and grade 1 (Median 6.6 weeks/year) than CFS grade 3 (Median 2.4 weeks/year), CFS grades 4 and 5 (Median time 0 week/year).
Assessment of DED symptoms by VAS showed a worsening of patient's discomfort from the time treatment was first stopped to the time it was restarted except pain which remained relatively low and stable. The median global VAS score increased from the time treatment was first stopped (23.3%) to the time treatment was restarted (45.1%).
No significant changes have been observed in the other secondary endpoints (TBUT, lissamine green staining and Schirmer test, NEI-VFQ and EQ-5D) over the course of the extension study.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with IKERVIS in all subsets of the paediatric population in dry eye disease (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

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

Blood concentrations of IKERVIS were measured using a specific high-pressure liquid chromatography-mass spectrometry assay. In 374 patients from the two efficacy studies, plasma concentrations of ciclosporin were measured before administration and after 6 months (SICCANOVE study and SANSIKA study) and 12 months of treatment (SANSIKA study). After 6 months of ocular instillation of IKERVIS once per day, 327 patients had values below the lower limit of detection (0.050 ng/mL) and 35 patients were below the lower limit of quantification (0.100 ng/mL). Measurable values not exceeding 0.206 ng/mL were measured in eight patients, values considered to be negligible. Three patients had values above the upper limit of quantification (5 ng/mL) however they were already taking oral ciclosporin at a stable dose, which was allowed by the studies' protocol. After 12 months of treatment, values were below the low limit of detection for 56 patients and below the low limit of quantification in 19 patients. Seven patients had measurable values (from 0.105 to 1.27 ng/mL), all considered to be negligible values. Two patients had values above the upper limit of quantification, however they were also on oral ciclosporin at a stable dose since their inclusion in the study.

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.

Effects in non-clinical studies were observed only with systemic administration or at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Medium-chain triglycerides
Cetalkonium chloride
Glycerol
Tyloxapol
Poloxamer 188
Sodium hydroxide (for pH adjustment)
Water for injections

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

After first opening the bottle the in-use shelf life is 3 months.
Store below 25°C.

6.4 Special precautions for storage

Do not freeze.
Store below 25°C.
For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

IKERVIS is supplied sterile in a white low density polyethylene bottle and white nozzle with tamper evident system.

The following pack sizes are available: Carton containing 1 bottle of 5 mL with 2.5 mL fill, carton containing 1 bottle of 11 mL with 4.5 mL fill or carton containing 1 bottle of 11 mL with 7 mL fill.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

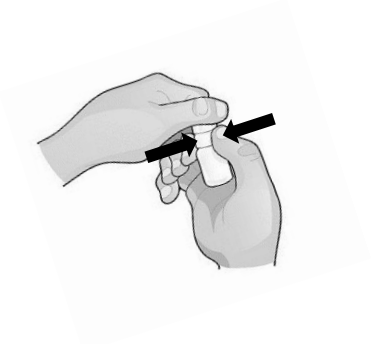
Instructions for use

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, drop one drop to 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 of the emulsion.



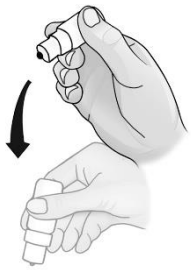
2. Tilt your head backwards and hold the bottle above your eye.

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 in order to ensure delivery of subsequent drops.



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

At the end of the in-use shelf life of the medicine, there could 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.

7. MARKETING AUTHORISATION HOLDER

SANTEN Oy
Niittyhaankatu 20
33720 Tampere
Finland

8. MARKETING AUTHORISATION NUMBERS

EU/1/15/990/003
EU/1/15/990/004
EU/1/15/990/005

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19 March 2015
Date of latest renewal: 09 March 2020

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. MANUFACTURER(S) 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. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

EXCELVISION
27 RUE DE LA LOMBARDIERE, ZI LA LOMBARDIERE
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 (PSURs)**

The requirements for submission of PSURs 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

OUTER CARTON CONTAINING SINGLE-DOSE CONTAINERS

1. NAME OF THE MEDICINAL PRODUCT

IKERVIS 1 mg/mL eye drops, emulsion
ciclosporin

2. STATEMENT OF ACTIVE SUBSTANCE

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.
30 single-dose containers
90 single-dose containers

5. METHOD AND ROUTE OF ADMINISTRATION

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

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

Remove contact lenses before use.

8. EXPIRY DATE

EXP
Discard any opened individual single-dose container with any remaining emulsion 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 NUMBERS

EU/1/15/990/001 30 single-dose containers
EU/1/15/990/002 90 single-dose containers

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

ikervis

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON CONTAINING ONE BOTTLE

1. NAME OF THE MEDICINAL PRODUCT

IKERVIS 1 mg/mL eye drops, emulsion
ciclosporin

2. STATEMENT OF ACTIVE SUBSTANCE

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 2.5 mL
1 x 4.5 mL
1 x 7 mL

5. METHOD AND ROUTE 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

Remove contact lenses before use.

8. EXPIRY DATE

EXP
Discard 3 months 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 NUMBERS

EU/1/15/990/003
EU/1/15/990/004
EU/1/15/990/005

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

ikervis

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

IKERVIS 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.
After opening of the aluminium pouches, the single-dose containers should be kept in the pouches in order to protect from light and avoid evaporation.
Discard any opened individual single-dose container with any remaining emulsion 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

IKERVIS 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

0.3 mL

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

BOTTLE LABEL

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

IKERVIS 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

1 x 2.5 mL
1 x 4.5 mL
1 x 7 mL

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

IKERVIS 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 IKERVIS is and what it is used for
2. What you need to know before you use IKERVIS
3. How to use IKERVIS
4. Possible side effects
5. How to store IKERVIS
6. Contents of the pack and other information

1. What IKERVIS is and what it is used for

IKERVIS contains the active substance, ciclosporin. Ciclosporin belongs to a group of medicines known as immunosuppressive agents that are used to reduce inflammation.

IKERVIS is used to treat adults with severe keratitis (inflammation of the cornea, the transparent layer in the front part of the eye). It is used in those patients who have dry eye disease, which has not improved despite treatment with tear substitutes (artificial tears).

Talk to a doctor if you do not feel better or if you feel worse.

You should visit your doctor at least every 6 months to assess the effect of IKERVIS.

2. What you need to know before you use IKERVIS

Do NOT use IKERVIS
- if you are allergic to ciclosporin or 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 IKERVIS for dropping in your eye(s).

Talk to your doctor or pharmacist before using IKERVIS
- if you have previously had an eye infection by the herpes virus that might have damaged the transparent front part of the eye (cornea).
- if you are taking any medicines containing steroids.
- if you are taking any medicines to treat glaucoma.

Contact lenses can further damage the transparent front part of the eye (cornea). Therefore, you should remove your contact lenses at bedtime before using IKERVIS; you can reinsert them when you wake up.

Children and adolescents
IKERVIS should not be used in children and adolescents below 18 years old.

Other medicines and IKERVIS
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 with IKERVIS as these might increase the risk of side effects.

IKERVIS eye drops should be used **at least 15 minutes** after any other eye drops are used.

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.

IKERVIS **should not be used** if you are pregnant.

If you could become pregnant you must use contraception while using this medicine.

IKERVIS 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 blurred immediately after using IKERVIS eye drops. If this happens, wait until your vision clears before you drive or use machines.

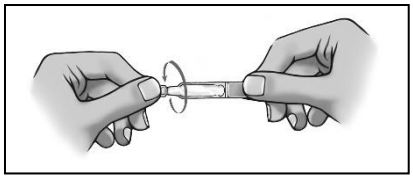
IKERVIS contains cetalkonium chloride
This medicine contains 0.05 mg cetalkonium chloride in 1 mL. You should remove contact lenses before using this medicine and you can reinsert them when you wake up. Cetalkonium chloride may cause eye irritation. If you feel abnormal eye sensation, stinging or pain in the eye after using this medicine, talk to your doctor.

3. How to use IKERVIS

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

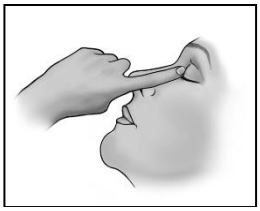
The recommended dose is one drop in each affected eye, once daily at bedtime.

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



1

2



3

- Wash your hands.
- If you wear contact lenses, take them out at bedtime before using the drops; you can reinsert them when you wake up.
- Open the aluminium pouch, which contains 5 single-dose containers.
- Take one single-dose container from the aluminium pouch.
- Gently shake the single dose container prior to use.
- Twist off the cap **(picture 1)**.
- Pull down your lower eyelid **(picture 2)**.
- Tilt your head back and look up at the ceiling.
- Gently squeeze one drop of the medicine onto your eye. Make sure you do not touch your eye with the tip of the single-dose container.
- Blink a few times so that the medicine covers your eye.
- After using IKERVIS, press a finger into the corner of your eye by the nose and close gently the eyelids for 2 minutes **(picture 3)**. This helps to stop IKERVIS getting into the rest of the body.
- If you use drops in both eyes, repeat the steps for your other eye.
- Discard the single dose container as soon as you have used it, even if there is still some medicine left in it.
- The remaining single-dose containers should be kept in the aluminium pouch.

If a drop misses your eye, try again.

If you use more IKERVIS 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 IKERVIS, continue with the next dose as planned. Do not use a double dose to make up for the forgotten dose. Do not use more than one drop each day in the affected eye(s).

If you stop using IKERVIS without speaking to your doctor, the inflammation of the transparent front part of your eye (known as keratitis) will not be controlled and could lead to impaired vision.

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:

The most common side effects are in and around the eyes.

Very common (may affect more than 1 in 10 people)
- Eye pain,
- Eye irritation

Common (may affect up to 1 in 10 people)
- Redness of the eyelid,
- Watery eyes,
- Eye redness,
- Blurred vision,
- Swelling of the eyelid,
- Redness of the conjunctiva (thin membrane covering the front part of the eye),
- Itching in the eye

Uncommon (may affect up to 1 in 100 people)
- Discomfort in or around the eye when the drops are put into the eye, including feeling that there is something in the eye,
- Irritation or swelling of the conjunctiva (thin membrane covering the front part of the eye),
- Tear disorder,
- Eye discharge,
- Irritation or inflammation of the conjunctiva (thin membrane covering the front part of the eye),
- Inflammation of the iris (coloured part of the eye) or eyelid,
- Deposits in the eye,
- Abrasion to the outer layer of the cornea,
- Red or swollen eyelids,
- Cyst in the eyelid,
- Immune response or scarring in the cornea,
- Itching in the eyelid,
- Bacterial infection or inflammation of the cornea (transparent front part of the eye),
- Painful rash around the eye caused by the herpes zoster virus,
- Headache

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 IKERVIS

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 outer carton, the aluminium pouch and on the single-dose containers after “EXP”. The expiry date refers to the last day of that month.

Do not freeze.
Store below 25°C.
After opening of the aluminium pouches, the single-dose containers should be kept in the pouches in order to protect from light and avoid evaporation. Discard any opened individual single-dose container with any remaining emulsion 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 IKERVIS contains
- The active substance is ciclosporin. One millilitre of IKERVIS contains 1 mg of ciclosporin.
- The other ingredients are medium-chain triglycerides, cetalkonium chloride, glycerol, tyloxapol, poloxamer 188, sodium hydroxide (for pH adjustment) and water for injections.

What IKERVIS looks like and contents of the pack
IKERVIS 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 and 90 single-dose containers.
Not all pack sizes may be marketed.

Marketing Authorisation Holder
SANTEN Oy
Niittyhaankatu 20
33720 Tampere
Finland

Manufacturer
EXCELVISION
Rue de la Lombardière
ZI la Lombardière
F-07100 Annonay
France

SANTEN Oy
Kelloportinkatu 1
33100 Tampere
Finland

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

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Santen Oy
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България
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Тел.: +359 (0) 888 755 393

Česká republika
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Danmark
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Lietuva
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Luxembourg/Luxemburg
Santen Oy
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Tel: + 353 (0) 16950008

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Sími: + 358 (0) 3 284 8111

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Nederland
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Österreich
Santen Oy
Tel: +43 (0) 720116199

Polska
Santen Oy
Tel.: +48(0) 221042096

Portugal
Santen Oy
Tel: + 351 308 805 912

România
Santen Oy
Tel: +358 (0) 3 284 8111

Slovenija
Santen Oy
Tel: + 358 (0) 3 284 8111

Slovenská republika
Santen Oy
Tel: +358 (0) 3 284 8111

Suomi/Finland
Santen Oy
Puh/Tel: +358 (0) 974790211

Sverige
Santen Oy
Tel: +46 (0) 850598833

United Kingdom (Northern Ireland)
Santen Oy
Tel: +353 (0) 16950008
(UK Tel: +44 (0) 345 075 4863)

This leaflet was last revised in

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

IKERVIS 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 IKERVIS is and what it is used for
2. What you need to know before you use IKERVIS
3. How to use IKERVIS
4. Possible side effects
5. How to store IKERVIS
6. Contents of the pack and other information

1. What IKERVIS is and what it is used for

IKERVIS contains the active substance, ciclosporin. Ciclosporin belongs to a group of medicines known as immunosuppressive agents that are used to reduce inflammation.

IKERVIS is used to treat adults with severe keratitis (inflammation of the cornea, the transparent layer in the front part of the eye). It is used in those patients who have dry eye disease, which has not improved despite treatment with tear substitutes (artificial tears).

Talk to a doctor if you do not feel better or if you feel worse.

You should visit your doctor at least every 6 months to assess the effect of IKERVIS.

2. What you need to know before you use IKERVIS

Do NOT use IKERVIS
- if you are allergic to ciclosporin or 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 IKERVIS for dropping in your eye(s).

Talk to your doctor or pharmacist before using IKERVIS
- if you have previously had an eye infection by the herpes virus that might have damaged the transparent front part of the eye (cornea).
- if you are taking any medicines containing steroids.
- if you are taking any medicines to treat glaucoma.

Contact lenses can further damage the transparent front part of the eye (cornea). Therefore, you should remove your contact lenses at bedtime before using IKERVIS; you can reinsert them when you wake up.

Children and adolescents
IKERVIS should not be used in children and adolescents below 18 years old.

Other medicines and IKERVIS
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 with IKERVIS as these might increase the risk of side effects.

IKERVIS eye drops should be used **at least 15 minutes** after any other eye drops are used.

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.

IKERVIS **should not be used** if you are pregnant.

If you could become pregnant you must use contraception while using this medicine.

IKERVIS 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 blurred immediately after using IKERVIS eye drops. If this happens, wait until your vision clears before you drive or use machines.

IKERVIS contains cetalkonium chloride
This medicine contains 0.05 mg cetalkonium chloride in 1 mL. You should remove contact lenses before using this medicine and you can reinsert them when you wake up. Cetalkonium chloride may cause eye irritation. If you feel abnormal eye sensation, stinging or pain in the eye after using this medicine, talk to your doctor.

3. How to use IKERVIS

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

The recommended dose is one drop in each affected eye, once daily at bedtime.

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

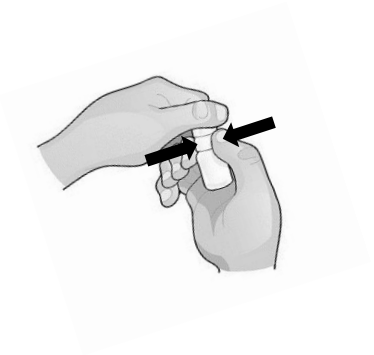
Before administration of the eye drops:

- 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.



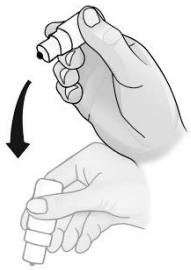
2. Tilt your head backwards and hold the bottle above your eye.

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.

8. At the end of the 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.

If a drop misses your eye, try again.

If you use more IKERVIS 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 IKERVIS, continue with the next dose as planned. Do not use a double dose to make up for the forgotten dose. Do not use more than one drop each day in the affected eye(s).

If you stop using IKERVIS without speaking to your doctor, the inflammation of the transparent front part of your eye (known as keratitis) will not be controlled and could lead to impaired vision.

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:

The most common side effects are in and around the eyes.

Very common (may affect more than 1 in 10 people)
- Eye pain,
- Eye irritation

Common (may affect up to 1 in 10 people)
- Redness of the eyelid,
- Watery eyes,
- Eye redness,
- Blurred vision,
- Swelling of the eyelid,
- Redness of the conjunctiva (thin membrane covering the front part of the eye),
- Itching in the eye

Uncommon (may affect up to 1 in 100 people)
- Discomfort in or around the eye when the drops are put into the eye, including feeling that there is something in the eye,
- Irritation or swelling of the conjunctiva (thin membrane covering the front part of the eye),
- Tear disorder,
- Eye discharge,
- Irritation or inflammation of the conjunctiva (thin membrane covering the front part of the eye),
- Inflammation of the iris (coloured part of the eye) or eyelid,
- Deposits in the eye,
- Abrasion to the outer layer of the cornea,
- Red or swollen eyelids,
- Cyst in the eyelid,
- Immune response or scarring in the cornea,
- Itching in the eyelid,
- Bacterial infection or inflammation of the cornea (transparent front part of the eye),
- Painful rash around the eye caused by the herpes zoster virus,
- Headache

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 IKERVIS

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 outer carton and on the 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, in order to prevent infections, you must throw away the bottle at the latest after 3 months. 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 IKERVIS contains
- The active substance is ciclosporin. One millilitre of IKERVIS contains 1 mg of ciclosporin.
- The other ingredients are medium-chain triglycerides, cetalkonium chloride, glycerol, tyloxapol, poloxamer 188, sodium hydroxide (for pH adjustment) and water for injections.

What IKERVIS looks like and contents of the pack
IKERVIS 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 2.5 mL, 4.5 mL or 7 mL of the medicine and each pack contains one bottle. Not all pack sizes may be marketed.

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