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 (see contact details below).

HPRA Pharmacovigilance
Website: www.hpra.ie

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

01/2022

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