ikervis®
1mg/mL eye drops, emulsion
(ciclosporin 1mg/1mL)

1. NAME OF THE MEDICINAL PRODUCT
IKERVIS® 1mg/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. PRODUCT DESCRIPTION
IKERVIS 1mg/ml, eye drops, emulsion is a sterile, preservative-free, positively-charged, oil in water emulsion drug product that contains the drug substance Ciclosporin at a concentration of 1mg/ml. The emulsion is milky-white in appearance.

4. CLINICAL PARTICULARS

4.1 Therapeutic indication
I. Treatment of severe keratitis in adult patients with dry eye disease, which has not improved despite treatment with tear substitutes (see section 5.1).
II. Treatment of severe vernal keratoconjunctivitis (VKC) in children and adolescents from 4 to 18 years old (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
I.Treatment of severe keratitis in dry eye disease

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 instill 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 in severe keratitis 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 adult patients with dry eye disease, which has not improved despite treatment with tear substitutes.

II. Treatment of severe vernal keratoconjunctivitis (VKC)
Children from 4 years of age through adolescence
The recommended dose is one drop of IKERVIS 4 times a day (morning, noon, afternoon and evening) to be applied to each affected eye during the VKC season. Response to Vernal Keratoconjunctivitis (VKC) treatment should be re-assessed at 4 months, where a decision can be made to continue treatment. 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 IKERVIS in children below 4 years in the treatment of severe keratoconjunctivitis.

Patients with renal or hepatic impairment
The effect of IKERVIS 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. 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 (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. 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

I. Treatment of severe keratitis in dry eye disease
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 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.

II. Treatment of severe vernal keratoconjunctivitis (VKC)

Contact lenses
Patient wearing contact lenses have not been studied. Therefore, the use of IKERVIS with contact lenses is not recommended.

Concomitant therapy
Co-administration of IKERVIS with eye drops containing corticosteroids may potentiate the effects of IKERVIS on the immune system. However, in clinical studies, 18 patients received IKERVIS (4 times daily) in co-administration of eye drops containing corticosteroids and no increase in the risk of adverse reactions related to the immune system was identified. Therefore, cautions should be exercised when corticosteroids are administered concomitantly with IKERVIS. (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 IKERVIS is used for more than 12 months.
IKERVIS 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.

III. Excipient (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

Tabulated list of adverse reactions

The following adverse reactions listed in tables 1 and 2 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).

I) Treatment of severe keratitis in dry eye disease

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.

Table 1 *Treatment of severe keratitis in dry eye disease*

MedDRA system organ class	MedDRA 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).

II) Treatment of severe vernal keratoconjunctivitis (VKC)

Summary of the safety profile

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

Table 2 *Treatment of severe VKC*

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.
	Very common	Eye pain.

Eye disorders	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.

4.9 Overdose

A topical overdose is not likely to occur after ocular administration. Systemic exposure to IKERVIS following topical ocular administration has been shown to be negligible. If overdose with IKERVIS occurs, it may be flushed from the eye(s) with water and treatment should be symptomatic and supportive.

5.0 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, 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 synthesis of pro-inflammatory cytokines such as IL-2. 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.

Clinical efficacy and safety

I) Treatment of severe keratitis in dry eye disease
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 -1.81 with IKERVIS *vs.* -1.48 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.

There is evidence from a French cohort temporary authorization for use (ATU) programme suggesting that of patients with severe keratitis previously treated with anionic and hospital-compounded ciclosporin formulations, up to 50% showed further improvements in signs and symptoms after switching to IKERVIS. This treatment benefit was also observed across all patient subpopulation in the programme, regardless of ciclosporin treatment history or underlying etiology.

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 for dry eye disease (see section 4.2 for information on paediatric use).

II) Treatment of severe vernal keratoconjunctivitis (VKC)

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 randomized to 4 drops (high dose) or 2 drops (low dose) of ciclosporin 1mg/ml eye drops emulsion and 2 drops or 4 drops of vehicle for the first 4 months (Period 1). Patients randomized to the vehicle group were switched to ciclosporin 1mg/ml eye drops emulsion (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 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.

In 166 patients with VKC 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 ciclosporin 1 mg/mL eye drops emulsion 4 times daily (n=50), 20 patients had values below the lower limit of detection (0.050 ng/mL) and 13 patients had values below the lower limit of quantification (0.100 ng/mL). Quantifiable values not exceeding 0.670 ng/mL were measured in 14 patients, values considered to be negligible. Ciclosporinemia was not measured for 3 patients. At Month 12, (n= 68 patients) values were below the lower limit of detection for 38 patients and below the lower limit of quantification in 10 patients. 12 patients had measurable values (maximum 0.291 ng/mL), all considered to be negligible values. Ciclosporinemia was not measured for 8 patients.

In the low dose group, after 4 months of ocular instillation of ciclosporin 1 mg/mL eye drops emulsion 2 times daily (n= 47 patients), 34 patients had values below the lower limit of detection (0.050 ng/mL) and 7 patients had values below the lower limit of quantification (0.100 ng/mL). Quantifiable values not exceeding 0.336 ng/mL were measured in 5 patients, values considered to be negligible. Ciclosporinemia was not measured for 1 patient. At Month 12 (n= 61 patients), values were below the lower limit of detection for 47 patients and below the lower limit of quantification in 6 patients. 5 patients had measurable values (maximum 0.300 ng/mL), all considered to be negligible values. Ciclosporinemia was not measured for 3 patients.

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.

6.0 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 store above 30°C. Protect from light. Do not freeze.
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. PRODUCT REGISTRATION HOLDER
SANTEN PHARMA MALAYSIA SDN. BHD.
Unit #23A-10, Q Sentral
No. 2A, Jalan Stesen Sentral 2, Kuala Lumpur Sentral,
50470 Kuala Lumpur, Malaysia.

8. MANUFACTURER
MANUFACTURED BY EXCELVISION
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9. DATE OF REVISION OF THE TEXT

Apr 2024