▼ This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems

# AUSTRALIAN PRODUCT INFORMATION – IKERVIS® (CICLOSPORIN) EYE DROPS, EMULSION

## 1 NAME OF THE MEDICINE

Ciclosporin

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One mL of IKERVIS® emulsion contains 1 mg (0.1%) of ciclosporin.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

## 3 PHARMACEUTICAL FORM

Eye drops, emulsion.

Milky white liquid.

## 4 CLINICAL PARTICULARS

### 4.1 THERAPEUTIC INDICATIONS

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

## 4.2 DOSE AND METHOD OF ADMINISTRATION

Treatment should be initiated by an ophthalmologist or appropriately qualified healthcare professional with expertise in the diagnosis, assessment and treatment of keratitis associated with dry eye disease (see Section 4.4 SPECIAL PRECAUTIONS AND WARNINGS FOR USE).

### Dosage

*Adults*

The recommended dose is one drop of IKERVIS® 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).

*Paediatric Patients*

IKERVIS® has not been studied in patients below 18 years of age.

*Elderly Patients*

The elderly population has been studied in clinical studies. No dosage adjustment is required.

*Renal Impairment*

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

*Hepatic Impairment*

The effect of IKERVIS has not been studied in patients with hepatic impairment. However, no special considerations are 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 in one patient 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 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

If more than one topical ophthalmic medicinal product is being used, the medicinal products must be administered at least 5 minutes apart. IKERVIS® should be administered last (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

## 4.3 CONTRAINDICATIONS

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

Ocular or peri-ocular malignancies or premalignant conditions

Active or suspected ocular or peri-ocular infection. Treatment with IKERVIS® should not be initiated or continued until all signs of infection have cleared.

## 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

A comprehensive eye examination should be performed to determine the aetiology of symptoms. Any reversible underlying conditions, not associated with dry eye disease, should be treated prior to initiating treatment with IKERVIS®.

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 IKERVIS® in the treatment of patients with glaucoma. Caution should be exercised when treating these patients concomitantly with IKERVIS®, especially with beta-blockers, which are known to decrease tear secretion.

Co-administration of IKERVIS® with eye drops containing corticosteroids may potentiate the effects of IKERVIS® on the immune system. Therefore, caution should be exercised when corticosteroids are administered concomitantly with IKERVIS® (see section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Effects on the immune system

Ophthalmic medicinal products, which affect the immune system, including ciclosporin, may affect host defences against local infections and malignancies.

## 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

## 4.6 FERTILITY, PREGNANCY AND LACTATION

**Effects on fertility**

There is no data on the effects of IKERVIS® on human fertility.

Male and female fertility were unaffected by ciclosporin in rats at oral doses up to 15 mg/kg/day (more than 2000 times higher than the maximum recommended human ophthalmic dose, based on body surface area-adjusted doses for a 50 kg subject).

## Women of childbearing potential/contraception in females

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

## Use in pregnancy - Category C

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

Ciclosporin has been shown to be embryo- and fetotoxic in rats and rabbits at doses toxic to dams (rat at 30 mg/kg per day and rabbit at 100 mg/kg per day orally). Toxicity was indicated by increased pre- and postnatal mortality and reduced fetal weight together with related skeletal retardations. In the well-tolerated dose range (rats up to 17 mg/kg per day and rabbits up to 30 mg/kg per day orally, more than 2500 times higher than the maximum recommended human ophthalmic dose, based on body surface area-adjusted doses for a 50 kg subject) ciclosporin did not demonstrate embryolethal or teratogenic effects.

In two published research studies, rabbits exposed to ciclosporin in utero (10 mg/kg/day subcutaneously, more than 3000 times higher than the maximum recommended human ophthalmic dose, based on body surface area-adjusted doses for a 50 kg subject) had reduced numbers of nephrons. These rabbits exhibited renal hypertrophy, systemic hypertension and progressive renal insufficiency when examined between 11 and 35 weeks of age in one study.

The clinical relevance of these findings to the ocular use of IKERVIS® is unknown as the systemic absorption of ciclosporin following administration of IKERVIS® was found to be either below the limit of detection or, when detected, considered to be negligible (see Section 5.2 PHARMACOKINETIC PROPERTIES).

However, IKERVIS® is not recommended during pregnancy unless the potential benefit to the mother outweighs the potential risk to the fetus.

## Use in lactation

Following oral administration, ciclosporin is excreted in breast milk. There is insufficient information on the effects of IKERVIS® on breastfed 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 breastfeeding or to discontinue/ abstain from IKERVIS® therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

## 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 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). Patients should be advised not to drive or use machines until their vision has cleared.

## 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

In five clinical studies including 532 patients who received IKERVIS® and 398 who received IKERVIS® vehicle (control), IKERVIS® was administered at least once a day in both eyes, for up to one year. The most common adverse reactions were 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.

The majority of adverse reactions reported in clinical studies with the use of IKERVIS® were ocular and mild to moderate in severity.

Tabulated list of adverse reactions

The 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).

**IKERVIS® ciclosporin 0.1% ophthalmic emulsion**

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

**IKERVIS® ciclosporin 0.1% ophthalmic emulsion**

The tabulated data on the most frequent adverse events (in particular the ocular AEs) for Ikervis compared to vehicle is presented below:

| TEAEs related to treatment: Studies N09F0502, NVG08B112, NVG06C103 and NVG10E117 | | | |
|---|---|---|---|
| Body system | Preferred Term | IKEVIS 0.1% N=532 | Vehicle N=398 |
| Eye disorders | Conjunctival hyperaemia | 9 ( 1.7) | 3 ( 0.8) |
| | Conjunctival oedema | 2 ( 0.4) | |
| | Conjunctivitis | | 2 ( 0.5) |
| | Corneal infiltrates | 1 ( 0.2) | |
| | Corneal scar | 1 ( 0.2) | |
| | Deposit eye | 1 ( 0.2) | |
| | Erythema of eyelid | 9 ( 1.7) | 5 ( 1.3) |
| | Eye discharge | 2 ( 0.4) | 2 ( 0.5) |
| | Eye irritation | 93 (17.5) | 23 ( 4.3) |
| | Eye pain | 101 (19.0) | 23 (4.3) |
| | Eye pruritus | 9 (1.7) | 3 (0.6) |
| | Eyelid oedema | 7 ( 1.3) | 2 ( 0.5) |
| | Eyelid pruritus | 1 ( 0.2) | 1 ( 0.3) |
| | Foreign body sensation in eyes | 4 (0.7) | 2 ( 0.5) |
| | Keratitis | 1 ( 0.2) | 1 ( 0.3) |
| | Lacrimal disorder | 5 ( 0.9) | 4 ( 1.0) |
| | Lacrimation increased | 26 (4.9) | 2 (0.5) |
| | Ocular discomfort | 2 ( 0.4) | 2 ( 0.4) |
| | Ocular hyperaemia | 20 (3.8) | 4 ( 1.0) |
| | Photophobia | 4 ( 0.8) | 4 ( 1.0) |
| | Vision blurred | 6 (1.1) | 4 ( 1.0) |
| | Visual acuity reduced | 5 (0.9) | 7 ( 1.8) |

| TEAEs related to treatment: Studies N09F0502, NVG08B112, NVG06C103 and NVG10E117 | | | |
|---|---|---|---|
| General disorders and administration site conditions | Instillation site reaction | 3 (0.6) | 1 (0.3) |
| Infections and infestations | Herpes zoster ophthalmic | 1 (0.2) | |
| | Keratitis bacterial | 1 (0.2) | |
| Nervous system disorders | Headache | 5 (0.9) | |

Description of selected adverse reactions

*Eye Pain*

Eye pain was 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 CONTRAINDICATIONS). Cases of infections have been reported uncommonly in association with the use of IKERVIS®.

As a precautionary measure, action should be taken to reduce systemic absorption (see section 4.2 DOSE AND METHOD OF ADMINISTRATION).

## Adverse Event Reporting

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

### 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.

For information on the management of overdose, contact the Poison Information Centre on 13 11 26 (Australia).

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 PHARMACODYNAMIC PROPERTIES

**Mechanism of action**

Ciclosporin is a calcineurin inhibitor immunosuppressant agent when administered systemically. Ciclosporin has been shown to have an anti-inflammatory effect whereby it inhibits the production and/or release of pro-inflammatory cytokines and has been shown to up-regulate the release of anti-inflammatory cytokines. In patients with dry eye disease, topical administration of ciclosporin is believed to exert an immunomodulatory effect, although its exact mechanism of action in dry eye disease is not known.

**Clinical trials**

The efficacy and safety of IKERVIS® were evaluated in two pivotal, Phase III, randomised, double-masked, vehicle-controlled clinical studies in adult dry eye disease (DED, keratoconjunctivitis sicca) patients with keratitis. Each study included assessment of both an objective sign (keratitis) and subjective symptoms of the disease as part of the primary efficacy endpoint.

**SICCANOVE Study:**

The first pivotal study, the SICCANOVE study, randomised 492 DED patients with moderate to severe keratitis (defined as a corneal fluorescein staining (CFS) score of 2 to 4 as measured on the modified Oxford scale) to receive either IKERVIS® or vehicle once-daily, at bedtime, for 6 months. The co-primary endpoints of this study were change in CFS score and change in global score of ocular discomfort unrelated to study medication instillation, both measured at Month 6. The mean improvement in CFS scores was statistically significantly greater with IKERVIS® than vehicle (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 analogue scale) showed no significant difference between IKERVIS and vehicle (-12.82 vs -11.21 respectively, p=0.808).

In patients with a baseline CFS score of 4 (n = 85) (severe disease), the percentage of co-responders with improvement in both sign and symptoms (defined as patients with at least 2 grades improvement in CFS on the modified Oxford scale and at least 30% improvement in Ocular Surface Disease Index (OSDI)) was 32.56% vs 7.14% at Month 6 for the IKERVIS® and vehicle groups respectively (p=0.003, post-hoc analysis).

**SANSIKA study:**

The second pivotal study, the SANSIKA study, randomised 246 dry eye disease patients with severe keratitis (defined as a CFS score of 4 on the modified Oxford scale) to receive one drop of IKERVIS® or vehicle once-daily, at bedtime, for 6 months. The average duration of severe DED prior to study start was 8 – 9 years. Following completion of the initial 6 Month double-masked phase of the study, patients in the vehicle group were switched to IKERVIS® for a further 6 month open label follow-up.

The primary efficacy outcome was a composite endpoint consisting of the proportion of patients achieving both a two-grade or greater improvement in keratitis (measured by CFS) and a 30% improvement in symptoms (measured by the OSDI) by Month 6. At the end of the initial 6 month treatment period, the proportion of responders in the IKERVIS® group was 28.6%, compared with 23.1% in the vehicle group. The difference was not statistically significant (p = 0.326).

A significantly greater improvement in CFS score was observed at Month 6 in the IKERVIS group compared with vehicle. The adjusted mean difference in CFS scores between the two groups was -0.35 (-1.76 vs -1.42 for the IKERVIS and vehicle groups respectively; p = 0.037). An improvement in favour of IKERVIS was also observed at Month 3 (p = 0.024).

With regard to improvement in symptoms, there was no significant difference between IKERVIS and vehicle groups at Month 6 as measured using the OSDI (-13.6 vs -14.1 respectively. The improvement from baseline to Month 6 for both groups exceeded the

minimal clinically important difference (MCID) for OSDI for severe OSDI symptoms at baseline.

The proportion of IKERVIS-treated patients with at least a 3-grade improvement in CFS score at Month 6 was 31.2%, compared with 13.2% of vehicle treated subjects (post-hoc analysis). Patients who recorded a CFS score of 1 or lower after 6 months treatment achieved almost complete or complete corneal clearing respectively.

A reduction in the ocular surface inflammation assessed with Human Leukocyte Antigen-DR (HLA-DR) expression, was observed at Month 6 in favour of IKERVIS®.

**Post-SANSIKA study**

Following 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 extension of the SANSIKA Study. In this study patients received either treatment with IKERVIS® or no treatment depending on their 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 improvement following discontinuation of treatment with IKERVIS®. Treatment was discontinued once a patient's CFS score (on the modified Oxford scale) had improved by at least 2 grades with respect to the SANSIKA study baseline score of CFS grade 4.

67 patients were enrolled (37.9% of the 177 patients who completed the SANSIKA study). 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. Recurrence of severe keratitis was observed in 35% and 48% of patients who had received IKERVIS® for 12 months or 6 months respectively in the SANSIKA study.

## 5.2 PHARMACOKINETIC PROPERTIES

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

## Absorption

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 lower limit of detection for 56 patients and below the lower 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

### Genotoxicity

Ciclosporin was not genotoxic in the Ames Test, the V79-HGPRT Test, the micronucleus test in mice and Chinese hamsters, the chromosome-aberration tests in Chinese hamster bonemarrow, the mouse dominant lethal assay, and the DNA-repair test in sperm from treated mice. An *in vitro* sister chromatid exchange (SCE) assay using human lymphocytes gave indications of a positive effect for ciclosporin at high concentrations.

### Carcinogenicity

Systemic carcinogenicity studies have been carried out in rats and mice. In a 78-week mouse study, at oral doses of 1, 4 and 16 mg/kg per day (more than 1200 times higher than the maximum recommended human ophthalmic dose, based on body surface area-adjusted doses for a 50 kg subject), a trend towards increased incidences of lymphomas at the highest dose studied was observed. In another study with ARK mice treated with higher ciclosporin doses in the diet, ciclosporin accelerated the development of lymphomas.

In a 24-month rat study, conducted with oral doses of 0.5, 2 and 8 mg/kg per day (up to at least 1200 times the maximum recommended human ophthalmic dose, based on body surface area-adjusted doses for a 50 kg subject), no significant increase in tumour incidence was reported, though the study had limited sensitivity. Ciclosporin enhanced the development of lymphomas induced in two strains of male mice by single whole body irradiation or N-methyl-n-nitrosurea.

# 6 PHARMACEUTICAL PARTICULARS

## 6.1 LIST OF EXCIPIENTS

Medium chain triglycerides

Cetalkonium chloride

Glycerol

Tyloxapol

Poloxamer

Sodium hydroxide (to adjust pH)

Water for injections

## 6.2 INCOMPATIBILITIES

Not applicable (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS)

## 6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG).
The expiry date can be found on the packaging.

## 6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C. Do not freeze. Protect from light.

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) ampoules presented in a sealed laminate aluminium pouch.

One pouch contains five single-dose ampoules. IKERVIS® is for single use in one patient only. Discard any residue after opening.

Pack sizes: 30 single-use ampoules (5 connected ampoules per pouch, 6 pouches per carton).

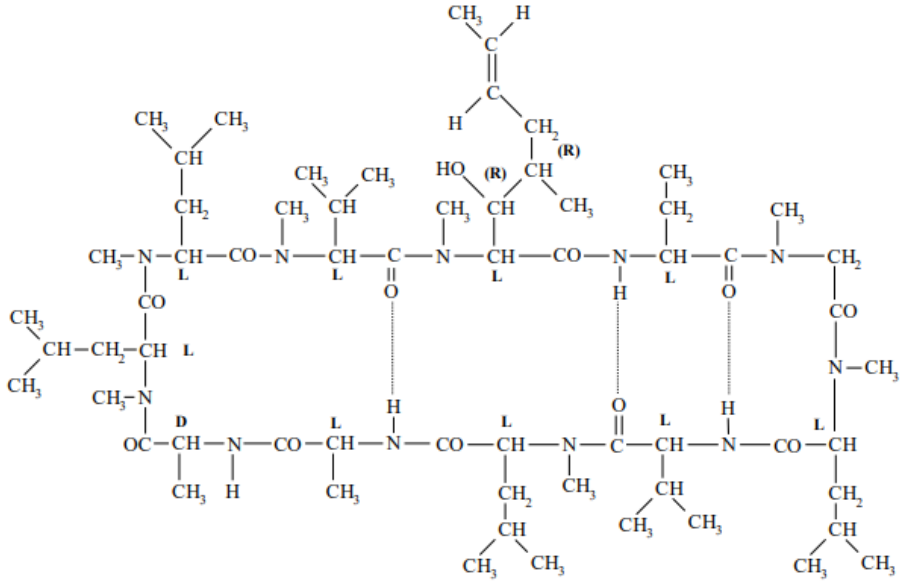
## 6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

## 6.7 PHYSICOCHEMICAL PROPERTIES

**Chemical structure**

The chemical structure of ciclosporin:



**CAS number**

59865-13-3

## 7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 (S4): Prescription Only Medicine

## 8 SPONSOR

Seqirus Pty Ltd
ABN 26 160 735 035
63 Poplar Road
Parkville, VIC 3052
Australia
Telephone: 1800 642 865
www.seqirus.com.au

## 9 DATE OF FIRST APPROVAL

15 December 2020

## 10 DATE OF REVISION

| Section changed | Summary of new information |
|---|---|
| | |
| | |
| | |

*IKERVIS is a registered trademark of Santen SAS*