# Summary of Product Characteristics

## 1 NAME OF THE VETERINARY MEDICINAL PRODUCT

Sporimune 50 mg/ml oral solution for cats and dogs

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains:
**Active substance:**

| | |
|---|---|
| Ciclosporin | 50mg |

**Excipient(s):**

| | |
|---|---|
| Ethanol, anhydrous (E-1510) | 100mg |
| all-rac-alfa-Tocopheryl acetate (E-307) | 1.00mg |

## 3 PHARMACEUTICAL FORM

Oral solution.
Colourless to yellowish oily solution

## 4 CLINICAL PARTICULARS

### 4.1 Target Species

Dog, cat.

### 4.2 Indications for use, specifying the target species

Treatment of chronic manifestations of atopic dermatitis in dogs.
Symptomatic treatment of chronic allergic dermatitis in cats.

### 4.3 Contraindications

Do not use in cases of hypersensitivity to the active substance or any of the excipients.
Do not use in dogs less than six months of age or less than 2 kg in weight.
Do not use in cases with a history of malignant disorders or progressive malignant disorders.
Do not vaccinate with a live vaccine during treatment or within a two-week interval before or after treatment. (see also sections 4.5 Special precautions for use and 4.8 Interaction with other medicinal products).
Do not use in cats infected with FeLV or FIV.

## 4.4 Special warnings for each target species

Consideration should be given to the use of other measures and/or treatments to control moderate to severe pruritus when initiating therapy with ciclosporin.

## 4.5 Special precautions for use

Special precautions for use in animals
Clinical signs of atopic dermatitis in dogs and allergic dermatitis in cats such as pruritus and skin inflammation are not specific for this disease. Therefore other causes of dermatitis such as ectoparasitic infestations, other allergies which cause dermatological signs (e.g. flea allergic dermatitis or food allergy) or bacterial and fungal infections should be evaluated and eliminated where possible. It is good practice to treat flea infestations before and during treatment of atopic and allergic dermatitis.

A complete clinical examination should be performed before treatment.
Any infections should be properly treated before initiation of treatment. Infections occurring during treatment are not necessarily a reason for drug withdrawal, unless the infection is severe.

Particular attention must be paid to vaccination. Treatment with the veterinary medicinal product may interfere with vaccination efficacy. In the case of inactivated vaccines, it is not recommended to vaccinate during treatment or within a two-week interval before or after administration of the product. For live vaccines see also section 4.3 Contraindications.

It is not recommended to use other immunosuppressive agents concomitantly.

In laboratory animals, ciclosporin is liable to affect the circulating levels of insulin and to cause an increase in glycaemia. In the presence of suggestive signs of diabetes mellitus, the effect of treatment on glycaemia must be monitored. If signs of diabetes mellitus are observed following the use of the product, e.g. polyuria or polydipsia, the dose should be tapered or discontinued and veterinary care sought. The use of ciclosporin is not recommended in diabetic animals

While ciclosporin does not induce tumours, it does inhibit T-lymphocytes and therefore treatment with ciclosporin may lead to an increased incidence of clinically apparent malignancy due to the decrease in antitumour immune response. The potentially increased risk of tumour progression must be weighed against the clinical benefit. If lymphadenopathy is observed in animals being treated with ciclosporin, further clinical investigations are recommended and treatment discontinued if necessary.
Dogs

Closely monitor creatinine levels in dogs with severe renal insufficiency.

Cats
Allergic dermatitis in cats can have various manifestations, including eosinophilic plaques, head and neck excoriation, symmetrical alopecia and/or miliary dermatitis.

The immune status of the cats to FeLV and FIV infections should be assessed before treatment.

Cats that are seronegative for *T. gondii* may be at risk of developing clinical toxoplasmosis if they become infected while under treatment. In rare cases this can be fatal. Potential exposure of seronegative cats or cats suspected to be seronegative to *Toxoplasma* should therefore be minimised (e.g. keep indoors, avoid raw meat or scavenging). Ciclosporin was shown to not increase *T. gondii* oocyte shedding in a controlled laboratory study. In cases of clinical toxoplasmosis or other serious systemic illness, stop treatment with ciclosporin and initiate appropriate therapy.

Clinical studies in cats have shown that decreased appetite and weight loss may occur during ciclosporin treatment. Monitoring of body weight is recommended. Significant reduction in body weight may result in hepatic lipidosis. If persistent, progressive weight loss occurs during treatment it is recommended to discontinue treatment until the cause has been identified.
The efficacy and safety of ciclosporin has neither been assessed in cats less than 6 months of age nor weighing less than 2.3 kg.

Special precautions to be taken by the person administering the veterinary medicinal product to animals
Accidental ingestion of this product may lead to nausea and/or vomiting. To avoid accidental ingestion, the product must be used and kept out of reach of children. Do not leave unattended filled syringe in the presence of children. Any uneaten medicated cat food must be disposed of immediately and the bowl washed thoroughly. In case of accidental ingestion, particularly by a child, seek medical advice immediately and show the package leaflet or the label to the physician.
Ciclosporin can trigger hypersensitivity (allergic) reactions. People with known hypersensitivity to ciclosporin should avoid contact with the product.
Irritation to eyes is unlikely. As precautionary measure avoid contact with eyes. In case of contact, rinse thoroughly with clean water. Wash hands and any exposed skin after use

**4.6 Adverse reactions (frequency and seriousness)**

Dogs

Gastrointestinal disturbances such as vomiting, mucoid or soft faeces and diarrhoea are observed very commonly. They are mild and transient and generally do not require the cessation of the treatment.
Other undesirable effects may be observed uncommonly: lethargy or hyperactivity, anorexia, mild to moderate gingival hyperplasia, skin lesions such as verruciform lesions or change of hair coat, red and swollen pinnae, muscle weakness or muscle cramps. These effects generally resolve spontaneously after treatment is stopped.
In very rare cases diabetes mellitus has been observed, reported mainly in West Highland White Terriers.
As for the subject of malignancy, please see sections 4.3 Contraindications and 4.5 Special precautions for use.

Cats
In 2 clinical studies with 98 cats treated with ciclosporin the following undesirable effects were observed:
Very common: gastrointestinal disturbances such as vomiting and diarrhoea. These are generally mild and transient and do not require the cessation of the treatment.
Common: lethargy, anorexia, hypersalivation, weight loss and lymphopenia. These effects generally resolve spontaneously after treatment is stopped or following a decrease in the dosing frequency.
As for the subject of malignancy, please see sections 4.3 Contraindications and 4.5 Special precautions for use.
Side effects may be severe in individual animals.

The frequency of adverse reactions is defined using the following convention:
- very common (more than 1 in 10 animals treated displaying adverse reaction(s))
- common (more than 1 but less than 10 animals in 100 animals treated)
- uncommon (more than 1 but less than 10 animals in 1,000 animals treated)
- rare (more than 1 but less than 10 animals in 10,000 animals treated)
- very rare (less than 1 animal in 10,000 animals treated, including isolated reports).

**4.7 Use during pregnancy, lactation or lay**

In laboratory animals, at doses which induce maternal toxicity (rats at 30 mg/kg bw and rabbits at 100 mg/kg bw) ciclosporin was embryo- and foetotoxic, as indicated by increased pre- and postnatal mortality and reduced foetal weight together with skeletal retardations. In the well-tolerated dose range (rats at up to 17 mg/kg bw and rabbits at up to 30 mg/kg bw) ciclosporin was without embryolethal or teratogenic effects.
The safety of the drug has neither been studied in breeding male cats or dogs nor in pregnant or lactating female cats or dogs. In the absence of such studies in the target species, it is recommended to use the drug in breeding cats or dogs only upon a positive risk/benefit assessment by the veterinarian.

Ciclosporin passes the placenta barrier and is excreted via milk. Therefore the treatment of lactating bitches or queens is not recommended.

## 4.8 Interaction with other medicinal products and other forms of interactions

Various substances are known to competitively inhibit or induce the enzymes involved in the metabolism of ciclosporin, in particular cytochrome P450 (CYP 3A 4). In certain clinically justified cases, an adjustment of the dosage of the veterinary medicinal product may be required. Ketoconazole is known to increase the blood concentration of ciclosporin in cats and dogs which is considered to be clinically relevant. During concomitant use of ketoconazole and ciclosporin the veterinarian should consider as a practical measure to double the treatment interval if the animal is on a daily treatment regime.
Macrolides such as erythromycin may increase the plasma levels of ciclosporin up to twofold.
Certain inducers of cytochrome P450, anticonvulsants and antibiotics (e.g. trimethoprim/sulfadimidine) may lower the plasma concentration of ciclosporin.
Ciclosporin is a substrate and an inhibitor of the MDR1 P-glycoprotein transporter. Therefore, the co-administration of ciclosporin with P-glycoprotein substrates such as macrocyclic lactones (e.g. ivermectin and milbemycin) could decrease the efflux of such drugs from blood-brain barrier cells, potentially resulting in signs of CNS toxicity. In clinical studies with cats treated with ciclosporin and selamectin or milbemycin, there did not appear to be an association between these drugs' concomitant use and neurotoxicity.
Ciclosporin can increase the nephrotoxicity of aminoglycoside antibiotics and trimethoprim. The concomitant use of ciclosporin is not recommended with these active ingredients.
Particular attention must be paid to vaccination (see sections 4.3 Contraindications and 4.5 Special precautions for use).
Concomitantuse of immunosuppressive agents: see section 4.5 Special precautions for use.

## 4.9 Amounts to be administered and administration route

For oral use.
Before starting treatment, an evaluation of all alternative treatment options should be made.
To ensure administration of the correct dosage bodyweight should be determined as accurately as possible.
At first use: replace the original screw cap of the bottle with the separately delivered screw cap. Fill the correct dosing syringe by pulling the plunger until it reaches the graduation corresponding to the correct body weight of the animal. After administration of the veterinary medicinal product close bottle tightly with cap, wash the measuring syringe with water and let it dry.

Dosage and method of administration

Dogs

The mean recommended dose of ciclosporin is 5 mg per kg body weight (0.25 ml oral solution per 2.5 kg bodyweight). The veterinary medicinal product should be given at least 2 hours before or after feeding.

The product should be administered directly into the dog's mouth on the back of the tongue using the graduated dosing syringe supplied (1 ml oral solution contains 50 mg ciclosporin) and delivering the entire dose.

Cats

The recommended dose of ciclosporin is 7 mg/kg body weight (0.14 ml of oral solution per kg) and should initially be administered daily. The frequency of administration should subsequently be reduced depending on the response. The veterinary medicinal product can be given either mixed with food or directly into the mouth. If given with food, the solution should be mixed with half the normal amount of food consumed using the graduated dosing syringe supplied. (1 ml oral solution contains 50 mg ciclosporin), preferably after a sufficient period of fasting to ensure complete consumption by the cat. When the medicated feed is fully consumed the rest of the food may be given.

Should the cat not accept the product mixed with food, it should be given by inserting the syringe directly into the cat's mouth and delivering the entire dose. If the cat only partially eats the product mixed with food, administration of the product directly into the mouth using the graduated dosing syringe must only be continued the next day.

Duration and frequency of administration

The product will initially be given daily until a satisfactory clinical improvement is seen (assessed by intensity of pruritus and lesion severity - excoriations, miliary dermatitis, eosinophilic plaques and/or self-induced alopecia). This will generally be the case within 4-8 weeks. If no response is obtained within the first 8 weeks, the treatment should be stopped.

Once the clinical signs of atopic/allergic dermatitis are satisfactorily controlled, the preparation can then be given every other day as a maintenance dose. The veterinarian should perform a clinical assessment at regular intervals and adjust the frequency of administration to the clinical response obtained.

In some cases where the clinical signs are controlled with every-other-day dosing, the veterinarian can decide to give the veterinary medicinal product every 3 to 4 days. The lowest effective frequency of dosing should be used to maintain the remission of clinical signs.

Adjunct treatment (e.g. medicated shampoos, fatty acids) may be considered before reducing the dosing interval. Patients should be regularly re-evaluated and alternative treatment options reviewed.

Treatment may be stopped when the clinical signs are controlled. Upon recurrence of clinical signs, treatment should be resumed at daily dosing, and in certain cases repeated treatment courses may be required.

### 4.10 Overdose (symptoms, emergency procedures, antidotes), if necessary

There is no specific antidote and in case of signs of overdose the animal should be treated symptomatically.
Dogs:
No undesirable effects beyond those that were seen under recommended treatment have been observed in the dog with a single oral dose of up to 5 times of what is recommended.
In addition to what was seen under recommended dosage, the following adverse reactions were seen in case of overdose for 3 months or more at 4 times the mean recommended dosage: hyperkeratotic areas especially on the pinnae, callous-like lesions of the foot pads, weight loss or reduced weight gain, hypertrichosis, increased erythrocyte sedimentation rate, decreased eosinophil values. Frequency and severity of these signs are dose dependent.
The signs are reversible within 2 months following cessation of treatment.
Cats:
The following adverse events were seen in the case of repeated administration of the active substance for 56 days at 24 mg/kg (more than 3x the recommended dose) or for 6 months at up to 40 mg/kg (more than 5x the recommended dose): loose/soft faeces, vomiting, mild to moderate increases in absolute lymphocyte counts, fibrinogen, activated partial thromboplastin time (APTT), slight increases in blood glucose and reversible gingival hypertrophy. The frequency and severity of these signs were generally dose and time dependent. At 3x the recommended dose administered daily for nearly 6 months, changes in ECG (conduction disturbances) may occur in very rare cases. They are transient and not associated with clinical signs. Anorexia, recumbency, loss of skin elasticity, few or absent faeces, thin and closed eye lids may be observed in sporadic cases at 5x the recommended dose.

### 4.11 Withdrawal period(s)

Not applicable.

## 5 PHARMACOLOGICAL or IMMUNOLOGICAL PROPERTIES

Pharmacotherapeutic group: Immunosuppressants; Calcineurin inhibitors; Ciclosporin.
ATCvet code: QL04AD01.

## 5.1 Pharmacodynamic properties

Ciclosporin (also known as ciclosporin, ciclosporin, ciclosporin A, CsA) is a selective immunosuppressor. It is a cyclic polypeptide consisting of 11 amino acids, has a molecular weight of 1203 daltons and acts specifically and reversibly on T lymphocytes.
Ciclosporin exerts anti-inflammatory and antipruritic effects in the treatment of allergic or atopic dermatitis. Ciclosporin has been shown to preferentially inhibit the activation of T-lymphocytes on antigenic stimulation by impairing the production of IL-2 and other T-cell derived cytokines. Ciclosporin also has the capacity to inhibit the antigen-presenting function on the skin immune system. It likewise blocks the recruitment and activation of eosinophils, the production of cytokines by keratinocytes, the functions of Langerhans cells, the degranulation of mast cells and therefore the release of histamine and pro-inflammatory cytokines.
Ciclosporin does not depress haematopoiesis and has no effect on the function of phagocytic cells.

## 5.2 Pharmacokinetic particulars

Absorption
*Dogs*
The bioavailability of ciclosporin is about 35% in dogs. The peak plasma concentration is reached within 1hour. The bioavailability is better and less subject to individual variations if ciclosporin is administered to fasted animals rather than at mealtimes.

*Cats*
The bioavailability of ciclosporin administered to cats fasted for 24 hours (mixed with a small amount of food) or just after feeding was 29% and 23% respectively. The peak plasma concentration is generally reached within 1 to 2 hours when given to fasted cats. After oral administration of ciclosporin via the food to fasted cats, peak plasma concentrations were reached within 1.5 to 5 hours. The absorption can be delayed by several hours when given after feeding. In spite of differences in the pharmacokinetics of the drug given mixed with food or directly into the mouth of fed cats, it has been shown that the same clinical response is obtained.

Distribution
*Dogs*
In dogs, the volume of distribution is about 7.8 l/kg. Ciclosporin is widely distributed to all tissues. Following repeated daily administration to dogs, ciclosporin concentration in the skin is several times higher than in blood.

*Cats*

In cats, the volume of distribution at steady state is about 3.3 l/kg. Ciclosporin is widely distributed to all tissues, including the skin.

Metabolism
Ciclosporin is metabolised mainly in the liver by cytochrome P450 (CYP 3A 4), but also in the intestine. Metabolism takes place essentially in the form of hydroxylation and demethylation, leading to metabolites with little or no activity.
Unchanged ciclosporin represents about 25% of circulating blood concentrations in the course of the first 24 hours in dogs.

Elimination
Elimination is mainly via the faeces. A small portion of the administered dose is excreted in the urine as inactive metabolites. In dogs, elimination half-life ranges from about 10-20 hours. No significant accumulation was observed in blood of dogs treated for one year. In cats, a slight bioaccumulation related to the long half-life of the drug (approximately 24h) is observed with repeated dosing. The steady state in cats is reached within 7 days, with a bioaccumulation factor in the range of 1.0 to 1.72 (typically 1-2).
In cats, there are large inter-individual variations in plasma concentrations. At the recommended dosage, ciclosporin plasma concentrations are not predictive of the clinical response, therefore monitoring of blood levels is not recommended.

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Ethanol, anhydrous (E-1510)
all-rac-alfa-Tocopheryl acetate (E-307)
Diethylene glycol monoethyl ether
Oleoyl macrogolglycerides
Macrogolglycerol hydroxystearate

### 6.2 Major incompatibilities

In the absence of compatibility studies, this veterinary medicinal product must not be mixed with other veterinary medicinal products.

### 6.3 Shelf-life

Shelf-life of the veterinary medicinal product as packaged for sale: 2 years
Shelf-life after first opening the immediate packaging: 6 months

### 6.4 Special precautions for storage

Do not refrigerate.
Store in the original container in order to protect from light.
The product contains fat components from natural origin which can become solid at lower temperatures. A turbidity or jelly-like formation may occur below 15°C which is however reversible at temperatures up to 25°C. However, this does not affect either the dosing or the efficacy and safety of the product.

### 6.5 Nature and composition of immediate packaging

Brown glass bottles (type III) of 25, 50 or 100 ml, closed with a child resistant closure (PP screw cap with a Teflon inlay).
One bottle and a dispenser set (consisting of a child resistant HDPE screw cap and a 1 ml PP dosing syringe for cats and a 5 ml PP dosing syringe for dogs) packed in a cardboard box.
Not all pack sizes may be marketed.

### 6.6 Special precautions for the disposal of unused veterinary medicinal products or waste materials derived from the use of such products

Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal products should be disposed of in accordance with local requirements.

## 7 MARKETING AUTHORISATION HOLDER

Le Vet Beheer B.V.
Wilgenweg 7
3421 TV Oudewater
Netherlands

## 8 MARKETING AUTHORISATION NUMBER(S)

VPA10475/004/001

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19 July 2013
Date of last renewal: 20 July 2018

## 10 DATE OF REVISION OF THE TEXT

October 2018