1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Modulis 100 mg/mL oral solution for dogs

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains:
Active substance:
Ciclosporin ..... 100 mg
Excipients:

Qualitative composition of excipients and other constituents	**Quantitative composition if that information is essential for proper administration of the veterinary medicinal product**
all-rac-α-tocopherol (E-307)	1 mg
Ethanol, anhydrous (E-1510)	
Propylene glycol (E-1520)	
Macrogolglycerol hydroxystearate	
Glycerol monolinoleate	

Clear to slightly yellow opalescent solution. A veil, minor flakes or slight sediment may be observed.

3. CLINICAL INFORMATION

3.1 Target species

Dogs

3.2 Indications for use for each target species

Treatment of chronic manifestations of atopic dermatitis in dogs.

3.3 Contraindications

Do not use in cases of hypersensitivity to ciclosporin or to 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 3.5 “Special precautions for use” and 3.8 “Interaction with other medicinal products”).

3.4 Special warnings

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

3.5 Special precautions for use

Special precautions for safe use in the target species:
Clinical signs of atopic dermatitis such as pruritus and skin inflammation are not specific for this disease and 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 ruled out before treatment is started. It is good practice to treat flea infestations before and during treatment of atopic dermatitis.
It is recommended to clear bacterial and fungal infections before administering the veterinary medicinal product. However, infections occurring during treatment are not necessarily a reason for drug withdrawal, unless the infection is severe.
A complete clinical examination should be performed before treatment. As ciclosporin inhibits Tlymphocytes and though it does not induce tumors, it may lead to increased incidences of clinically apparent malignancy due to the decrease in antitumor immune response. Lymphadenopathy observed on treatment with ciclosporin should be regularly monitored.
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 veterinary medicinal 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 dogs.
Closely monitor creatinine levels in dogs with severe renal insufficiency.
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 veterinary medicinal product. For live vaccines see also section 3.3 'Contraindications'. It is not recommended to use other immunosuppressive agents concomitantly.

Special precautions to be taken by the person administering the veterinary medicinal product to animals:
Accidental ingestion of this veterinary medicinal product may lead to nausea and/or vomiting. To avoid accidental ingestion, the veterinary medicinal product must be used and kept out of reach of children. Do not leave unattended filled syringe in the presence of children. 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 veterinary medicinal 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.

Special precautions for the protection of the environment: Not applicable.

3.6 Adverse events

Dogs:

Common (1 to 10 animals / 100 animals treated):	Mucous stool[1], soft stool[1]
Uncommon (1 to 10 animals / 1,000 animals treated):	Hyperactivity[1] Skin lesion[1] e.g. verruciform lesion, hair change, Muscle weakness[1], musculoskeletal cramp[1]

[1] These effects generally resolve spontaneously after treatment is stopped.

Rare (1 to 10 animals / 10,000 animals treated):	Vomiting[2]
Very rare (<1 animal / 10,000 animals treated, including isolated reports):	Diarrhoea[2], gingival hyperlasia[2] Lethargy[2], anorexia[2] Pinnal irritation[2] Diabetes mellitus[3]

[2]These signs are mild and transient and generally do not require the cessation of the treatment. [3]Mainly in West Highland White terriers

Reporting adverse events is important. It allows continuous safety monitoring of a veterinary medicinal product. Reports should be sent, preferably via a veterinarian, to either the marketing authorisation holder or its local representative or the national competent authority via the national reporting system. See the package leaflet for respective contact details.

3.7 Use during pregnancy, lactation or lay

Pregnancy and lactation:
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 fetotoxic, 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 dogs nor in pregnant or lactating female dogs. In the absence of such studies in the dog, it is recommended to use the drug in breeding 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 is not recommended.

3.8 Interaction with other medicinal products and other forms of interaction

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 at 5-10 mg/kg is known to increase the blood concentration of ciclosporin in dogs up to five-fold, 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 dog is on a daily treatment regime.
Macrolides 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 coadministration 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 Central nervous system toxicity.
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 3.3 “Contraindications” and 3.5 “Special precautions for use”). Concomitant use of immunosuppressive agents: see section 35 “Special precautions for use”.

3.9 Administration routes and dosage

Oral use.
Before starting treatment, an evaluation of all alternative treatment options should be made.
The mean recommended dose of ciclosporin is 5 mg/kg body weight corresponding to 0.5 ml of solution for 10 kg of body weight.

The veterinary medicinal product will initially be given daily until a satisfactory clinical improvement is seen. This will generally be the case within 4 weeks. If no response is obtained within the first 8 weeks, the treatment should be stopped.
Once the clinical signs of atopic 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, essential 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.
The veterinary medicinal product should be given at least 2 hours before or after feeding.

The veterinary medicinal product is administered directly into the mouth.

Instructions for use:
Push down and unscrew bottle top.
Insert the dosing syringe into the plastic adapter.



Turn the bottle/syringe upside down and slowly pull the plunger down until the white line on the plunger corresponds to the dose prescribed by your veterinarian. The syringe is graduated in kg and ml.

By pushing the plunger in, empty the contents of the syringe directly into the mouth. Introduce the syringe either to the side of the mouth or over the tongue.

If necessary, wipe the outside of the syringe with a dry tissue and dispose of used tissue immediately. Close the bottle.

For the 5 and 15 ml vials
Volume to be administered using 1 ml syringe: 0.05 ml/kg, i.e. 1 graduation/kg.

For the 30 and 50 ml vials
Volume to be administered using 2 ml syringe: 0.1 ml/2 kg, i.e. 1 graduation/2 kg

To ensure a correct dosage, body weight should be determined as accurately as possible.

3.10 Symptoms of overdose (and where applicable, emergency procedures, and antidotes)

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 6 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.
There is no specific antidote and in case of signs of overdose the dog should be treated symptomatically.
The signs are reversible within 2 months following cessation of treatment.

3.11. Special restrictions for use and special conditions for use, including restrictions on the use of antimicrobial and antiparasitic veterinary medicinal products in order to limit the risk of development of resistance

Not applicable.

3.12 Withdrawal periods

Not applicable.

4. PHARMACOLOGICAL INFORMATION

4.1 ATCvet code: QL04AD01.

4.2 Pharmacodynamics

Ciclosporin (also known as cyclosporin, cyclosporine, cyclosporine 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 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 proinflammatory cytokines.
Ciclosporin does not depress haematopoiesis and has no effect on the function of phagocytic cells.

4.3 Pharmacokinetics

Absorption
The bioavailability of ciclosporin is about 35%. The peak plasma concentration is reached within 1 to 2 hours. The bioavailability is better and less subject to individual variations if ciclosporin is administered to fasted animals rather than at mealtimes.
Distribution

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. 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.
Excretion
Excretion is mainly via the faeces. Only 10% is excreted in the urine, mostly in the form of metabolites. No significant accumulation was observed in blood of dogs treated for one year.

5. PHARMACEUTICAL PARTICULARS

5.1 Major incompatibilities

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

5.2 Shelf life

Shelf life of the veterinary medicinal product as packaged for sale:
Vial of 5 ml : 18 months
Vials of 15 ml, 30 ml, 50 ml : 30 months
Shelf life after first opening the immediate packaging: 3 months

5.3 Special precautions for storage

Keep the bottle in the outer carton.
Storage in the refrigerator should be avoided.
The veterinary medicinal product contains fat components from natural origin which can become solid at lower temperatures. A jelly-like formation may occur below 20°C which is however reversible at temperatures up to 30°C. Minor flakes or a slight sediment may still be observed. However, this does neither affect the dosing nor the efficacy and safety of the product.

5.4 Nature and composition of immediate packaging

An amber Type III glass bottle, closed with a child resistant tamper-evident HDPE screw cap, fitted with a transparent LDPE insert, plus a syringe for oral use (transparent natural polypropylene barrel and white HDPE plunger).

5 ml bottle with 1 ml oral syringe in a cardboard box
15 ml bottle with 1 ml oral syringe in a cardboard box
30 ml bottle with 2 ml oral syringe in a cardboard box
50 ml bottle with 2 ml oral syringe in a cardboard box

Not all pack sizes may be marketed.

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

Medicines should not be disposed of via wastewater or household waste.

Use take-back schemes for the disposal of any unused veterinary medicinal product or waste materials derived thereof in accordance with local requirements and with any national collection systems applicable to the veterinary medicinal product concerned.

6. NAME OF THE MARKETING AUTHORISATION HOLDER

Ceva Santé Animale

7. MARKETING AUTHORISATION NUMBER(S)

VPA10815/043/001

8. DATE OF FIRST AUTHORISATION

22/04/2016

9. DATE OF THE LAST REVISION OF THE SUMMARY OF THE PRODUCT CHARACTERISTICS

20/03/2026

10. CLASSIFICATION OF VETERINARY MEDICINAL PRODUCTS

Veterinary medicinal product subject to prescription.
Detailed information on this veterinary medicinal product is available in the Union Product Database (https://medicines.health.europa.eu/veterinary).