NEW

Modulis® for Dogs

(cyclosporine oral solution) USP MODIFIED

100 mg/mL

15mL 30mL 50mL

Modulis® for Cats

(cyclosporine oral solution) USP MODIFIED

100 mg/mL

4.7mL 15mL

Modulis® is the *only* brand with liquid cyclosporine solution for both dogs and cats.

- Easy to administer
- Precise oral dosing
  1mL and 3mL dosing syringes*

ORAL SOLUTION

*Use only with syringes provided with product.

Why choose Modulis® for Dogs

(cyclosporine oral solution) USP MODIFIED

and/or

Modulis® for Cats

(cyclosporine oral solution) USP MODIFIED

- Allows precise dosing by pet's weight, to help avoid under-dosing or over-dosing
- Oral solution easy to administer
- Cost effective treatment

NEW Modulis® (cyclosporine oral solution) USP Modified				
Dog body weight	**Dosage***	**Form**	**Precise dosing by weight**	**Small volume to administer**
20 lb	0.45 mL	LIQUID	YES	YES
65 lb	1.48 mL	LIQUID	YES	YES
Cat body weight	**Dosage***			
10 lb	0.32 mL	LIQUID	YES	YES

*Based on initial dosing. Please read product inserts for complete dosing and administration.

Modulis® for Dogs and Modulis® for Cats is a systemic immunosuppressant that may increase the susceptibility to infection and the development of neoplasia.

MODULIS® for Dogs

PRODUCT INDICATION: MODULIS® for Dogs is indicated for the control of atopic dermatitis in dogs weighing at least 4 lbs. (1.8 kg) body weight.

IMPORTANT SAFETY INFORMATION: For oral use in dogs only. Do not use in dogs with a history of neoplasia, hypersensitivity to cyclosporine, or in reproducing dogs. MODULIS® for Dogs is a systemic immunosuppressant and may increase susceptibility to infection and the development of neoplasia. Killed vaccines are recommended. Use with caution in dogs with diabetes mellitus or renal insufficiency, and with drugs that affect the dog's metabolism. Gastrointestinal problems and gingival hyperplasia may occur at the initial recommended dose. The most common adverse reactions are vomiting and diarrhea. Safety and effectiveness have not been established in dogs less than 6 months of age or less than 4 lbs. body weight. Wear gloves during administration and wash hands after administration. For full prescribing information, see package insert or visit modulis.cevaconnect.com.

MODULIS® for Cats

PRODUCT INDICATION: MODULIS® for Cats is indicated for the control of feline allergic dermatitis as manifested by excoriations (including facial and neck), miliary dermatitis, eosinophilic plaques, and self-induced alopecia in cats at least 6 months of age and at least 3 lbs (1.4 kg) in body weight.

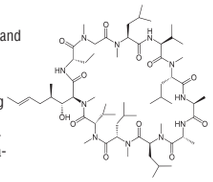
IMPORTANT SAFETY INFORMATION: For oral use in cats only. Do not use in cats with a history or suspicion of malignant disorders, feline leukemia virus (FeLV) or feline immunodeficiency virus (FIV) infection, or hypersensitivity to cyclosporine. Do not use in breeding cats, pregnant or lactating queens. Do not use with other immunosuppressive agents. MODULIS® for Cats is a systemic immunosuppressant and may increase susceptibility to infection, development of neoplasia, and decrease response to vaccination. Persistent, progressive weight loss may result in hepatic lipidosis; monitoring of body weight is recommended. Potential exposure of seronegative cats to T. gondii should be avoided. Use with caution in cats with diabetes mellitus or renal insufficiency, and with drugs that affect the cat's metabolism. The most common adverse reactions were vomiting, weight loss, diarrhea, and loss of appetite. Wash hands after administration. For full prescribing information, see package insert or visit modulis.cevaconnect.com.

MOD-100-24v1

Modulis® for Dogs

(cyclosporine oral solution) USP MODIFIED

100 mg/mL



Caution: Federal law restricts this drug to use by or on the order of a licensed veterinarian. Keep this and all drugs out of the reach of children.

Description: MODULIS® for Dogs (cyclosporine oral solution) USP MODIFIED is an oral form of cyclosporine that immediately forms a microemulsion in an aqueous environment. Cyclosporine, the active ingredient in MODULIS® for Dogs, is a cyclic polypeptide, immune modulating agent consisting of 11 amino acids. It is produced as a metabolite by the fungal species *Beauveria nivea*.

Chemically, cyclosporine A is designated Cyclo[[(E)-(2S, 3R, 4R)-3-hydroxy- 4-methyl-2-(methylamino)-6-octenoyl]-L-2-aminobutryl -N-methylglycyl- N -methyl-L-leucyl-L-valyl-N-methyl-L-leucyl-L-alanyl-D-ananyl-N-methyl -L- leucyl- N-methyl-L-leucyl-N-methyl-L-valyl].

The structural formula is:

Indication: MODULIS® for Dogs is indicated for the control of atopic dermatitis in dogs weighing at least 4 lbs. (1.8 kg) body weight.

Dosage and Administration: Always provide the Instructions for Assembling the Dispensing System and Preparing a Dose of MODULIS® for Dogs and the Information for Dog Owners with prescription.

The initial dose of MODULIS® for Dogs is 5 mg/kg/day as a single daily dose for 30 days. Following this initial daily treatment period, the dose of MODULIS® for Dogs may be tapered by decreasing the frequency of dosing to every other day or twice weekly, until a minimum frequency is reached which will maintain the desired therapeutic effect. MODULIS® for Dogs should be given at least one hour before or two hours after a meal. If a dose is missed, the next dose should be administered (without doubling) as soon as possible, but dosing should be no more frequent than once daily. The dispensing system includes oral dosing syringes to accompany MODULIS® for Dogs:

- For dogs 4 lbs to 40 lbs, use the 1 mL syringe: The 1 mL syringe is graduated in 1 pound (lb) increments. To dose the dog, the syringe should be filled to the nearest 1 lb graduation corresponding to the dog's body weight in lbs (round down to the nearest whole lb if 0.1 to 0.4 lb, or round up to the nearest whole lb if 0.5 to 0.9 lb). Each 1-lb graduation on the 1 mL syringe delivers a volume of 0.023 mL, providing 2.3 mg/lb (5 mg/kg) dose.
- For dogs 41 lbs to 125 lbs, use the 3 mL syringe: The 3 mL syringe is graduated in 5 pound (lb) increments. To dose the dog, the syringe should be filled to the nearest 5 lb graduation corresponding to the dog's body weight in lbs (round down to the nearest whole lb if 0.1 to 0.4 lb, or round up to the nearest whole lb if 0.5 to 0.9 lb). Each 5-lb graduation on the 3 mL syringe delivers a volume of 0.115 mL, providing 2.3 mg/lb (5 mg/kg) dose.

Do not rinse or clean the oral dosing syringe between uses.

Note: Always close the bottle with the child-resistant screw cap after each use.

The 1 mL syringe is graduated in 1 lb increments corresponding to 0.023 mL/lb. This syringe is for dosing dogs 4 to 40 lb. The 1 mL syringe will be included with the 4.7, 15, and 30 mL bottles.

The 3 mL syringe is graduated in 5 lb increments corresponding to 0.115 mL/5 lb. This syringe is for dosing dogs 41 to 125 lb. The 3 mL syringe will be included with the 30 and 50 mL bottles.

(See **Instructions for Assembling the Dispensing System and Preparing a Dose of MODULIS® for Dogs**)

Contraindications: MODULIS® for Dogs is contraindicated for use in dogs with a history of neoplasia. Do not use in dogs with a hypersensitivity to cyclosporine.

Warnings: MODULIS® for Dogs (cyclosporine oral solution) is a systemic immunosuppressant that may increase the susceptibility to infection and the development of neoplasia.

Human Warnings: Not for human use. Keep this and all drugs out of reach of children.

For use only in dogs. Wear gloves during administration.

Special precautions to be taken when administering MODULIS® for Dogs:

Do not eat, drink, smoke, or use smokeless tobacco while handling MODULIS® for Dogs.

Wash hands after administration.

In case of accidental ingestion, seek medical advice immediately and provide the package insert or the label to the physician.

People with known hypersensitivity to cyclosporine should avoid contact with MODULIS® for Dogs.

Precautions: The safety and effectiveness of cyclosporine has not been established in dogs less than 6 months of age or less than 4 lbs body weight. MODULIS® for Dogs is not for use in breeding dogs, pregnant or lactating bitches.

As with any immunomodulation regimen, exacerbation of sub-clinical neoplastic and infectious conditions may occur.

Gastrointestinal problems and gingival hyperplasia may occur at the initial recommended dose. (See **Animal Safety**).

MODULIS® for Dogs may cause elevated levels of serum glucose and should be used with caution in cases with diabetes mellitus. If signs of diabetes mellitus develop following the use of MODULIS® for Dogs, consideration should be given to tapering or discontinuing the dose.

MODULIS® for Dogs should be used with caution with drugs that affect the P-450 enzyme system. Simultaneous administration of MODULIS® for Dogs with drugs that suppress the P-450 enzyme system, such as azoles (e.g. ketoconazole), may lead to increased plasma levels of cyclosporine.

Since the effect of cyclosporine use on dogs with compromised renal function has not been studied, MODULIS® for Dogs should be used with caution in dogs with renal insufficiency.

There have been reports of convulsions in human adult and pediatric patients receiving cyclosporine, particularly in combination with high dose methylprednisolone. (See Animal Safety).

Killed vaccines are recommended for dogs receiving MODULIS® for Dogs because the impact of cyclosporine on the immune response to modified live vaccines is unknown. (See Animal Safety).

Adverse Reactions: A total of 265 dogs were included in the field study safety analysis. One hundred and eleven (111) dogs were treated with placebo for the first 30 days. For the remainder of the study, all dogs received cyclosporine capsules.

Fourteen dogs withdrew from the study due to adverse reactions. Four dogs withdrew from the study after vomiting. One dog each withdrew from the study after diarrhea; vomiting, diarrhea and pruritus; vomiting, depression and lethargy; lethargy, anorexia and hepatitis; gingival hyperplasia, lethargy, polyuria/polydipsia and soft stool; seizure; sebaceous cyst; pruritus; erythema; or otitis externa.

Vomiting and diarrhea were the most common adverse reactions occurring during the study. In most cases, signs spontaneously resolved with continued dosing. In other cases, temporary dose modifications (brief interruption in dosing, divided dosing, or administration with a small amount of food) were employed to resolve signs.

Persistent otitis externa, urinary tract infections, anorexia, gingival hyperplasia, lymphadenopathy and lethargy were the next most frequent adverse events observed. Gingival hyperplasia regressed with dose tapering. Owners of four dogs reported seizures while dogs were receiving cyclosporine. In one dog, seizures were the result of a brain tumor diagnosed one month into the study. Another dog experienced seizures before and after the study.

Otitis externa, allergic otitis, or pinna erythema, with or without exudates, commonly accompanies atopy. Many dogs entered the study with otitis externa, which did not resolve without otic treatment. New cases of otitis externa, allergic otitis, or pinna erythema developed while dogs were receiving cyclosporine. However, the incidence rate was lower with cyclosporine compared to placebo. A change in the dose frequency was not necessary when new cases occurred.

Number of Dogs Displaying Each Clinical Observation in the Field Study

Clinical Sign	% out of 265)	Clinical Sign	% out of 265)
Vomiting	30.9%	Anorexia	3.0%
Diarrhea	20.0%	Lethargy	2.3%
Persistent Otitis Externa	6.8%	Gingival Hyperplasia	2.3%
Urinary Tract Infection	3.8%	Lymphadenopathy	2.3%

The following clinical signs were reported in less than 2% of dogs treated with cyclosporine in the field study: constipation, flatulence, Clostridial organisms in the feces, nausea, regurgitation, polyuria/polydipsia, strong urine odor, proteinuria, pruritus, erythema/flushed appearance, pyoderma, sebaceous adenitis, crusty dermatitis, excessive shedding, coarse coat, alopecia, papillomas, histiocytoma, granulomatous mass or lesion, cutaneous cyst, epulis, benign epithelial tumor, multiple hemangioma, raised nodule on pinna, seizure, shaking/trembling, hind limb twitch, panting, depression, irritability, hyperactivity, quieter, increased light sensitivity, reluctance to go outside, weight loss, hepatitis.

The following clinical signs were observed in 1.5-4.5% of dogs while receiving the placebo: vomiting, diarrhea and urinary tract infection. The following clinical signs were observed in less than 1% of dogs receiving the placebo: anorexia, otitis externa, cutaneous cysts, corneal opacity, lymphadenopathy, erythema/flushed appearance.

Clinical Pathology Changes: During the study, some dogs experienced changes in clinical chemistry parameters while receiving cyclosporine, as described in the following table:

Clinical Chemistry	% Affected (out of 265)	Clinical Chemistry	% Affected (out of 265)
Elevated Creatinine	7.8%	Hypercholesterolemia	2.6%
Hyperglobulinemia	6.4%	Hypoalbuminemia	2.3%
Hyperphosphatemia	5.3%	Hypocalcemia	2.3%
Hyperproteinemia	3.4%	Elevated BUN	2.3%

In addition, the following changes in clinical chemistry parameters were noted in less than 2% of dogs: hypernatremia; hyperkalemia, elevated ALT, elevated ALP, hypercalcemia and hyperchloremia. These clinical pathology changes were generally not associated with clinical signs.

Post-approval Experience: (Rev 2014)

The following adverse events are based on post-approval adverse drug experience reporting. Not all adverse reactions are reported to FDA CVM. It is not always possible to reliably estimate the adverse event frequency or establish a causal relationship to product exposure using this data. The following adverse events are grouped by body system and are presented in decreasing order of reporting frequency.

Gastrointestinal: Emesis, diarrhea, gingival hyperplasia, hemorrhagic diarrhea, abdominal pain, hematemesis, digestive tract hemorrhage, hypersalivation, retching, flatulence, tenesmus, intestinal stasis, digestive tract hypermotility, melena, pancreatitis, involuntary defecation

General: Lethargy, anorexia, weight loss, polydipsia, hyperthermia, pale mucous membrane, general pain, collapse, dehydration, edema

Dermatologic: Pruritus, dermatitis and eczema, alopecia, erythema, papilloma, bacterial skin infection, skin lesion, skin and/or appendage neoplasm, pigmentation disorder, hair change, hyperkeratosis, histiocytoma, fungal skin infection, dermal cyst(s), desquamation

Behavioral: Hyperactivity, behavioral changes, anxiety, vocalization, aggression, inappropriate urination, disorientation

Neurologic: Muscle tremor, convulsion, ataxia, paresis

Respiratory: Tachypnea, dyspnea, cough

Urologic: Polyuria, urine abnormalities (hematuria, urinary tract infection, proteinuria, glucosuria, decreased urine concentration) urinary incontinence, cystitis, renal failure, renal insufficiency

Immune: Urticaria, anaphylaxis, allergic edema

Blood and lymphatic: Lymphadenopathy, anemia, hypoalbuminemia, leukopenia

Hepatic: Elevated Liver Enzymes, hepatopathy, hepatomegaly, hepatitis

Musculoskeletal: Lameness, limb weakness, myositis

Ear and labyrinth: Otitis externa

Cardio-vascular: Tachycardia

Endocrine: Diabetes mellitus, hyperglycemia

In some cases, death/euthanasia has been reported as an outcome of the adverse events listed above.

Neoplasms have been reported in dogs taking cyclosporine, including reports of lymphoma/lymphosarcoma and mast cell tumor. It is unknown if these were preexisting or developed *de novo* while on cyclosporine.

Diabetes mellitus has been reported; West Highland White Terriers are the most frequently reported breed.

To report suspected adverse drug events, for technical assistance or to obtain a copy of the Safety Data sheet, contact Ceva Animal Health, LLC at 1-800-999-0297 or ceva.com.

For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or http://www.fda.gov/reportanimalae.

Clinical Pharmacology: Cyclosporine is an immunosuppressive agent that has been shown to work via suppression of T-helper and T-suppressor cells and inhibition of interleukin-2.

It does not depress hematopoiesis or the function of phagocytic cells.

A decrease in CD4 and CD8 cells was not seen in dogs receiving 20 mg/kg/day of cyclosporine for 56 days. MODULIS® for Dogs is not a corticosteroid or an antihistamine.

Metabolism: Cyclosporine is extensively metabolized by the cytochrome P-450 enzyme system in the liver, and to a lesser degree in the gastrointestinal tract and the kidney.

The metabolism of cyclosporine can be altered by the co-administration of a variety of agents (See *Precautions*).

Effectiveness Field Study: A multisite, placebo controlled, double masked, field study was conducted in the United States and Canada using 16 investigators. Two hundred sixty five (265) dogs aged 1-10 years, weighing 4-121 lbs received either cyclosporine capsules at 5 mg/kg/day or placebo capsules. After 30 days, placebo dogs were switched to cyclosporine capsules.

Dogs were treated with cyclosporine capsules for a total of 4 months. No additional therapy with antihistamines, corticosteroids or medicated shampoos was permitted.

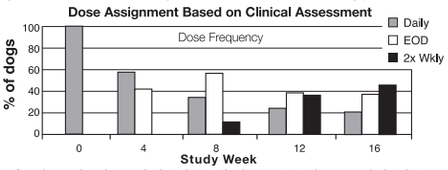
Evaluations for pruritus and for skin lesions to derive a Canine Atopic Dermatitis Extent and Severity Index (CADESI) score occurred at enrollment and at monthly intervals.

One hundred ninety-two (192) dogs were included in the statistical analysis of effectiveness.

At the end of the 30 day placebo controlled period, CADESI scores of dogs treated with cyclosporine capsules improved by 45% from enrollment, while CADESI scores of dogs treated with placebo worsened by 9%. Seventy-four percent (74%) of cyclosporine capsule treated dogs showed improvement in their pruritus scores over the first 30 day period, while only 24% of the placebo treated dogs showed an improvement. Owner and Veterinary Global Assessment in response to treatment also demonstrated statistically significant ($p<0.0001$) improvement. After 4 weeks of therapy, Owner and Veterinary Global Assessments showed approximately twice as much improvement in the cyclosporine capsule treated dogs as compared to placebo treated dogs.

Improvements in pruritus accompanied by 50% or 75% improvements in CADESI scores resulted in dose reductions to every other day or twice weekly respectively. Not all dogs were able to decrease to twice weekly dosing. Some animals required upward or downward dosage adjustments during the study. Such adjustments should be expected during therapy of this disease. Dogs unable to decrease from once daily dosing after 60 days were considered dose reduction failures for the purposes of the study.

The results of dose assignments, based on the study criteria, for each 4-week dosing period, are shown in the graph.



Analysis of blood levels of cyclosporine drawn during the study demonstrated no correlation between blood cyclosporine levels and CADESI scores or pruritus; therefore monitoring blood cyclosporine levels is not an appropriate predictor of effectiveness.

Animal Safety: In a 52-week oral study with dose levels of 0, 1, 3, and 9 times the target initial daily dose, emesis, diarrhea and weight loss were seen in all cyclosporine treated groups with increasing frequency as the dose increased.

Multilocular papilloma-like lesions of the skin were observed in 5 out of 8 high dose animals between weeks 20 and 40. These changes regressed spontaneously after drug was withdrawn.

Other findings in the mid and high dose animals included swollen gums due to chronic gingivitis and periodontitis, lower serum albumin and higher cholesterol, triglyceride, IgA and IgG. Hematological findings consisted of anemia and decreased leukocyte counts in a few high dose animals. Erythrocyte sedimentation rates were increased at all dose levels in a dose dependent fashion. Notable histopathological findings were limited to lymphoid atrophy, hypertrophic gums (from gingivitis) and slight regenerative changes of the renal tubular epithelium in high dose animals. The findings were shown to be reversible during a 12-week recovery phase of the study.

In a 90-day study with cyclosporine, dogs were dosed in one of two patterns: either 1, 3, or 5X the maximum recommended target initial daily dose for 90 days, or 1, 3, or 5X the maximum recommended target initial daily dose for 30 days followed by tapering to mimic the recommended clinical dosing pattern. The maximum recommended dose, when administered for 90 days causes callus-like lesions on the footpads, red/swollen pinnae, mild to moderate gingival proliferation, hyperkeratotic areas on the integument, hair loss, salivation, vomiting, and diarrhea/abnormal stools. These clinical signs lessened in severity or resolved as the drug was tapered to a lower dose. Increased erythrocyte sedimentation rate, hyperproteinemia, hyperglobulinemia, hypoalbuminemia, hypocalcemia, hypophosphatemia, and hypomagnesemia were observed at three and five times the maximum recommended dose. These resolved as the dose was tapered. When administered at higher than the maximum recommended dose, raised skin lesions, papilloma-like areas on the integument, popliteal lymph node enlargement, and weight loss were also seen. There were no cyclosporine related changes in urinalysis, ECG, blood pressure, or ophthalmologic exams.

Gross necropsy revealed epithelial changes consistent with those seen on physical examination. Proliferation of gingiva and toe pad epithelium was seen in all cyclosporine dosed groups, and was seen in a dose dependent fashion. The degree of the proliferation was greater in dogs in the non-tapered groups as compared to the tapered groups.

Similar changes were noted on histopathologic examination of the cutaneous changes seen on physical examination. These lesions were characterized by epidermal hyperplasia, chronic dermatitis and hyperkeratosis.

Methylprednisolone combination: Twenty-four dogs were administered 1 mg/kg/day methylprednisolone alone for 14 days followed by 20 mg/kg/day cyclosporine either alone or in combination with methylprednisolone, or placebo for 14 days. There was no evidence of seizures/convulsions or neurological signs.

Vaccination effect: The effect of cyclosporine administration on the immunological response to vaccination was evaluated in a study in which 16 dogs were dosed with either cyclosporine at 20 mg/kg/day (4X the initial daily dose) or placebo for 56 days. All dogs were vaccinated on Day 27 with a killed commercial rabies virus and a multivalent vaccine (DHLPP) which included a modified live virus. Antibody titers for rabies, canine distemper, canine adenovirus type 2, parainfluenza, parvovirus, *Leptospira canicola,* and *Leptospira icterohaemmorrhagiae* were examined on Days 0, 27 (prior to vaccination), 42 and 56. Quantification of CD4, CD8, and CD3 T-lymphocytes was analyzed.

Clinical changes included soft stool and dermatologic changes consistent with those seen in previous studies. Antibody titers did not rise in dogs treated with cyclosporine or the placebo for any component of the multivalent vaccine which included a modified live virus while all animals demonstrated a significant increase in antibody rabies titer by Day 42 or 15 days post-revaccination. No effect was seen on T-lymphocytes.

Storage Conditions: MODULIS® for Dogs should only be dispensed in the original container and stored at controlled room temperature between 59 and 77°F (15-25°C). Modulis® for Dogs does not require refrigeration. Once opened, use contents within 9 weeks for the 4.7 mL container and 16 weeks for the 15, 30, and 50 mL containers.

How Supplied: MODULIS® for Dogs is supplied in glass amber bottles of 4.7, 15, 30, and 50 mL at 100 mg/mL.

A dispensing system is included **(**See **Instructions for Assembling the Dispensing System and Preparing a Dose of MODULIS® for Dogs)**.

Manufactured for: Ceva Animal Health, LLC. Lenexa, KS 66215.

Approved by FDA under ANADA # 200-743

Instructions for Assembling the Dispensing System and Preparing a Dose of MODULIS® for Dogs (cyclosporine oral solution) USP MODIFIED

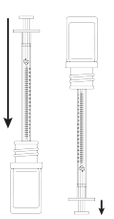
Assembling the Dispensing System

The dispensing system consists of 2 parts:

1. A bottle containing the medicine, fitted with a pre-inserted plastic adapter and a screw cap to close the bottle after use. Do not remove the adapter from the neck of the bottle. It must remain in place for the duration of use.
2. An oral dosing syringe that fits into the top of the plastic adapter to withdraw the prescribed dose of the medicine from the bottle. The oral dosing syringe comes with a plastic cap. Save the plastic cap to protect the oral dosing syringe during storage between each use.

Note: To prepare a dose, carefully follow the instructions for **Preparing a Dose of Medicine.**

Preparing a Dose of Medicine.



3. Insert syringe 4. Pull plunger down

1. Push and turn the child-resistant screw cap to open the bottle. **Note:** Always close the bottle with the child-resistant screw cap after use.
2. Remove the plastic cap and check that the plunger of the oral dosing syringe is pushed all the way down.
3. Keep the bottle upright and insert the oral dosing syringe firmly into the plastic adapter.
4. Invert the bottle/syringe, and slowly pull the plunger down so that the oral dosing syringe fills with the medicine.
5. **Expel any large bubbles by pushing and pulling the plunger a few times. The presence of a few tiny bubbles is not important for dose accuracy.**
6. Withdraw the dose of medicine prescribed by your veterinarian. The scale on the oral dosing syringe corresponds to the dog's body weight.

Note: If the prescribed dose is more than the maximum volume marked on the oral dosing syringe, you will need to reload the syringe to withdraw the full dose.

7. Return the bottle/syringe to the upright position, and gently remove the oral dosing syringe from the plastic adapter.

You can now place the oral dosing syringe over a small amount of food or introduce the syringe in the mouth of your cat and push the medicine out of the syringe.

See Information for Dog Owners for complete administration instructions.

Do not rinse or clean the oral dosing syringe between uses. Replace the plastic cap to store the oral dosing syringe between each use.

MODULIS® for Dogs should only be dispensed in the original container and stored between 59 and 77°F (15 - 25°C). MODULIS® for Dogs does not require refrigeration. Once opened, use contents within 9 weeks for the 4.7 mL container and 16 weeks for the 15, and 30 mL containers.

Keep out of reach of children!

Always close the bottle with the child-resistant screw cap after use. To provide a child-resistant closure, push down on the child-resistant screw cap as you turn it.

MOD-101-24v1
Made in Germany

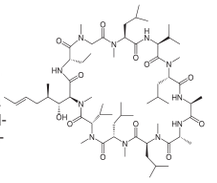
Modulis® for Cats

(cyclosporine oral solution) USP MODIFIED

100 mg/mL

Caution:
Federal law restricts this drug to use by or on the order of a licensed veterinarian.

Description:
MODULIS® for Cats (cyclosporine oral solution) USP MODIFIED is an oral formulation of cyclosporine that immediately forms a microemulsion in an aqueous environment. Cyclosporine, the active ingredient in MODULIS® for Cats, is a cyclic polypeptide, immune modulating agent consisting of 11 amino acids. It is produced as a metabolite by the fungal species *Beauveria nivea*.



Chemically, cyclosporine A is designated Cyclo[[(E)-(2S, 3R, 4R)-3-hydroxy- 4-methyl-2-(methylamino)-6-octenoyl]-L-2-aminobutryl -N-methylglycyl- N -methyl-L-leucyl-L-valyl-N-methyl-L-leucyl-L-alanyl-D-ananyl-N-methyl -L- leucyl- N-methyl-L-leucyl-N-methyl-L-valyl].
The structural formula is:

Indication:
MODULIS® for Cats is indicated for the control of feline allergic dermatitis as manifested by excoriations (including facial and neck), miliary dermatitis, eosinophilic plaques, and self-induced alopecia in cats at least 6 months of age and at least 3 lbs (1.4 kg) in body weight.

Dosage and Administration:
Always provide the Instructions for Assembling the Dispensing System and Preparing a Dose of MODULIS® for Cats and the Information for Cat Owners with prescription.
The initial dose of MODULIS® for Cats is 3.2 mg/lb/day (7 mg/kg/day) as a single daily dose for a minimum of 4 to 6 weeks or until resolution of clinical signs. Following this initial daily treatment period, the dose of MODULIS® for Cats may be tapered by decreasing the frequency of dosing to every other day or twice weekly to maintain the desired therapeutic effect. MODULIS® for Cats should be administered directly on a small amount of food or orally just after feeding. Whenever possible, MODULIS® for Cats should be administered on a consistent schedule with regard to meals and time of day. If a dose is missed, the next dose should be administered (without doubling) as soon as possible, but dosing should be no more frequent than once daily.
The dispensing system includes an oral dosing syringe graduated in 1 lb increments. To dose the cat, the syringe should be filled to the nearest 1 lb corresponding to the cat's body weight (round down if 0.1 to 0.4 lb, round up if 0.5 to 0.9 lb). Each pound graduation on the syringe delivers a volume of 0.032 mL providing 3.2 mg/lb. **Do not rinse or clean the oral dosing syringe between uses.**
(See **Instructions for Assembling the Dispensing System and Preparing a Dose of MODULIS® for Cats**)

Contraindications:
Do not use in cats with a history of malignant disorders or suspected malignancy. Do not use in cats infected with feline leukemia virus (FeLV) or feline immunodeficiency virus (FIV).
Do not use in cats with a hypersensitivity to cyclosporine.

Warnings:
MODULIS® for Cats is a systemic immunosuppressant that may increase the susceptibility to infection and the development of neoplasia. One of 205 field study cats died of the effusive form of feline infectious peritonitis. (See **Adverse Reactions**)
Persistent, progressive weight loss that resulted in hepatic lipidosis occurred in 2 of 205 cats on treatment with cyclosporine in field studies. Monitoring of body weight is recommended. (See **Adverse Reactions**)

Human Warnings:
Not for human use. Keep this and all drugs out of reach of children. **For use only in cats.**

Special precautions to be taken when administering MODULIS® for Cats:
Do not eat, drink, smoke, or use smokeless tobacco while handling MODULIS® for Cats.
Wash hands after administration.
In case of accidental ingestion, seek medical advice immediately and provide the package insert or the label to the physician.
People with known hypersensitivity to cyclosporine should avoid contact with MODULIS® for Cats.

Precautions:
The safety and effectiveness of MODULIS® for Cats has not been established in cats less than 6 months of age or less than 3 lbs (1.4 kg) body weight.
MODULIS® for Cats is not for use in breeding cats, pregnant or lactating queens.
Cats should be tested and found to be negative for FeLV and FIV infections before treatment.
As with any immunosuppressive regimen, exacerbation of sub-clinical neoplastic and infectious conditions may occur. MODULIS® for Cats is not for use with other immunosuppressive agents.
Cats that are seronegative for *Toxoplasma gondii* may be at risk of developing clinical toxoplasmosis if they become infected while under treatment, which can be fatal. In a controlled laboratory study, cats seronegative for *T. gondii* were administered cyclosporine and subsequently infected with *T. gondii*, resulting in increased susceptibility to infection and subsequent expression of toxoplasmosis. Cyclosporine did not increase *T. gondii* oocyst shedding (see **Animal Safety**). Potential exposure of seronegative cats to *T. gondii* should be avoided (e.g. keep indoors, avoid raw meat or scavenging).
In cases of clinical toxoplasmosis or other serious systemic illness, stop treatment with cyclosporine and initiate appropriate therapy.
MODULIS® for Cats may cause elevated levels of serum glucose, creatinine, and urea nitrogen. MODULIS® for Cats should be used with caution in cases with diabetes mellitus or renal insufficiency.
MODULIS® for Cats should be used with caution with drugs that affect the P-450 enzyme system. Simultaneous administration of MODULIS® for Cats with drugs that suppress the P-450 enzyme system, such as azoles (e.g. ketoconazole), may lead to increased plasma levels of cyclosporine.
Treatment with MODULIS® for Cats may result in decreased immune response to vaccination. Naïve cats may not develop protective titers during treatment (see **Animal Safety**).

Adverse Reactions:
The clinical safety of cyclosporine was assessed in a masked, controlled 6-week field study followed by a 12-week open-labeled dose-tapering field study. In these two field studies, 205 cats received treatment with cyclosporine for up to 126 days.
Two cats died or were euthanized within two weeks following study exit. One cat was diagnosed with the effusive form of feline infectious peritonitis and died following normal study exit, and one cat with pre-existing anemia that worsened during the study was diagnosed with aplastic anemia and euthanized because of a poor prognosis for recovery.
Fourteen of the 205 cats (6.8%) were withdrawn from the studies due to the occurrence of an adverse reaction. Adverse reactions in these 14 cats included weight loss, anorexia, vomiting, diarrhea, hypersalivation, lethargy, hepatic lipidosis and jaundice, upper respiratory signs, ocular discharge, cough, toxoplasmosis, lymphopenia, anemia, bacterial dermatitis, seizure, ataxia, and small cell gastrointestinal lymphoma.
The most commonly reported adverse reaction was vomiting. In most cases, vomiting spontaneously resolved with continued dosing. Adverse reactions occurred most often with daily dosing compared to other dosing regimes.
Adverse reactions reported with greater than 2% frequency in the two field studies.

Adverse Reaction*	Number (Percent) of Cases n= 205	Adverse Reaction*	Number (Percent) of Cases n= 205
Vomiting/Retching/Regurgitation	72 (35.1%)	Behavioral Disorder (hiding, hyperactivity, aggression)	18 (8.8%)
Weight Loss	42 (20.5%)	Ocular Discharge/Epiphora/Conjunctivitis	14 (6.8%)
Diarrhea	31 (15.1%)	Sneezing/Rhinitis	11 (5.4%)
Anorexia/Decreased Appetite	29 (14.1%)	Gingivitis/Gingival Hyperplasia	9 (4.4%)
Lethargy/Malaise	28 (13.6%)	Polydipsia	6 (2.9%)
Hypersalivation	23 (11.2%)		

*Cats may have experienced more than one type or occurrence of a reaction during the studies.

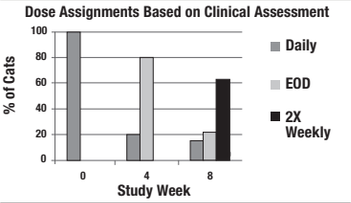
The following adverse reactions were reported in less than or equal to 2% of cats treated with cyclosporine in the two field studies: bacterial dermatitis, hepatic lipidosis and jaundice, gastrointestinal small cell lymphoma, constipation, cough, toxoplasmosis, muscle wasting, muscle tremors, ataxia, convulsion, polyuria, urinary tract infection, inappropriate urination or defection, seborrhea, worsening otitis externa, papilloma, leukotrichia (whitening of hair) and excessive hair growth, anemia, lymphopenia, worsening monocytosis, worsening neutrophilia, hyperglobulinemia, increased serum creatinine and urea nitrogen, and increased alanine aminotransferase.

Contact Information:
To report suspected adverse events, for technical assistance or to obtain a copy of the safety data sheet (SDS), contact Ceva Animal Health at 1-800-999-0297 or www.ceva.us. For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS, or www.fda.gov/reportanimalae.

Information for Cat Owners:
Owners should be advised to discontinue MODULIS® for Cats and contact their veterinarian in case of signs of serious illness and/or persistent, progressive weight loss. Owners should be informed of the risks of increased susceptibility to infection and the development of neoplasia, and they should be provided advice on how to avoid exposure of their cat to *Toxoplasma gondii* infection.

Clinical Pharmacology:
Cyclosporine is an immunosuppressive agent that has been shown to work via suppression of T-helper and T-suppressor cells and inhibition of interleukin-2. It does not depress hematopoiesis or the function of phagocytic cells. Cyclosporine is not a corticosteroid or antihistamine.
Following an intravenous dose of 2 mg/kg in a 24-hour fasted state, clearance of cyclosporine A in cats was 0.199 L/kg x h and half life was ~24 hours. After oral administration, the terminal elimination half life has been estimated to be as short as 6.8 to longer than 40 hours in some normal healthy cats.
The bioavailability of cyclosporine is highly variable both within and between cats. A pharmacokinetic study showed no consistent difference in the mean extent of drug absorption when administered orally to fed or fasted cats or mixed in with food.
Blood levels of cyclosporine in field studies were highly variable, even among cats with similar clinical response, suggesting no generalizable correlations can be made between cats with regard to blood cyclosporine levels and clinical response (effectiveness and safety). Nevertheless, individual differences in the relationship between drug exposure and clinical response may exist. Therefore, to minimize individual fluctuations in drug absorption, MODULIS® for Cats should be administered on a consistent schedule with regard to meals and time of day.

Effectiveness:
A masked, controlled field study was conducted at 24 sites from various geographic locations in the United States and Canada. In this study, 217 client-owned cats with clinical signs consistent with allergic dermatitis (miliary dermatitis, excoriations including facial or neck, self-induced alopecia and eosinophilic plaques) along with non-seasonal localized or generalized pruritus, were randomly assigned in a 2:1 ratio and received either cyclosporine or a control solution (the excipients of Cyclosporine Oral Solution, USP without the cyclosporine). Owners administered treatment in a small amount of food or directly in the cat's mouth just after feeding once daily for up to 6 weeks. No additional therapy with antihistamines, corticosteroids or medicated shampoos was permitted.
Effectiveness was evaluated in 181 cats. Cats in the cyclosporine treatment group had a 65.1% reduction in mean total lesion score, compared to cats in the control treatment group, which had a 9.2% reduction in mean total lesion score. The percent of cats identified as treatment success by the Owner was 78.6% in the cyclosporine group compared to 26.2% in the control group. Compared to the control group, the cyclosporine group had improved mean ratings for Investigator assessment of overall improvement, Owner and Investigator assessment of pruritus, and number of body regions with lesions.
After drop-out from or completion of the masked 6-week field study, 191 cats were enrolled in a 12-week open-labeled field study to evaluate dose tapering of cyclosporine. The graph below shows the dose assignments for each 4-week dosing period. At study entry, all cats were assigned daily doses. At Week 4, cats were assigned daily or every other day (EOD) dosing, based on clinical improvement. At Week 8, cats were assigned daily, EOD, or twice weekly (2X Weekly) dosing for the final month of the study. Cats with poor responses exited the study at Weeks 4 and 8. At study exit at Week 12, 62.9%, 21.6%, and 15.5% of the remaining 97 evaluable cats were on twice weekly, EOD, and daily dosage regimens, respectively.



Cyclosporine was used in conjunction with various medications including a macrocyclic lactone and other antiparasitic agents, systemic antimicrobials, and topical skin and otic cleansers and antimicrobials.

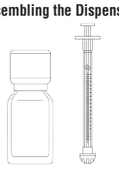
Animal Safety:
In a 6-month safety study, forty (20 male and 20 female) 6-month old cats were randomized into 5 treatment groups and administered 0, 8, 16, 24 or 40 mg/kg/day cyclosporine (0, 1, 2, 3 or 5X the maximum therapeutic dose). An intermittent interventricular conduction disturbance was noted on electrocardiogram in one 3X and one 5X treatment group cat following 6 months of dosing. A 5X cat was euthanized after two weeks of treatment following a rapidly-declining clinical condition including recumbency, inappetance, dehydration, and decreased body weight. A post-mortem examination showed a healing rib fracture and bone marrow hypocellularity characterized by a moderate reduction in the number of bone marrow cells from multiple lineages. Hematology parameters drawn prior to euthanasia for this cat did not reveal abnormalities indicative of bone marrow hypocellularity. A 5X female cat presented with abdominal fibroadenomatous nodules during the study. Lymphoma of the kidneys and a mesenteric lymph node were present on necropsy in one 5X male, which is likely related to the immunosuppressive effects of cyclosporine treatment. Activated partial thromboplastin time (APTT) was prolonged in treated cats when compared to control cats.
A safety study was conducted to evaluate the effect of cyclosporine on the development of vaccine titers following vaccination in cats. Thirty-two cats (16 males and 16 females) were randomized into two treatment groups. Group 1 cats served as the control group and were sham dosed. Group 2 cats were administered cyclosporine at a dose of 24 mg/kg (3X the maximum therapeutic dose) orally once daily for 56 days. All cats were approximately 7 months of age at the start of the study and previously vaccinated against feline calici virus (FCV), feline panleukopenia virus (FPV), feline leukemia virus (FeLV), feline herpes virus-1 (FHV-1) and rabies with the final pre-treatment vaccines administered 16 weeks prior to treatment with cyclosporine. Cats were naïve to the feline immunodeficiency virus (FIV) vaccine, which was administered after 28 days on cyclosporine. After booster vaccinations on Day 28, titers for FCV, FPV, FeLV, FHV-1 and rabies were decreased in cyclosporine treated cats compared to control cats, but these titers remained adequate in both treatment groups. In contrast, cats on high-dose cyclosporine failed to develop titers to the novel vaccine (FIV). An increase in incidence and frequency of diarrhea, vomiting, and salivation were noted in Group 2 cats. One female cat treated with cyclosporine was observed to be in estrus during the study compared to 5 of the female control cats. One cat treated with cyclosporine was noted as having a slow or absent startle reflex, displayed ataxia, had small lymph nodes, thin body condition, and gas and fluid filled loops of intestine. Lymphocyte counts were lower in treated cats when compared to control. APTT was prolonged in treated cats when compared to control cats. Cholesterol, glucose, total protein, blood urea nitrogen, and creatinine values were elevated in cyclosporine treated cats with values just above the normal reference range. Glucosuria was noted in three treated animals that also had hyperglycemia.
A safety study was conducted to evaluate the effects of cyclosporine on the clinical course of *Toxoplasma gondii*. Thirty domestic short-haired cats (15 males and 15 females) ranging in age from 1-2 years were randomized into three treatment groups. Group 1 cats served as the control group and were administered placebo. Group 2 cats were administered placebo for 84 days followed by treatment with cyclosporine for 42 days. Group 3 cats were treated with cyclosporine for 126 days. Cyclosporine was administered at a target dose of 7.5 mg/kg orally once daily. All cats were infected with *T. gondii* cysts on Study Day 42.
One cat was found dead and another was euthanized (both in Group 3) within six weeks following infection due to complications related to toxoplasmosis. Clinical signs typical of *T. gondii* infection, including bloody feces, lethargy, and vomiting/regurgitation, were also seen in most of the remaining cats, but resolved within six weeks following infection. Decreases in body weight and food consumption were seen in some cats from each group, but these changes were reversible as the animals recovered from clinical toxoplasmosis.
APTT was prolonged in Group 2 and 3 cats receiving cyclosporine when compared to Group 1 cats. Cholesterol, glucose and total protein/globulin values were elevated in cyclosporine treated cats. Ocular changes consistent with toxoplasmosis were seen in one to two cats in each group. The oocyst shedding period and number of oocysts shed were increased in Group 1 and 2 cats compared to Group 3 cats. All inoculated cats developed *T. gondii* IgG antibodies; IgM titers were detected in only 3 cats.
Post-mortem examinations revealed mild to moderate inflammation in the central nervous system and pulmonary tissues, with the highest incidence and severity generally following this trend: Group 3 > Group 2 > Group 1. Lesions were consistent with *T. gondii* infection and were more prevalent in males than females. *T. gondii* organisms were only detected histopathologically in the tissues of the two Group 3 cats that died of toxoplasmosis.

Storage Information:
MODULIS® for Cats should only be dispensed in the original container and stored at controlled room temperature between 59 and 77°F (15-25°C). Modulis® for Cats does not require refrigeration. Once opened, use contents within 9 weeks for the 4.7 mL container and 16 weeks for the 15 and 30 mL containers.

How Supplied:
MODULIS® for Cats (cyclosporine oral solution) USP MODIFIED is supplied in glass amber bottles of 4.7, 15, and 30 mL at 100 mg/mL. A dispensing system is included (See **Instructions for Assembling the Dispensing System and Preparing a Dose of MODULIS® for Cats**).
Manufactured for: Ceva Animal Health, LLC. Lenexa, KS 66215.
Approved by FDA under ANADA # 200-744

Instructions for Assembling the Dispensing System and Preparing a Dose of MODULIS® for Cats (cyclosporine oral solution) USP MODIFIED

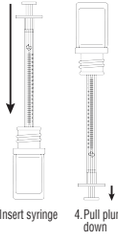
Assembling the Dispensing System



The dispensing system consists of 2 parts:
1. A bottle containing the medicine, fitted with a pre-inserted plastic adapter and a screw cap to close the bottle after use. Do not remove the adapter from the neck of the bottle. It must remain in place for the duration of use.
2. An oral dosing syringe that fits into the top of the plastic adapter to withdraw the prescribed dose of the medicine from the bottle. The oral dosing syringe comes with a plastic cap. Save the plastic cap to protect the oral dosing syringe during storage between each use.

Note: To prepare a dose, carefully follow the instructions for **Preparing a Dose of Medicine.**

Preparing a Dose of Medicine.



3. Insert syringe 4. Pull plunger down

1. Push and turn the child-resistant screw cap to open the bottle. **Note:** Always close the bottle with the child-resistant screw cap after use.
2. Remove the plastic cap and check that the plunger of the oral dosing syringe is pushed all the way down.
3. Keep the bottle upright and insert the oral dosing syringe firmly into the plastic adapter.
4. Invert the bottle/syringe, and slowly pull the plunger down so that the oral dosing syringe fills with the medicine.
5. **Expel any large bubbles by pushing and pulling the plunger a few times. The presence of a few tiny bubbles is not important for dose accuracy.**
6. Withdraw the dose of medicine prescribed by your veterinarian. The scale on the oral dosing syringe corresponds to the cat's body weight.

Note: If the prescribed dose is more than the maximum volume marked on the oral dosing syringe, you will need to reload the syringe to withdraw the full dose.
7. Return the bottle/syringe to the upright position, and gently remove the oral dosing syringe from the plastic adapter.

You can now place the oral dosing syringe over a small amount of food or introduce the syringe in the mouth of your cat and push the medicine out of the syringe.
See Information for Cat Owners for complete administration instructions.
Do not rinse or clean the oral dosing syringe between uses. Replace the plastic cap to store the oral dosing syringe between each use.

MODULIS® for Cats should only be dispensed in the original container and stored between 59 and 77°F (15 - 25°C). MODULIS® for Cats does not require refrigeration. Once opened, use contents within 9 weeks for the 4.7 mL container and 16 weeks for the 15, and 30 mL containers.
Close the bottle with the child-resistant screw cap after use.

Keep out of reach of children!

Always close the bottle with the child-resistant screw cap after use. To provide a child-resistant closure, push down on the child-resistant screw cap as you turn it.

MOD-102-24v1
Made in Germany