Veterinary Medicinal Product

MODULIS 100 MG/ML ORAL SOLUTION FOR DOGS

PART I B

Pharmaceutical Form

Oral solution

Veterinary Medicinal Product

MODULIS 100 MG/ML ORAL SOLUTION FOR DOGS

PART I B

SUMMARY OF THE PRODUCT CHARACTERISTICS

Pharmaceutical Form

Oral solution

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Modulis 100 mg/ml oral solution for dogs
Modulis 100 mg/ml (FR)
Modulis vet 100 mg/ml oral solution for dogs (DK, SE, FI, NO)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipient(s):
all-rac-α-tocopherol (E-307) .....1 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

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

4. CLINICAL PARTICULARS

4.1 Target species

Dogs

4.2 Indications for use, specifying the target species

Treatment of chronic manifestations of atopic dermatitis in dogs.

4.3 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 4.5 “Special precautions for use” and 4.8 “Interaction with other medicinal products”).

4.4 Special warnings for each target species

Consideration should be given to the use of other measures and/or treatment 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 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 T-lymphocytes 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 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 product. For live vaccines see also section 4.3 “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 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. 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)

Gastrointestinal disturbances such as vomiting were reported rarely in spontaneous reports. Diarrhoea, lethargy, anorexia, gingival disorder and pinnal irritation were reported very rarely in spontaneous reports.
These signs are mild and transient and generally do not require the cessation of the treatment. Diabetes mellitus has been reported very rarely in spontaneous reports, mainly in West highland white terriers.
Mucoid or soft faeces were observed commonly during the development studies and not in the spontaneous pharmacovigilance reports. Hyperactivity, skin lesions such as verruciform lesions or change of hair coat, muscle weakness or muscle cramps were observed uncommonly during the development studies and not in the spontaneous pharmacovigilance reports.These effects generally resolve spontaneously after treatment is stopped.

As for the subject of malignancy, please see sections 4.3 “contraindications” and 4.5 “special precautions for use”.

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 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.

4.8 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 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 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 4.3 “Contraindications” and 4.5 “Special precautions for use”). Concomitant use 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.
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.

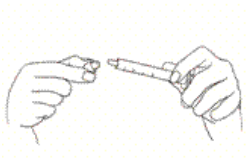
The product is administered directly into the mouth.

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 and insert the syringe into the specific cap to protect from any contamination and to avoid any spillage of remaining product.



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

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

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.

4.11 Withdrawal period(s)

Not applicable.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Antineoplastic and immunomodulating agents, immunosuppressants, calcineurin inhibitors, ciclosporin.

ATCvet code: QL04AD01.

5.1 Pharmacodynamic properties

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 pro-inflammatory cytokines.
Ciclosporin does not depress haematopoiesis and has no effect on the function of phagocytic cells.

5.2 Pharmacokinetic particulars

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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

all-rac-α-tocopherol (E-307)
Ethanol, anhydrous (E-1510)
Propylene glycol (E-1520)
Macrogolglycerol hydroxystearate
Glycerol monolinoleate

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:
5 ML bottle : 18 months

15ml, 30 ml and 50 ml bottles : 30 months
Shelf life after first opening the immediate packaging: 3 months

6.4. Special precautions for storage

Keep the bottle in the outer carton.
Storage in the refrigerator should be avoided.
The 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.

6.5 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) with a white polypropylene cap.

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.

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

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

7. MARKETING AUTHORISATION HOLDER

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10 DATE OF REVISION OF THE TEXT

PROHIBITION OF SALE, SUPPLY AND/OR USE

To be completed in accordance with national requirements.

A. LABELLING

BOX

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Modulis 100 mg/ml oral solution for dogs
Modulis 100 mg/ml (FR)
Modulis vet 100 mg/ml oral solution for dogs (DK, SE, FI, NO)
Ciclosporin

2. STATEMENT OF ACTIVE SUBSTANCES

Ciclosporin ..... 100 mg/ml

3. PHARMACEUTICAL FORM

Oral solution

4. PACKAGE SIZE

5 ml
15 ml
30 ml
50 ml

5. TARGET SPECIES

Dogs

6. INDICATION(S)

7. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

8. WITHDRAWAL PERIOD

9. SPECIAL WARNING(S), IF NECESSARY

Read the package leaflet before use.

10. EXPIRY DATE

EXP {month/year}
Once opened, use by …
Shelf-life after first opening the immediate packaging: 3 months

11. SPECIAL STORAGE CONDITIONS

Storage in the refrigerator should be avoided.
Keep the bottle in the outer carton.

12. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCTS OR WASTE MATERIALS, IF ANY

Disposal: read package leaflet

13. THE WORDS "FOR ANIMAL TREATMENT ONLY" AND CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE, IF APPLICABLE

For animal treatment only. To be supplied only on veterinary prescription.

14. THE WORDS "KEEP OUT OF THE SIGHT AND REACH OF CHILDREN"

Keep out of the sight and reach of children.

15. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

16. MARKETING AUTHORISATION NUMBER(S)

17. MANUFACTURER'S BATCH NUMBER

Batch:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Modulis 100 mg/ml oral solution for dogs
Modulis 100 mg/ml (FR)
Modulis vet 100 mg/ml oral solution for dogs (DK, SE, FI, NO)
Ciclosporin

2. QUANTITY OF THE ACTIVE SUBSTANCE(S)

Ciclosporin ..... 100 mg/ml

3. CONTENTS BY WEIGHT, BY VOLUME OR BY NUMBER OF DOSES

5 ml
15 ml
30 ml
50 ml

4. ROUTE(S) OF ADMINISTRATION

Oral route

5. WITHDRAWAL PERIOD

6. BATCH NUMBER

Batch number

7. EXPIRY DATE

EXP {month/year}
Once opened, use by …
Once opened use the product within 3 months.

8. THE WORDS "FOR ANIMAL TREATMENT ONLY"

For animal treatment only.

B. PACKAGE LEAFLET

PACKAGE LEAFLET:

Modulis 100 mg/ml oral solution for dogs

1. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER AND OF THE MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE, IF DIFFERENT

Marketing authorisation holder

Manufacturer responsible for batch release:

Ceva Santé Animale Boulevard de la Communication Zone Autoroutière 53950 Louverné France	Laboratoires Biové 3 rue de Lorraine 62510 Arques France	Ceva Santé Animale ZI Très-Le-Bois 22 600 Loudeac France

a mis en forme : Surlignage

2. NAME OF THE VETERINARY MEDICINAL PRODUCT

Modulis 100 mg/ml oral solution for dogs
Modulis 100 mg/ml (FR)
Modulis vet 100 mg/ml oral solution for dogs (DK, SE, FI, NO)
Ciclosporin

3. STATEMENT OF THE ACTIVE SUBSTANCE(S) AND OTHER INGREDIENT(S)

Each ml contains:
Active substance:
Ciclosporin .....100 mg
Excipient(s):
all-rac-α-tocopherol (E-307) .....1 mg

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

4. INDICATION(S)

Treatment of chronic manifestations of atopic dermatitis in dogs.
This is a type of allergic skin disease in dogs and is caused by allergens such as house dust mites or pollens which stimulate an excessive immune response. Ciclosporin reduces the inflammation and itching associated with atopic dermatitis.

5. 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 “Special precautions for use” and “Interaction with other medicinal products”).

6. ADVERSE REACTIONS

Gastrointestinal disturbances such as vomiting were reported rarely in spontaneous reports. Diarrhoea, lethargy, anorexia, gingival disorder and pinnal irritation were reported very rarely in spontaneous reports.
These signs are mild and transient and generally do not require the cessation of the treatment.
Diabetes mellitus has been reported very rarely in spontaneous reports, mainly in West highland white terriers.
Mucoid or soft faeces were observed commonly during the development studies and not in the spontaneous pharmacovigilance reports. Hyperactivity, skin lesions such as verruciform lesions or change of hair coat, muscle weakness or muscle cramps were observed uncommonly during the development studies and not in the spontaneous pharmacovigilance reports.These effects generally resolve spontaneously after treatment is stopped.

As for the subject of malignancy, please see sections “contraindications” and “special precautions for use”.

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)

If you notice any side effects, even those not already listed in this package leaflet or you think that the medicine has not worked, please inform your veterinary surgeon.
Alternatively you can report via your national reporting system {national system details}.

7. TARGET SPECIES

Dogs

8. DOSAGE FOR EACH SPECIES, ROUTE(S) AND METHOD OF ADMINISTRATION

For 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, 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.

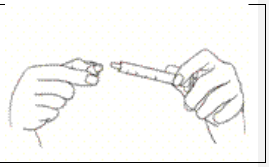
9. ADVICE ON CORRECT ADMINISTRATION

The veterinary medicinal product should be given at least 2 hours before or after feeding.
The 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 and insert the syringe into the specific cap to protect from any contamination and to avoid any spillage of remaining product.	

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

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

10. WITHDRAWAL PERIOD

Not applicable

11. SPECIAL STORAGE PRECAUTIONS

Keep out of the sight and reach of children.

Keep the bottle in the outer carton.
Discard any remaining product 3 months after opening.
Do not use this veterinary medicinal product after the expiry date which is stated on the carton and vial label, after “EXP”. The expiry date refers to the last day of that month.

Storage in the refrigerator should be avoided.
The 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.

12. SPECIAL WARNING(S)

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

Special precautions for use in animals
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 T-lymphocytes 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 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 product. For live vaccines see also section “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 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. 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.

Use during pregnancy, lactation or lay
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.

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 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 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 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 “Contraindications” and “Special precautions for use”). Concomitant use of immunosuppressive agents: see section “Special precautions for use”.

Overdose (symptoms, emergency procedures, antidotes), if necessary
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.

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

13. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCT OR WASTE MATERIALS, IF ANY

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

14. DATE ON WHICH THE PACKAGE LEAFLET WAS LAST APPROVED

15. OTHER INFORMATION

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.

For any information about this veterinary medicinal product, please contact the local representative of the marketing authorisation holder.