For the use only of a Registered Veterinary Practitioner, Hospital or Laboratory

ICHMUNE C®

(Capsules 25,50,100mg and Oral Solution IP 100 mg/ml)

Composition:
Each soft gelatin capsule of **ICHMUNE C® 25mg** contains:
Cyclosporine IP 25 mg
Color: Ferric Oxide Red.
Each soft gelatin capsule of **ICHMUNE C® 50mg** contains:
Cyclosporine IP 50 mg
Color: Ferric Oxide Red and Ferric Oxide Black
Each soft gelatin capsule of **ICHMUNE C® 100mg** contains:
Cyclosporine IP 100 mg
Color: Ferric Oxide Red
Each ml of **ICHMUNE C® Oral Solution** contains:
Cyclosporine I.P. 100 mg
In a Palatable base

Category: Potent Immunosuppressive Agent

Indications:
- ICHMUNE C® is indicated for the treatment of atopic dermatitis in dogs.
- ICHMUNE C® can also be used as an aid in the treatment of perianal fistulae in dogs. A perianal fistula is a syndrome of inflammation, ulceration and draining sinuses in the perianal (around the anus) region of dogs. If is thought to be an immune-mediated condition.
- Symptomatic treatment of chronic allergic dermatitis in cats

Contraindications:
Do not use in cases of hypersensitivity to the active substance 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 cats infected with Feline Leukemia Virus (FeLV) or Feline Immunodeficiency Virus (FIV).
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 “Special precautions for use“ and “Interaction with other medicinal products").

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

Special precautions for use
(i) Special precautions for use in animals

Clinical signs of atopic dermatitis in dogs and allergic dermatitis in cats such as pruritus and skin inflammation are not specific for these diseases. Other causes of dermatitis such as ecto-parasitic 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 or allergic dermatitis.

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

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.
In laboratory animals, cyclosporine is liable to affect the circulating levels of insulin and to cause an increase in glycaemia. If signs of diabetes mellitus are observed following the use of the product, e.g. polyuria, polydipsia, the dose should be tapered or discontinued and veterinary care sought.
In the presence of suggestive signs of diabetes mellitus, the effect of treatment on glycaemia must be monitored.

The use of cyclosporine is not recommended in diabetic animals.
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.

Dogs: Closely monitor creatinine levels with severe renal insufficiency.
Cats: Allergic dermatitis in cats can have various manifestations, including eosinophilic plaques, head and neck excoriation, symmetrical alopecia and/or miliary dermatitis.

The immune status of the cats to FeLV and FIV infections should be assessed before treatment.
Cats that are seronegative for T. gondii may be at risk of developing clinical toxoplasmosis if they become infected while under treatment. In rare cases this can be fatal. Potential exposure of seronegative cats or cats suspected to be seronegative to Toxoplasma should therefore be minimised (e.g. keep indoors, avoid raw meat or scavenging). However, in a controlled laboratory study, treatment with cyclosporine did not reactivate oocyst shedding in cats previously exposed to T. gondii. In cases of clinical toxoplasmosis or other serious systemic illness, stop treatment with cyclosporine and initiate appropriate therapy.

Clinical studies in cats have shown that decreased appetite and weight loss may occur during cyclosporine treatment. Monitoring of body weight is recommended. Significant reduction in body weight may result in hepatic lipidosis. If persistent, progressive weight loss occurs during treatment it is recommended to discontinue treatment until the cause has been identified.

The efficacy and safety of cyclosporine has neither been assessed in cats less than 6 months of age nor weighing less than 2.3 kg.

(ii)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 oral syringe in the presence of children. Any uneaten medicated cat food must be disposed of immediately and the bowl washed thoroughly. In case of accidental ingestion, particularly by a child, seek medical advice immediately and show the package leaflet or the label to the physician. Cyclosporine can trigger hypersensitivity (allergic) reactions. People with known hypersensitivity to cyclosporine should avoid contact with the product. This product may cause irritation in case of eye contact. Avoid contact with eyes. In case of contact, rinse thoroughly with clean water.
Wash hands and any exposed skin after use.
Adverse reactions:
Regarding malignancy, please see sections "Contraindications" and “Special precautions for use".
Dogs: The occurrence of adverse reactions is uncommon. The most commonly observed undesirable effects are gastrointestinal disturbances such as vomiting, mucoid or soft faeces and diarrhoea. They are mild and transient and generally do not require the cessation of the treatment. Other undesirable effects may be observed uncommonly: lethargy or hyperactivity, anorexia, mild to moderate gingival hyperplasia, skin reactions such as verruciform lesions or change of hair coat, red and swollen pinnae, muscle weakness or muscle cramps. Mild and transient salivation can be observed following treatment administration. These effects generally resolve spontaneously after treatment is stopped. In very rare cases diabetes mellitus has been observed, especially in West Highland White Terriers.

Cats: In cats treated with cyclosporine the following undesirable effects were observed:
Very common: gastrointestinal disturbances such as vomiting and diarrhoea, accompanied by weight loss. These are generally mild and transient and do not require the cessation of the treatment. Increased appetite was also commonly observed.

Common: lethargy, anorexia, hyper salivation, hyperactivity, polydipsia, gingival hyperplasia and lymphopaenia. These effects generally resolve spontaneously after treatment is stopped or following a decrease in the dosing frequency.
Side effects may be severe in individual animals.

The frequency of adverse reactions is defined using the following convention:
- very common (more than 1 in 10 animals treated displaying adverse reaction(s))
- common (more than 1 but less than 1 0 animals in 1 00 animals treated)
- uncommon (more than 1 but less than 1 0 animals in 1 ,000 animals treated)
- rare (more than 1 but less than 1 0 animals in 1 0,000 animals treated)
- very rare (lessthan1 animal in 1 0,000 animals treated, including isolated reports).

Use during pregnancy, lactation or lay:
The safety of the drug has neither been studied in male dogs or cats used for breeding nor in pregnant or lactating bitches and queens. In the absence of such studies, it is recommended to use the drug in breeding animals only upon a positive benefit/risk assessment by the responsible veterinarian.
Pregnancy: In laboratory animals, at doses which induce maternal toxicity (rats at 30 mg/kg BW and rabbits at 1 00 mg/kg BW) cyclosporine was embryo- and foetotoxic, as indicated by increased pre- and postnatal mortality and reduced foetal weight together with skeletal retardations. In the well-tolerated dose range (rats at up to 17 mg/kg BW and rabbits at up to 30 mg/kg BW) cyclosporine was without embryolethal or teratogenic effects. Therefore the treatment of pregnant bitches and queens is not recommended.
Lactation: In laboratory animals cyclosporine crosses the placenta barrier and is excreted via milk. Therefore the treatment of lactating bitches and queens is not recommended.

Interactions 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 cyclosporine, in particular cytochrome P450 (CYP 3A4). In certain clinically justified cases, an adjustment of the dosage of the veterinary medicinal product may be required.
The compound class of azoles (e.g. ketoconazole) is known to increase the blood concentration of cyclosporine in dogs and cats, which is considered to be clinically relevant. Ketoconazole at 5-10 mg/kg is known to Increase the blood concentration of cyclosporine In dogs up to five-fold. During concomitant use of ketoconazole and cyclosporine the veterinarian should consider as a practical measure to double the treatment Interval If the dog is on a daily treatment regime.

Macrolides such as erythromycin may increase the plasma levels of cyclosporine up to two fold.
Certain Inducers of cytochrome P450, anticonvulsants and antibiotics (e.g. trimethoprim/sulfadimidine) may lower the plasma concentration of cyclosporine.

Cyclosporine is a substrate and an Inhibitor of the MDR1 P-glycoprotein transporter. Therefore, the co-administration of cyclosporine with P-glycoprotein substrates such as macrocyclic lactones, e.g. ivermectin and milbemycin, could decrease the efflux of such drugs from blood-brain barrier cells, potentially resulting in signs of CNS toxicity.

Cyclosporine can increase the nephrotoxicity of aminoglycoside antibiotics and trimethoprim. The concomitant use of cyclosporine is not recommended with these active ingredients. Particular attention must be paid to vaccination (see "Contraindications" and "Special precautions for use") and to concomitant use of other immunosuppressive agents (see "Special precautions for use").

Amounts to be administered and administration route:
For oral use:
Before starting treatment, an evaluation of all alternative treatment options should be made.
Dogs: The recommended dose of cyclosporine is 5 mg/kg body weight (0.05 ml of oral solution per kg BW) and should initially be administered daily. The frequency of administration should subsequently be reduced depending on the response. The product should initially be given daily until a satisfactory clinical improvement is seen. This will generally be the case within 4-8 weeks. If no response is obtained withinthefirst8 weeks, the treatment should be stopped. Once the clinical signs of atopic dermatitis are satisfactorily controlled, the product can then be given every second day. 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 second day dosing, the veterinary surgeon can decide to give the product every 3 to 4 days. The lowest effective frequency of dosing should be used to maintain the remission of clinical signs.

Patients should be regularly re-evaluated and alternative treatment options reviewed. Adjunct treatment (e.g. medicated shampoos, fatty acids) maybe considered before reducing the dosing interval. The duration of treatment should be adjusted according to treatment response. 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. Insert the oral syringe directly into the dog's mouth

If giving ICHMUNE C® capsules, the dosage guide is as below:

Body Weight (kg)	ICHMUNE C 25mg	ICHMUNE C 50mg	ICHMUNE C 100mg
4 – 8kg	1		
8 – 15kg		1	
15 – 29kg			1
29 – 36kg		1	1
36 – 55kg			2

If using ICHMUNE C® Oral Solution
Dosages for dogs: For the 30 ml / 50ml vials (3 ml syringe graduated every 0.1 ml) (See dosage guide)

At standard dosage of 5mg/kg, Volume to be administered: 0.05ml/kg

Dosage Guide: Ichmune C 100 mg/ml Oral Solution for Dogs

Wt (kg)	Dose (ml)	Wt (kg)	Dose (ml)	Wt (kg)	Dose (ml)	Wt (kg)	Dose (ml)	Wt (kg)	Dose (ml)
2	0.1	18	0.9	34	1.7	50	2.5	66	3.3
4	0.2	20	1.0	36	1.8	52	2.6	68	3.4
6	0.3	22	1.1	38	1.9	54	2.7	70	3.5
8	0.4	24	1.2	40	2.0	56	2.8	72	3.6
10	0.5	26	1.3	42	2.1	58	2.9	74	3.7
12	0.6	28	1.4	44	2.2	60	3.0	76	3.8
14	0.7	30	1.5	46	2.3	62	3.1	78	3.9
16	0.8	32	1.6	48	2.4	64	3.2	80	4.0

Cats: The recommended dose of cyclosporine is 7 mg/kg body weight (0.07 ml of oral solution per kg) and should initially be administered daily. The frequency of administration should subsequently be reduced depending on the response. The product should initially be given daily until a satisfactory clinical improvement is seen (assessed by Intensity of pruritus and lesion severity - excoriations, miliary dermatitis, eosinophilic plaques and/or self-induced alopecia). This will generally be the case within 4-8 weeks. Severe prolonged pruritus may induce a state of anxiety and subsequent excessive grooming behaviour. In such cases, despite an improvement in pruritus upon administration of the treatment, the resolution of self - induced alopecia may be delayed. Once the clinical signs of allergic dermatitis are satisfactorily controlled, the product can then be given every second day. In some cases where the clinical signs are controlled with every second day dosing, the veterinary surgeon can decide to give the product every 3 to 4 days. The lowest effective frequency of dosing should be used to maintain the remission of clinical signs.

Patients should be regularly re-evaluated and alternative treatment options reviewed. The duration of treatment should be adjusted according to treatment response. 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 product can be given either mixed with food or directly into the mouth. If given with food, the solution should be mixed with a small amount of food, preferably after a sufficient period of fasting to ensure complete consumption by the cat.
Should the cat not accept the product mixed with food, it should be given by inserting the oral syringe directly into the cat's mouth

and delivering the entire dose. In case the cat only partially consumes the product mixed with food, administration of the product with the oral syringe should be resumed only the next day. Any uneaten medicated cat food must be disposed of immediately and the bowl washed thoroughly.
The efficacy and tolerability of this product was demonstrated in clinical studies with a duration of 4.5 months.

Dosage for cats:
As the efficacy and safety of cyclosporine have not been assessed in cats weighing less than 2.3 kg (see "Special considerations for use"), administration of the product to cats weighing less than 2.3 kg should be according to a benefit-risk assessment by the responsible veterinarian.

Dosage Guide: Ichmune C® 100 mg/ml Oral Solution for cats
At standard dosage of 7 mg/kg

Wt (kg)	Dose (ml)	Wt (kg)	Dose (ml)
2.1	0.15	9.3	0.65
2.9	0.2	10.0	0.7
3.6	0.25	10.7	0.75
4.3	0.3	11.4	0.8
5	0.35	12.1	0.85
5.7	0.4	12.8	0.90
6.4	0.45	13.5	0.95
7.1	0.5	14.3	1.00
7.9	0.55		
8.6	0.6		

For the 30 ml vial (3 ml oral syringe graduated every 0.1 ml)
At standard dosage of 7 mg/kg

Weight (kg)	Dose(ml)
2.9	0.2
4.3	0.3
5.7	0.4
7.1	0.5
8.6	0.6
10.0	0.7
11.4	0.8
12.8	0.90
14.3	1.00

Overdose:
There is no specific antidote and in cases of signs of overdose the animal should be treated symptomatically.

Dogs: No undesirable effects beyond those that were seen under recommended treatment have been observed in the dog with a single oral dose of upto 5times what is recommended. In addition to what was seen under recommended dosage, the following adverse reactions were seen in case of overdose for 3 months or more at 4 times the mean recommended dosage: hyperkeratotic areas especially on the pinnae, callous -like lesions of the foot pads, weight loss or reduced weight gain, hypertrichosis, increased erythrocyte sedimentation rate, decreased eosinophil values. Frequency and severity of these signs are dose dependent. The signs are reversible within 2 months following cessation of treatment.

Cats: The following adverse events were seen in the case of repeated administration for56 days at 24 mg/kg (more than 3x the recommended dose) or for 6 months at up to 40 mg/kg (more than 5x the recommended dose): loose/soft faeces, vomiting, mild to moderate increases in absolute neutrophil counts, fibrinogen, activated partial thromboplastin time (APTT), slight increases in blood glucose and reversible gingival hypertrophy. Increased appetite was observed for both dose regimens. At ransient increase followed by a decrease in lymphocyte counts was observed in treated cats, combined with a greater occurrence of palpable small peripheral lymph nodes. This may reflect immunosuppression following prolonged exposure to cyclosporine. APTT was prolonged in cats administered at least twice the recommended dose of cyclosporine. The frequency and severity of these signs were generally close and time dependent. At 3x the recommended dose administered daily for nearly 6 months, changes in ECG (conduction disturbances) commonly occur. They are transient and not associated with clinical signs. Anorexia, recumbency, loss of skin elasticity, few or absent faeces, thin and closed eye lids may be observed in sporadic cases at 5x the recommended dose.

Withdrawal periods: Not applicable

Pharmacology
Pharmacodynamic properties
Cyclosporine (also known as ciclosporin, 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. Cyclosporine exerts anti-inflammatory and antipruritic effects in the treatment of atopic dermatitis. Cyclosporine 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. Cyclosporine also has the capacity to inhibit the antigen-presenting function of 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. Cyclosporine does not depress haematopoiesis and has no effect on the function of phagocytic cells.

Pharmacokinetic properties
Dogs:
Absorption: The bioavailability of cyclosporine is about 35%. The peak plasma concentration is reached within 1 to 2 hours. The bioavailability is better and less subiect to individual variations if cyclosporine is administered to fasted animals rather than at mealtimes.
Distribution: The volume of distribution is about 7.8 L/kg. Cyclosporine is widely distributed to all tissues. Following repeated daily administration to dogs, cyclosporine concentration in the skin is several times higher than in blood.
Metabolism: Unchanged cyclosporine represents about 25% of circulating blood concentrations in the course of the first 24 hours. Cyclosporine is metabolised mainly in the liver by cytochrome P450 (CYP3A4), but also in the intestine.

Metabolism takes place essentially in the form of hydroxylation and demethylation, leading to metabolites with little or no activity.
Elimination: Elimination is mainly via the faeces. Only 1 0% is excreted in the urine, mostly in the form of metabolites.
No significant accumulation was observed in blood of dogs treated for one year.

Cats:
Absorption: The bioavailability of orally administered cyclosporine is between 25 and 29% in cats. The peak blood concentrations is generally reached within 1 to 2 hours when given to fasted cats. Blood drug concentration-time curves are not dose proportional at dose levels greater than the recommended dose. There is a less than proportional increase in C_{max} and AUC over the dose range 8m 40 mg/kg.
Distribution: The volume of distribution at steady state is about 1 .7—2.1 L/kg.
Metabolism: cyclosporine is metabolized in the liver by cytochrome P450 3A enzymes.
Elimination: The terminal elimination phase half-life is 8-11 h. There is no significant accumulation of cyclosporine beyond the first week of treatment.

In the cat, there are large inter-individual variations in blood cyclosporine concentrations. At the recommended dosage, cyclosporine plasma concentrations are not predictive of the clinical response, therefore monitoring of blood levels is not recommended.

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

Presentation:

ICHMUNE C® 25mg, ICHMUNE C® 50mg, ICHMUNE C® 100mg – Strip of 6 capsules
ICHMUNE C® Oral Solution - 30 ml and 50 ml Bottle with dosing syringe.

Storae: Store at a temperature between 25°C and 35°C, protect from light and moisture.
Do not refrigerate.

Keep out of reach of children

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

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SAVAVET
Shaping the Future

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