PROFESSIONAL INFORMATION - VETERINARY MEDICINE

SCHEDULING STATUS S4

PROPRIETARY NAME AND DOSAGE FORM

Cyclavance 100 mg/ml Oral Solution

COMPOSITION

Each 1 ml contains ciclosporin 100 mg.

Excipients: All-rac-α-tocopherol (E-307), glycerol monolinoleate, ethanol, anhydrous (E-1510), macrogolglycerol hydroxystearate, propylene glycol (E-1520).

CLASS OF MEDICINE

C 21 Immune Modulating Agents

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

Ciclosporin is a selective immunosuppressor. It is a cyclic polypeptide consisting of 11 amino acids, has a molecular weight of 1203 daltons and acts specifically and reversibly on T-lymphocytes.

Ciclosporin exerts anti-inflammatory and antipruritic effects in the treatment of allergic and 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 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.

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

Pharmacokinetic properties

Dogs:

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: 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: Unchanged ciclosporin represents about 25 % of circulating blood concentrations in the course of the first 24 hours.

Ciclosporin 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 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.

Cats:

Absorption: The bioavailability of orally administered ciclosporin is between 25 and 29 % in cats.

The peak blood concentration is generally reached within 1 to 2 hours when given to fasted cats. Blood substance 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 8 to 40 mg/kg.

Distribution: The volume of distribution at steady state is about 1,7 – 2,1 L/kg.

Metabolism: Ciclosporin is metabolised in the liver by cytochrome P450 3A enzymes.

Elimination: The terminal elimination phase half-life is 8 - 11 hours.

There is no significant accumulation of ciclosporin beyond the first week of treatment.

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

INDICATIONS

In dogs and cats:

Treatment of chronic manifestations of atopic dermatitis in dogs.

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 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 WARNINGS AND SPECIAL PRECAUTIONS and INTERACTIONS).

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).

WARNINGS AND SPECIAL PRECAUTIONS

Warnings: None

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 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 or allergic dermatitis.

A complete clinical examination should be performed prior to treatment. While ciclosporin does not induce tumours, it does inhibit T-lymphocytes and therefore treatment with ciclosporin may lead to an increased incidence of clinically apparent malignancy due to the decrease in anti-tumour 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 CYCLAVANCE, further clinical investigations are recommended and treatment discontinued if necessary.

It is recommended to clear bacterial and fungal infections before administering CYCLAVANCE. However, infections occurring during treatment are not necessarily a reason for medicine withdrawal, unless the infection is severe.

In laboratory animals, ciclosporin 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 CYCLAVANCE, 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 CYCLAVANCE is not recommended in diabetic animals.

Particular attention must be paid to vaccination. Treatment with CYCLAVANCE 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 CYCLAVANCE. For live vaccines see also 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 ciclosporin 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 ciclosporin and initiate appropriate therapy.
Clinical studies in cats have shown that decreased appetite and weight loss may occur during CYCLAVANCE 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 CYCLAVANCE 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 medicine to animals

Accidental ingestion of CYCLAVANCE may lead to nausea and/or vomiting. To avoid accidental ingestion, CYCLAVANCE 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 doctor. CYCLAVANCE can trigger hypersensitivity (allergic) reactions. People with known hypersensitivity to ciclosporin should avoid contact with CYCLAVANCE. CYCLAVANCE 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.

WITHDRAWAL PERIOD IN CASE OF FOOD PRODUCING ANIMALS

Not applicable.

INTERACTIONS

Various substances are known to competitively inhibit or induce the enzymes involved in the metabolism of ciclosporin, in particular cytochrome P450 (CYP3A4). In certain clinically justified cases, an adjustment of the dosage of CYCLAVANCE may be required.
The compound class of azoles (e.g. ketoconazole) is known to increase the blood concentration of ciclosporin 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 ciclosporin in dogs up to five-fold. During concomitant use of ketoconazole and CYCLAVANCE 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 CYCLAVANCE up to two-fold. Certain inducers of cytochrome P450, anticonvulsants and antibiotics (e.g. trimethoprim/ sulfadimidine) may lower the plasma concentration of CYCLAVANCE.
Ciclosporin is a substrate and an inhibitor of the MDR1 P-glycoprotein transporter. Therefore, the co-administration of CYCLAVANCE with P-glycoprotein substrates such as macrocyclic lactones, e.g. ivermectin and milbemycin, could decrease the efflux of such medicines from blood-brain barrier cells, potentially resulting in signs of CNS toxicity.
CYCLAVANCE can increase the nephrotoxicity of aminoglycoside antibiotics and trimethoprim. The concomitant use of CYCLAVANCE is not recommended with these active ingredients.
In dogs, no toxicological interactions between CYCLAVANCE and prednisolone (at anti-inflammatory doses) are expected.

Particular attention must be paid to vaccination (see CONTRAINDICATIONS and WARNINGS and SPECIAL PRECAUTIONS) and to concomitant use of other immunosuppressive agents (see WARNINGS and SPECIAL PRECAUTIONS).

PREGNANCY AND LACTATION

The safety of CYCLAVANCE 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 CYCLAVANCE 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 100 mg/kg BW) ciclosporin was embryo- and foetotoxic, as indicated by increased pre- and postnatal mortality and reduced foetal weight together with skeletal retardations. In the well-tolerated dose range (rats at up to 17 mg/kg BW and rabbits at up to 30 mg/kg BW) ciclosporin was without embryolethal or teratogenic effects. Therefore the treatment of pregnant bitches and queens is not recommended.

Lactation: In laboratory animals ciclosporin crosses the placenta barrier and is excreted via milk. Therefore the treatment of lactating bitches and queens is not recommended.

DOSAGE AND DIRECTIONS FOR USE

For oral use.

Before starting treatment, an evaluation of all alternative treatment options should be made.

Dogs:

The recommended dose of CYCLAVANCE 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.

CYCLAVANCE 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 within the first 8 weeks, the treatment should be stopped.

Once the clinical signs of atopic dermatitis are satisfactorily controlled, CYCLAVANCE 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 CYCLAVANCE 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) may be 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.

Dosages for dogs:

For the 5 and 15 ml vials (1 ml oral syringe graduated every 0,05 ml)

At standard dosage of 5 mg/kg

Weight (kg)		**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Dosage (ml)		0,1	0,15	0,2	0,25	0,3	0,35	0,4	0,45	0,5
Weight (kg)	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**
Dosage (ml)	0,55	0,6	0,65	0,7	0,75	0,8	0,85	0,9	0,95	1
Weight (kg)	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**
Dosage (ml)	1,05	1,1	1,15	1,2	1,25	1,3	1,35	1,4	1,45	1,5

Weight (kg)	**31**	**32**	**33**	**34**	**35**	**36**	**37**	**38**	**39**	**40**
Dosage (ml)	1,55	1,6	1,65	1,7	1,75	1,8	1,85	1,9	1,95	2
Weight (kg)	**41**	**42**	**43**	**44**	**45**	**46**	**47**	**48**	**49**	**50**
Dosage (ml)	2,05	2,1	2,15	2,2	2,25	2,3	2,35	2,4	2,45	2,5
Weight (kg)	**51**	**52**	**53**	**54**	**55**	**56**	**57**	**58**	**59**	**60**
Dosage (ml)	2,55	2,6	2,65	2,7	2,75	2,8	2,85	2,9	2,95	3
Weight (kg)	**61**	**62**	**63**	**64**	**65**	**66**	**67**	**68**	**69**	**70**
Dosage (ml)	3,05	3,1	3,15	3,2	3,25	3,3	3,35	3,4	3,45	3,5
Weight (kg)	**71**	**72**	**73**	**74**	**75**	**76**	**77**	**78**	**79**	**80**
Dosage (ml)	3,55	3,6	3,65	3,7	3,75	3,8	3,85	3,9	3,95	4

For the 30 and 50 ml vials (3 ml oral syringe graduated every 0,1 ml)

At standard dosage of 5 mg/kg

Weight (kg)	**2**	**4**	**6**	**8**	**10**
Dosage (ml)	0,1	0,2	0,3	0,4	0,5
Weight (kg)	**12**	**14**	**16**	**18**	**20**
Dosage (ml)	0,6	0,7	0,8	0,9	1
Weight (kg)	**22**	**24**	**26**	**28**	**30**
Dosage (ml)	1,1	1,2	1,3	1,4	1,5
Weight (kg)	**32**	**34**	**36**	**38**	**40**
Dosage (ml)	1,6	1,7	1,8	1,9	2
Weight (kg)	**42**	**44**	**46**	**48**	**50**

Dosage (ml)	2,1	2,2	2,3	2,4	2,5
Weight (kg)	**52**	**54**	**56**	**58**	**60**
Dosage (ml)	2,6	2,7	2,8	2,9	3
Weight (kg)	**62**	**64**	**66**	**68**	**70**
Dosage (ml)	3,1	3,2	3,3	3,4	3,5
Weight (kg)	**72**	**74**	**76**	**78**	**80**
Dosage (ml)	3,6	3,7	3,8	3,9	4

Cats:

The recommended dose of CYCLAVANCE 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.

CYCLAVANCE 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, CYCLAVANCE 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 CYCLAVANCE 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.

CYCLAVANCE 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 CYCLAVANCE 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 CYCLAVANCE mixed with food, administration of CYCLAVANCE 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 CYCLAVANCE was demonstrated in clinical studies with a duration of 4,5 months.

Dosage for cats:

As the efficacy and safety of CYCLAVANCE have not been assessed in cats weighing less than 2,3 kg (see WARNINGS and SPECIAL PRECAUTIONS), administration of CYCLAVANCE to cats weighing less than 2,3 kg should be according to a benefit-risk assessment by the responsible veterinarian.

For the 5, 15, 30 and 50 ml vials (1 ml oral syringe graduated every 0,05 ml)

At standard dosage of 7 mg/kg

Weight (kg)	**2,1**	**2,9**	**3,6**	**4,3**	**5,0**	**5,7**	**6,4**	**7,1**
Dosage (ml)	0,15	0,2	0,25	0,3	0,35	0,4	0,45	0,5

Weight (kg)	**7,9**	**8,6**	**9,3**	**10,0**	**10,7**	**11,4**	**12,1**	**12,8**	**13,6**	**14,3**
Dosage (ml)	0,55	0,60	0,65	0,70	0,75	0,80	0,85	0,90	0,95	1,00

For the 30 and 50 ml vials (3 ml oral syringe graduated every 0,1 ml)

At standard dosage of 7 mg/kg

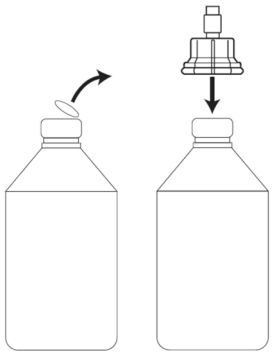
Weight (kg)	**2,9**	**4,3**	**5,7**	**7,1**	**8,6**	**10,0**	**11,4**	**12,8**	**14,3**
Dosage (ml)	0,2	0,3	0,4	0,5	0,6	0,7	0,8	0,9	1,0

INSTRUCTIONS FOR USE

Dogs: CYCLAVANCE should be given at least 2 hours before or after feeding. Insert the oral syringe directly into the dog's mouth.

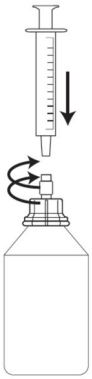
Cats: CYCLAVANCE can be given either mixed with food or directly into the mouth in cats.

1 Retrieve the plastic cap and insert firmly the plastic dispenser.

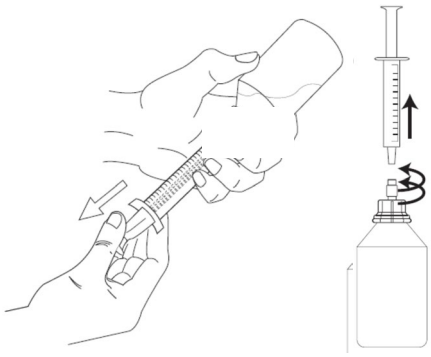


The plastic dispenser should remain in place.

2 Keep the bottle upright and insert the oral dosing syringe firmly into the plastic dispenser.



3 Turn the bottle upside down and slowly pull the plunger up so that the oral dosing syringe fills with the product.
Withdraw the dose of medicine prescribed by your veterinarian.



Return the bottle to its upright position and remove the oral dosing syringe by gently twisting it out of the plastic dispenser.

4 You can now introduce the syringe in the mouth of your animal and push the medicine out of the syringe.
Do not rinse or clean the oral dosing syringe between uses.

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.

Note: For cats, you can also give the product mixed with food

Keep out of the sight and reach of children

If necessary, the user can wipe the outside of the oral syringe with a dry tissue and dispose of used tissue immediately.

SIDE EFFECTS

Regarding malignancy, please see CONTRAINDICATIONS and WARNINGS and SPECIAL PRECAUTIONS.

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 CYCLAVANCE 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, hypersalivation, 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 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).

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

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

Dogs: No undesirable effects beyond those that were seen under recommended treatment have been observed in the dog with a single oral dose of up to 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. The signs are reversible within 2 months following cessation of treatment.

Cats: The following adverse events were seen in the case of repeated administration for 56 days at 24 mg/kg (more than 3 times the recommended dose) or for 6 months at up to 40 mg/kg (more than 5 times 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. A transient 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 CYCLAVANCE. APTT was prolonged in cats administered at least twice the recommended dose of CYCLAVANCE. The frequency and severity of these signs were generally dose and time dependent. At 3 times 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 eyelids may be observed in sporadic cases at 5 times the recommended dose.

IDENTIFICATION

Clear to slightly yellow oral solution.

PRESENTATION

Amber glass (type III) bottles closed with a 20 mm bromobutyl stopper and an aluminum cap with flip-off.

5 ml bottle with a dispenser set consisting of a polycarbonate dispenser cap with a silicone valve and a 1 ml polypropylene syringe graduated in increments of 0,05 ml, packaged in a cardboard box.

15 ml bottle with a dispenser set consisting of a polycarbonate dispenser cap with a silicone valve and a 1 ml polypropylene syringe graduated in increments of 0,05 mL, packaged in a cardboard box.

30 ml bottle, with two dispenser sets consisting of a polycarbonate dispenser cap with a silicone valve and both 1 ml and 3 ml polypropylene syringes graduated in increments of respectively 0,05 ml and 0,1 ml, packaged in a cardboard box.

50 ml bottle, with two dispenser sets consisting of a polycarbonate dispenser cap with a silicone valve and both 1 ml and 3 ml polypropylene syringes graduated in increments of respectively 0,05 ml and 0,1 ml, packaged in a cardboard box.

STORAGE INSTRUCTIONS

Store at or below 25 °C.

Do not refrigerate.

A jelly-like formation may occur below 15 °C which is however reversible at temperatures up to 25 °C without affecting the quality of CYCLAVANCE.

After first opening: Do not store above 25 °C.

REGISTRATION NUMBER

To be allocated.

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

Virbac RSA (Pty) Ltd

Private Bag X115

Halfway House

1685

DATE OF PUBLICATION OF THE PACKAGE INSERT

Date of registration: TBA