1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Zycortal 25 mg/ml prolonged-release suspension for injection for dogs

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance:
Desoxycortone pivalate 25 mg/ml

Excipients:
Chlorocresol 1 mg/ml

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Prolonged-release suspension for injection.
Opaque white suspension.

4. CLINICAL PARTICULARS

4.1 Target species

Dogs.

4.2 Indications for use, specifying the target species

For use as replacement therapy for mineralocorticoid deficiency in dogs with primary hypoadrenocorticism (Addison's disease).

4.3 Contraindications

Do not use in cases of hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings for each target species

Before starting treatment with the veterinary medicinal product, it is important that Addison's disease has been definitively diagnosed. Any dog presenting with severe hypovolaemia, dehydration, pre-renal azotaemia and inadequate tissue perfusion (also known as "Addisonian crisis") must be rehydrated with intravenous fluid (saline) therapy before starting treatment with the veterinary medicinal product.

4.5 Special precautions for use

Special precautions for use in animals

Use with caution in dogs with congestive heart disease, severe renal disease, primary hepatic failure or oedema.

Special precautions to be taken by the person administering the veterinary medicinal product to animals

Avoid contact with the eyes and skin. In case of accidental spillage onto the skin or eyes, wash the affected area with water. If irritation occurs, seek medical advice immediately and show the package leaflet or the label to the physician.

This veterinary medicinal product may cause pain and swelling at the injection site if accidentally self-administered.

This veterinary medicinal product may cause adverse effects on male reproductive organs and, as a result, fertility.

This veterinary medicinal product may cause adverse developmental effects on unborn children and neonates.

Pregnant and breast-feeding women should avoid administration of this veterinary medicinal product.

In case of accidental self-injection, seek medical advice immediately and show the package leaflet or the label to the physician.

4.6 Adverse reactions (frequency and seriousness)

Polydipsia and polyuria were very common adverse reactions in a clinical trial. Inappropriate urination, lethargy, alopecia, panting, vomiting, decreased appetite, anorexia, decreased activity, depression, diarrhoea, polyphagia, shaking, tiredness and urinary tract infections were common adverse reactions in a clinical trial.
Injection site pain has been reported uncommonly in post-authorisation spontaneous reports following the administration of Zycortal.
Pancreas disorders have been reported rarely in post-authorisation spontaneous reports following use of Zycortal. The concurrent administration of glucocorticoids may contribute to these signs.

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

The safety of the veterinary medicinal product has not been established during breeding, pregnancy or lactation. Therefore, use only according to the benefit/risk assessment by the responsible veterinarian.

4.8 Interaction with other medicinal products and other forms of interaction

Use with caution when administering Zycortal concurrently with medicinal products which affect either serum sodium or potassium concentrations, or cellular transportation of sodium or potassium, for example: trimethoprim, amphotericin B, digoxin or insulin.

4.9 Amounts to be administered and administration route

Subcutaneous use.

Prior to use, gently shake the vial to resuspend the veterinary medicinal product.

Use an appropriately graduated syringe to accurately administer the required dose volume. This is particularly important when injecting small volumes.

Zycortal replaces the mineralocorticoid hormones only. Dogs with combined glucocorticoid and mineralocorticoid deficiency should also receive a glucocorticoid such as prednisolone taking into account the current scientific knowledge.

Zycortal is intended for long term administration at intervals and doses dependent upon individual response. Tailor the dose of Zycortal and the concurrently administered glucocorticoid replacement therapy to the individual dog based on clinical response and normalization of Na^+ and K^+ serum concentrations.

Initial dose of Zycortal:
The initial dose is 2.2 mg/kg body weight, administered by subcutaneous injection.

Interim monitoring visit:
Re-evaluate the dog and measure the serum sodium/potassium ratio (Na^+/K^+ ratio) approximately 10 days after the first dose (which is the time to maximum concentration (T_{max}) of desoxycortone). If the dog's clinical signs have worsened or not resolved, adjust the dose of glucocorticoid and/or investigate other causes of the clinical signs.

Second dose of Zycortal:
At approximately 25 days after the first dose, re-evaluate the dog and measure the Na^+/K^+ ratio.

- If the dog is both clinically normal and has a normal Na^+/K^+ ratio (i.e. 27 to 32) on Day 25, adjust the dose based on the Day 10 Na^+/K^+ ratio using the guidelines in Table 1, below.

- If the dog is clinically normal and has a Na^+/K^+ ratio > 32 on Day 25, either adjust the dose based on the Day 10 Na^+/K^+ ratio according to Table 1 or delay the dose (see **Prolonging the dosing interval**).

- If the dog is either not clinically normal or if the Na^+/K^+ ratio is abnormal on Day 25, adjust the dose of glucocorticoid or Zycortal (see **Subsequent doses and long term management**).

Table 1: Day 25: Administering the Second Dose of Zycortal

If the Day 10 Na^+/K^+ ratio is:		**25 days after the first dose, administer Zycortal, as follows:**
≥ 34	Do not administer Dose 2 on Day 10.	Decrease dose to: 2.0 mg/kg body weight
32 to < 34		Decrease dose to: 2.1 mg/kg body weight
27 to < 32		Continue 2.2 mg/kg body weight
≥ 24 to < 27		Increase dose to: 2.3 mg/kg body weight
< 24		Increase dose to: 2.4 mg/kg body weight

Prolonging the dosing interval:
If the dog is clinically normal and the Day 25 Na^+/K^+ ratio is > 32, it is possible to prolong the dosing interval instead of adjusting the dose as described in Table 1. Evaluate the electrolytes every 5–9 days until the Na^+/K^+ ratio is < 32, and then administer 2.2 mg/kg of Zycortal.

Subsequent doses and long term management:
Once the optimal dose and dosing interval have been determined, maintain the same regimen. If the dog develops abnormal clinical signs or Na^+ or K^+ serum concentrations, use the following guidelines for subsequent doses:

- Clinical signs of polyuria/polydipsia: Decrease the glucocorticoid dose first. If the polyuria/polydipsia persists and the Na^+/K^+ ratio is >32, then decrease the dose of Zycortal without changing the dosing interval.

- Clinical signs of depression, lethargy, vomiting, diarrhoea or weakness: Increase the glucocorticoid dose.

- Hyperkalaemia, hyponatremia or Na^+/K^+ ratio < 27: Decrease the Zycortal dosing interval by 2–3 days or increase the dose.

- Hypokalaemia, hypernatremia or Na^+/K^+ ratio > 32: Decrease the Zycortal dose.

Prior to a stressful situation, consider temporarily increasing the dose of glucocorticoid.

In the clinical trial, the mean final dose of desoxycortone pivalate was 1.9 mg/kg (range 1.2–2.5 mg/kg) and the mean final dosing interval was 38.7 ± 12.7 days (range 20–99 days) with the majority of dogs having a dosing interval between 20 and 46 days.

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

When given to dogs at three to five times the recommended dose, injection site reactions characterised by erythema and oedema occurred.

As expected from the pharmacodynamic effects, escalating doses of desoxycortone are associated with a dose-related trend for increased serum sodium, and decreased blood urea nitrogen, serum potassium and urine specific gravity. Polyuria, polydipsia may be observed.

Hypertension has been observed in dogs receiving 20 mg/kg of desoxycortone pivalate.

There is no specific antidote. In case of signs of overdose, the dog should be treated symptomatically, and subsequent doses reduced.

4.11 Withdrawal period(s)

Not applicable.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: corticosteroids for systemic use, mineralocorticoids
ATCvet code: QH02AA03

5.1 Pharmacodynamic properties

Desoxycortone is a corticosteroid with primarily mineralocorticoid activity, similar to aldosterone. In the kidney, desoxycortone causes sodium and chloride ion retention, and hydrogen and potassium ion excretion, creating an osmotic gradient. The osmotic gradient promotes water absorption from the renal tubules resulting in increased extracellular fluid volume, leading to blood volume expansion, improved venous return to the heart, and increased cardiac output.

5.2 Pharmacokinetic particulars

After subcutaneous administration of desoxycortone pivalate at a dose of 11 mg/kg body weight (five times the recommended dosage), the plasma half-life (mean ± standard deviation) is approximately 17 ± 7 days, with a maximum concentration (C_{max}) of 13.2 ± 5 ng/ml, and time to maximum concentration (T_{max}) of 10 ± 3.5 days.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Methylcellulose
Sodium carboxymethylcellulose

Polysorbate 60
Sodium chloride
Chlorocresol
Water for injections

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: 3 years.
Shelf life after first opening the immediate packaging: 4 months.

6.4. Special precautions for storage

Do not store above 30 °C.
Do not freeze.

6.5 Nature and composition of immediate packaging

Type I glass vial (4 ml) with a coated chlorobutyl rubber stopper and aluminium seal with a plastic flip-off cap.

Pack size of 1.

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 products should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Dechra Regulatory B.V.
Handelsweg 25
5531 AE Bladel
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/2/15/189/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 06/11/2015.
Date of last renewal:

10. DATE OF REVISION OF THE TEXT

Detailed information on this veterinary medicinal product is available on the website of the European Medicines Agency (http://www.ema.europa.eu/).

PROHIBITION OF SALE, SUPPLY AND/OR USE

Not applicable.