ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

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

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

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

Pregnant and breast-feeding women should avoid administration of this 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)

In a clinical trial, very common adverse reactions were polydipsia and polyuria. Common reactions were inappropriate urination, lethargy, alopecia, panting, vomiting, decreased appetite, anorexia, decreased activity, depression, diarrhoea, polyphagia, shaking, tiredness and urinary tract infections. Pancreas disorders have been reported very rarely 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 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 in accordance with standard texts.

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 dosage 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: 120 days.

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 (containing 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.

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.

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. STATEMENT OF THE MRLs

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Dales Pharmaceuticals Limited
Snaygill Industrial Estate
Keighley Road
Skipton
North Yorkshire
BD23 2RW
United Kingdom

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Veterinary medicinal product subject to prescription.

C. STATEMENT OF THE MRLs

Not applicable.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGE

CARDBOARD CARTON

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

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

2. STATEMENT OF ACTIVE SUBSTANCES

desoxycortone pivalate 25 mg/ml

3. PHARMACEUTICAL FORM

Prolonged-release suspension for injection

4. PACKAGE SIZE

4 ml

5. TARGET SPECIES

Dogs

6. INDICATION(S)

Read the package leaflet before use.

7. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
Read the package leaflet before use.

8. WITHDRAWAL PERIOD(S)

9. SPECIAL WARNING(S), IF NECESSARY

Read the package leaflet before use.

10. EXPIRY DATE

EXP {month/year}
Once broached, use by __/__/__

11. SPECIAL STORAGE CONDITIONS

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

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

Dechra Regulatory B.V.
Handelsweg 25
NL-5531 AE Bladel

16. MARKETING AUTHORISATION NUMBER(S)

EU/2/15/189/001

17. MANUFACTURER'S BATCH NUMBER

Lot {number}

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Zycortal 25 mg/ml prolonged-release suspension for injection
desoxycortone pivalate

2. QUANTITY OF THE ACTIVE SUBSTANCE(S)

Desoxycortone pivalate 25 mg/ml

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

4 ml

4. ROUTE(S) OF ADMINISTRATION

SC

5. WITHDRAWAL PERIOD(S)

6. BATCH NUMBER

Lot {number}

7. EXPIRY DATE

EXP {month/year}

8. THE WORDS "FOR ANIMAL TREATMENT ONLY"

For animal treatment only.

B. PACKAGE LEAFLET

PACKAGE LEAFLET:
Zycortal 25 mg/ml prolonged-release suspension for injection 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:
Dechra Regulatory B.V.
Handelsweg 25
5531 AE Bladel
The Netherlands

Manufacturer responsible for batch release:
Dales Pharmaceuticals Limited
Snaygill Industrial Estate
Keighley Road
Skipton
North Yorkshire
BD23 2RW
United Kingdom

2. NAME OF THE VETERINARY MEDICINAL PRODUCT

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

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

Active substance:
Desoxycortone pivalate 25 mg/ml

Excipients:
Chlorocresol 1 mg/ml

Zycortal is an opaque white suspension.

4. INDICATION(S)

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

5. CONTRAINDICATIONS

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

6. ADVERSE REACTIONS

In a clinical trial, very common adverse reactions were polydipsia (excessive drinking) and polyuria (excessive urination). Common reactions were inappropriate urination, lethargy, alopecia (hair loss),

panting, vomiting, decreased appetite, anorexia, decreased activity, depression, diarrhoea, polyphagia (excessive eating), shaking, tiredness and urinary tract infections.
Pancreas disorders have been reported very rarely 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).

If you notice any serious effects or other effects not mentioned in this package leaflet, please inform your veterinary surgeon.

7. TARGET SPECIES

Dogs.

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

Subcutaneous use.

Prior to use, gently shake the vial to resuspend the 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 in accordance with standard texts.

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 Zycortal 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.

9. ADVICE ON CORRECT ADMINISTRATION

Not applicable.

10. WITHDRAWAL PERIOD(S)

Not applicable.

11. SPECIAL STORAGE PRECAUTIONS

Keep out of the sight and reach of children.
Do not store above 30 °C.
Do not freeze.
Do not use this veterinary medicinal product after the expiry date which is stated on the carton and the vial after EXP.
Shelf life after first opening the container: 120 days.

12. SPECIAL WARNING(S)

Special precautions for use in animals:

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

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.

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

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

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

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

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

Pregnancy and lactation:

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.

Interaction with other medicinal products and other forms of interaction:

Use 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, or digoxin or insulin.

Overdose (symptoms, emergency procedures, antidotes):

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 and 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.

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

Medicines should not be disposed of via wastewater or household waste.

Ask your veterinary surgeon how to dispose of medicines no longer required. These measures should help to protect the environment.

14. DATE ON WHICH THE PACKAGE LEAFLET WAS LAST APPROVED

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

15. OTHER INFORMATION

Type I glass vial (containing 4 ml) with a coated chlorobutyl rubber stopper and aluminium seal with a plastic flip-off cap.
Pack size of 1.

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