Australian Government
Australian Pesticides and Veterinary Medicines Authority

PERMIT TO ALLOW SUPPLY AND MINOR USE OF AN UNREGISTERED AGVET CHEMICAL PRODUCT FOR TREATMENT OF PITUITARY-DEPENDENT HYPERADRENOCORTICISM AND ADRENAL CARCINOMA IN DOGS

PERMIT NUMBER – PER84048

This permit is issued to the Permit Holder in response to an application granted by the APVMA under section 112 of the Agvet Codes of the jurisdictions set out below. This permit allows a Supplier (as indicated) to possess the product for the purposes of supply and to supply the product to a person who can use the product under permit. This permit also allows a person, as stipulated below, to use the product in the manner specified in this permit in the designated jurisdictions. This permit also allows the Permit Holder, the Supplier (if not one and the same) and any person stipulated below to claim that the product can be used in the manner specified in this permit.

THIS PERMIT IS IN FORCE FROM 16 FEBRUARY 2017 TO 31 MAY 2025

Permit Holder and Supplier:
DECHRA VETERINARY PRODUCTS (AUSTRALIA) PTY LTD
2 Cal Close
SOMERSBY NSW 2250

Additional Suppliers:
CENVERSA SERVICES PTY LTD
26 Binney Rd
KINGS PARK NSW 2148

LYPPARD AUSTRALIA LTD
14-16 Fiveways Blvd
KEYSBOROUGH VIC 3173

PROVET PTY LTD
48 Bell-Are Ave
NORTHGATE QLD 4013

Persons who can use the product under this permit:
This product is to be used by or under the direction of a registered veterinary surgeon for animals in their care as permitted in the jurisdiction in which they practice their profession.

CONDITIONS OF USE

Products to be used:
APEX MITOTANE 500
AN UNREGISTERED PRODUCT
Containing: 500 mg/tablet MITOTANE as the only active constituent.

Jurisdiction:
All States and Territories.

Directions for Use:

User Safety Information:

WEAR GLOVES WHEN HANDLING PRODUCT OR EMPTY CONTAINER.

Wash hands if skin contact occurs.

Precautions:

Adrenal insufficiency may develop in dogs treated with mitotane especially in response to trauma or illness. Adrenal steroid replacement should be considered in these patients. Dog owners should keep a small supply of prednisolone for use in emergencies (dose rate is 1-2 mg/kg orally).

Treatment should be temporarily discontinued immediately following shock or severe trauma. Exogenous steroids may be necessary in such circumstances.

Mitotane is a strong inducer of cytochrome P-450 3A4. This may affect the dosage requirements of concomitant medications that are also substrates of these enzymes.

The product should be used with caution in dogs with liver disease and in dogs that have demonstrated a previous hypersensitivity to the product.

Adverse Events:

Some adverse events that have been associated with the use of mitotane in dogs include: weakness, vomiting, anorexia, diarrhoea, ataxia, Addisonian crisis and occasionally neurological signs. Adverse events are generally related to low serum cortisol concentrations, and thus may resolve in treatment with glucocorticoids.

Permit Holder's Dosage Recommendations:

Use as directed by the prescribing veterinarian for the treatment of pituitary dependent hyperadrenocorticism and for the palliative treatment of adrenal carcinoma in dogs.

Tablets should be given with food.

The dose rate used to treat pituitary dependent hyperadrenocorticism is individualised to the patient and is dependent on choice of protocol for treatment (i.e. complete chemical adrenalectomy versus partial chemical adrenalectomy) and individualised response to treatment. A common protocol used to treat pituitary dependent hyperadrenocorticism is as follows:

Induction Phase:

50 mg/kg by mouth divided twice daily for 5-7 days as an induction dose. Water consumption, appetite and general demeanour should be monitored during this phase and if any of these parameters change for longer than 12 hours, therapy should be stopped and an ACTH stimulation test performed 48 hours after the last dose. ACTH stimulation testing should be performed after the induction phase (usually after 5 days) before proceeding with further induction or maintenance phase. The aim of treatment is to have both pre and post cortisol

measurements in the normal resting range.

Maintenance Phase:

25-50 mg/kg by mouth once or twice weekly for maintenance. An ACTH stimulation test should be performed once every 8-12 weeks to ensure adequate control is being maintained.

A recommended protocol used in the palliative treatment of adrenal carcinoma is as follows: 50-75 mg/kg by mouth daily in divided doses for 10-14 days. The dose is then adjusted depending on individual response to therapy.

Treatment protocols should be carried out under close monitoring by the prescribing veterinarian.

Please refer to the Client Instructional Handout For Mitotane Therapy provided by the prescribing veterinarian.

Additional Conditions:
This permit allows for the use of a product in a manner specified on the permit. Persons who wish to prepare for use and/or use products for the purposes specified in this permit must read, or have read to them, the details and conditions of this permit. Unless otherwise stated, the use of the product must be in accordance with the product label at **Attachment 1**.

1. The Permit Holder or Secondary Suppliers, on behalf of the Permit Holder must only supply the product to a registered veterinary surgeon after receiving from them a signed, written request (request form) stating the veterinary surgeon's registration number, specifying the quantity of the product requested and containing the following statement immediately above the place for the veterinary surgeon's signature:

   I agree to:
   1. keep a register of all treatments using the product, recording the date, amount of product dispensed, patient and client details (including name, address and phone contact) (register);
   2. make the register available on request to State/Territory Government Chemical Coordinators and the APVMA;
   3. report any adverse experiences associated with the use of this product in writing to the Permit Holder within five (5) working days of the occurrence of any such adverse experience; and
   4. supply a completed copy of the Client Instructional Handout For Mitotane Therapy with each prescription of the product.

2. If there is a registered product available for the disease in the target animals, the attending veterinarian should document the evidence or justification to support the claim that the currently registered product is not achieving adequate efficacy at combating the disease, that the side effects are excessive, or clinical justification that the permit product is preferred for the specific patient.

3. The Permit Holder must not supply a total of more than 3,000 units (1 unit is 1 bottle of 50 tablets) of product during the period in which the permit is in force.

4. When the Permit Holder or Secondary Suppliers, on behalf of the Permit Holder, supplies the product to a veterinary surgeon, the Permit Holder or Secondary Suppliers, on behalf of the Permit Holder, must:
   4.1 give a copy of this permit, including these conditions, to the veterinary surgeon; and
   4.2 request the veterinary surgeon in writing to read the permit, in particular the permit conditions, before using the product.

5. The Permit Holder or Secondary Suppliers, on behalf of the Permit Holder must retain all request forms and make them available to the APVMA upon request.

6. The Permit Holder or Secondary Suppliers, on behalf of the Permit Holder must report any adverse experience associated with the use of the product to the APVMA as soon as possible and no later than five (5) working days after becoming aware of any such adverse experience.

7. The Permit Holder must maintain a compilation of adverse events reported to the Permit Holder or to the Secondary Suppliers, and this must be submitted to the APVMA upon application for renewal of the permit.

8. The Permit Holder must supply the product in a container that must:
    a. be impervious to, and incapable of chemical reaction with, its contents when under conditions of temperature and pressure that are likely to be encountered in normal service; and
    b. have sufficient strength and impermeability to prevent leakage of its contents during handling, transport and storage under normal handling conditions; and
    c. if it is intended to be opened more than once, be able to be securely and readily closed and reclosed; and
    d. have sufficient excess capacity to prevent it from breaking if its contents expand during handling, transport or storage; and
    e. enable all or any part of its contents to be removed or discharged in such a way that, with the exercise of no more than reasonable care, the contents cannot:
        (i)harm any person; or
        (ii)have an unintended effect that is harmful to the environment.
9. The Permit Holder must supply the product in a container that is child-proof.
10. Attached to the container must be a label which is consistent in content to the label in Attachment 1.
11. The shelf life of this product is 30 months from the date of formulation, when stored below 30°C (Room Temperature). The appropriate expiry date must appear on the label.

Issued by the Australian Pesticides and Veterinary Medicines Authority
Note: Version 2 issued to update holder name – 16/1/2019. Permit expiry date 30/04/2021
26/05/2021 – Permit updated to update permit conditions, and increase the number of units that may be supplied. Permit expiry extended to 31/05/2025. Permit issued as Version 3.

Attachment 1

Signal heading:	PRESCRIPTION ANIMAL REMEDY KEEP OUT OF REACH OF CHILDREN FOR ANIMAL TREATMENT ONLY
Product name:	**APEX MITOTANE 500**
Active constituent/s:	**Each tablet contains Mitotane 500mg**
Statement of claims:	**This product is NOT registered and is only available under APVMA permit to a registered veterinarian for use in the treatment of pituitary-dependant hyperadrenocorticism in dogs and in the palliative treatment of adrenal carcinoma under relevant State prescribing laws. READ THE PERMIT BEFORE USING THIS PRODUCT.**
Net contents:	**50 tablets**
Directions for Use Heading:	**DOSAGE: As directed by the prescribing veterinarian (see permit for details)**
Restraints:	**N/A**
Contraindications:	**N/A**
Precautions:	**Adrenal insufficiency may develop in dogs treated with mitotane especially in response to trauma or illness. Adrenal steroid replacement should be considered in these patients. Dog owners should keep a small supply of prednisolone for use in emergencies (dose rate is 1-2 mg/kg orally).** **Treatment should be temporarily discontinued immediately following shock or severe trauma. Exogenous steroids may be necessary in such conditions.** **Mitotane is a strong inducer of cytochrome P-450 3A4. This may affect the dosage requirements of concomitant medications that are also substrates of these enzymes.** **The product should be used with caution in dogs with liver disease and in dogs that have demonstrated a previous hypersensitivity to the product.**
Side effects:	**Some adverse events that have been associated with the use of Mitotane in dogs include: weakness, vomiting, anorexia, diarrhoea, ataxia, Addisonian crisis and occasionally neurological signs. Adverse events are generally related to low serum cortisol concentrations, and thus may resolve with treatment with glucocorticoids.**
Dosage & administration:	**Dosage recommendations: Use as directed by the prescribing veterinarian for the treatment of pituitary dependent hyperadrenocorticism and for the palliative treatment of adrenal carcinoma in dogs.** **Tablets should be given with food.**

	The dose rate used to treat pituitary dependent hyperadrenocorticism is individualised to the patient and is dependent on choice of protocol for treatment (ie complete chemical adrenalectomy versus partial chemical adrenalectomy) and individualised response to treatment. A common protocol used to treat pituitary dependent hyperadrenocorticism is as follows: **Induction phase: 50mg/kg by mouth divided twice daily for 5-7 days as an induction dose. Water consumption, appetite and general demeanour should be monitored during this phase and if any of these parameters change for longer than 12 hours, therapy should be stopped and an ACTH stimulation test performed 48 hours after the last dose. ACTH stimulation testing should be performed after the induction phase (usually after 5 days) before proceeding with further induction or maintenance phase. The aim of treatment is to have both pre and post cortisol measurements in the normal resting range.** **Maintenance phase: 25-50 mg/kg by mouth once or twice weekly for maintenance. An ACTH stimulation test should be performed once every 8-12 weeks to ensure adequate control is being maintained.** **A recommended protocol used in the palliative treatment of adrenal carcinoma is as follows: 50-75 mg/kg by mouth daily in divided doses for 10-14 days. The dose is then adjusted depending on individual response to therapy.** **Treatment protocols should be carried out under close monitoring by the prescribing veterinarian.** **Please refer to the Client Instructional Handout for Mitotane Therapy provided by the prescribing veterinarian.**
General directions:	**N/A**
Withholding Period/s:	**N/A**
Trade Advice:	**N/A**
Safety Directions:	**WEAR GLOVES WHEN HANDLING PRODUCT OR EMPTY CONTAINER.** **Wash hands if skin contact occurs.**
First Aid:	**If poisoning occurs contact a doctor or Poisons Information Centre phone Australia 131 126**
Additional user safety:	**N/A**
Environmental statements:	**N/A**
Disposal:	**Dispose of empty container by wrapping with paper and putting in garbage.**
Storage:	**Store below 30°C (room temperature)**
Name & address:	**Apex Laboratories Pty Ltd** **2 Cal Close Somersby NSW 2250 Australia**