Australian Government
Australian Pesticides and Veterinary Medicines Authority

PERMIT TO ALLOW SUPPLY AND MINOR USE OF A VETERINARY CHEMICAL PRODUCT

PERMIT NUMBER - PER14876

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. If this permit were not issued, supply of The Product as specified below would constitute an offence under section **78** of the Agvet Code. 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 4 AUGUST 2014 TO 4 AUGUST 2015.

Permit Holder:
ZOETIS AUSTRALIA PTY LTD
Level 6, 5 Rider Boulevard,
Rhodes, NSW 2138

Suppliers:
Zoetis Australia P/L and veterinary medicine distributors approved by, and acting on behalf of, Zoetis Australia P/L.

Persons who are authorised to use The Product under this permit:
Registered veterinary surgeons who are accredited through the completion of the Equivac HeV Vaccine e-learning module.

The Product:
EQUIVAC HeV HENDRA VIRUS VACCINE FOR HORSES
Containing: 100µg /mL of Hendra virus G glycoprotein as the only active constituent.

Directions for Use:

Animal	Purpose	Dose
Horses	Aid in the prevention of clinical disease caused by Hendra virus.	1 mL 3-6 weeks apart in horses 4 months of age and above, followed by 6 monthly booster

Jurisdiction

All States and Territories.

Withholding Period

N/A.

CONDITIONS

Supply

1. Zoetis must supply The Product in a container that complies with the requirements of Reg 18(1)(a-e) of the Agricultural and Veterinary Chemicals Code Regulations. Attached to the container must be a label bearing the relevant label particulars as indicated in **Attachment 1,** and showing an expiry date not greater than 15 months from the date of manufacture.

2. The Product may only be supplied by Zoetis or veterinary medicine distributors approved by and acting on behalf of Zoetis must keep and maintain the list of distributors and must make such records available to the APVMA on request.

3. Zoetis Australia Pty Ltd and the veterinary medicine distributors approved by and acting on behalf of Zoetis are authorised to supply only to registered veterinary surgeons whom Zoetis has trained and accredited on the use ***of The Product***

4. On each occasion The Product is supplied to an authorised veterinary surgeon, Zoetis must make, a record containing the following particulars:

    - Name, address and telephone number of the registered veterinary surgeon
    - Certificates of vaccination
    - Vaccine inventory, including full auditable details of quantity of stock manufactured, supplied, used or returned; batch numbers; date supplied.

5. On each occasion The Product is supplied, Zoetis must maintain the HeV Vaccine National Online Registry with information which includes, breed, sex, age, the unique microchip identification of each vaccinated horse and the batch number of The Product.

6. It is a condition of this permit that Zoetis allow CVOs access to the information in the HeV Vaccine Online Registry at all times. The same information must be provided to the APVMA on request.

7. The customer declaration letter in **Attachment 2** must accompany the permit document for each batch of EQUIVAC HeV HENDRA VIRUS VACCINE supplied.

8. Zoetis must record any reported adverse reaction, including lack of efficacy, resulting from the use of the vaccine. Pfizer Animal Health must fully investigate and report all adverse reactions to the APVMA's Coordinator, Adverse Experience Reporting Program within 48 hours of receiving an adverse reaction report.
   Freecall: 1800 700 583 (within Australia) - charges apply for calls made from mobile phones
   Fax: +61 2 6210 4776
   Email: aerp@apvma.gov.au

9. From each batch of The Product Zoetis must retain and store samples at the recommended temperature for at least two years past the nominal expiry date, to allow for testing as part of the required investigation of adverse reactions.

Use

10. Persons who wish to prepare for use and/or use the vaccine for the purposes specified in this permit must read, or have read to them, the label at **Attachment 1,** and particularly the information included in page 1 of the permit and the Conditions of the permit.

11. Registered veterinary surgeons, who are authorised to use The Product, are permitted to vaccinate only horses that are permanently identified by a microchip carrying a unique identification sequence.

12. On each occasion a registered veterinary surgeon vaccinates a horse with The Product, he/she must enter a record of each vaccination into the HeV Vaccine National Online Registry (managed by Zoetis) within 48 hours of vaccination. The record must include:

    - Details of each vaccinated horse, such as breed, sex, age, batch of vaccine used and the unique microchip identification
    - Location of the horse at the time of vaccination
    - Name, address and telephone number of owner or manager.

13. Registered veterinary surgeons must report to Zoetis any adverse reactions, including lack of efficacy, resulting from the use of The Product within 48 hours of either observing or being notified of an adverse reaction.

Issued by

Dr John Owusu
Principal Evaluator
Veterinary Medicines Program

Attachment 1

LABEL (1 mL syringe)

Equivac HeV Hendra Virus Vaccine for Horses
(B) 7347-
(E) mth/yr

FOR ANIMAL TREATMENT ONLY
Equivac HeV Hendra Virus Vaccine for Horses
100 µg sG-protein/mL
READ ENCLOSED LEAFLET
CAUTION: Avoid accidental self-injection
Store at 2° to 8°C (Refrigerate).
APVMA Permit No. PER13510

1 mL (Zoetis logo)

(B) 7347-
(E) mth/yr

(item numbers and version)

LABEL (10 mL vial)

KEEP OUT OF REACH OF CHILDREN
READ SAFETY DIRECTIONS
FOR ANIMAL TREATMENT ONLY

Equivac HeV Hendra Virus Vaccine for Horses
10 Doses
10 mL
100 µg sG-protein/mL
READ ENCLOSED LEAFLET
CAUTION: Avoid accidental self-injection
Store at 2° to 8°C (Refrigerate. Do not freeze).

(Zoetis logo)
APVMA Permit No. 13510

(B) 7347-
(E)mth/yr
(item numbers and version)

CARTON (20 dose pack x 1 mL Syringe/ 10 mL vial)

Main Panel:

KEEP OUT OF REACH OF CHILDREN
READ SAFETY DIRECTIONS
FOR ANIMAL TREATMENT ONLY

Equivac HeV Hendra Virus Vaccine for Horses
1 x 1 mL Syringe/Vial (10 mL vial)
(horse picture)
100 µg sG-protein per mL
0.1 mg/mL Thiomersal added
For active immunisation of horses against Hendra Virus as an aid in the prevention of clinical disease caused by Hendra virus.
(Zoetis logo)
CAUTION: Avoid accidental self-injection

Side Panel 1: **READ THE ENCLOSED LEAFLET BEFORE USING THIS PRODUCT**

DIRECTIONS FOR USE
Contents must be left in outer package until immediately before use.
For Intramuscular Use Only
Dose: 1 mL
MEAT WITHHOLDING PERIOD NIL

SAFETY DIRECTIONS
Caution: Care should be taken to avoid accidental self-injection and needle-stick injury when administering this product. In the event of accidental self-injection, seek medical advice immediately.
Personal Protective Equipment (PPE) should be worn whenever Hendra virus disease is suspected even in vaccinated horses as no vaccine can provide a guaranteed protection

(Bar Code)

Store between 2^{o}C and 8^{o}C (Refrigerate. Do not freeze). Protect from light.
(B) 7347-
EXPIRY
mth/yr (Item numbers and version)

Side Panel 2: **Equivac HeV Hendra Virus Vaccine for Horses**
Zoetis Australia Pty Ltd
Level 6, 5 Rider Boulevard, Rhodes, NSW 2138, Australia
Australian Technical Services Toll Free 1800 814 883
https://www.zoetis.com.au/home/
APVMA Permit Number: PER13510
1 x 1 mL Syringe/vial (10 Doses, 10 mL) (Recycle logo)

Side Panel 3: **Equivac HeV Hendra Virus Vaccine for Horses**
1 x 1 mL Syringe/Vial

(10 Doses, 10 mL)
(Zoetis logo)

Side Panel 4: **Equivac HeV Hendra Virus Vaccine for Horses**
Disposal: Dispose of empty syringes and needles by immediately placing into a designated and appropriately labelled ‘sharps’ container.

1 x 1 mL Syringe/Vial (10 Doses, 10 mL)

(Recycle logo)

LEAFLET

KEEP OUT OF REACH OF CHILDREN
READ SAFETY DIRECTIONS
FOR ANIMAL TREATMENT ONLY

Equivac® HeV Hendra Virus Vaccine for Horses

For active immunisation of horses against Hendra Virus as an aid in the prevention of clinical disease caused by Hendra virus.

This vaccine is under development at Zoetis Veterinary Medicine Research and Development. Equivac HeV Hendra virus vaccine for horses contains soluble forms of G glycoprotein [sG] of Hendra Virus adjuvanted with immunostimulating complex. Each mL of vaccine provides 100 µg G glycoprotein of Hendra Virus [sG – protein]. Thiomersal 0.1 mg/mL has been added as a preservative.

Trials have shown complete protection when vaccinated horses were subject to lethal challenge with a virulent strain of Hendra virus. All vaccinated animals were protected from clinical signs of disease. Equivac HeV Hendra virus vaccine for horses is used as an aid to prevent clinical disease in horses caused by Hendra virus, and also to reduce viral shedding. Following vaccination, horses produce antibodies that neutralise the Hendra virus by binding to the G protein of the virus, rendering it unavailable for attachment to the cells of the animal and thereby preventing infection.

Equivac HeV Hendra virus vaccine for horses does not contain genetically modified organisms and there is no live or inactivated Hendra virus in this product.

DIRECTIONS FOR USE
Contraindications and Precautions
The effect of this product on pregnant mares or on horses intended for breeding is not known.

There is no data to support the use of this vaccine in sick horses.

The effectiveness of Equivac HeV vaccine in the face of Hendra virus disease outbreak has not been studied.

Personal Protective Equipment (PPE) should be worn whenever HeV is suspected even in vaccinated horses as no vaccine can provide a guaranteed protection

Dosage and Administration
The dose on all occasions is **1 mL injected intramuscularly in horses 4 months of age and older**. The most convenient site for injection is the centre of the side of the neck. Before the vaccine is injected, the proposed site of inoculation on the horse's skin may be cleaned by swabbing with cotton-wool soaked in a suitable antiseptic solution, such as methylated spirits.

For primary immunisation two doses of vaccine should be administered 3 to 6 weeks apart. Effective levels of serological antibodies for the control of Hendra virus infection develops approximately 21 days after administration of the second dose of vaccine. Primary immunisation should be completed in advance of when the desired vaccination effect is needed.

When horses were challenged with Hendra virus approximately six months after receiving the primary vaccination course, 100% of the horses were found to be fully protected from clinical signs of Hendra virus disease.

At this stage, data to support greater than six months duration of protection is not available. Therefore, Zoetis recommends that a booster dose of the vaccine be administered 6 months after the completion of the primary immunisation course.

Summary of Dosing Schedule

Vaccination Type	**Timing Interval**
First Dose	Day 1
Second Dose	Day 21 - 42
Booster Dose	6 months after the date of the second dose
Followed by 6 monthly boosters	

Interaction
Compatibility studies with concurrent use of other veterinary products have not yet been performed.

Side Effects
Transient swelling may develop at the site of vaccination in some horses but should resolve within one week without treatment.

In some horses transient post-vaccination reactions including injection site reaction, pain, increase in body temperature, lethargy, inappetance, and muscle stiffness have also been observed. Rarely reported symptoms have included urticaria, mild peripheral oedema and mild transient colic. Symptoms may vary in severity and on some occasions may require veterinary intervention.

Systemic allergic reactions such as anaphylaxis are thought to occur rarely with all vaccines and may require parenteral treatment with adrenaline, corticosteroid and antihistamine as appropriate and should be followed with appropriate supportive therapy.

Efficacy
Clinical trials of Equivac® HeV vaccine containing either 100 µg or 50 µg sG in a prime-boost regime resulted in seroconversion in all vaccinated horses. Following challenge of a limited number of vaccinated horses with a lethal dose of HeV at least 6 months after the completion of the primary immunisation course, immunised horses remained clinically well throughout the period of observation (7-9 days post challenge). By contrast, non-vaccinated control animals showed clinical signs consistent with HeV infection from 4 days following challenge.

In the initial efficacy trials, there was no evidence of viral shedding by immunised horses after Hendra virus challenge, as reflected by PCR negative test results on all daily clinical samples. In non-immunised (control) horses or (surrogate control) guinea pigs, after challenge viral genome was detected in respiratory secretions during the incubation period as well as in oral and rectal swabs, urine and blood at disease onset (horses) or in major organs and blood on day 5 after exposure to the virus (guinea pigs). Following euthanasia of immunized horses (7 to 9 days post challenge, and 1-3 days after clinical signs first became apparent in control animals), there was no evidence of HeV viral replication in any tissue of immunised horses collected at post mortem examination, after what would be expected to be the period of acute infection. In contrast, HeV genome and antigen were distributed widely among the tissues of control animals including horses in a pattern consistent with acute HeV infection, and vasculopathy typical of HeV infection was also identified. Clinical, histological and immunohistological findings corroborate a diagnosis of acute HeV infection in these animals.

At approximately 6 months post-vaccination, when horses were challenged with Hendra virus via the intranasal route, all were protected from clinical signs of Hendra virus disease. In addition, virus was not reisolated from any clinical samples (collected pre-and post-mortem) from any of the horses, and there was no evidence of virus spreading beyond the site of administration (i.e. the

upper respiratory tract). In non-immunised (surrogate control) ferrets, viral infection was detected and all succumbed to acute Hendra virus infection.

In summary all vaccinated animals were protected from disease against a virulent challenge with Hendra virus until 1-3 days after the onset of acute disease in unvaccinated horses.

To demonstrate the immunogenicity of the vaccine under field conditions two trials were conducted. Horses were given two single doses of the vaccine by intramuscular injection on Days 0 and 21. 100% of vaccinated animals in both trials seroconverted, confirming that two doses of Equivac HeV given 3 weeks apart are sufficient to generate an antibody response in horses from 4 months of age. Serum neutralising antibody levels on day 42 (3 weeks after the 2nd dose of vaccine) in all vaccinated horses from both trials were equivalent to those seen in the earlier efficacy studies by challenge as described above, in which vaccinated horses were shown to be protected from challenge with Hendra virus.

An evaluation of the serological antibody response resulting from the administration of different vaccination schedules [2 doses 3 weeks apart, 2 doses 6 weeks apart, and 3 doses 4 weeks apart] using the Hendra virus vaccine Equivac HeV in horses was also carried out. Serological antibody response data suggested that two doses of Equivac HeV given 3 or 6 weeks apart are equally effective in generating protective levels of antibody in horses. In all vaccinated horses serum HeV neutralizing antibody titres measured from blood samples taken approximately 3 weeks and 5 weeks after animals received the final vaccination were comparable to those seen in the challenge studies described above, in which vaccinated horses were shown to be protected from challenge with Hendra virus. Hence, two doses of Equivac HeV can be administered between 3 to 6 weeks apart.

Safety
The safety profile of Equivac HeV was assessed in completely randomized, negatively controlled safety trials in foals aged between 4 and 6 months and in adult horses (aged between 3 and 23 years). For overdose safety, foals were given one double dose of Equivac HeV by intramuscular injection on Day 42, having previously received two single dose injections on Days 0 and 21. All foals remained healthy throughout the course of the study, with no evidence of decreased appetite, altered demeanor or abnormal gait. One animal in the vaccinate group recorded a high rectal temperature following the double dose; however this was short-lived, having resolved by the following morning. In addition one of the control animals demonstrated marked pyrexia at the same time point, which indicates that this event may not be vaccine related. There were no visible, palpable or discharging injection sites in any of the study animals at any point throughout the study, and the vaccine did not appear to cause any pain at the injection site at any stage, even when administered as a double dose. There were no systemic vaccine reactions or other abnormal reactions to the vaccine and no adverse events were reported throughout the course of the study.

Of the adult horses, 3.4% of animals in the vaccinate group had an injection site reaction following the first dose of vaccine. 34.5% of animals were recorded as having visible and/or palpable injection site reactions the day after the second dose of vaccine was administered, as did one animal in the control group (administered saline as a placebo). By Day 28 (7 days post-vaccination) these had all resolved, apart from one small intradermal lesion (measuring 0.004cm^3) that may not have been vaccine related. No painful injection site reactions were recorded at any stage and all horses remained healthy. There were no systemic vaccine reactions or other abnormal reactions to the vaccine and no adverse events were reported throughout the course of the study. In summary, the vaccine has been demonstrated to be safe in horses from 4 months old.

MEAT WITHHOLDING PERIOD N/A

SAFETY DIRECTIONS
Caution: In the event of an outbreak of Hendra virus appropriate personal safety precautions should be implemented and strictly enforced even around vaccinated horses.

Personal Protective Equipment (PPE) should be worn whenever Hendra virus disease is suspected even in vaccinated horses as no vaccine can provide a guaranteed protection

Additional User Safety
Take care to avoid accidental self-injection
Accidental self-administration may result in local bruising, pain and swelling. In the event of self-administration, seek medical attention and show the package leaflet or the label, to the Medical Practitioner.

FIRST AID
If poisoning occurs, contact a doctor or Poisons Information Centre. Phone Australia 131126.

This material may cause a mild allergic reaction in sensitive individuals on skin contact. Avoid skin contact. If skin or hair contact occurs, remove contaminated clothing and flush skin and hair with running water. If splashed in eyes, wash out immediately with water.

STORAGE
Store between 2°C and 8°C (Refrigerate. Do not freeze). Protect from light.

DISPOSAL
Dispose of containers and syringes by wrapping in paper and putting in garbage. Discarded needles should immediately be placed in a designated and appropriately labelled 'sharps' container.

NOTE
This vaccine has been tested for potency, sterility and safety before issue but it must be stressed that the correct vaccination procedure in the field is equally important if secondary injection-related infection is to be prevented. Very occasionally, pathogenic organisms from the animal's skin or lying dormant in the animal's tissues are activated at the time of vaccination and are able to initiate a local infection at the site of injection. This may lead to the horse's death, but fortunately is of rare occurrence. To the maximum extent permitted by law, Zoetis does not accept any claim, loss, liability, cost or expense in respect of:

(a) Disability or death of horses following vaccination as a result of failure to use the correct vaccination procedure described on the label.
(b) The failure of any horse to conceive or maintain a pregnancy following use of The Product.

Zoetis Australia Pty Ltd
Level 6, 5 Rider Boulevard, Rhodes, NSW 2138, Australia
Australian Technical Services Toll Free 1800 814 883
https://www.zoetis.com.au/
APVMA Permit Number: PER13510

(item number and version) (Recycling logo) (Month, Year)

Label:

PRODUCT NAME: Equivac® HeV Hendra Virus Vaccine for Horses	**PAGE:** 10 **OF** 7
DESCRIPTION: Cartons:1 X 1mL, 10mL; Labels: 1 mL,10mL; Leaflets: Single dose, Multidose	**APVMA Permit No:** PER13510
PRODUCT CODES: 73470209 (1mL, 20 dose pack), 73471301(10mL)	**Versions:** E
NOTES: Cartons, labels and leaflet	**DATE:** July 2014

Text contained within () represents alternative pack sizes. Text contained above this line does not appear on labelling.

Attachment 2

Zoetis Australia Research and Manufacturing Pty Ltd
ABN: 32 158 433 053
45 Poplar Road
Parkville Vic 3052

DECLARATION

APVMA Permit Number: **14876**

Trade Name: **Equivac HeV Hendra Virus Vaccine for Horses**

Zoetis has obtained permission from the Australian Pesticides and Veterinary Medicines Authority (APVMA) to use labels with permit number PER13510 for the supply of Equivac HeV Hendra Virus Vaccine for Horses under permit number PER14876.

For technical enquiries regarding this product please contact Zoetis Australian Technical Services Toll Free 1800 814 883.

Name: Sean Griffiths
Company: Zoetis Australia Research and Manufacturing Pty Ltd
Position: Site Quality Operations Leader

Signature: Date: