AUSTRALIAN PRODUCT INFORMATION

RABIPUR (INACTIVATED RABIES VIRUS VACCINE) POWDER FOR INJECTION

1 NAME OF THE MEDICINE

RABIPUR Inactivated Rabies Virus vaccine

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

RABIPUR is an inactivated rabies virus vaccine, derived from the fixed-virus strain, Flury LEP. The virus is propagated in a Purified Chick Embryo Cell (PCEC) culture, inactivated using β-propiolactone and purified via centrifugation.

Each 1.0 mL dose of the reconstituted vaccine contains no less than 2.5 IU of inactivated rabies virus, in accordance with the World Health Organisation requirements.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

Powder for injection.

The reconstituted vaccine is clear to slightly opalescent and colourless to slightly pink.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

For active immunisation against rabies virus, including:

a) Pre-exposure immunisation,

b) Post-exposure treatment following exposure to rabies virus.

4.2 DOSE AND METHOD OF ADMINISTRATION

Recommended dosages, as outlined below, are the same for children, adolescents and adults.

Dosage

Pre-exposure Prophylaxis

Primary immunisation

In previously unvaccinated persons, an initial course of pre-exposure prophylaxis consists of three doses (each of 1.0 mL) administered on days 0, 7 and 21 *or* 28.

Booster doses

In persons with ongoing risk of exposure to rabies virus, the following general guidance is provided:

- Testing for neutralising antibodies by the Rapid Focus-Fluorescent Inhibition Test (RFFIT) at 6-month intervals is usually recommended if the risk of exposure to rabies virus is high (e. g. Laboratory staff working with rabies virus).
- In persons who are considered to be at continuing risk of exposure to rabies (e.g. veterinarians and their assistants, wildlife workers, hunters), a serological test should usually be performed at least every 2 years, with shorter intervals if appropriate to the perceived degree of risk.
- In above mentioned cases, a booster dose should be given should the antibody titre fall below 0.5 IU/mL.
- Alternatively, in persons with ongoing risk of rabies exposure, booster doses may be offered every 2 to 5 years without serological testing.

RABIPUR may be used for booster vaccination after prior immunisation with human diploid cell rabies vaccine.

Post-exposure treatment

Post-exposure immunisation should begin as soon as possible after exposure and should be accompanied by local measures to the site of inoculation so as to reduce the risk of infection.

Immediate wound treatment:

In order to remove as much of the rabies virus as possible, immediately cleanse the wound with soap and flush thoroughly with water. Then treat with alcohol (70 %) or an iodine tincture. Where possible, bite injuries should not be closed with a suture, or only sutured to secure apposition. Prophylaxis against tetanus should be administered when necessary.

In cases where passive immunisation is also indicated, as much of the recommended dose of HRIG as is anatomically feasible should be applied as deeply as possible in and around the wound. Any remaining HRIG should be injected intramuscularly at a site distant from the site of vaccine administration (preferably intragluteally).

Previously fully immunised individuals:

For WHO exposure categories II and III, and in category I cases where there is uncertainty regarding the correct classification of exposure (see Table 1 below), two doses (each of 1.0 mL) should be administered on both day 0 and day 3. On a case by case basis, schedule A (see Table 2 below) may be applied if the last dose of vaccine was given more than two years previously.

Table 1: Immunisation schedules appropriate to different types of exposure (Published by World Health Organisation, 2002)

Exposure Category	Type of contact with suspect or confirmed rabid domestic or wild animal, or animal unavailable for observation[(a)]	Recommended treatment
I	Touching or feeding of animals Licks on intact skin Touching of inoculated animal lure with intact skin	None, if reliable case history is available. In case of unreliable case history, treat according to schedule A (see Table 2).
II	Nibbling of uncovered skin Minor scratches or abrasions without bleeding Licks on broken skin Touching of inoculated animal lure with damaged skin	Administer vaccine immediately [(b)] as in schedule A (see Table 2). In case of uncertainty and/or exposure in a high-risk area, administer active and passive treatment as in schedule B (see Table 2). (see also footnote [c])
III	Single or multiple transdermal bites or scratches Contamination of mucous membrane with saliva (i. e. licks) Touching of inoculated animal lure with mucous membrane or fresh skin wound	Administer rabies immunoglobulin and vaccine immediately [(b)] as in schedule B (see Table 2). (see also footnote [c])

a) Exposure to rodents, rabbits and hares seldom, if ever, requires specific anti-rabies treatment.

b) If an apparently healthy dog or cat in or from a low-risk area is placed under observation, it may be justified to delay specific treatment.

c) Stop treatment if animal is a cat or dog and remains healthy throughout an observation period of 10 days or if animal is euthanised and found to be negative for rabies by appropriate laboratory techniques. Except in the case of threatened or endangered species, other domestic and wild animals suspected as rabid should be euthanised and their tissues examined using appropriate laboratory techniques.

Individuals non-immunised or with uncertain immune status

Depending on the WHO category as in Table 1, treatment according to schedules A or B (see Table 2 below) may be required for previously non-immunised persons and for those who have received fewer than 3 doses of vaccine or who have received a vaccine of doubtful potency.

Table 2: Post-exposure treatment of subjects with no or uncertain immune status

Schedule A Active immunisation after exposure is required	*Schedule B* Active and passive immunisation after exposure are required
One injection of RABIPUR i.m. on days: 0, 3, 7, 14, 28 (5-doses schedule) Or One dose of RABIPUR is given into the right deltoid muscle and one dose into the left deltoid muscle on day 0, and one dose is applied into the deltoid muscle on days 7 and 21 (2-1-1 regimen). In small children the vaccine is to be given into the thighs.	Administer RABIPUR as in schedule A + 1 × 20 IU/kg body weight human rabies immunoglobulin* concomitantly with the first dose of RABIPUR. If HRIG is not available at the time of the first vaccination it must be administered not later than 7 days after the first vaccination.

**** Observe manufacturer's instructions regarding administration***

Immunocompromised patients and patients with a particularly high risk of contracting rabies

For immunocompromised patients, those with multiple wounds and/or wounds on the head or other highly innervated areas, and those for whom there is a delay before initiation of treatment, it is recommended that:

- The days 0, 3, 7, 14 and 28 immunisation regimen should be used for these cases
- Two doses of vaccine may be given on day 0. That is, a single dose of 1.0 mL vaccine should be injected into the right deltoid and another single dose into the left deltoid muscle. In small children, one dose should be given into the anterolateral region of each thigh.

Severely immunosuppressed patients may not develop an immunologic response after rabies vaccination. Therefore, prompt and appropriate wound care after exposure is an essential step in preventing death. In addition, rabies immunoglobulin should be administered in all immunosuppressed patients experiencing Category II and Category III wounds.

For immunocompromised patients, the neutralising antibody titre should be measured 14 days after the first injection. Patients with a titre that is less than 0.5 IU/mL should be given another two doses of vaccine simultaneously as soon as possible. Further checks on the

antibody titre should be made and further doses of vaccine should be administered as necessary.

Method of administration

Reconstitution:

The vaccine should be visually inspected both before and after reconstitution for any foreign particulate matter and/or change in physical appearance. The vaccine must not be used if any change in the appearance of the vaccine has taken place.

The powder for solution should be reconstituted by addition of the diluent supplied using a sterile syringe supplied. The reconstituted vaccine is clear to slightly opalescent and colourless to slightly pink. One sterile syringe and needle is supplied with each dose packed. The reconstituted vaccine must be carefully agitated prior to injection and should be used immediately with any unused vaccine or waste material suitably disposed.

The vial of vaccine contains negative pressure. After reconstitution of the vaccine, it is recommended to unscrew the syringe from the needle to eliminate the negative pressure. After that, the vaccine can be easily withdrawn from the vial. It is not recommended to induce excess pressure, since over-pressurization will create the problems in withdrawing the proper amount of the vaccine.

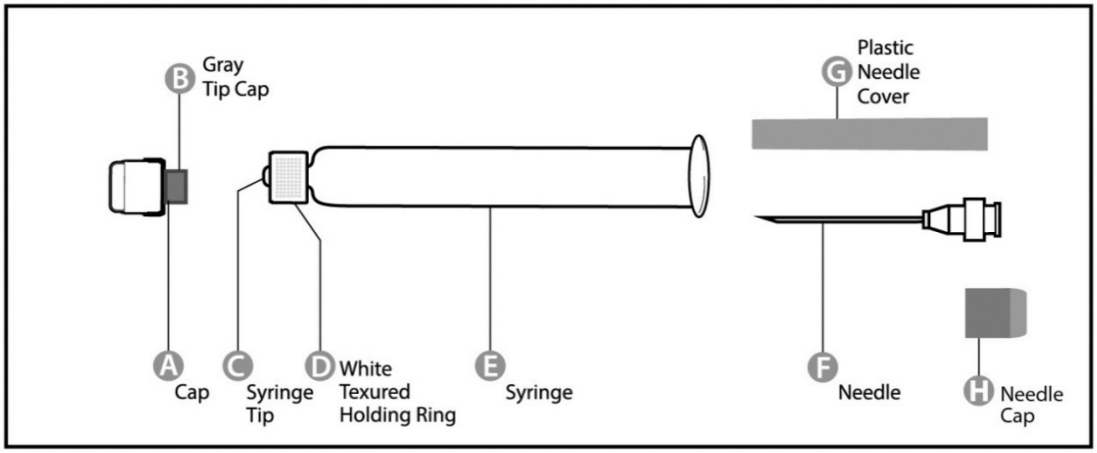
Administration:

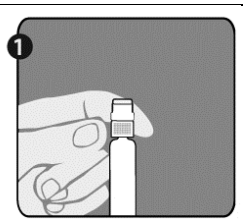
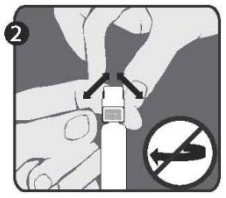
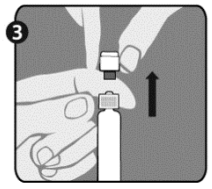
The vaccine must be given by intramuscular injection into the deltoid muscle, or into the anterolateral region of the thigh in small children. The vaccine must not be given by intragluteal injection.

Product is for single use in one patient only.

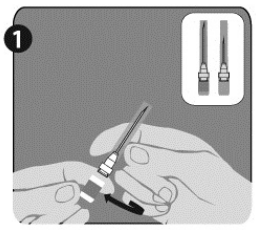
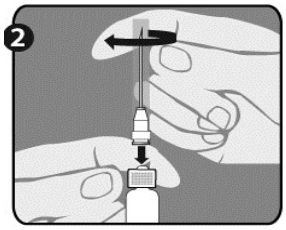
Instructions for use and handling:

Administration of RABIPUR presented in a pre-filled syringe



Step 1: With one hand, hold the syringe (E) with the cap pointing upward. Be sure to hold the syringe by the white textured holding ring (D).	
Step 2: With the other hand, grasp the cap (A) and firmly rock it back and forth to break its connection to the holding ring (D). **Do not twist or turn the cap.**	
Step 3: Lift up to remove the cap (A) and the attached gray tip cap (B). Be careful not to touch the sterile syringe tip (C).	

Needle application (these instructions apply to both provided needles)

Step 1: Twist to remove the cap (H) from the reconstitution needle. Do not remove the plastic cover (G). **This needle is the longer of the two needles.**	
Step 2: With one hand, firmly hold syringe (E) by white textured holding ring (D). With your other hand, insert needle (F) and twist clockwise until it locks into place. Once needle is locked, remove its plastic cover (G). The syringe (E) is now ready for use.	

After completing the reconstitution of the vaccine, remove the cap from the administration needle (as explained in step 1 for the reconstitution needle) and replace the reconstitution needle with the administration needle.

4.3 CONTRAINDICATIONS

a) Pre-exposure immunisation

RABIPUR is contraindicated in subjects with a known severe hypersensitivity to any of the components of the vaccine, including chicken eggs, chicken protein, bovine gelatin, neomycin, chlortetracycline and amphotericin B (amphotericin).

Vaccination should be delayed in subjects suffering from an acute febrile illness. Minor infections are not a contraindication to vaccination.

b) Post-exposure treatment

In view of the fatal outcome of clinically manifest rabies, any suspicion of infection should always lead to treatment. Subjects that have a severe hypersensitivity to components of the vaccine should not receive the vaccine for post-exposure treatment unless a suitable alternative vaccine is not available, in which case all injections should be administered with close monitoring and with facilities for emergency treatment available.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

For intramuscular injection only.

Serious systemic anaphylactic reactions, including cases of anaphylactic shock, have been reported in temporal association with RABIPUR.

Serious neurological events, such as encephalitis, Guillain-Barré-Syndrome, meningitis, multiple sclerosis, myelitis, paresis, and retrobulbar neuritis have been reported (<1:100,000) in temporal association with RABIPUR.

If complications arise following any of the series of injections in the schedule, do not continue with further vaccine doses until the cause of the complications have been clarified.

As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of a rare anaphylactic event following the administration of the vaccine.

In patients with known hypersensitivity to constituents of the vaccine receiving post-exposure treatment, appropriate remedial facilities for treating anaphylactic shock should always be available during immunisation, or alternatively another equivalent modern cell culture rabies vaccine should be used.

A history of allergy to eggs or a positive skin test to ovalbumin does not necessarily indicate that a subject will be allergic to RABIPUR. However, subjects who have a history of a severe hypersensitivity reaction to eggs or egg products should not receive the vaccine for pre-exposure prophylaxis.

Patients who are immunocompromised, including those receiving immunosuppressive therapy or high dose corticosteroids, may not mount an adequate response to rabies vaccine. Therefore, it is recommended that serological responses should be monitored in such patients and additional doses given as necessary.

Anxiety-related reactions, including vasovagal reactions (syncope), hyperventilation or stress-related reactions, may occur in association with vaccination as a psychogenic response to the needle injection (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). It is important that procedures are in place to avoid injury from fainting.RABIPUR may contain residual amounts of the antibiotics neomycin, chlortetracycline and amphotericin B (amphotericin).

The vaccine is unlikely to produce an effect on ability to drive and use machines.

Adherence to treatment guidelines, as outlined below, are of utmost importance in order to minimise risk of rabies disease. However, in very few cases development of rabies disease despite correct treatment has been reported. Direct inoculation of the rabies virus into nerve endings has been discussed as an explanation for these rare cases.

As with other vaccines, a protective immune response may not be achieved in all patients who receive the vaccine.

Use in the elderly

See Section 4.2 DOSE AND METHOD OF ADMINISTRATION.

Paediatric use

See Section 4.2 DOSE AND METHOD OF ADMINISTRATION.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Other vaccines, which are deemed clinically essential, may be given at the same time as RABIPUR. Different injectable vaccines should be administered into separate injection sites. Do not mix vaccines within the same syringe.

For patients receiving immunosuppressive therapy, or with congenital or acquired immunodeficiency, the response to the vaccination may be reduced or absent.

Immunosuppressive therapy during post-exposure treatment should be avoided.

Anti-rabies immunoglobulins may attenuate the effects of concomitantly administered rabies vaccine. Therefore it should only be administered once at the recommended dose.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No reproductive toxicity studies have been performed with RABIPUR.

Use in pregnancy

(Pregnancy Category B2)

Animal embryofetal development studies have not been conducted with the vaccine. It is not known whether the vaccine can cause foetal harm when administered to a pregnant woman or can effect reproductive capacity. For pre-exposure vaccination, RABIPUR should not be given to a pregnant woman, unless benefits outweigh potential risks and vaccination is clearly needed, as might occur in high risk situations.

Pregnancy is never a contraindication to post-exposure rabies vaccination. In post-exposure situations the vaccine should be given as recommended.

No cases of harm attributable to use of this vaccine during pregnancy have been observed in mothers or children.

Use in lactation

It is not known whether RABIPUR is excreted in human milk. Caution should be exercised when the vaccine is administered to a nursing mother.

It is advisable to carefully weigh expected benefits against potential risks prior to prophylactic administration of RABIPUR during lactation.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The vaccine is unlikely to produce an effect on ability to drive and use machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

As with all vaccines and as outlined below, RABIPUR administration may cause unintended reactions. However, not all events occurring after vaccination are causally related to the vaccine. For any unexpected effects while taking RABIPUR, contact your physician or pharmacist.

Adverse Drug Reaction Overview

In very rare cases, neurological and neuroparalytical events and cases of hypersensitivity have been reported in temporal association with administration of RABIPUR.

The most commonly occurring adverse reactions are injection-site reactions, such as injection-site erythema, induration and pain; flu-like symptoms, such as asthenia, fatigue, fever, headache, myalgia and malaise; arthralgia, dizziness, lymphadenopathy, nausea, and rash.

A patient’s risk of acquiring rabies must be carefully considered before deciding to discontinue vaccination.

Clinical Trials Experience

As clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a vaccine cannot be directly compared to rates in the clinical trials of another vaccine and may not reflect the rates observed in practice. The adverse

reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to vaccine use and for approximating rates.

In a comparative trial in normal volunteers, Dreesen *et al* (Vaccine. 1989;7:397-400) described their experience with RABIPUR compared to a human diploid cell culture rabies vaccine (HDCV). Nineteen subjects received RABIPUR and 20 received HDCV. The most commonly reported adverse reaction was pain at the injection site, reported in 45% of the HDCV group, and 34% of the RABIPUR group. Localised lymphadenopathy was reported in about 15% of each group. The most common systemic reactions were malaise (15% RABIPUR group versus 25% HDCV group), headache (10% RABIPUR group versus 20% HDCV group), and dizziness (15% RABIPUR group versus 10% HDCV group).

In a recent study in the USA, 83 subjects received RABIPUR and 82 received HDCV. Again, the most common adverse reaction was pain at the injection site in 80% in the HDCV group and 84% in the RABIPUR group. The most common systemic reactions were headache (52% RABIPUR group versus 45% HDCV group), myalgia (53% RABIPUR group versus 38% HDCV group) and malaise (20% RABIPUR group versus 17% HDCV group). None of the adverse events were serious, almost all adverse events were of mild or moderate intensity.

Other common adverse events reported in clinical trials

The data from clinical trials described below reflect exposure to RABIPUR in 1307 subjects, including 355 subjects in pre-exposure vaccination settings and 952 patients, who received RABIPUR for post-exposure prophylaxis. RABIPUR was studied primarily in single-blind, randomised controlled trials. The population studied was mainly Caucasian and Asian, ranging from healthy infants to healthy adults with an equal gender distribution. Patients only received intramuscular administration of RABIPUR.

Body System	**Frequency**	**Adverse Reactions (Clinical Trials, n=1307)**
General disorders and administration-site condition	Very common (≥1/10)	Injection-site reaction, injection-site induration
	Common (≥1/100 and <1/10)	Asthenia, fever, fatigue, influenza-like illness, injection-site erythema
	Rare ≥1/10,000 and <1/1,000	Chills
Skin and subcutaneous tissue disorders	Very common (≥ 1/10)	Rash
	Common (≥1/100 and <1/10)	Urticaria
	Rare ≥1/10,000 and <1/1,000	Hyperhidrosis

Body System	Frequency	Adverse Reactions (Clinical Trials, n=1307)
Musculoskeletal and connective tissue disorders	Common (≥1/100 and <1/10)	Arthralgia, Myalgia
Gastrointestinal disorders	Common (≥1/100 and <1/10)	Gastrointestinal disorders (such as nausea, vomiting, diarrhoea or abdominal pain)
Metabolism and Nutrition Disorders	Common (≥1/100 and <1/10)	Decreased appetite
Immune System Disorders	Rare ≥1/10,000 and <1/1,000	Hypersensitivity
Nervous System Disorders	Rare ≥1/10,000 and <1/1,000	Paraesthesia

Post-Marketing Adverse Drug Reactions

Those adverse reactions identified during post-approval use of RABIPUR can be found in the following table. As these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to vaccine exposure. Decisions to include these reactions in labelling are typically based on one or more of the following factors: 1) seriousness of the reaction, 2) frequency of reporting, or 3) strength of causal connection to vaccine exposure, or a combination of these factors.

Adverse reactions information (post-marketing)

Body System	Adverse Reactions (only observed in post-approval use, n ≥ 10,000,000); frequency < 1: 1,000 for all events
General disorders and administration-site condition	Chills, sweating
Cardiac disorders	Circulatory reactions (such as palpitations or hot flush)
Ear and labyrinth disorders	Vertigo
Eye disorders	Visual disturbance
Nervous system disorders	Paraesthesia

Body System	Adverse Reactions (only observed in post-approval use, n ≥ 10,000,000); frequency < 1: 1,000 for all events
	Nervous system disorders (such as encephalitis, paresis or Guillain-Barré-Syndrome), presyncope, syncope
Immune system disorders	Allergic reactions (such as anaphylaxis, bronchospasm, oedema, pruritus, rash or urticaria)
	Type III hypersensitivity-like symptoms
Musculoskeletal and connective tissue disorders	Pain in limbs, limb swelling
Skin and subcutaneous tissue disorders	Angioedema

Once initiated, rabies prophylaxis should not be interrupted or discontinued because of local or mild systemic adverse reactions to rabies vaccine. Usually such reactions can be successfully managed with anti-inflammatory and antipyretic agents.

In post-marketing experience to November 2004 (a period in which approximately 33 million doses have been distributed) 47 deaths due to rabies were reported in persons who had been received post-exposure treatment with RABIPUR. In all but three cases WHO recommendations for post-exposure treatment had not been followed. The other three cases involved severe exposures such as facial bites.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Injection of the vaccine induces production of an antibody titre that markedly exceeds 0.5 IU/mL of serum, the threshold considered to provide adequate protection. As the antibody

concentration slowly falls, booster doses are required to maintain antibody levels above the acceptable level of 0.5 IU/mL.

Clinical trials

Pre-exposure Immunisation

The immunogenicity of RABIPUR has been demonstrated in clinical trials conducted in Europe, North America and Asia. When administered according to the recommended immunisation schedule (days 0, 7, 21 *or* 28), 100% of subjects attained an adequate titre of 0.5 IU/mL by day 28 or earlier. Persistence of antibody titres ≥ 0.5 IU/mL for up to 2 years after immunisation with RABIPUR has been measured in clinical trials.

Table 3 details the serum antibody titres of subjects, vaccinated according to the pre-exposure vaccination dosage regimen with either RABIPUR or Human Diploid Cell rabies Vaccine (HDCV). These data demonstrate that RABIPUR causes production of antibodies, with geometric mean titres (GMT) greater than 0.5 IU/mL by Day 28. The study also demonstrated no statistically significant difference in GMT following vaccination with either type of vaccine.

Table 3. Antibody titres following pre-exposure vaccination with RABIPUR and HDCV

Day	Rabies Antibody conc (IU/mL)	RABIPUR (n=82)	HDCV (n=79)
0	GMT Range	0.25 0.25 – 0.25	0.25 0.25 – 0.25
28	GMT Range	9.3 0.8 – 68.0	12.0 2.0 – 95.0
49	GMT Range	25.3 3.0 – 70.0	25.8 4.0 – 120.0

In other studies, long term antibody titres following pre-exposure vaccination with RABIPUR were evaluated in 36 patients. The study showed that 2 years post-vaccination, the antibody GMTs remained above 0.5 IU/mL for 64% of recipients vaccinated. Antibody titre data is provided in Table 4.

Table 4. Long term antibody titres following vaccination with RABIPUR

	Day 0 (n=36)	Day 28 (n=36)	Day 48 (n=36)	Day 90 (n=34)	Year 2 (n=28)
Minimum Titre (IU/mL)	<0.02	0.58	4.48	0.90	0.05
Geometric Mean Titre (GMT) (IU/mL)	<0.02	2.47	12.73	5.06	0.80
No. of subjects with titre ≥0.5 IU/mL	0	36	36	34	18
% of subjects with GMT ≥0.5 IU/mL	0	100.0	100.0	100.0	64

Post-exposure Immunisation

Clinical studies in patients exposed to rabies virus have demonstrated that RABIPUR, when used in the recommended post-exposure WHO schedule of 5 x 1.0 mL Intramuscular injections (on days 0, 3, 7, 14, 28), provided protective titres of neutralising antibodies (>0.5 IU/mL) in 98% of patients within 14 days and in 100% of patients by day 30. Similar results were obtained in several studies with healthy volunteers who had been given the WHO recommended post-exposure regimen ("simulated" post-exposure immunisation). Table 5 details the proportion of subjects who developed a protective antibody titre (≥0.5 IU/mL) following vaccination in accordance with the post-exposure regimen.

Table 5. Proportion of subjects achieving a protective antibody titre following post-exposure vaccination with RABIPUR

Day	No of subjects with GMT ≥0.5 IU/mL (n=37)
7	11 / 37 (29.7%)
14	35 / 37 (94.6%)
30	36 / 36 (100.0%)
90	36 / 36 (100.0%)
365	33 / 34 (97.1%)

One study followed cohorts of patients presenting with bites from laboratory proven rabid animals for one year. No case of rabies was observed in this patient population. Some patients received passive immunisation with Human Rabies Immunoglobulin (HRIG) 20 - 30 IU/kg body weight, or Equine Rabies Immune Globulin (ERIG), 40 IU/kg body weight, at the time of the first vaccine dose. Analysis of the data concluded that the addition of either HRIG or ERIG caused a slight decrease in GMTs when compared to subjects not receiving the immunoglobulin; this slight decrease was deemed neither clinically relevant nor statistically significant.

Booster Immunisation

The ability of RABIPUR to boost antibody titres in previously immunised subjects has been examined through clinical studies. Data from one study demonstrated that after one booster dose, a 10-fold or higher increase in GMTs on day 30 were observed in subjects previously vaccinated with HDCV. A significant increase was observed among all vaccinees with antibody titres of > 0.5 IU/mL at baseline on day 0. Table 6 details the GMT’s for this trial.

Table 6. Antibody titres following booster immunisation with RABIPUR

	Group A	Group B	Group C	Group D
Median GMT (IU/mL) – Day 0	1.50	0.40	2.20	1.57
Median GMT (IU/mL) – Day 28	15.05	11.00	6.85	14.20

Group A – *Pre-exposure immunisation with HDCV <1 year prior to study*
Group B – *Pre-exposure immunisation with HDCV <2 years prior to study*
Group C – *Pre-exposure immunisation with HDCV <5 years prior to study*
Group D – *Post-exposure immunisation with HDCV <1 year prior to study*

Data from an additional booster vaccination study demonstrated that individuals known to have been previously immunised with a PCEC vaccine or Human Diploid Cell Vaccine (HDCV), developed a rapid anamnestic response when boosted with RABIPUR. A booster response was observed on day 7 for all individuals. One RABIPUR intramuscular booster dose resulted in a significant increase in antibody titers in all subjects, regardless of whether they had received RABIPUR or HDCV as the primary vaccine. More than one year after primary immunisation, one or two IM doses of RABIPUR induced a 10-fold or higher increase in GMTs by day 7. On day 21 post-booster, the GMTs of subjects that received two booster doses of vaccine were higher than those that received one booster dose of vaccine.

Table 7. Antibody titre data following one or two booster doses of RABIPUR

Day		RABIPUR Booster Day 0		RABIPUR Booster Days 0, 3	
		n	Rabies Ab (IU/mL)	n	Rabies Ab (IU/mL)
-3	Geometric Mean Titre	69	2.33	67	1.84
3	Geometric Mean Titre	69	2.87	67	2.07
7	Geometric Mean Titre	69	51.23	66	51.67
21	Geometric Mean Titre	68	120.91	66	151.63

5.2 PHARMACOKINETIC PROPERTIES

Not relevant for vaccines.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No genotoxicity studies have been performed with RABIPUR.

Carcinogenicity

No carcinogenicity studies have been performed with RABIPUR.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Each 1.0 mL dose of the reconstituted vaccine also contains the following excipients:

- trometamol (3.5 mg),
- sodium chloride (4.5 mg),
- disodium edetate (0.25 mg),
- monopotassium glutamate (0.9 mg),
- polygeline (10.5 mg),
- sucrose (60 mg)
- water for injections (1.0 mL).

The quantities of each excipient (excluding water for injection) will vary dependent on virus concentration in the harvested material.

Contains no antimicrobial agent.

The antibiotics neomycin, chlortetracycline and amphotericin B (amphotericin) are used in the manufacturing process of this vaccine and may be present in trace amounts.

The manufacture of this product includes exposure to bovine derived materials. No evidence exists that any case of vCJD (considered to be the human form of bovine spongiform encephalitis) has resulted from the administration of any vaccine product.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store vaccine at 2°C - 8°C (in a refrigerator). Do not freeze.

Store diluent below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

RABIPUR is available in the following pack sizes:

- 1 single dose lyophilised vaccine vial (type 1 glass) with a stopper (chlorobutyl) with 1 single dose ampoule (type 1 glass) containing diluent (1.0 mL). A sterile syringe and needle used for dilution of vaccine and administration are enclosed.

- 5 single dose lyophilised vaccine vials (type 1 glass) with a stopper (chlorobutyl) with 5 single dose ampoules (type 1 glass) containing diluent (1.0 mL). Five sterile syringes and

needles used for dilution of vaccine and administration are enclosed in the five dose pack.

- 1 single dose lyophilised vaccine vial (type 1 glass) with a stopper (chlorobutyl), with 1 single dose disposable pre-filled syringe (type 1 glass) with a plunger-stopper (bromobutyl) containing diluent (1.0 mL), without needle and with a tip-cap (bromobutyl). With 1 administration needle for injection and one needle for reconstitution.

Not all pack sizes and presentations may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

No data available.

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription only medicine

8 SPONSOR

GlaxoSmithKline Australia Pty Ltd
Level 4, 436 Johnston Street
Abbotsford, Victoria
AUSTRALIA 3067

MANUFACTURED BY:

GSK Vaccines and Diagnostics GmbH
P.O. Box 16 30
D-35006 Marburg
Germany

9 DATE OF FIRST APPROVAL

25 July 2005

10 DATE OF REVISION

13 April 2018

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All	PI re-format and editorial changes
4.2	Addition of appearance of reconstituted vaccine, and instructions for handling and reconstitution

4.4	Addition of precaution on protective immune response
6.5	Addition of new presentation

Version 4