NEW ZEALAND DATA SHEET

1 VERORAB 3.25 IU POWDER AND DILUENT FOR SUSPENSION FOR INJECTION

Inactivated Rabies Virus Vaccine

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Verorab is a Purified Vero Rabies Vaccine referred as PVRV.

Verorab is a sterile stable freeze-dried solution of purified and inactivated rabies virus from Wistar strain PM/WI38 1503-3M. It is cultured on Vero cell, inactivated with Beta-propiolactone and purified by ultracentrifugation.

One dose of vaccine contains 3.25 international units (IU) of rabies antigen (in vitro potency measured using G protein content by ELISA method) (corresponds to ≥ 2.5 IU by NIH test).

Excipient with known effect:

Phenylalanine .....4.1 micrograms

No adjuvant or preservative are added.

Verorab meets the World Health Organization (WHO) requirements for manufacture of biological substances.

For the full list of excipients, see Section 6.1.

The antibiotics neomycin, streptomycin and polymyxin are used in the manufacturing process of this vaccine and may be present in trace amounts.

3 PHARMACEUTICAL FORM

Powder and diluent for suspension for injection.

The powder is a white homogeneous pellet.

The diluent for suspension for injection is 0.4% sodium chloride solution, which is a clear and colourless solution.

After reconstitution, Verorab is limpid and homogeneous.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Verorab is indicated for pre-exposure prophylaxis against rabies.

Verorab is indicated for post-exposure prophylaxis against rabies.

Verorab should be used in accordance with official local recommendations.

4.2 DOSE AND METHOD OF ADMINISTRATION

4.2.1 General

The dose and dosing schedule is identical for adults and paediatric population. The vaccine is administered by intramuscular (IM) injection, in the deltoid area for adults and children or the anterolateral area of the thigh muscle in infants and toddlers.

For dosing in immunocompromised individuals refer to Section 4.2.2 – Special populations.

For further information, refer to the official local recommendations.

Once the vaccine is reconstituted with 0.5 mL of diluent, one intramuscular (IM) dose consists of 0.5 mL of reconstituted vaccine and one intradermal (ID) dose consists of 0.1 mL of reconstituted vaccine per injection site.

4.2.1.1 Pre-exposure prophylaxis (PrEP)

For primary pre-exposure prophylaxis, individuals can be vaccinated according to one of the vaccination schedules presented in Table 1, Table 2 and according to official local recommendations when available:

Table 1 - Pre-exposure IM vaccination schedules

	D0	D7	D21 or D28
Three-dose regimen IM route - 0.5 mL	1 dose	1 dose	1 dose
Two-dose regimen [a] IM route - 0.5 mL	1 dose	1 dose	

a This regimen should not be used for immunocompromised individuals (see Section 4.2.2.3.1)

Table 2 - Pre-exposure ID vaccination schedules

	D0	D7	D21 or D28
Three-dose regimen ID route - 0.1 mL	1 dose	1 dose	1 dose
Two-dose regimen [a] ID route - 0.1 mL	2 doses [b]	2 doses [b]	

a This regimen should not be used for immunocompromised individuals (see Section 4.2.2.3.1)

b One injection in each arm (for adults and children) or each anterolateral thigh (infants and toddlers)

In addition, booster doses and/or regular serology testing of neutralising antibodies may be indicated according to official local recommendations. A booster dose consists of one dose of 0.5 mL given by intramuscular route or one dose of 0.1 mL given by intradermal route. Follow official local recommendation.

4.2.1.2 Post-exposure prophylaxis (PEP)

Post-exposure prophylaxis should be initiated as soon as possible after suspected rabies exposure. In all cases, proper wound care (thorough flushing and washing of all bite wounds and scratches with soap or detergent and copious amounts of water and/or virucidal agents) must be performed immediately or as soon as possible after exposure. It must be performed before administration of rabies vaccine or rabies immunoglobulin, when they are indicated.

The rabies vaccine administration must be performed strictly in accordance with the category of exposure, the patient immune status, and the animal status for rabies (according to official local recommendations, see Table 3 for WHO recommendations).

In addition, tetanus prophylaxis and a course of antibiotics to prevent superinfections may be required according to official local recommendations.

Table 3 - WHO category of severity of exposure

Category of exposure	Type of exposure to a domestic or wild animal suspected or confirmed to be rabid or animal unavailable for testing	Recommended post-exposure prophylaxis
I	Touching or feeding of animals Licks on intact skin (no exposure)	None, if reliable case history is available[a]
II	Nibbling of uncovered skin Minor scratches or abrasions without bleeding (exposure)	Administer vaccine immediately Stop treatment if animal remains healthy throughout an observation period of 10 days[b] or is proven to be negative for rabies by a reliable laboratory using appropriate diagnostic techniques. Treat as category III if bat exposure involved.
III	Single or multiple transdermal[c] bites or scratches, contamination of mucous membrane or broken skin with saliva from animal licks, exposures due to direct contact with bats. (severe exposure)	Administer rabies vaccine immediately, and rabies immunoglobulin, preferably as soon as possible after initiation of post-exposure prophylaxis. Rabies immunoglobulin can be injected up to 7 days after administration of first vaccine dose. Stop treatment if animal remains healthy throughout an observation period of 10 days or is proven to be negative for rabies by a reliable laboratory using appropriate diagnostic techniques.

a If an apparently healthy dog or cat in or from a low-risk area is placed under observation, treatment may be delayed.

b This observation period applies only to dogs and cats. Except for threatened or endangered species, other domestic and wild animals suspected of being rabid should be euthanised and their tissues examined for the presence of rabies antigen by appropriate laboratory techniques.
c Bites especially on the head, neck, face, hands and genitals are category III exposures because of the rich innervation of these areas.

4.2.1.2.1 Post-exposure prophylaxis of non-immunised individuals or incompletely immunised individuals

Individuals not previously immunised can be vaccinated according to one of the vaccination schedules presented in Table 4 in accordance with the official local recommendations:

Table 4 - Post-exposure vaccination schedules in non-immunised individuals or incompletely immunised individuals

	D0	D3	D7	D14	D21	D28
5-dose Essen regimen IM route - 0.5 mL	1 dose	1 dose	1 dose	1 dose		1 dose
Zagreb regimen IM route - 0.5 mL	2 doses[a]		1 dose		1 dose	
Updated Thai Red Cross regimen ID route - 0.1 mL	2 doses[b]	2 doses[b]	2 doses[b]			2 doses[b]
Institute Pasteur Cambodia regimen ID route - 0.1 mL	2 doses[b]	2 doses[b]	2 doses[b]			
One week, four-site regimen ID route - 0.1 mL	4 doses[c]	4 doses[c]	4 doses[c]			

a one injection in each of the two deltoids (for adults and children) or anterolateral thigh sites (infants and toddlers)
b to be injected in 2 distinct sites, if possible contra-laterally.
c to be injected in 4 distinct sites

For category III exposure (see Table 3), rabies immunoglobulin should be given in association with vaccine. In this case, each dose of the vaccine should be administered at a body site that is distant from the immunoglobulin administration sites, if possible.

Vaccination should not be discontinued unless the animal is declared not rabid according to a veterinarian assessment (supervision of animal and/or laboratory analysis).

4.2.1.2.2 Post-exposure prophylaxis of previously immunised individuals

According to WHO recommendation, previously immunised individuals are patients who can document previous complete PrEP (pre-exposure prophylaxis) or PEP (post-exposure prophylaxis) and patients who discontinued a PEP series after at least two doses of a cell culture or embryonated egg-based rabies vaccine.

These individuals should receive one dose of vaccine intramuscularly (vaccine dose 0.5 mL) or intradermally (vaccine dose 0.1 mL) on each of days 0 and 3. Alternatively, 4 intradermal injections (vaccine dose 0.1 mL) can be given at 4 distinct sites at D0.

Rabies immunoglobulin is not indicated for previously immunised individuals.

Official local recommendations should be followed for conditions of utilization of these abbreviated schedules.

4.2.2 Special populations

4.2.2.1 Paediatric population

There is no dose adjustment needed for paediatric population.

4.2.2.2 Elderly

There is no dose adjustment needed for patients over the age of 65.

4.2.2.3 Immunocompromised individuals

The following recommendation should be followed for immunocompromised individuals. See also Section 4.8.

4.2.2.3.1 Pre-exposure prophylaxis

For immunocompromised individuals, a 3-dose regimen should be used (see Section 4.2.1.1) and serology testing of neutralising antibodies should be performed 2 to 4 weeks after the last dose, to assess the possible need for an additional dose of the vaccine.

4.2.2.3.2 Post-exposure prophylaxis

For immunocompromised individuals requiring post-exposure prophylaxis, administer one of the full vaccination schedules listed in Table 4 (Section 4.2.1.2.1. Post-exposure prophylaxis of non-immunised individuals or incompletely immunised individuals). Rabies immunoglobulin should be given in association with the vaccine for both categories II & III exposures (see Table 3).

Method of administration

The vaccine is administered by the intramuscular route, in the deltoid area for adults and children or the anterolateral area of the thigh muscle in infants and toddlers.

It can also be administered by intradermal (ID) route preferably on upper arm or forearm. Do not inject in the gluteal area.

Do not inject by the intravascular route.

For instructions on reconstitution of the vaccine before administration, see Section 6.6.

4.3 CONTRAINDICATIONS

Pre-exposure prophylaxis

Known systemic hypersensitivity reaction to any component (i.e. as defined under Section 2 and Section 6.1) of Verorab or after previous administration of the vaccine or a vaccine containing the same components.

Vaccination must be postponed in case of febrile or acute disease.

Post-exposure prophylaxis

Since declared rabies infection generally results in death, there are no contraindications to post-exposure vaccination.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Protection

As with any vaccine, vaccination with Verorab may not protect 100% of vaccinated individuals.

In order to reach a sufficient antibodies level of protection, recommendations for the use of Verorab must be strictly followed (see Section 4.2) as an insufficient immune response may lead to fatal cases of rabies.

Immunocompromised individuals

In individuals with congenital or acquired immunodeficiency, the immune response to the vaccine may be inadequate. Therefore, it is recommended to monitor serologically RVNA (Rabies Virus Neutralising Antibodies) level in such individuals to ensure that an acceptable immune response has been induced. Additional doses should be given as necessary (see Section 4.2.2.3).

Moreover, if post-exposure vaccination is needed, only full schedule of vaccination should be administered (listed in Section 4.2.1.2.1. Post-exposure prophylaxis of non-immunised individuals or incompletely immunised individuals). In addition, rabies immunoglobulin should be given in association with the vaccine for category II & III exposures (see Section 4.2.2.3).

Administration precautions

Before the injection of any biological, the person responsible for administration must take all precautions known for the prevention of allergic or any other reactions. As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of an anaphylactic event following administration of the vaccine.

As a precautionary measure, adrenaline (epinephrine) injection (1:1000) must be immediately available in case of unexpected anaphylactic or serious allergic reactions.

It is essential that intradermal administration of Verorab is carried out only by medical staff trained in this technique in order to ensure that the vaccine is delivered intradermally. For the intradermal route appropriate syringe and needle should be used. Do not inject by the intravascular route. Ensure that the needle does not enter a blood vessel.

Neomycin, streptomycin and polymyxin

As each dose may contain undetectable traces of neomycin, streptomycin and polymyxin which are used during vaccine production, caution must be exercised when the vaccine is administered

to individuals with hypersensitivity to those antibiotics (and other antibiotics of the same class, if appropriate).

Apnoea

The potential risk of apnoea and the need for respiratory monitoring for 48-72 hours should be considered when administering the primary immunization series to very premature infants (born ≤ 28 weeks of gestation) and particularly for those with a previous history of respiratory immaturity.

Anxiety-related reactions

Anxiety-related reactions, including vasovagal reactions (syncope), hyperventilation or stress-related reactions can occur following, or even before, any vaccination as a psychogenic response to the needle injection. This can be accompanied by several neurological signs such as transient visual disturbance and paraesthesia. It is important that procedures are in place to avoid injury from fainting.

Traceability

In order to improve the traceability of biological medicinal products, the name and batch number of the administered product should be clearly recorded.

Use in the elderly

See Section 4.2.2.2 .

Paediatric use

See Section 4.2.2.1. The clinical trial program in paediatrics did not include children aged less than 28 days (see Section 5.1 – Clinical trials – Paediatric population).

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Immunosuppressive treatment, including long-term systemic corticosteroid therapy, may interfere with antibody production and cause the failure of the vaccination. It is therefore advisable to perform a serological test 2 to 4 weeks after the last injection. (See Section 4.2.2.3).

Verorab can be administered simultaneously with a typhoid polysaccharide Vi vaccine in two separate injection sites.

Separate injection sites and separate syringes must be used in case of concomitant administration with any other medicinal product, including rabies immunoglobulins.

As rabies immunoglobulin interferes with development of immune response to the vaccine, the recommendation of administration of rabies immunoglobulin must be strictly followed.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Verorab has not been evaluated for impairment of male or female fertility.

Use in pregnancy – Category B2

Animal reproductive studies have not been conducted with Verorab. Data on the use of this vaccine in pregnant women are limited.

Pre-exposure prophylaxis

Verorab should be given to pregnant women only if clearly needed and following an assessment of the risks and benefits.

Post-exposure prophylaxis

Due to the severity of the disease, pregnancy is not a contraindication.

Use in lactation

It is not known whether this vaccine is excreted in human milk.

Pre-exposure prophylaxis

Caution must be exercised when Verorab is administered to a nursing mother.

Post-exposure prophylaxis

Due to the severity of the disease, lactation is not a contraindication.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effects on the ability to drive or use machines have been performed.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Adverse reaction information is derived from clinical trials and worldwide post-marketing experience.

Within each system organ class the adverse reactions are ranked under headings of frequency, using the following CIOMS frequency rating:

- Very common ≥ 10%;
- Common ≥ 1 and < 10%;
- Uncommon ≥ 0.1 and < 1%;
- Rare ≥ 0.01 and < 0.1%;
- Very rare < 0.01%;
- Not known (cannot be estimated from available data).

4.8.1 Clinical trials

In clinical studies, more than 13,000 study participants (from 2 months through 98 years of age) received at least one dose of Verorab.

A pooled analysis has been performed on 4 randomised, controlled clinical studies sharing the same safety standards, integrating data from 1151 study participants (17 infants/toddlers younger than 24 months of age, 510 children and adolescents and 624 adults from 18 through 60 years of age). In these studies, the vaccine was given by intramuscular route (N=477) or by intradermal route (N=674). In one of the studies using intradermal route (N=599), most of the study participants received Equine Rabies Immunoglobulin (ERIG) concurrently with the first dose of Verorab.

The adverse reactions were generally of mild intensity and appeared within 3 days after vaccination. Most reactions resolved spontaneously within 1 to 3 days after onset. Most frequent systemic adverse reactions in all age groups (except infants/toddlers) were headache, malaise and myalgia. Injection site reactions (pain, erythema and swelling) were more frequent following ID injection compared to IM injection. Injection site pain was the most frequent injection site reactions for both routes of administration.

The table below presents the frequencies of solicited adverse reaction (recorded within 7 days) and unsolicited adverse reactions (recorded within 28 days), reported following any dose of Verorab. Injection site reactions are presented according to the route of administration (IM or ID). The systemic reactions are presented grouped.

Table 5 - Solicited and Unsolicited Systemic and Injection Site Adverse Reactions up to 28 days after any dose of Verorab (pooled safety analysis)

Adverse Reactions	**Adults** 18 years and older N=624[(a)]	**Pediatric population** Less than 18 years old N=527[(b)], including 17 study participants younger than 24 months of age
	% † - Frequency	% † - Frequency
SOC: Blood and lymphatic system disorders		
Lymphadenopathy	Common - 1.0 %	Common - 1.1 %
SOC: Immune system disorders		
Hypersensitivity reactions (e.g. rash, urticaria, pruritus)	Uncommon – 0.8 %	Uncommon – 0.6%

Adverse Reactions	Adults 18 years and older N=624[a]	Pediatric population Less than 18 years old N=527[b], including 17 study participants younger than 24 months of age
	% † - Frequency	% † - Frequency
SOC: Gastrointestinal disorders		
Nausea	Uncommon – 0.2%	-
Abdominal pain	Uncommon – 0.2%	Uncommon – 0.2%
Diarrhea	Uncommon - 0.3 %	-
Vomiting	-	Uncommon – 0.6%
SOC: General disorders and administration site conditions		
Injection site pain - IM route - ID route	 Very common- 21.9% Very common- 58.8%	 Very common- 17.0% Very common- 57%
Injection site erythema - IM route - ID route	 Common- 2.0% Very common- 12.3%	 Common- 1.8% Very common- 50.8%
Injection site pruritus - IM route - ID route	 Common- 1.0% Common- 1.3%	- Uncommon – 0.6%
Injection site swelling - IM route - ID route	 Common- 2.3% Common- 5.3%	 Common- 2.3% Very common- 24.4%
Injection site induration - IM route - ID route	 Common- 1.0% -	- -
Injection site haematoma - IM route - ID route	- Uncommon – 0.3%	- -
Malaise	Very common- 33.9%	Very common- 24.4%
Pyrexia	Common – 4.2%	Common – 9.9 %
Asthenia	Uncommon - 0.8 %	-
Chills	Uncommon - 0.2 %	Uncommon - 0.2 %
Inconsolable Crying (in infants/toddlers only)	-	Very common- 23.5%
SOC: Nervous system disorders		
Headache	Very common- 34.6%	Very common- 24.3%
Dizziness /vertigo	Uncommon - 0.3 %	-
Somnolence (in infants/toddlers only)	-	Very common – 17.6 %

Adverse Reactions	Adults 18 years and older N=624[a]	Pediatric population Less than 18 years old N=527[b], including 17 study participants younger than 24 months of age
	% † - Frequency	% † - Frequency
Irritability (in infants/toddlers only)	-	Very common – 35.3 %
SOC: Metabolism and nutrition disorders		
Decreased appetite	Uncommon – 0.2%	Uncommon – 0.9 %
SOC: Musculoskeletal and connective tissue disorders		
Myalgia	Very common- 30.1%	Very common- 21.6%

a IM route: N=306; ID route: N=318

b IM route: N=171; ID route: N=356

†: For each reaction, the frequency has been defined by the number of study participants experiencing the reaction at least once during the observation period divided by the number of study participants with available data.

For a comprehensive overview of vaccine safety, additional relevant adverse reactions from other studies not selected for pooled safety analysis have been included. Their frequencies are estimated based on total number of study participants included in the clinical studies, where safety of Verorab was evaluated (a total of more than 5000 study participants, including more than 1000 children younger than 18 years of age; split by age group was not available for all studies).

Table 6 - Additional Adverse Reactions from other Clinical Studies

Adverse Reactions	Adults 18 years and older N > 2600	Pediatric population Less than 18 years old N > 1000
	% - Frequency	% - Frequency
SOC: General disorders and administration site conditions		
Influenza-like symptoms	Common- 1.1%	-
SOC: Nervous system disorders		
Insomnia (in infants/toddlers only)	-	Common - 8.5%
SOC: Musculoskeletal and connective tissue disorders		
Arthralgia	Uncommon - 0.3%	-
SOC: Respiratory system disorders		
Dyspnea	Rare - 0.08%	-

Data from post-marketing experience

Based on spontaneous reporting, the following additional events have been reported during the commercial use of Verorab. These events have been very rarely reported, however exact incidence rate cannot be precisely calculated, their frequency is qualified as 'Not known".

Immune sytem disorders

- Anaphylactic reactions, angioedema

Ear and labyrinth disorders

- Sudden sensorineural hearing loss

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 https://pophealth.my.site.com/carmreportnz/s/.

4.9 OVERDOSE

For risk assessment and advice on the management of overdose, please contact the National Poisons Centre on 0800 POISON (0800 764 766).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

ATC code: J07BG01 Rabies, inactivated, whole virus

Mechanism of action

Protection after vaccination is provided by the induction of rabies virus neutralising antibodies (RVNA).

Clinical trials

Clinical studies were conducted to assess the immunogenicity of the vaccine in both pre-exposure and post-exposure situations. A RVNA titre ≥ 0.5 IU/ml, considered by WHO to confer protection, was used as a proof of protective antibody level.

Pre-exposure prophylaxis

The pre-exposure schedule, 3 doses on D0, D7 and D28 (or D21) by intramuscular (IM) route has been assessed in several clinical studies in adult and paediatric populations.

After the vaccination series, all vaccinees reached a RVNA titre ≥ 0.5 IU/mL.

A ten-year follow-up in 49 study participants who received the 3-injections protocol, followed by a booster dose at 1 year showed the maintenance of seroconversion up to 10 years in more than 95% of vaccinees.

The one-week pre-exposure schedule by IM route (one 0.5-mL dose at D0 and one 0.5-mL dose at D7) was assessed in Study VAJ00001 in 75 study participants (including 35 children from 2 to 17 years). At D21, 98.6% study participants reached RVNA titre ≥ 0.5 IU/mL.

One year later, following a simulated PEP with two 0.5-mL doses injected 3 days apart (at D0 and D3) by IM route, a high and rapid anamnestic response was demonstrated in all study participants from D7.

In 5 other supportive studies conducted with Verorab in a total of 392 study participants in the context of a 3-dose regimen assessment (at D0, D7, D21 or D28) by IM route, all study participants reached a RVNA titre ≥ 0.5 IU/mL, at D21 or D28, after the 2 doses (at D0 and D7), just before injection of the third dose.

The one-week pre-exposure schedule by intradermal (ID) route (two 0.1-mL doses at D0 and two 0.1-mL doses at D7) was assessed in Study VAJ00001 in 75 study participants (including 36 children from 2 to 17 years). At D21, 97.2% of study participants reached RVNA titre ≥ 0.5 IU/mL.

One year later, following a simulated PEP with two 0.1-mL doses injected 3 days apart (at D0 and D3) by ID route, a high and rapid anamnestic response was demonstrated in all study participants from D7, except one study participant who remained seronegative at every time points despite completing all study vaccinations.

In another supportive study conducted in 430 study participants who received one 0.1-mL dose of Verorab at D0 and one 0.1-mL dose at D7 by ID route, 99.1% of study participants reached RVNA titre ≥ 0.5 IU/mL at D21.

Post-exposure prophylaxis

Two post-exposure intramuscular schedules (5- dose Essen regimen [D0, D3, D7, D14 and D28] and 4-dose Zagreb regimen [2 doses on D0, then 1 dose each on D7 and D21], and immunoglobulin as appropriate) have been assessed in several clinical studies in both adult and paediatric populations. Almost all vaccinees reached a RVNA titre ≥ 0.5 IU/mL at D14.

In the phase III trial RAB40, including 600 exposed study participants aged from 11 months through 50 years of age, two intradermal PEP schedules were tested: one-week 4-site regimen (4 doses each on D0, D3 and D7) with and without ERIG at D0, and Thai Red Cross (TRC) regimen (2 doses each on D0, D3, D7 and D28) with ERIG at D0. Institute Pasteur Cambodia regimen (2 doses each on D0, D3 and D7) was also documented at D14, as part of TRC regimen. Almost all vaccinees reached RVNA titre ≥ 0.5 IU/mL at D14.

Five years after the RAB40 trial and before the simulated PEP was received, a protective level of RVNA was maintained in more than 84% of study participants. These study participants received the one-week 4-site regimen with or without ERIG and maintained a RVNA titre of ≥ 0.5 IU/mL in 84.8% (112/132) and 97.6% (123/126) of study participants, respectively. In those who received the TRC regimen with ERIG, a protective level of RVNA was maintained in 64.1% (82/128) of study participants. Eleven days after simulated PEP with the “single-visit 4-dose” ID regimen, all of the study participants had a RVNA titre ≥ 0.5 IU/mL.

The IPC regimen was also assessed in a real-life setting study (RAB56) in 112 exposed study participants aged from 3 to 71 years of age, who received Verorab. Fourteen study participants received concomitantly ERIG at D0. All study participants (n=112) reached RVNA titer ≥ 0.5 IU/mL at both D14 and D28.

In Study VAJ00001, the simulated PEP vaccination given 1 year after a one-week (D0, D7) IM and ID PrEP vaccination, induced a high and rapid anamnestic response in all study participants from D7 (except one study participant vaccinated by ID route, who remained seronegative at every time points despite completing all study vaccinations).

Effectiveness of Verorab has been evaluated in 44 adult study participants bitten by confirmed rabid animals. The study participants received the vaccine according to 5-dose Essen regimen (D0, D3, D7, D14 and D28 by IM route) and immunoglobulin as appropriate. None of these study participants developed the disease.

Effectiveness of Verorab was also confirmed in two studies that used administration schedules recommended in the past. In the first study, 106 study participants received 6 IM injections on D0, D3, D7, D14, D28, and D91. In the second study, 40 study participants received ID injections at the two deltoid sites on D0, D3, D7 and at 1 site on D28 and D90. All study participants received immunoglobulin as appropriate. They all were bitten by confirmed rabid animals, and none of them developed the disease.

Paediatric population

There is no clinically significant difference in immunogenicity of the vaccine in paediatric population comparing to adults.

Pre-exposure prophylaxis

In the study VAJ00001 assessing the one-week pre-exposure schedule by intradermal route (two 0.1-mL doses of Verorab at D0 and two 0.1-mL doses at D7) or by IM route (one 0.5-ml dose of Verorab at D0 and one 0.5-mL dose at D7) in 71 children from 2 to 17 years of age, all children reached RVNA titre ≥ 0.5 IU/mL at D21.

One year later, following a simulated PEP with two doses injected 3 days apart (at D0 and D3) by IM or ID route, a high and rapid anamnestic response was demonstrated in all study participants from D7.

Post-exposure prophylaxis

In the phase III study (RAB40) assessing the two ID PEP schedules, one-week 4-site regimen (4 doses of 0.1 mL each on D0, D3 and D7) with and without ERIG at D0, and TRC regimen (2 doses of 0.1 mL each on D0, D3, D7 and D28) with ERIG at D0 and also documenting IPC regimen (2 doses of 0.1 mL each on D0, D3 and D7) at D14 as part of TRC regimen, a total of 319 exposed children aged from 11 months to 17 years of age received Verorab. At D14, all children with available data reached RVNA titer ≥ 0.5 IU/mL. Eleven days after simulated PEP with “single-visit 4-dose” ID regimen, all children had RVNA titer ≥ 0.5 IU/mL.

In the real-life setting study (RAB56) also assessing the IPC regimen, a total of 55 exposed children from 3 years of age received Verorab. At both D14 and D28, all children (n=55) reached RVNA titer ≥ 0.5 IU/mL.

5.2 PHARMACOKINETIC PROPERTIES

No pharmacokinetic studies have been performed.

5.3 PRECLINICAL SAFETY DATA

Data in animals, including single dose and repeated dose studies revealed no unexpected findings and no target organ toxicity.

Genotoxicity

No genotoxicity studies have been performed with Verorab.

Carcinogenicity

No carcinogenicity studies have been performed with Verorab.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Each 0.5 mL dose of the reconstituted vaccine also contains the following excipients:

- Maltose
- 20% albumin solution
- Basal Medium Eagle[1]
- Sodium chloride
- Water for injections

[1]Basal Medium Eagle: mixture of mineral salts, vitamins, dextrose and amino-acids including L-Phenylalanine

Contains no antimicrobial agent.

Hydrochloric acid and/or sodium hydroxide can be used for pH adjustment. These components are only present in trace amount.

The antibiotics neomycin, streptomycin and polymyxin are used in the manufacturing process of this vaccine and may be present in trace amounts.

6.2 INCOMPATIBILITIES

This vaccine must not be mixed with other medicinal products.

6.3 SHELF LIFE

48 months.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store in a refrigerator (2°C – 8°C). Do not freeze.

Store protected from light.

6.5 NATURE AND CONTENTS OF CONTAINER

Verorab is available in the following pack size:

- Powder in vial (Type I glass) with a stopper (chlorobutyl) and a cap + 0.5 mL of diluent in prefilled syringe (Type I glass) with attached needle with a plunger-stopper (chlorobutyl or bromobutyl). Box of 1.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

Instructions for preparation and administration

1. Remove the seal of the vial of lyophilised powder.
2. Inject the diluent into the vial of lyophilised powder.
3. Gently swirl the vial until homogeneous suspension of the powder is obtained.
   The reconstituted vaccine should be limpid, homogeneous, and free from particles.
4. Remove and discard the syringe that was used for vaccine reconstitution and use a new syringe with a new needle to withdraw the reconstituted vaccine.
5. Replace the needle used to withdraw the reconstituted vaccine by a new needle for intramuscular or intradermal injection.
6. The length of the needle used for vaccine administration should be adapted to the individual and to the route of administration.

If Verorab is used via intramuscular route, once reconstituted, the vaccine must be used immediately.

If Verorab is used via intradermal route, vaccine may be used up to 6 hours after reconstitution provided it is maintained at no more than 25°C and protected from light. After reconstitution with the solvent, using aseptic technique, each dose of vaccine should be withdrawn from a vial. The vaccine is for single use only and must not be reused. Discard any remaining unused contents.

After use, any remaining vaccine and container must be disposed of safely, preferably by heat inactivation or incineration, according to locally agreed procedure.

6.7 PHYSICOCHEMICAL PROPERTIES

No data available.

7 MEDICINE SCHEDULE

Prescription only medicine

8 SPONSOR

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9 DATE OF FIRST APPROVAL

14 March 2024

10 DATE OF REVISION

12 January 2026

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.2	Editorial adjustments
4.4	Editorial adjustments
4.6	Editorial adjustments
4.8	The word “subjects” has been replaced by “study participants”
4.9	Updated overdose statement
5.1	Addition of RAB56 study results supporting PEP ID regimens in adult and paediatric populations and of RAB40 study results in paediatric populations
6.6	Minor editorial adjustments to instructions for use