PROFESSIONAL INFORMATION

SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

VERORAB powder and diluent for suspension for injection

Inactivated rabies vaccine prepared on Vero cells.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 0,5 mL dose of reconstituted vaccine contains:

Active substance:

3,25 IU* rabies virus (WISTAR rabies PM/WI 38 1503-3M strain) produced on Vero cell lines and inactivated with beta-propiolactone and purified by ultracentrifugation.

Contains sugar: 26,3 mg maltose per dose (following reconstitution).

For the full list of excipients, see section 6.1.

* IU = International Unit. *In vitro* potency measured using G protein content by ELISA method.

3. PHARMACEUTICAL FORM

Freeze-dried powder and diluent for suspension for injection.

The powder is a white homogenous pellet.

The diluent is a limpid (clear) solution.

After reconstitution, VERORAB is a limpid, homogenous suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

VERORAB is indicated for pre-exposure and post-exposure prophylaxis against rabies in all age groups (see section 4.2 and 5.1).

VERORAB should be used in accordance with official local recommendations.

Generally, pre-exposure prophylaxis should be offered to people at high risk of exposure such as

those working in rabies diagnostic or research laboratories, veterinarians, animal handlers potentially exposed to rabid animals, as well as other people (especially children) living in or travelling to high-risk areas.

4.2 Posology and method of administration

Posology

One dose consists of 0,5 mL of reconstituted vaccine administered by the intramuscular route.

Pre-exposure prophylaxis

The pre-exposure immunisation course consists of 3 injections at Day 0, Day 7 and either Day 21 or Day 28 by intramuscular route (0,5 mL).

In addition, booster doses may be indicated according to official local recommendations.

Booster doses are determined based on the risk of exposure and on serological tests in accordance with official recommendations. Follow official local recommendation for booster doses.

Post-exposure prophylaxis

Post-exposure prophylaxis should be initiated as soon as possible after suspected rabies exposure.

Prompt local treatment of wounds is very important and must be performed immediately following the bite. Recommended first-aid procedures include immediate and thorough washing of the wound for a minimum of 15 minutes with soap and water, detergent, povidone iodine or other substances of proven lethal effect on rabies virus. If soap or an antiviral agent is not available, the wound should be thoroughly and extensively washed with water. It must be performed before administration of rabies vaccine or rabies immunoglobulin, when they are indicated.

The preventative vaccination must be administered under medical supervision and should be started as soon as possible after exposure.

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 1 below for WHO recommendations).

In both previously immunised or non-immunised subjects, the treatment should be completed with the administration of anti-tetanus prophylaxis treatment if necessary and a course of antibiotics to prevent superinfections.

Table 1: 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.

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
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.

Table 2: Actions to be taken following possible exposure to rabies infection

Circumstances	Course of action concerning		Remarks
	The animal	**The patient**	
Animal unavailable			
Suspect or non-suspect		To be placed under	Treatment** is always

circumstances		medical supervision for treatment	completed
Dead animal			
Suspect or non-suspect circumstances	Send the brain to an approved laboratory for analysis	To be placed under medical supervision for treatment	Treatment** is discontinued if the analyses are negative or, otherwise, continued
Live animal			
Suspect or non-suspect circumstances	Place under veterinary supervision*	Decision to delay anti-rabies treatment	Treatment** is continued according to the veterinary supervision of the animal
Suspect circumstances	Place under veterinary supervision*	To be placed under medical supervision for treatment	Treatment** is discontinued if the veterinary supervision invalidates the initial doubts or, otherwise, continued

* According to WHO recommendations, the minimum observation period under veterinary supervision for dogs and cats is 10 days.

** Treatment is recommended according to the severity of the wound: see Table 1.

Post-exposure prophylaxis of previously non-immunised individuals

Individuals not previously immunised can be vaccinated according to one of the vaccination schedules presented in Table 3 (see Method of administration).

Table 3: Post-exposure vaccination schedules in previously non-immunised individuals

	Day 0	Day 3	Day 7	Day 14	Day 21	Day 28
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	

[a] One injection in each of the two deltoids (for adults and children) or anterolateral thigh sites (infants and toddlers).

For category III exposure (see Table 1), rabies immunoglobulin should be given in association with the vaccine in non-immunised subjects. In this case, the vaccine should be administered contra-laterally, if possible.

Vaccination must not be discontinued unless the animal is declared not rabid by a reliable laboratory using appropriate diagnostic techniques.

Refer to the professional information of the rabies immunoglobulins used.

Post-exposure prophylaxis of previously immunised individuals

According to WHO recommendations, these 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) on each of Days 0 and 3 (for immunocompromised individuals, see section under Special Populations).

Rabies immunoglobulin is not indicated for previously immunised individuals.

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

Special populations

Paediatric population

There are no specificities to dose or vaccination schedule, for the paediatric population.

Immunocompromised individuals

The following recommendation should be followed for immunocompromised individuals (see section 4.4 and 4.5).

Pre-exposure prophylaxis:

For immunocompromised individuals, serology testing of neutralising antibodies should be performed 2 to 4 weeks after the vaccination, to assess the possible need for an additional dose of the vaccine.

If the result of the test shows an antibody titre < 0,5 IU/mL, an additional injection is justified.

Post-exposure prophylaxis:

For immunocompromised individuals, only the full vaccination schedule (listed in Post-exposure prophylaxis of previously non-immunised individuals – Table 2) should be administered.

Rabies immunoglobulin should be given in association with the vaccine for both categories II & III exposures.

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.

Do not inject in the gluteal area.

Do not inject by the intravascular route.

For instructions on reconstitution of VERORAB before administration, see section 6.6.

4.3 Contraindications

Pre-exposure prophylaxis

Known systemic hypersensitivity reaction to any of the components of VERORAB or after previous

administration of the vaccine or a vaccine containing the same components (see section 6.1).
Vaccination must be postponed in case of febrile or acute illness.

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

As each dose may contain undetectable traces of neomycin, streptomycin and polymyxin, which is used during vaccine production, caution must be exercised when the vaccine is administered to subjects with hypersensitivity to those antibiotics (and other antibiotics of the same class, if appropriate).

Protection

As with any vaccine, vaccination with VERORAB may not protect 100 % of vaccinated individuals. In order to reach sufficient antibody levels 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 (see section 4.5). 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 Special populations).

Moreover, if post-exposure vaccination is needed, only full schedule of vaccination should be administered (listed in Post-exposure prophylaxis of previously non-immunized individuals). In addition, rabies immunoglobulin should be given in association with the vaccine for category II & III

exposures (see section 4.2 Special populations above).

Administration precautions

Do not inject by the intravascular route. Ensure that the needle does not enter a blood vessel.

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 (1:1 000) must be immediately available in case of unexpected anaphylactic or serious allergic reactions.

Apnoea

The potential risk of apnoea and the need for respiratory monitoring for 48 – 72 hours should be considered when administering the primary immunisation 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.

Excipient information

VERORAB contains 41 micrograms phenylalanine per 0,5 mL dose which is equivalent to 0,68 micrograms/kg for a 60 kg person. Phenylalanine may be harmful for people with phenylketonuria (PKU), a rare genetic disorder in which phenylalanine builds up because the body cannot remove it properly.

VERORAB contains less than 1 mmol of potassium (39 mg) and less than 1 mmol of sodium (23 mg) per dose, that is to say it is essentially potassium free and sodium free.

Neomycin, streptomycin and polymyxin

Each dose may contain undetectable traces of neomycin, streptomycin and polymyxin, which are used during vaccine production.

4.5 Interaction with other medicines and other forms of interaction

Immunosuppressive treatment, including long-term systemic corticosteroid therapy may interfere with antibody production and cause vaccination failure. It is therefore advisable to perform a serological test 2 to 4 weeks after the last injection (see section 4.4 Immunocompromised individuals).

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

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

Pregnancy

Pre-exposure prophylaxis

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

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

Post exposure prophylaxis

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

Breastfeeding

Pre-exposure prophylaxis

It is not known whether this vaccine is excreted in human milk. Caution must be exercised when VERORAB is administered to a nursing mother.

Post-exposure prophylaxis

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

Fertility

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

4.7 Driving a vehicle or performing other hazardous tasks

Post-vaccination dizziness was frequently reported (see section 4.8). It can temporarily affect the ability to drive or use machines.

4.8 Undesirable effects

Summary of the safety profile

Over 13 000 subjects, including approximately 1 000 children and adolescents under the age of 18, have received at least one dose of VERORAB in clinical studies.

Adverse reactions were generally moderate in intensity and occurred within 3 days of vaccination. Most reactions resolved spontaneously within 1 to 3 days of their onset.

The most common adverse reactions, in all age groups (except infants/young children less than 24 months) were headache, malaise, myalgia and pain at the injection site.

Tabulated list of adverse reactions

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 (≥ 1/10); common (≥ 1/100 and < 1/10); uncommon (≥ 1/1 000 and < 1/100); rare ≥ 1/10 000 and 1/1 000); very rare < 1/10 000), not known (cannot be estimated from available data).

Table 4: 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 = 546	**Paediatric population** Less than 18 years old N = 455, including 17 subjects younger than 24 months of age
	Frequency * (%)	Frequency * (%)
Blood and lymphatic system disorders		
Lymphadenopathy	Common (1,1 %)	Common (1,3 %)
Immune system disorders		
Hypersensitivity reactions (e.g. rash, urticaria, pruritus)	Uncommon (0,9 %)	Uncommon (0,7 %)
Metabolism and nutrition disorders		
Decreased appetite	Uncommon (0,2 %)	Common (1,1 %)
Nervous system disorders		
Headache	Very common (37,5 %)	Very common (24,4 %)
Dizziness/vertigo	Uncommon (0,4 %)	-
Somnolence (in infants/toddlers only)	-	Very common (17,6 %)

Adverse reactions	Adults 18 years and older N = 546	Paediatric population Less than 18 years old N = 455, including 17 subjects younger than 24 months of age
Irritability (in infants/toddlers only)	-	Very common (35,3 %)
Gastrointestinal disorders		
Nausea	Uncommon (0,2 %)	-
Abdominal pain	Uncommon (0,2 %)	Uncommon (0,2 %)
Diarrhoea	Uncommon (0,4 %)	-
Vomiting	-	Uncommon (0,7 %)
Musculoskeletal and connective tissue disorders		
Myalgia	Very common (33,2 %)	Very common (22,9 %)
General disorders and administration site conditions		
Injection site pain	Very common (22,2 %)	Very common (14,0 %)
Injection site erythema	Common (2,3 %)	Common (2,2 %)
Injection site pruritus	Common (1,1 %)	-
Injection site swelling	Common (2,6 %)	Common (2,9 %)
Injection site induration	Common (1,1 %)	-
Malaise	Very common (33,9 %)	Very common (24,4 %)
Pyrexia	Common (4,8 %)	Common (9,9 %)
Asthenia	Uncommon (0,9 %)	-
Chills	Uncommon (0,2 %)	Uncommon (0,2 %)
Inconsolable crying (in infants/toddlers only)	-	Very common (23,5 %)

* For each reaction, the frequency has been defined by the number of subjects experiencing the reaction at least once during the observation period divided by the number of subjects 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 subjects included in the clinical studies, where safety of VERORAB was evaluated (a total of more than 5 000 subjects, including more than 1 000 children younger than 18 years of age; split by age group was not available for all studies).

Table 5: Additional adverse reactions from other clinical studies

Adverse reactions	**Adults** 18 years and older N > 2 600	**Paediatric population** Less than 18 years old N > 1 000
	Frequency (%)	Frequency (%)
Nervous system disorders		
Insomnia (in infants/toddlers only)	-	Common (8,5 %)
Respiratory, thoracic and mediastinal disorders		
Dyspnoea	Rare (0,08 %)	-
General disorders and administration site conditions		
Influenza-like symptoms	Common (1,1 %)	-
Musculoskeletal and connective tissue disorders		
Arthralgia	Uncommon (0,3 %)	-

Data from post-marketing experience

Based on spontaneous reporting, the following additional events are reported very rarely following commercial use of VERORAB. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate the frequency or establish a causal relationship of exposure to VERORAB.

Immune system disorders: anaphylactic reactions, angioedema.

Ear and labyrinth disorders: sudden sensorineural hearing loss.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of VERORAB is important. It allows continued monitoring of the benefit/risk balance of VERORAB. Health care providers are asked to report any suspected adverse reactions to:

- The Pharmacovigilance Unit at Sanofi: za.drugsafety@sanofi.com (email) or 011 256 3700 (tel), or
- SAHPRA via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Not documented.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 30.2 Antigens.

ATC Code: J07BG01 Rabies, inactivated, whole virus.

Inactivated vaccine used for the prevention of rabies in individuals at a risk of infection and for treatment after confirmed or possible infection with rabies virus.

Mechanism of action

Clinical studies were conducted to assess the immunogenicity of the vaccine in both pre-exposure and post-exposure situations. A rabies neutralising antibody 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 Day 0, Day 7 and Day 28 (or Day 21) by IM route has been assessed in several clinical studies. After the vaccination series, all vaccinees have reached a rabies neutralising antibody titre ≥ 0,5 IU/mL.

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

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 on each 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 rabies neutralising antibody titre ≥ 0,5 IU/mL at D14.

Effectiveness of VERORAB has been evaluated during several studies conducted in both children and adults and using the recommended WHO schedules. Subjects bitten by confirmed rabid animals were given VERORAB and immunoglobulin as appropriate. None of these subjects developed the disease.

Paediatric population

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

5.2 Pharmacokinetic properties

No pharmacokinetic studies were performed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Freeze-dried powder pellet

Maltose (sugar) (see section 2)

Human albumin

BME medium**

Hydrochloric acid (pH adjustment)

Sodium hydroxide (pH adjustment).

** BME: Basal Medium Eagle: mixture of mineral salts, vitamins, dextrose and amino acids including L-phenylalanine.

May contain traces of polymyxin B, streptomycin and neomycin, used in the manufacturing process (see Warnings and precautions).

Diluent

Sodium chloride

Water for injection.

No preservative or adjuvant is added.

6.2 Incompatibilities

Rabies immunoglobulins or any other product and the rabies vaccine must never be combined in the same syringe or injected into the same site.

VERORAB must not be mixed with other medicinal products or other vaccines.

6.3 Shelf life

3 years.

If VERORAB is administered via the IM route, once reconstituted, the vaccine must preferably be used immediately.

6.4 Special precautions for storage

Store in the refrigerator between 2 °C and 8 °C. Do not freeze.

Keep the vial and prefilled syringe in the carton until required for use to protect from light.

For storage conditions after reconstitution, see section 6.3.

6.5 Nature and contents of container

Each box contains an inserted leaflet with:

Immunising dose: 1 vial (Type I glass) with grey chlorobutyl stopper and a blue aluminium flip-off

cap containing freeze-dried powder pellet.

Diluent: 1 prefilled syringe (Type I glass with a chlorobutyl or bromobutyl plunger stopper) with a needle, containing 0,5 mL of diluent.

6.6 Special precautions for disposal and other handling

Handling instructions

- Remove the seal of the vial of lyophilised powder.
- Screw the plunger rod into the syringe, if provided separately.
- Attach the reconstitution needle to the syringe (for syringe without attached needle).
- Inject the diluent into the vial of lyophilised (freeze-dried) powder.
- Gently swirl the vial until homogeneous suspension of the powder is obtained.
- The reconstituted vaccine should be limpid, homogeneous and free from particles.
- Remove and discard the syringe that was used for vaccine reconstitution.
- Use a new syringe with a new needle to withdraw the reconstituted vaccine.
- Replace the needle used to withdraw the reconstituted vaccine by a new needle for intramuscular injection. The length of the needle used for vaccine administration should be adapted to the patient.

7. HOLDER OF CERTIFICATE OF REGISTRATION

sanofi-aventis south africa (pty) ltd

Hertford Office Park, Building 1, 5th Floor

90 Bekker Road, Midrand 2196

South Africa

MANUFACTURER

SANOFI PASTEUR

VERORAB: 1541 Avenue Marcel Merieux, 69280, Marcy L'Etoile, France

Diluent: Parque Industrial de Incarville, 27100 Val de Reuil – France

8. REGISTRATION NUMBER

V/30.1/220

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

March 1989

10. DATE OF REVISION OF THE TEXT

12 December 2024

SADC INFORMATION

BOTSWANA:	S2	Reg. No.: BOT 0700952
NAMIBIA:	NS2	Reg. No.: 06/30.1/0021
ZIMBABWE:	PP	Reg. No.: 87/18.2/2048