1. NAME OF THE MEDICINAL PRODUCT

Verorab, powder and solvent for suspension for injection

Rabies vaccine, inactivated

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

After reconstitution, with 0.5 mL of solvent, 1 vial contains:

Rabies virus*, WISTAR Rabies PM/WI38 1503-3M strain (inactivated) ..... 3.25 IU**

* Produced in VERO cells

** Quantity measured according to the ELISA test by comparison with the international standard

Excipient with known effects:
Phenylalanine .....4.1 micrograms

For the full list of excipients, see section 6.1.

Verorab may contain traces of polymyxin B, streptomycin, and neomycin, which are used in the manufacturing process (see section 4.3).

3. PHARMACEUTICAL FORM

Powder and solvent for suspension for injection.

Before reconstitution, the powder is a uniform white colour.

The solvent is a clear, colourless solution.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Verorab is indicated for the prevention of rabies in children and adults. It can be used before and after exposure to the rabies virus, as a primary vaccination or as a booster dose.

Pre-Exposure Prevention of Rabies (Pre-Exposure Vaccination)
Pre-exposure vaccination should be offered to subjects at high risk of contamination by the rabies virus.

All those at permanent risk, such as the personnel of a diagnostic, research or production laboratory working with the rabies virus, should be vaccinated. A serological test is recommended every 6 months (see section 4.4).

Pre-exposure vaccination should also be considered for subjects at frequent risk of exposure to the rabies virus, such **as:**
- veterinarians, veterinarians' assistants, and animal handlers
- those who, either by profession or leisure activity, are in contact with species such as dogs, cats, skunks, raccoons, bats or other species likely to have rabies. Examples of such people are gamekeepers, hunters, forestry workers, speleologists and taxidermists.
- adults and children living or travelling in enzootic areas.

A serological test can be performed every 2 to 3 years for those subject to discontinuous exposure.
In areas where the enzootic level of rabies is low, veterinarians and their assistants (including students), animal handlers and wildlife officers (gamekeepers) are considered to be at occasional risk of exposure and should receive a primary vaccination against rabies.
Serological tests for rabies antibodies should be performed at regular intervals in accordance with the subject's risk of exposure.

Systematic booster injections should be administered in accordance with the subject's risk of exposure. The frequency of booster injections is described in section 4.2.

Post-Exposure Prevention of Rabies (Post-Exposure Vaccination)
Upon the slightest risk of rabies contamination, post-exposure vaccination should be performed as soon as possible.

In some countries, vaccination must be performed in a specialized rabies treatment centre. Post-exposure treatment includes local, non-specific treatment of the injury, passive immunisation with rabies immunoglobulins (RIGs) and vaccination, depending on the type of injury and the status of the animal (see Tables 1 and 2).

Table 1: Course of Action Depending on the Status of the Animal

Circumstances	**Course of Action Regarding**	**Comments**	
	The animal	**The patient**	
Animal unavailable **Suspect or non-suspect circumstances**		To be taken to a rabies treatment centre for treatment	Treatment[(b)] is always completed
Dead animal **Suspect or non- suspect circumstances**	Send the brain to an approved laboratory for analysis	To be taken to a rabies treatment centre for treatment.	Treatment[(b)] is discontinued if the analyses are negative or, otherwise, continued
Live animal **Non-suspect circumstances**	Place under veterinary supervision[(a)]	Decision to delay rabies treatment	Treatment[(b)] is adapted according to the results of veterinary supervision of the animal
Suspect circumstances	Place under veterinary supervision[(a)]	To be taken to a rabies treatment centre for treatment.	Treatment[(b)] is discontinued if veterinary supervision invalidates the initial doubts, or, otherwise, continued

[(a)] Veterinary supervision includes 3 certificates, drawn up on D0, D7, and D14, declaring the absence of signs of rabies. According to WHO recommendations, the minimum observation period under veterinary supervision for dogs and cats is 10 days.
[(b)] Treatment is recommended depending on the severity of the wound: see Table below.

Table 2: WHO Guidelines on Post-Exposure Treatment Depending on Wound Severity

Category of severity	**Type of contact with a wild[(a)] or domestic animal presumed or confirmed rabid or an animal that cannot be placed under supervision**	**Recommended treatment**
I	Touching or feeding of animals Licks on intact skin	None, if a reliable case history can be obtained
II	Nibbling of uncovered skin Minor scratches or abrasions without bleeding Licks on broken skin	Administer vaccine immediately[(b)]
III	Single or multiple transdermal bites or scratches Contamination of mucous membrane with saliva (i.e., licks)	Administer rabies immunoglobulins and vaccine immediately[(b)]

(a) Contact with rodents, rabbits, or hares does not normally necessitate specific rabies treatment.
(b) Discontinue treatment if the animal is in good health after 10 days of observation (for cats and dogs) or if, after the animal has been euthanized, the results of the search for rabies by the appropriate laboratory techniques are negative.

4.2 Posology and Method of Administration

Posology:

VERORAB can be administered to adults and children, using the same posology.
The vaccination schedule should be adapted in accordance with the circumstances of vaccination and the subject's rabies immune status.

4.2.1. Pre-Exposure Vaccination

Three doses of VERORAB (0.5 ml) should be administered on D0, D7 and D28 or D21.

Booster Injection after Pre-Exposure Vaccination

A VERORAB booster injection (0.5 ml) should be administered one year after primary vaccination, followed by a booster injection every 5 years (see Table 3).

Table 3: Recommendations for Primary Vaccination and Booster Injections

Primary vaccination	3 Injections	D0, D7 and D28*
1st booster injection	1 year later	
Subsequent booster injections	Every five years	

* *The D28 injection can be administered on D21.

VERORAB can be administered as a booster injection after primary vaccination with a cell culture rabies vaccine (a rabies vaccine prepared on VERO cells or prepared on human diploid cells (HDCV)).

4.2.2. Post-Exposure Vaccination

First Aid: Local Treatment of the Wound

All bites and scratches should be immediately flushed out and washed with soap or detergent. Doing so can enable efficient elimination of the rabies virus at the infection site. A 70 % alcohol solution, a tincture (or solution) of iodine, or a 0.1 % quaternary ammonia solution can then be applied (provided that there are no remaining traces of soap, because these two products neutralize each other).

Depending on the severity of the injuries, rabies immunoglobulins (RIGs) may have to be administered in association with the vaccine. In this case, refer to the instructions for use in the RIG package leaflet.

If necessary, treatment can be supplemented by the administration of a tetanus prophylaxis treatment and/or antibiotherapy.

Fully Immunised Subjects

Two booster doses of VERORAB (0.5 ml) should be administered on D0 and D3. Administration of rabies immunoglobulins (RIGs) is not necessary and should not be performed in this case, since booster injection is always followed by an anamnestic response. Previously immunised subjects should be able to document the following:

- Full pre- or post-exposure rabies vaccination, by a cell culture vaccine or
- A documented rabies antibody titre ≥ 0.5 IU/ml

In case of doubt, if the booster injection was administered more than 5 years ago, or in the case of incomplete vaccination, the patient should not be considered to be completely immunised, and complete post-exposure treatment should be initiated.

Table 4: Recommendations for Post-Exposure Rabies Vaccination Depending on Previous Vaccinations

Vaccination within the last 5 years (with a cell culture rabies vaccine)	2 injections: D0 and D3
Vaccination more than 5 years ago or incomplete vaccination	5 injections: on D0, D3, D7, D14 and D28, with RIG administration if necessary

Non-Immunised Subjects

Five doses of VERORAB (0.5 ml) should be administered on D0, D3, D7, D14 and D28. Rabies immunoglobulins (RIGs) should be administered concomitantly with the first injection in the case of a severe injury (category III, according to the WHO rabies risk classification).

It can be administered later, but not after the 7th day of vaccination. Equine and human immunoglobulins can be used with VERORAB. The internationally recognized RIG posology is as follows:

Human rabies immunoglobulins: 20 IU/kg of body weight Equine rabies immunoglobulins: 40 IU/kg of body weight

Because RIGs may partially inhibit active antibody production, no more than the recommended dose should be administered.

The vaccine should be injected contralaterally to the RIG administration sites.

In enzootic rabies areas, the administration of two vaccine injections on D0 may be justified,
e.g. in the case of lesions that are extremely severe or located near the nervous system, or when the subject is immunodeficient or did not come in for a medical consultation immediately after exposure.

Method of administration

Precautions to be taken before handling or administering the medicinal product.

The vaccine is administered via the intramuscular route, in the anterolateral region of the thigh muscle in infants and young children and in the deltoid muscle in older children and adults.

Do not inject in the buttocks region.

Do not inject via the intravascular route.

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

4.3. Contraindications

Pre-exposure prophylaxis

Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1, to polymyxin B, streptomycin, neomycin or to an antibiotic of the same class, to a previous administration or to a vaccine containing the same components.

Vaccination should be postponed in the event of acute or febrile illness.

Post-exposure prophylaxis

Due to the always-fatal course of declared rabies infection, post-exposure vaccination has no contraindications.

4.4. Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name of the administered product should be clearly recorded. It is recommended to record the batch number as well.

Special warnings

Like all vaccines, Verorab may not protect 100% of those vaccinated.

To be used with caution in individuals with a known allergy to polymyxin B, streptomycin or neomycin (present in trace amounts in the vaccine). or to an antibiotic of the same class.

Precautions for use

Recommendations relating to the injection regimen should be followed exactly.

Serological tests (in order to assess the seroconversion of subjects) should be used in accordance with official recommendations.

When the vaccine is administered to subjects with known immunodeficiency due to an immunosuppressive disease or concomitant immunosuppressive treatment (including corticosteroids), serological tests should be performed 2 to 4 weeks after vaccination in order to ensure a protective immune response has been induced. In the case of post-exposure vaccination, a complete course of vaccination should be administered. Rabies immunoglobulins should also be administered in combination with the vaccine in the event of any category II and III exposure (see Section 4.2).Do not inject by the intravascular route: make sure the needle does not penetrate a blood vessel.

As with any vaccine injection, in the event of a rare anaphylactic reaction occurring after administration of the vaccine, appropriate medical treatment should be available immediately, and the patient should be monitored, particularly in post-exposure vaccination in subjects with known hypersensitivity to polymyxin B, streptomycin, or neomycin, or to an antibiotic of the same class.

As with any vaccine injection, Verorab should be administered with caution in patients with thrombocytopaenia or coagulation disorders, as intramuscular injection may lead to bleeding in these subjects.

Anxiety-related reactions, including vasovagal reactions (syncope), hyperventilation or stress-related reactions, may occur after, or even before, any vaccination, as a psychogenic reaction to the injection with a needle. This may be accompanied by several neurological signs, such as a transient vision disorder and paraesthesia. It is important that measures are in place to prevent injury in the event of fainting.

Verorab contains phenylalanine, potassium and sodium

VERORAB contains 4.1 micrograms of phenylalanine per 0.5 mL dose equivalent to 0.068 micrograms/kg in a 60 kg person. Phenylalanine may be dangerous for individuals with phenylketonuria (PKU), a rare genetic disease characterised by a defect in the elimination of phenylalanine and its accumulation in the body.

Verorab contains less than 1 mmol (39 mg) of potassium, and less than 1 mmol (23 mg) of sodium per dose; that is, it is considered to be essentially "potassium-free" and "sodium-free".

Paediatric population

The potential risk of apnoea and the need for respiratory monitoring for 48-72 hours should be carefully considered when administering the primary vaccination doses in very premature infants (born ≤ 28 weeks of pregnancy gestation or less) and particularly for those with a history of respiratory immaturity.

4.5. Interaction with other medicinal products and other forms of interaction

Immunosuppressive treatments, including long-term systemic corticosteroid therapy, may interfere with the production of antibodies and lead to vaccination failure. It is therefore recommended that a serological test is performed 2 to 4 weeks after the last injection (see section 4.2).

Verorab may be combined with a Vi polysaccharide typhoid vaccine during the same vaccination session by using two different injection sites.

Rabies immunoglobulins or any other product and the rabies vaccine should never be combined in the same syringe or administered at the same site (see section 6.2).

Given that rabies immunoglobulins interfere with the development of the immune response to the rabies vaccine, the recommendations for administration of rabies immunoglobulins must be strictly followed.

4.6. Fertility, pregnancy and lactation

Pregnancy

There is limited data on the use of VERORAB in pregnant women. No animal reproductive toxicity studies have been performed with this vaccine.

Pre-exposure prophylaxis

Because of the severity of the disease, the vaccine should only be administered during pregnancy if really needed and after an assessment of the risk/benefit ratio, in accordance with the usual vaccination schedule.

Post-exposure prophylaxis

Because of the severity of the disease, the vaccine may be administered during pregnancy.

Breast-feeding

It is unknown whether VERORAB is excreted in human milk. No risks have been identified nor are expected for breastfed infants.

VERORAB may be administered to a breast-feeding woman after an assessment of the risk/benefit ratio.

Fertility

Verorab has not been assessed in fertility studies.

4.7. Effects on ability to drive and use machines

Vertigo has commonly been reported after vaccination (see section 4.8). This may temporarily affect the ability to drive and use machines.

4.8. Undesirable effects

Summary of the tolerability profile

More than 13,000 subjects, including approximately 1,000 children and adolescents under 18 years of age, have received at least one dose of Verorab in clinical studies.

The undesirable effects were generally moderate in intensity and occurred within 3 days of vaccination. Most of the effects resolved spontaneously within 1 to 3 days of their appearance.

The most common undesirable effects in all age groups (except infants/young children less than 24 months of age) were headaches, malaise, myalgia and injection site pain. Pain was the most common reaction at the injection site.

Tabulated list of the undesirable effects

The undesirable effects listed below are those from clinical studies and post-marketing surveillance worldwide. Within each system organ class, the adverse events are classified by frequency according to the following convention:

- very common (≥ 1/10);
- common: (≥ 1/100 to <1/10);
- uncommon: (≥ 1/1,000 to <1/100);
- rare: (≥ 1/10,000 to <1/1,000);
- very rare (<1/10,000);
- Not known (cannot be estimated from the available data).

Undesirable effects	**Adults** ≥ 18 years	**Paediatric population** less than 18 years
	Frequency	**Frequency**
Blood and lymphatic system disorders		
Lymphadenopathy	Common	Common
Immune system disorders		
Allergic reactions (e.g., rash, urticaria, pruritus)	Uncommon	Uncommon
Anaphylactic reactions and angio-oedema	Not known	Not known
Metabolism and nutrition disorders		
Decreased appetite	Uncommon	Uncommon
Nervous system disorders		
Headache	Very common	Very common
Dizziness / Vertigo	Uncommon	-
Irritability (in infants / young children)	-	Very common
Somnolence (in infants / young children)	-	Very common
Insomnia (in infants / young children)	-	Common
Ear and labyrinth disorders		
Sudden loss of hearing which may persist	Not known	Not known
Respiratory, thoracic and mediastinal disorders		
Dyspnoea	Rare	-
Gastrointestinal disorders		
Nausea	Uncommon	-
Abdominal pain	Uncommon	Uncommon
Diarrhoea	Uncommon	-
Vomiting	-	Uncommon
Musculoskeletal and connective tissue disorders		
Myalgia	Very common	Very common
Arthralgia	Uncommon	-
General disorders and administration site conditions		
Injection site pain	Very common	Very common
Injection site erythema	Common	Common
Injection site pruritus	Common	-
Injection site swelling	Common	Common
Injection site induration	Common	-
Malaise	Very common	Very common
Flu-like syndrome	Common	
Fever	Common	Common
Asthenia	Uncommon	-
Chills	Uncommon	Uncommon
Inconsolable crying (in infants / young children)	-	Very common

Reporting of suspected adverse reactions

Reporting of suspected adverse reactions Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected

adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/

4.9. Overdose

No cases of overdose have been reported during clinical studies.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Rabies vaccines, ATC code: J07BG01.

Mechanism of action

Protection after vaccination is ensured by the induction of rabies neutralising antibodies.

Clinical studies have been conducted to assess the immunogenicity of the vaccine as pre- and post-exposure prophylaxis. A rabies neutralising antibody level of ≥ 0.5 IU/mL is considered to be protective by the WHO.

Pre-exposure prophylaxis

In clinical trials assessing a 3-dose vaccination schedule (D0, D7, and D28 (or D21)) in adults and children, an adequate immune response was obtained in all subjects with serum neutralising antibody titres ≥ 0.5 IU/mL on D14 after the end of primary vaccination.

A ten-year follow-up in 49 patients who had received a 3-dose regimen (D0, D7 and D28) followed by a booster dose at one year, demonstrated persistence of the immune response with neutralising antibody titres being maintained for up to 10 years in 96.9% of the vaccinated subjects.

The one-week IM pre-exposure regimen (0.5 mL dose on D0 and 0.5 mL dose on D7) was assessed in a study (VAJ00001) in 75 subjects (including 35 children aged 2 to 17 years).

On D21, 98.6% of the vaccinated subjects had achieved serum antibody levels ≥ 0.5 IU/mL.

One year later, following simulated post-exposure prophylaxis (PEP) with two 0.5 mL doses 3 days apart (on D0 and D3) via IM injection, a rapid and robust anamnestic response was demonstrated in all subjects from D7 (7 days after the 1st PPE dose).

During 5 additional studies conducted with VERORAB in a total of 392 subjects assessing the standard three-dose regimen (on D0, D7, and D21 or D28) by IM injection, all the subjects achieved serum antibody levels ≥ 0.5 IU/mL. after two doses (on D0 and D7), just before the third dose on D21 or D28.

Post-exposure prophylaxis

In clinical trials assessing the 5-dose intramuscular Essen regimen (D0, D3, D7, D14 and D28) and the 4-dose intramuscular Zagreb regimen (2 doses on D0 then one dose on D7 and one dose on D21) in children and adults, vaccination with VERORAB resulted in neutralising antibody titres (≥0.5 IU/mL) in almost all the vaccinated subjects on D14 and in all the subjects on D28.

The administration of human rabies immunoglobulin (HRIG) or equine rabies immunoglobulin (ERIG) at the same time as the rabies vaccine may cause a slight decrease in the mean neutralising antibody titre because of immune interference.

The efficacy of Verorab was assessed in 44 adult subjects bitten by rabid animals in a phase 4 clinical trial. Subjects received the vaccine according to the 5-dose Essen regimen (D0, D3, D7, D14 and D28 by IM injection) and immunoglobulins, if applicable. All the subjects were alive 3 years after the post-exposure prophylaxis.

Paediatric population

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

5.2. Pharmacokinetic properties

No pharmacokinetic studies have been performed.

5.3. Preclinical safety data

Animal data, including data from single-dose and repeat-dose studies , did not reveal any unexpected findings or target organ toxicity.

No animal reproductive toxicity studies have been performed with this vaccine.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Powder*:

Maltose.

20% human albumin solution.

Basal Medium Eagle: mixture of mineral salts (including potassium), vitamins, dextrose and amino acids (including L-phenylalanine).

Hydrochloric acid and sodium hydroxide for pH adjustment.

Water for injections.

* Composition of the powder before the freeze-drying step.

Solvent:

Sodium chloride.

Water for injections.

6.2. Incompatibilities

Rabies immunoglobulins or any other product and the rabies vaccine should never be combined in the same syringe or administered at the same site.

6.3. Shelf life

The expiry date of the product is indicated on the packaging materials.
After first opening / reconstitution, the product must be used immediately.

6.4. Special precautions for storage

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

Store in the original outer carton in order to protect from light.

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5. Nature and contents of container

Powder in a vial (Type I glass) fitted with a stopper (chlorobutyl) and a cap + 0.5 mL of solvent in a pre-filled syringe (Type I glass) fitted with a plunger-stopper with attached needle and needle cap. Box of 1 or 10.

6.6. Special precautions for disposal and other handling

Handling instructions:

- Remove the cap of the vial of lyophilised powder.
- Screw the plunger rod onto the syringe, if supplied separately.
- Inject the solvent into the vial of lyophilised powder.
- Gently stir the vial until a homogeneous suspension of powder is obtained.
- The reconstituted vaccine is a clear, homogeneous, particle-free liquid.
- Remove and discard the syringe used for reconstitution of the vaccine.
- Use a new syringe with a new needle to withdraw the reconstituted vaccine.
- Replace the needle used to withdraw the vaccine with a new needle for intramuscular injection.
- The length of the needle used to administer the vaccine must be adapted to the patient.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

8. MARKETING AUTHORISATION HOLDER AND IMPORTER AND ITS ADDRESS:

Sanofi Israel ltd. Greenwork Park, P.O Box 47, Yakum .

9. MARKETING AUTHORISATION NUMBER: 140-97-31875

Revised in April 2024 according to MoH guidelines.