1. NAME OF THE MEDICINAL PRODUCT

Verorab, powder and solvent for suspension for injection in prefilled syringe

Rabies vaccine, inactivated

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

After reconstitution, 1 dose (0.5 mL) contains:

Rabies virus*, WISTAR Rabies PM/WI38 1503-3M strain (inactivated)..... ≥ 2.5 IU**

* Produced in VERO cells

** Quantity measured according to the NIH test against the international standard

Excipient with known effect:
Phenylalanine .....41 micrograms

For the full list of excipients, see section 6.1.

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

3. PHARMACEUTICAL FORM

Powder and solvent for suspension for injection in prefilled syringe.

Before reconstitution, the powder is uniform white in 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, to streptomycin, to neomycin or to any antibiotic of the same class to a previous administration or to any vaccine containing the same components.

Vaccination should be postponed in case of febrile or acute diseases.

Post-exposure prophylaxis

Given the always-fatal outcome of the declared rabies infection, there are no contraindications to post-exposure vaccination.

4.4. Special warnings and precautions for use

Special warnings

As with all vaccines, Verorab may not protect 100% of vaccinated individuals.

Use with caution in people with known allergies to polymyxin B, to streptomycin, to neomycin (present as traces in the vaccine) or to any antibiotic of the same class.

Precautions for use

Injection-schedule recommendations should be followed scrupulously.

The need for serological tests (to assess seroconversion in subjects) should be determined in accordance with official recommendations.

When the vaccine is administered to subjects with a known immunodeficiency due to an immunosuppressive illness or a concomitant immunosuppressive treatment (such as corticosteroids), a serological test should be performed to ensure that an immune response indicative of protection has been induced. In the case of post-exposure vaccination, all vaccine doses should be administered. Rabies immunoglobulins should also be administered concomitantly with the vaccine in the event of any category II or III exposure (see section 4.2).

Do not inject via the intravascular route: make sure the needle does not penetrate a blood vessel.

As with all injectable vaccines, appropriate medical treatment and supervision must be readily available in case of a rare anaphylactic reaction after vaccine administration, particularly in case of post-exposure in subjects with a known hypersensitivity to polymyxin B, to streptomycin, to neomycin or to any antibiotic of the same class.

As with all injectable vaccines, Verorab should be administered with caution in subjects with thrombocytopenia or coagulation disorders as intramuscular injection may induce bleeding in these subjects.

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 faints.

Traceability

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

Verorab contains phenylalanine, potassium and sodium

Verorab contains 41 micrograms phenylalanine per 0.5 mL dose which is equivalent to 0.68 microgram/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 essentially 'potassium-free' and 'sodium-free'.

Paediatric population

The potential risk of apnoea with the need for respiratory monitoring for 48-72 h must be carefully taken into account when administering the primary vaccination doses in very premature infants (born at 28 weeks' gestation or less) and particularly in 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 to perform a serological test 2 to 4 weeks after vaccination.

Verorab may be administered concomitantly with a Vi polysaccharide typhoid vaccine during the same vaccination visit, using two different injection sites.

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

4.6. Fertility, pregnancy and lactation

Pregnancy

One animal toxicity study on reproduction and development led with another inactivated rabies vaccine produced in VERO cells, did not evidence any deleterious effect on female fertility and on pre- and post-natal development.

Clinical use of rabies vaccines (inactivated "WISTAR Rabies PM/WI38 1503-3M strain") during a limited number of pregnancies did not show any malformative or fetotoxic effects to date.

Pre-exposure prophylaxis

Given the seriousness of the disease, in case of high risk of contamination, vaccination should be performed during pregnancy, in compliance with the usual vaccination schedule.

Post-exposure prophylaxis

Given the seriousness of the disease, pregnancy is not a contraindication.

Lactation

This vaccine can be used during lactation.

Fertility

Verorab has not been evaluated in fertility studies.

4.7. Effects on ability to drive and use machines

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

The adverse reactions listed below were reported during clinical studies and worldwide post-marketing surveillance. Within each system organ class, adverse reactions are ranked under headings of frequency using the following convention:

- 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 the available data).

Adverse reactions	**Adults** ≥ 18 years	**Paediatric population** under 18 years old
	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 angioedema	Not known	Not known
Metabolism and nutrition disorders		
Decreased appetite	Uncommon	Common
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 hearing loss, 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
Influenza-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 were reported.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Rabies vaccines, ATC code: J07BG.

Mechanism of action

Protection after vaccination is provided by the induction of anti-rabies neutralising antibodies.

Clinical studies have been conducted to assess the immunogenicity of the vaccine for pre-exposure and post-exposure prophylaxis. A titre of anti-rabies neutralising antibodies ≥ 0.5 IU/mL is considered protective.

Pre-exposure prophylaxis

In clinical trials assessing a 3-dose regimen (D0, D7, D28 (or D21) by IM route) in adults and children, all subjects achieved an adequate immune response with anti-rabies neutralising antibody titres ≥ 0.5 IU/mL two weeks after the end of primary vaccination.

A ten-year follow-up in 49 subjects who received the vaccine according to a 3-dose schedule (D0, D7, D28) followed by a booster dose one year later showed the persistence of the immune response with anti-rabies neutralising antibody titres ≥ 0.5 IU/mL for up to 10 years in 96.9% of vaccinated subjects.

Post-exposure prophylaxis

In clinical trials assessing the 5-dose Essen regimen (D0, D3, D7, D14, D28 by IM route) and the 4-dose Zagreb regimen (2 doses at D0, then 1 dose at D7 and 1 dose at D21 by IM route) in adults and children, Verorab induced adequate titres of anti-rabies neutralising antibodies (≥ 0.5 IU/mL) in nearly all subjects at D14 and in all subjects at D28.

The administration of human rabies immunoglobulin (HRIG) or equine rabies immunoglobulin (ERIG) concomitantly with the rabies vaccine may cause slightly lower mean neutralising antibody titres due to immune interference.

The effectiveness of Verorab was evaluated in 44 adult subjects bitten by animals confirmed to be rabid. The subjects received the vaccine according to the 5-dose Essen regimen (D0, D3, D7, D14 and D28 by IM route) and immunoglobulins, where necessary. Three years after vaccination, none of the subjects had developed rabies.

Paediatric population

There are no clinically significant differences in the immunogenicity of the vaccine in the paediatric population compared to adults.

5.2. Pharmacokinetic properties

No pharmacokinetic studies were performed.

5.3. Preclinical safety data

Toxicity studies in animals (acute, subacute and chronic toxicity) do not indicate any toxic effects or target organ toxicity.

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 must never be combined in the same syringe or injected into the same site.

This medicinal product must not be mixed with other medicinal products or other vaccines.

6.3. Shelf life

The expiry date of the product is indicated on the packaging materials.
After reconstitution, the vaccine must be administered immediately.

6.4. Special precautions for storage

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

Store in the original outer package, protected from light.

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

6.5. Nature and contents of container

Powder in vial (Type I glass) with a stopper (chlorobutyl) and a cap + 0.5 mL of solvent in prefilled

syringe (Type I glass) with a plunger-stopper. 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 into the syringe, if provided separately.
- Inject the solvent into the vial of lyophilised powder.
- Shake the vial gently 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 vaccine by a new needle for intramuscular injection.
- The length of the needle used for vaccine administration should be adapted to the patient.

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

7. MANUFACTURER

SANOFI PASTEUR
14 Espace Henry Vallée, 69007 Lyon, France

8. MARKETING AUTHORISATION HOLDER

Medici Medical Ltd.
3 Hamachshev St., Netanya

9. MARKETING AUTHORISATION NUMBER: 140-97-31875-00

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