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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for suspension for injection in prefilled syringe.
Before reconstitution, the powder is a white and homogeneous pellet.
The solvent is a limpid 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 rabies prevention (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 diagnostic, research or production laboratories working on the rabies virus, should be vaccinated. Immunity should be maintained by booster doses and controlled by serological tests (see section 4.2).

Vaccination is also recommended for the following categories, given the frequency of exposure to risk:

- Veterinarians and veterinarians' assistants, animal handlers (including those manipulating bats) and forest warden (gamekeepers), taxidermists.
- People in contact with potentially rabid animal species (such as dogs, cats, skunks, raccoons, bats).
- Adults and children living in or travelling to enzootic areas.

Post-exposure rabies prevention (post-exposure vaccination)

Vaccination should be initiated immediately at the slightest risk of rabies contamination. It must imperatively be performed in a rabies center under medical supervision.

Post-exposure treatment includes local non-specific treatment of the wound, vaccination and passive immunisation with rabies immunoglobulins. The treatment should be adapted to the nature of the contact or of the wound, the condition of the animal and the patient's rabies vaccination status (see section 4.2).

Local treatment of the wound must be performed in all cases.

4.2. Posology and method of administration

Posology

One dose consists in the administration of 0.5 mL of vaccine via the intramuscular route.

The vaccination schedule should be adapted according to the circumstances of vaccination and the subject's rabies immunity status (see Tables 1 and 2).

Pre-exposure vaccination

Three doses of 0.5 mL of VERORAB are administered at D0, D7 and D28 for primary vaccination. The dose scheduled at D28 can be administered at D21.

This administration schedule follows WHO recommendations.
Booster doses and regular serological tests, to assess the subjects' seroconversion status, are recommended. The frequency of booster doses and tests is indicated in Table 1.

Each booster dose consists in the administration of one dose of 0.5 mL.

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

Table 1: Recommendations for pre-exposure treatment, depending on the nature of the risk.

RISK	NATURE OF RISK	TYPICAL POPULATION	PRE-EXPOSURE TREATMENT
CONTINUOUS	Virus present continuously, in high concentrations. Contamination by: aerosols, contact with mucous membrane, bites or scratches. Sources of exposure may be unknown.	Rabies research or production laboratory workers.	Primary vaccination. Serological tests every 6 months. Booster vaccinations when antibody levels are below the protective threshold*.
FREQUENT	Exposure usually episodic. Contamination by: aerosols, contact with mucous membrane, bites or scratches. Sources of exposure may be unknown.	Rabies diagnostic laboratory workers. Veterinarians, cavers, animal handlers and forest warden working in enzootic areas.	Primary vaccination. Booster vaccination after 1 year. Serological tests every 2 years. Subsequent booster vaccinations when antibody levels are below the protective threshold*.
INFREQUENT	Exposure often episodic. Contamination by: contact with mucous membrane, bites or scratches.	Veterinarians, animal handlers and forest warden working in areas of low enzooty. Travellers visiting enzootic areas. Veterinary students.	Primary vaccination. Booster vaccination after 1 year. Subsequent booster vaccinations every 5 years.

* When the level of neutralising antibodies is strictly below the protective threshold (0.5 IU/mL using the RFFIT - Rapid Fluorescent Focus Inhibition Test - method), a booster dose is necessary.

For immunodeficient subjects, a serological test should be performed 2 to 4 weeks after vaccination. If the test result shows antibody titers strictly below 0.5 IU/mL, an additional injection is justified.

Post-exposure vaccination

Post-exposure treatment includes local non-specific treatment of the wound, vaccination and passive immunisation with rabies immunoglobulins if necessary. The treatment should be adapted to the nature of the contact or of the wound (see Table 2), the condition of the animal (see Table 3) and the patient's rabies vaccination status.

First aid: local treatment of the wound

Local treatment of all bites and scratches is very important and must be performed immediately.

First aid recommendations include immediate flushing out of the wound for at least 15 minutes with water and soap, detergent, povidone iodine or any other substance with a proven destructive action on the rabies virus. If no soap or antiviral agents are available, the wound should be extensively flushed out with water.

If necessary, the treatment can be supplemented by the administration of a prophylactic tetanus treatment and an antibiotherapy in order to prevent the development of infections other than rabies.

Vaccination

Table 2: WHO guidelines on post-exposure treatment depending on the nature of contact and the seriousness of the wound

SERIOUSNESS	TYPE OF CONTACT	TYPE OF EXPOSURE	TREATMENT RECOMMENDED
I	Touching or feeding of animals. Licks on intact skin.	None	None if reliable case history is available.
II	Nibbling of uncovered skin. Minor scratches or abrasions without bleeding.	Minor	Administer vaccine immediately**.**
III	Single or multiple transdermal bites or scratches. Licks on broken skin. Contamination of mucous membrane with saliva (i.e. licks). Exposure to bats.	Severe	Administer rabies immunoglobulin and vaccine immediately.

Table 3: Course of action depending on the condition of the animal

Circumstances	Course of action regarding		Comments
	The animal	**The patient**	
Animal unavailable **Suspect or nonsuspect circumstances**		To be taken to a medical center that vaccinate against rabies for treatment.	Treatment (b) is always completed**.**
Dead animal **Suspect or nonsuspect circumstances**	Send the brain to an approved laboratory for analysis.	To be taken to a medical center that vaccinate against rabies for treatment.	Treatment (b) is discontinued if the tests are negative or, otherwise, continued
Live animal **Non-suspect circumstances**	Place under veterinary supervision (a).	Postpone rabies treatment.	Treatment (b) is continued according to the results of veterinary supervision of the animal.
Live animal **Suspect circumstances**	Place under veterinary supervision (a).	To be taken to a medical center that vaccinate against rabies for treatment.	Treatment (b) is discontinued if veterinary supervision invalidates initial doubts, or, otherwise, continued.

(a) 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 seriousness of the wound: see Table 2.

Post-exposure vaccination must be performed under medical supervision, only in a medical center that vaccinate against rabies and as soon as possible following exposure.

Vaccination of non-immunised subjects (subjects who did not receive pre-exposure vaccination)

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.

VERORAB must not be discontinued unless made possible by the animal's health status (see Table 3).

Rabies immunoglobulins should be administered at D0 concomitantly with the vaccine, in case of category III exposure (WHO classification, see Table 2). The rabies immunoglobulins posology is as follows :

- Human rabies immunoglobulins ..... 20 IU/kg of body weight,
- Equine rabies immunoglobulins ..... 40 IU/kg of body weight.

For more information, please see the Summary of Characteristics of the rabies immunoglobulins used.

When possible, the vaccine should be administered contra-laterally to the immunoglobulins administration sites.

For immunodeficient subjects in case of Category II exposure (WHO Classification, see Table 2), rabies immunoglobulins should also be administered concomitantly with the vaccine.

Vaccination of subjects already immunised (full pre-exposure vaccination confirmed).

If pre-exposure vaccination was performed less than 5 years before (cell culture rabies vaccine): two booster doses are administered at D0 and D3. Rabies immunoglobulins are not necessary.

If pre-exposure vaccination was performed more than 5 years before, if it is incomplete or in case of doubt, the subject's vaccination status is not considered as complete and a full post-exposure treatment should be started (see "Vaccination of non-immunised subjects").

If the patient is immunodeficient, a full post-exposure treatment should also be started (see "Vaccination of non-immunised subjects").

Paediatric population

VERORAB can be administered to children and to adults using the same posology.

Method of administration

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

The vaccine is administered via the intramuscular route, generally in the anterolateral region of the thigh muscle until the age of 12 months and in the deltoid muscle after this age.

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 vaccination

Hypersensitivity to the active substance 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 group, 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 vaccination

Given the 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 people vaccinated.

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 group.

Precautions for use

Injection-schedule recommendations should be followed scrupulously.

Serological tests (assay of neutralising antibodies using the RFFIT - Rapid Fluorescent Focus Inhibition Test - method) should be performed regularly (see Table 1).

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 2 to 4 weeks after vaccination (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 group.

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.

The potential risk of apnoea and the need for respiratory monitoring for 48-72 h 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. As the benefit of vaccination is high in this group of infants, vaccination should not be withheld or delayed.

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.

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

Corticosteroids and immunosuppressive treatments may interfere with the production of antibodies and lead to vaccination failure (see section 4.4).
Rabies immunoglobulins and vaccine must never be combined in the same syringe or administered at the same site (see section 6.2).
When possible, the vaccine should be administered contra-laterally to the immunoglobulins administration sites.

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

Lactation

This vaccine can be used during lactation.

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

Undesirable effects were reported during clinical studies and after commercial use.

Undesirable effects are ranked in terms of frequency:
- 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 including isolated cases.

Experience from clinical trials

Blood and lymphatic system disorders

Very common: adenopathy/lymphadenopathy.

Immune system disorders

Common: cutaneous allergic reactions such as rash, pruritus, oedema.
Uncommon: urticaria, angioedema, dyspnoea.

Nervous system disorders
Common: headache, dizziness, somnolence.

Gastrointestinal disorders

Common: abdominal pain, nausea.
Uncommon: diarrhoea.

Musculoskeletal and connective tissue disorders

Very common: myalgia.
Common: arthralgia, shivering.

General disorders and administration site conditions

Very common: Injection-site pain, fever, malaise.
Common: injection-site erythema, injection-site pruritus, injection-site haematoma, injection-site induration, asthenia, influenza-like syndrome.
Uncommon: injection-site swelling.

Experience after commercial use

In addition to the list above, the following undesirable effects were reported. Their exact incidence cannot be calculated as they were spontaneously reported. However, given the number of doses sold, the occurrence of these undesirable effects is very rare (<1/10 000).

Immune system disorders
Anaphylactic reactions, serum sickness-like reactions.

Nervous system disorders
Encephalopathy, convulsions.

Ear and labyrinth disorders
Sudden hearing loss.*
*Which may persist.

Respiratory, thoracic and mediastinal disorders
Apnoea in very premature infants (born ≤ 28 weeks of gestation) (see section 4.4).

Gastrointestinal disorders
Vomiting.

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: J07BG01.

Pre-exposure

The serum antibody level ≥ 0.5 IU/mL considered as protective by the WHO is achieved after injection of 3 doses at D0, D7 and D28 (or D21). This immunity should be maintained with booster doses.

Post-exposure

Post-exposure treatment was studied in adults exposed to the rabies virus. The subjects received 5 doses of the vaccine via the intramuscular route at D0, D3, D7, D14 and D28, as well as rabies immunoglobulins. In all subjects, the serum antibody level exceeded the threshold of 0.5 IU/mL, considered as protective by WHO, from the third injection at D14.
For subjects already immunised, the administration of 2 doses 3 days apart (D0 and D3) postexposure makes it possible to achieve a serum antibody level > 0.5 IU/mL, considered as protective by WHO. The administration of rabies immunoglobulins is not necessary in this case.
Slightly lower mean neutralizing antibody titres may be observed when human rabies immunoglobulins (HRIG) or equine rabies immunoglobulins (ERIG) are administered at the same time as the first two doses of rabies vaccine, in accordance with the Zagreb regimen.

5.2. Pharmacokinetic properties

No pharmacokinetic studies were performed.

5.3. Preclinical safety data

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

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Powder*: Maltose, human albumin, Basal Medium Eagle (mixture of mineral salts, vitamins, dextrose and amino-acids including L-Phenylalanine), Water for injections
* Composition of the powder before the freeze-drying step.

Solvent: Sodium chloride, Water for injections

6.2. Incompatibilities
The rabies immunoglobulins and the rabies vaccine must never be combined in the same syringe or injected at the same injection 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 (chlorobromobutyl or chlorobutyl or bromobutyl). Box of 1or 10.

6.6. Special precautions for disposal and other handling

To reconstitute the vaccine:
- Take the cap off the vial of powder.
- Inject the content of the prefilled syringe of solvent into the vial of powder.
- Shake gently in order to obtain a homogeneous vaccine suspension. The reconstituted vaccine appears as a limpid homogeneous liquid.
- Withdraw 0.5 mL of suspension and inject immediately.

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

The content of this leaflet was approved by the Ministry of Health in August 2010 and updated according to the guidelines of the Ministry of Health in March 2020.