

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) \geq 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 by appropriately trained medical staff.

Post-exposure treatment includes local non-specific treatment of the wound, vaccination and passive immunization 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 intradermal (ID) route may be used as an alternative. One intradermal dose consists of 0.1 mL of reconstituted vaccine, i.e. 1/5 of the intramuscular dose.

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 VERORAB are administered at D0, D7 and D28 for primary vaccination. The dose scheduled at D28 can be administered at D21.

The doses are administered either by IM or ID route. The Intradermal route must not be used for immunocompromised individuals (see section 4.3 Contraindications). Intramuscular injections are preferable if antimalarial chemoprophylaxis (e.g. chloroquine) is being used concurrently or there is a possibility of an immune-compromised state (antibody response may be impaired if the intradermal method is used).

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 IM 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	<p>Virus present continuously, in high concentrations.</p> <p>Contamination by: aerosols, contact with mucous membrane, bites or scratches.</p> <p>Sources of exposure may be unknown.</p>	Rabies research or production laboratory workers.	<p>Primary vaccination.</p> <p>Serological tests every 6 months.</p> <p>Booster vaccinations when antibody levels are below the protective threshold*.</p>

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 neutralizing 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 immunization 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 non-suspect circumstances		To be taken under medical supervision	Treatment ^(b) is always completed
Dead animal Suspect or non-suspect circumstances	Send the brain to an approved laboratory for analysis	To be taken under medical supervision	Treatment ^(b) is discontinued if the tests are negative or, otherwise, continued
Live animal Non-suspect circumstances	Place under veterinary supervision ^(a)	Subject to evaluation from appropriately trained medical staff	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 under medical supervision	Treatment ^(b) is discontinued if veterinary supervision invalidates initial doubts, or, otherwise,

			continued
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- (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 by appropriately trained medical staff, and as soon as possible following exposure.

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

- Essen regimen

Five doses of 0.5 mL of VERORAB are administered by IM route at D0, D3, D7, D14 and D28.

Or

- Zagreb regimen (schedule 2-1-1)

IM administration of four doses of 0.5 mL of VERORAB: one dose administered in the right deltoid region and one dose administered in the left deltoid region at D0, then one dose administered in the deltoid region at D7 and D21 (see section “**Method of administration**” for the administration site in young children)

Or

The 2-site intradermal regimen (known as updated Thai Red Cross regimen, 2-2-2-0-2), which prescribes 1 injection of 0.1 mL at 2 sites on days 0, D3, D7, and D28. The Intradermal route must not be used for immunocompromised individuals (see section 4.3 Contraindications).

Whatever the regimen used, vaccination must not be discontinued unless made possible by the animal’s health status.

Whatever the regimen used, 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 immunized (full pre-exposure vaccination confirmed)

If pre-exposure vaccination was performed with cell culture rabies vaccine, two booster doses are administered at D0 and D3 by IM route. Rabies immunoglobulins are not necessary. This schedule should not apply to immunocompromised patients (see “Vaccination of non-immunized subjects”).

If pre-exposure vaccination 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-immunized subjects”).

Intradermal schedule:

This vaccine is of sufficient potency to allow its safe use in the WHO recommended intradermal post-exposure regimen in countries where relevant national authorities have approved the intradermal route for rabies post-exposure treatment.

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.

The intradermal (ID) injection may be used as an alternative, in upper arm or forearm.

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.

The Intradermal route must not be used in the following instances:

- individuals receiving long term corticosteroid or other immunosuppressive therapy or chloroquine,
- immunocompromised individuals,
- individuals, particularly children, with severe wounds, especially to the head and neck or presenting late for consultation.

Post-exposure vaccination

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

The Intradermal route must not be used in the following instances:

- individuals receiving long term corticosteroid or other immunosuppressive therapy or chloroquine,
- immunocompromised individuals,
- individuals, particularly children, with severe wounds, especially to the head and neck or presenting late for consultation.

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 neutralizing 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 hours should be considered when administering the primary immunization series to very premature infants (born \leq 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.

Additional Precautions related to ID route:

It is essential that intradermal administration of VERORAB be carried out only by medical staff trained in this technique in order to ensure that the vaccine is delivered intradermally and not subcutaneously. For the intradermal route an appropriate graduated sterile syringe with needle (insulin type) should be used. Correct intradermal injection should result in a raised papule with an "orange peel" appearance.

If the vaccine is injected too deeply into the skin, and a papule is not seen, the needle should be withdrawn and reinserted nearby.

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: $\geq 1/10$
- Common: $\geq 1/100$ and $< 1/10$
- Uncommon: $\geq 1/1000$ and $< 1/100$
- Rare: $\geq 1/10\ 000$ 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 \leq 28 weeks of gestation) (see Section 4.4).

Gastrointestinal disorders

Vomiting.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

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 \geq 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 immunized, the administration of 2 doses 3 days apart (D0 and D3) post-exposure 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

20% human albumin solution

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

3 years.

After reconstitution, the vaccine must preferably be administered immediately.

If VERORAB is used via ID route, given that the vaccine does not contain a preservative, great care must be taken to avoid contamination of reconstituted vaccine. Vaccine may be used up to 8 hours after reconstitution provided it is maintained at 2°C to 8°C and protected from light. Unused vaccine must be discarded after 8 hours.

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 1 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 1 or 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.
- For IM injection, withdraw 0.5 mL of suspension and inject immediately.
- For ID injection, using aseptic technique, a 0.1 mL dose of vaccine may be withdrawn from a vial and the remainder used for another patient provided that the vial is stored in a refrigerator between + 2°C and + 8°C. A new sterile needle and syringe must be used to withdraw and administer each dose of vaccine for each patient to avoid cross infection.

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

7 DATE OF REVISION OF TEXT

December 2018

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