PRODUCT INFORMATION

VERORAB, powder and solvent for suspension for injection in prefilled syringe
Rabies vaccine, inactivated

ENGLISH TRANSLATION

Marketing Authorization Dates	Modified sections in SPC
24 July 2013	Notification of renewal (Section 9)
24 November 2014 (cancels French MA dated 18 June 2014)	Full document
25 August 2015	Annex I - 6.1 List of excipients Annex II – addresses and composition Annex IIIA and IIIB - addresses and composition Annex IIIA – section 10

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

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.

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 centre 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.

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

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 non-suspect circumstances**		To be taken to a rabies 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 centre 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 rabies centre for treatment	Treatment [(b)] is discontinued if veterinary supervision invalidates initial doubts, or, otherwise, continued

(a) In France, veterinary supervision includes 3 certificates, drawn up at 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 seriousness of the wound: see Table 2.

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

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

- Essen regimen

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

Or

- Zagreb regimen (schedule 2-1-1)

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).

Whatever the regimen used, vaccination must not be discontinued unless made possible by the animal's health status (see Table 3).

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 package leaflet 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).

Method of administration

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.

See Section 6.6 for the instructions on vaccine reconstitution.

4.3. Contraindications

Pre-exposure vaccination

Known hypersensitivity to the active substance, to any of the excipients, 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.

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. Pregnancy and lactation

Pregnancy

One animal toxicity study on reproduction and development led with the inactivated rabies vaccine VERORABVAX®, 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, œdema.
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.

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 suspected adverse reactions after authorisation 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: « Agence nationale de sécurité du médicament et des produits de santé (Ansm) et réseau des Centres Régionaux de Pharmacovigilance - Site internet : www.ansm.sante.fr ».

4.9. Overdose

No cases of overdose were reported.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Rabies vaccines.

ATC Code: J07B G

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) 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.

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

6.3. Shelf life

3 years.

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.

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 1.

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 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. MARKETING AUTHORISATION HOLDER

SANOFI PASTEUR
2 AVENUE PONT PASTEUR
69007 LYON
FRANCE

8. MARKETING AUTHORISATION NUMBER(S)

- 336 604-9 or 34009 604 9 9: 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 1.

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

- Date of first authorisation: 28 May 1985.
- Date of renewal of the authorisation: unlimited starting from 12 December 2010.

10. DATE OF REVISION OF THE TEXT

25 August 2015

11. DOSIMETRY

Not applicable.

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

Not applicable.

GENERAL CLASSIFICATION FOR SYPPLY

List I.

ANNEX II

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURING AUTHORISATION HOLDER(S) RESPONSIBLE FOR BATCH RELEASE

A.1. Name and address of the manufacturer(s) of the biological active substance(s)

SANOFI PASTEUR
PARC INDUSTRIEL D'INCARVILLE
27100 VAL DE REUIL
FRANCE

A.2. Name and address of the manufacturer(s) responsible for batch release

SANOFI PASTEUR
1541 AVENUE MARCEL MERIEUX
69280 MARCY L'ETOILE
FRANCE

OR

SANOFI PASTEUR
PARC INDUSTRIEL D'INCARVILLE
27100 VAL DE REUIL
FRANCE

B. CONDITIONS OF THE MARKETING AUTHORISATION

B.1. Conditions or restrictions regarding supply and use imposed on the marketing authorisation holder

List I.

B.2. Conditions or restrictions with regard to the safe and effective use of the medicinal product

Not applicable.

B.3. Other conditions

Not applicable.

C. SPECIFIC OBLIGATIONS TO BE FULFILLED BY THE MARKETING AUTHORISATION HOLDER

Not applicable.

D. QUALITATIVE AND QUANTITATIVE COMPOSITION IN EXCIPIENTS

Vial of powder*:

Maltose ..... 26.3 mg

20% human albumin solution ..... 0.125 mL

Basal Medium Eagle** ..... 0.025 mL

Water for injections ..... q.s. 0.5 mL

* Composition of the powder before the freeze-drying step

** Basal Medium Eagle is a mixture of mineral salts, vitamins, dextrose and amino-acids including L-Phenylalanine.

Prefilled syringe of solvent:

Sodium chloride ..... 2.0 mg

Water for injections ..... q.s. 0.5 mL

ANNEX IIIA

LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND ON THE IMMEDIATE PACKAGING

NATURE/TYPE Outer packaging or primary packaging

Outer packaging

1. NAME OF THE MEDICINAL PRODUCT

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

Rabies vaccine, inactivated

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. 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.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for suspension for injection (1 dose of powder in vial (≥ 2.5 IU) and 0.5 mL of solvent in prefilled syringe – box of 1).

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular route.

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Not applicable.

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

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

Store in the original outer package, protected from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Not applicable.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Holder

SANOFI PASTEUR
2, AVENUE PONT PASTEUR
69007 LYON
FRANCE

Distributor

SANOFI PASTEUR
2, AVENUE PONT PASTEUR
69007 LYON
FRANCE

Manufacturer

SANOFI PASTEUR
2, AVENUE PONT PASTEUR
69007 LYON
FRANCE

12. MARKETING AUTHORISATION NUMBER(S)

Authorised medicinal product N°:

13. BATCH NUMBER

Lot {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

List I.

15. INSTRUCTIONS ON USE

Rabies prevention, for vaccination before or after exposure.

16. INFORMATION IN BRAILLE

Not applicable.

PICTOGRAM TO APPEAR ON THE OUTER PACKAGING OR, IN THE ABSENCE OF OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

The pictogram must be in compliance with the decree of 8 August 2008 ordered in enactment of article R.5121-139 of the public health code and governing the affixing of a pictogram on the outer packaging of certain medicines and products.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

NATURE/TYPE Small immediate packaging

Vial of powder + prefilled syringe of solvent.

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

POWDER

<VERORAB, powder

Rabies vaccine, inactivated

IM after reconstitution>

SOLVENT

<Solvent for reconstitution of VERORAB>

2. METHOD OF ADMINISTRATION

Read the package leaflet.

3. EXPIRY DATE

EXP {MM/YYYY}

4. BATCH NUMBER

Lot {number}

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

Powder: <1 dose (≥ 2.5 IU) of inactivated rabies virus>

Solvent: <0.5 mL of 0.4% sodium chloride>

6. OTHER

Not applicable.

ANNEX IIIB

PACKAGE LEAFLET: INFORMATION FOR THE USER

Name of the medicinal product

VERORAB, powder and solvent for suspension for injection in prefilled syringe
Rabies vaccine, inactivated

Boxed text

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicinal product was prescribed for you only. Do not pass it on to others.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See Section 4.

Package leaflet summary

What is in this leaflet:

1. WHAT VERORAB IS AND WHAT IT IS USED FOR

Pharmacotherapeutic group

Pharmacotherapeutic group: rabies vaccines.

Therapeutic indications

VERORAB is indicated for the prevention of rabies in children and adults. It can be used before or 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 with the rabies virus, should be vaccinated. Immunity should be maintained by booster doses (see "Posology").

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 and 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 centre 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 "Posology"). Local treatment of the wound must be performed in all cases.

2. WHAT YOU NEED TO KNOW BEFORE YOU USE VERORAB

List of information necessary before taking the medicinal product

Not applicable.

Contraindications

Do not use VERORAB:

Pre-exposure vaccination:

- If you are allergic (hypersensitive) to any of the components of VERORAB or if you developed an allergic reaction during a previous injection of VERORAB or of any vaccine with the same composition
- If you are feverish or if you have an acute disease (in this case, it is preferable to postpone vaccination).

Post-exposure vaccination:

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

Precautions for use; special warnings

Take special care with VERORAB:

- As with all vaccines, VERORAB may not protect 100% of people vaccinated.
- VERORAB must not be administered via the intravascular route; make sure the needle does not penetrate a blood vessel.
- Use with caution if you are allergic to polymyxin, to streptomycin or to neomycin (present in trace amounts in the vaccine) or to any antibiotic of the same group.
- As with all injectable vaccines, appropriate medical treatment and supervision must be readily available in case of a rare anaphylactic reaction after vaccine administration.
- 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 decreased immunity (immunodeficiency), due to a suppressive disease or to a concomitant immunosuppressive treatment, a serological test should be performed 2 to 4 weeks after vaccination, see "Posology".
- VERORAB should be administered with caution to subjects with a decreased platelet level (thrombocytopenia) or clotting disorders, because of the risk of bleeding that may occur during intramuscular administration.

Interactions with other medicinal products

Using other medicines

Corticosteroids and immunosuppressive treatments may interfere with the production of antibodies and lead to vaccination failure, see "Take special care with VERORAB".

Rabies immunoglobulins and vaccine must never be combined in the same syringe or administered at the same site.

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

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Interactions with food and drinks

Not applicable.

Interactions with phytotherapy or alternative therapies

Not applicable.

Use during pregnancy and breast-feeding

Pregnancy and breast-feeding

Pregnancy

One animal toxicity study on reproduction and development, led with the inactivated rabies vaccine VERORABVAX®, did not evidence any deleterious effects 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.

Breast-feeding

This vaccine can be used during breast-feeding.

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Athletes

Not applicable.

Effects on the ability to drive or to use machines

Driving or using machines

Post-vaccination dizziness was frequently reported. This can temporarily affect the ability to drive or use machines.

List of excipients with recognised effect

Not applicable.

3. HOW TO USE VERORAB

Instructions for proper use

Not applicable.

Dosage, Method and/or route(s) of administration, Frequency of administration and Duration of treatment

Dosage

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

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

Always use exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

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.

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

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

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. 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

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

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 to a rabies 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 centre 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 rabies centre for treatment	Treatment (b) is discontinued if veterinary supervision invalidates initial doubts, or, otherwise, continued

(a) In France, veterinary supervision includes 3 certificates, drawn up at 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 seriousness of the wound: see Table 2.

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

- *Essen regimen*

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

- *Zagreb regimen (schedule 2-1-1)*

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.

Whatever the regimen used, vaccination must not be discontinued unless made possible by the animal's health status (see Table 3).

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 package leaflet of the rabies immunoglobulins used.

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

For immunodeficient subjects, in the 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 perfomed less than 5 years before (cell culture rabies vaccine) : two booster doses are administered at D0 and D3. Rabies immunoglobulins are not necessary.

This does not apply to immunodeficient subjects.

If pre-exposure vaccination was perfomed 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).

Method of administration

The vaccine is administered by 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.

If the Zagreb regimen is used, one dose should be administered in each deltoid muscle (left and right) in adults at D0, then one dose at D7 and D21.

VERORAB must not be injected in the buttocks region.

The vaccine must not be injected via the intravascular route.

Symptoms and instructions in the case of overdose

Not applicable.

Actions to be taken when one or more doses have been missed

Not applicable.

Risk of withdrawal syndrome

Not applicable.

4. POSSIBLE SIDE EFFECTS

Description of side effects

Like all medicines, VERORAB can cause side effects, although not everybody gets them.

- Increase in size of lymph nodes (adenopathy, lymphadenopathy).
- Allergic skin reaction as skin rash with itching (urticaria, pruritus), swelling (œdema). Allergic reaction with respiratory disorders (dyspnoea, angioedema). Anaphylactic reaction, serum sickness-like reaction.
- Headache (cephalalgia), dizziness, somnolence.
- Abdominal pain, nausea, diarrhoea, vomiting.
- Muscular pain (myalgia), joint pain (arthralgia).
- At the injection site: pain, erythema (redness) and induration, haematoma, swelling (œdema) and itching (pruritus).
- Fever (hyperthermia), shivering, malaise, influenza-like syndrome.
- Convulsions, encephalopathy.
- Fatigue (asthenia).
- In infants born very prematurely (at or before 28 weeks of gestation), respiratory pauses may occur during 2 to 3 days after vaccination.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system: "Agence nationale de sécurité du médicament et des produits de santé (Ansm) et réseau des Centres Régionaux de Pharmacovigilance - Site internet : www.ansm.sante.fr." By reporting side effects you can help provide more information on the safety of this medicine.

5. HOW TO STORE VERORAB

Keep out of the sight and reach of children.

Expiry date

Do not use VERORAB after the expiry date which is stated on the box. The expiry date refers to the last day of that month.

Storage conditions

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

Store in the original outer package, protected from light.

After reconstitution, the vaccine must be used immediately.

Where appropriate, warning against certain visible signs of deterioration

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

Full statement of the active substances and excipients

What VERORAB contains?

The active substance is:

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

The other ingredients are:

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.

Pharmaceutical form and contents

What VERORAB looks like and contents of the pack?

VERORAB is a powder and a solvent for suspension for injection (1 dose of powder in vial (≥ 2.5 IU) and 0.5 mL of solvent in prefilled syringe – Box of 1).

Name and address of the marketing authorisation holder and of the manufacturing authorisation holder responsible for batch release, if different

Holder

SANOFI PASTEUR
2, AVENUE PONT PASTEUR
69007 LYON
FRANCE

Distributor

SANOFI PASTEUR
2, AVENUE PONT PASTEUR
69007 LYON
FRANCE

Manufacturer

SANOFI PASTEUR
2, AVENUE PONT PASTEUR
69007 LYON
FRANCE

Names of the medicinal product in the Member States of the European Economic Area

Not applicable.

Date of approval of the package leaflet

This package leaflet was last approved on 08/2015.

Marketing authorisation under exceptional circumstances

Not applicable.

Internet Information

Detailed information on this medicinal product is available on the Internet site of Ansm (France) www.ansm.sante.fr.

Information intended for healthcare professionals

The following information is intended for healthcare professionals only:

Injection-schedule recommendations should be followed scrupulously.

To reconstitute the vaccine:
- Take the cap off the vial of powder.
- Inject the content of the prefilled syringe into the vial of powder.
- Shake gently in order to obtain a homogenous vaccine suspension. The reconstituted vaccine appears as a limpid homogenous 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.

Other

Medicinal product subject to medical prescription (List I).