Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Verorab, powder and solvent for suspension for injection.
Rabies vaccine, inactivated.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

After reconstitution with 0.5 mL solvent, 1 vial contains:
Rabies virus[a], WISTAR Rabies PM/WI38 1503-3M strain (inactivated)..... 3.25 IU[b]
[a] Produced in VERO cells
[b] Quantity measured according to the ELISA test against the international standard
Excipient with known effect:
Phenylalanine ..... 4.1 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.
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 pre-exposure and post-exposure prophylaxis of rabies in all age groups (see sections 4.2 and 5.1).
Verorab should be used according to official recommendations.

4.2 Posology and method of administration

Posology
The recommended dose is 0.5 mL of reconstituted vaccine intramuscularly (IM) (pre-exposure or post-exposure) or 0.1 mL of reconstituted vaccine intradermally (ID) (post-exposure only).

Pre-exposure prophylaxis
The primary pre-exposure immunisation course consists of three doses of 0.5 mL of Verorab administered by intramuscular route at days (D) D0, D7 and D28. The dose scheduled at D28 can be administered at D21, if necessary.
Booster doses are determined based on the risk of exposure and on serological tests to detect the presence of rabies virus-neutralising antibodies (≥ 0.5 IU/ml). A booster dose consists of one dose of 0.5 mL given by intramuscular route.
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)).

Post-exposure prophylaxis
Post-exposure prophylaxis should be initiated as soon as possible after suspected exposure to rabies.
In all cases, proper wound care (careful washing of all bites and scratches with soap or detergent and copious amounts of water and/or virucidal agents) must be performed immediately or as soon as possible after exposure. It must be performed before administration of vaccine or rabies immunoglobulins, when they are indicated.

Table 1: WHO Guide for post-exposure prophylaxis depending on severity of exposure (to be adapted according to local official recommendations).

Exposure category	Type of exposure to a domestic or wild animal, suspected or confirmed to be rabid or not available for testing	Post-exposure prophylaxis recommended
I	Touching or feeding of animals. Licks on intact skin (no exposure)	None if reliable case history is available.[(a)]
II	Nibbling of uncovered skin. Minor scratches or abrasions without bleeding (exposure)	Administer the rabies vaccine immediately. Discontinue treatment if the animal is in good health after the 10-day observation period[(b)] or if the rabies test performed using appropriate laboratory methods is negative. Treat as category III if bat exposure involved.
III	Single or multiple transdermal bites[(c)] or scratches, licks on broken skin or contamination of mucous membranes with saliva (licks), exposure to bats (severe exposure).	Administer the rabies vaccine immediately and rabies immunoglobulins, preferably as soon as possible after initiation of post-exposure prophylaxis. Rabies immunoglobulins can be injected up to 7 days after the first dose of vaccine is administered. Discontinue treatment if the animal is in good health after the 10-day observation period[(b)] or if the rabies test performed using appropriate laboratory methods is negative.

[(a)] If the animal is an apparently healthy dog or cat living in a low-risk area and placed under veterinary observation, treatment may be postponed.
[(b)] This observation period only applies to cats and dogs. With the exception of endangered or threatened species, domestic animals and wild animals suspected to have rabies should be euthanised and their tissues examined for the presence of rabies virus using appropriate laboratory methods.
[(c)] Bites, particularly to the head, neck, face, hands and genitals are classified as Category III exposure due to the extensive innervation of these parts of the body.

Post-exposure prophylaxis of non-immunised subjects
Non-immunised subjects may be vaccinated according to one of the vaccination regimens by intramuscular use (IM) or by intradermal use (ID) presented in table 2.

Table 2: Post-exposure prophylaxis of non-immunised subjects

	D0	D3	D7	D14	D21	D28
Intramuscular use (0.5 mL per dose)						
IM Essen protocol IM use – 0.5 mL/dose	1 dose	1 dose	1 dose	1 dose		1 dose
IM Zagreb protocol IM use – 0.5 mL/dose	2 doses[(a)]	-	1 dose	-	1 dose	-
Intradermal use[(d)] (0.1 mL per dose)						
New Thailand Red Cross (TRC) ID Regimen ID use – 0.1 mL/dose	2 doses[(b)]	2 doses[(b)]	2 doses[(b)]	-	-	2 doses[(b)]
Institute Pasteur of Cambodia (IPC) ID regimen ID use – 0.1 mL/dose	2 doses[(b)]	2 doses[(b)]	2 doses[(b)]	-	-	-
4-site 1-week ID regimen ID use – 0.1 mL/dose	4 doses[(c)]	4 doses[(c)]	4 doses[(c)]	-	-	-

[(a)] one IM injection in the anterolateral region of each thigh (in infants and young children) or in each deltoid (in older children and adults).
[(b)] to be injected in 2 separate sites, contralateral if possible.
[(c)] to be injected in 4 separate sites.
[(d)] See section 5.1

Irrespective of the regimen used, vaccination should not be discontinued unless the animal is declared free from rabies.

Rabies immunoglobulins should be administered concomitantly with the vaccine, in case of category III exposure (WHO classification, see Table 1). If possible, each dose of the vaccine should be administered at a body site distant from the immunoglobulin administration sites.

Post-exposure prophylaxis for already immunised subjects
In accordance with official recommendations, this applies to subjects who have already received pre-exposure prophylaxis or post-exposure prophylaxis or who discontinued post-exposure prophylaxis after receiving at least two doses of vaccine prepared in cell culture.

Subjects who have already been immunised must receive 1 dose of vaccine (0.5 mL intramuscularly or 0.1 mL intradermally) on D0 and 1 dose on D3. Alternatively, 4 intradermal injections of 0.1 mL may be administered in 4 separate sites on D0. Rabies immunoglobulins are not indicated in this case.

Immunocompromised subjects

- Pre-exposure prophylaxis

Blood tests for neutralising antibodies should be performed 2 to 4 weeks following the vaccination to assess the possible need for an additional dose of the vaccine.

- Post-exposure prophylaxis

A complete vaccine regimen should be administered post-exposure. Rabies immunoglobulin should be administered concomitantly with the vaccine in case of any category II or III exposure (see table 1).

Paediatric population
Children should receive the same dose as adults i.e. 0.5 mL intramuscularly (for pre-or post-exposure prophylaxis) or 0.1 mL intradermally (for post-exposure prophylaxis only).

Method of administration
For pre-exposure prophylaxis the vaccine must only be administered IM, whereas for post-exposure prophylaxis the vaccine can be administered IM or ID.

- Intramuscular use (IM)

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

- Intradermal use (ID)

The vaccine is administered preferably in the upper arm or the forearm.
Do not inject in the buttocks region.
Do not inject via the intravascular route.

Precautions to be taken before handling or administering the medicinal product
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

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

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 in subjects with known immunodeficiency, due to an immunosuppressive disease or a concomitant immunosuppressive treatment (including corticosteroids), blood tests must be performed 2 to 4 weeks after vaccination to ensure that a protective immunising response was obtained. In case of post-exposure vaccination, a complete vaccination regimen must be administered. Rabies immunoglobulin must also be administered concomitantly with the vaccine in case 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.

Prefilled syringes without attached needle
The tip caps of the prefilled syringes without attached needle contain a natural rubber latex derivative, which may cause severe allergic reactions in latex sensitive individuals.

Verorab contains phenylalanine, potassium and sodium
Verorab contains 4.1 micrograms phenylalanine per 0.5 mL dose which is equivalent to 0.068 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 (see section 4.2).

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
Data on the use of Verorab in pregnant women are limited. Animal developmental and reproductive toxicity studies have not been conducted with this vaccine.

Pre-exposure prophylaxis
Given the seriousness of the disease, vaccination should be given to pregnant women only if clearly needed and following an assessment of the risks and benefits, in compliance with the usual vaccination schedule

Post-exposure prophylaxis
Given the seriousness of the disease, the vaccine can be administered during pregnancy.

Lactation
It is unknown whether Verorab is excreted in human milk. No risk has been identified and is anticipated for infants receiving breast milk.
Verorab can be administered to breast-feeding women following an assessment of the risks and benefits.

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 effects in all age groups (except in infants/young children aged under 24 months) were headache, malaise, myalgia and pain at the injection site. Injection site reactions (pain, erythema and swelling) were more common after an ID injection than an IM injection. Pain was the most common injection site reaction for both administration routes.

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 (IM use)	Very common	Very common
Injection site pain (ID use)	Very common	Very common
Injection site erythema (IM use)	Common	Common
Injection site erythema (ID use)	Very common	Very common
Injection site pruritus (IM use)	Common	-
Injection site pruritus (ID use)	Common	Uncommon
Injection site swelling (IM use)	Common	Common
Injection site swelling (ID use)	Common	Very common
Injection site induration (IM use)	Common	-
Injection site haematoma (ID use)	Uncommon	
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 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 HPRA Pharmacovigilance Website: www.hpra.ie.

4.9 Overdose

No cases of overdose were reported in clinical trials.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Rabies vaccines, ATC code: J07BG01.

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 in post-exposure and pre-exposure prophylaxis. Rabies virus neutralising antibody levels of ≥ 0.5 IU/mL are considered to be protective by the WHO.

Pre-exposure prophylaxis
In clinical trials assessing a 3-dose vaccine regimen (D0, D7, D28 [or D21]) in both adults and children, all subjects achieved an adequate immune response, with serum neutralising antibody titres ≥ 0.5 IU/mL by D14 after the end of the primary vaccine regimen.
A ten-year follow-up in 49 patients who received a 3-dose regimen (D0, D7 and D28) followed by a booster dose at 1 year demonstrated a persistent immune response, with neutralising antibody titres maintained for 10 years in 96.9% of vaccinated subjects.

Post-exposure prophylaxis
In clinical trials assessing the 5-dose intramuscular Essen regimen (D0, D3, D7, D14 and D28) and the intramuscular 4-dose Zagreb regimen (2 doses on D0, then 1 dose on D7 and 1 dose on D21) in both children and adults, Verorab elicited neutralising antibody titres ≥ 0.5 IU/mL in almost all vaccinated subjects by D14 and in all subjects by D28.
During a phase-3 study including 600 exposed subjects aged from 11 months to 50 years, 2 intradermal post-exposure prophylaxis (PEP) regimens were tested: 1 regimen in 4 sites in 1 week (4 doses on D0, 4 doses on D3 and 4 doses on D7) with or without equine rabies immunoglobulin (ERIG) on D0, and the new Thailand Red Cross regimen (2 doses on D0, 2 doses on D3, 2 doses on D7 and 2 doses on D28) with equine rabies immunoglobulin (ERIG) on D0. The Institute Pasteur of Cambodia (IPC) regimen (2 doses on D0, D3 and D7) was also included in the Thailand Red Cross regimen up to D28. Almost all vaccinated subjects (98.8%) reached rabies neutralising antibody levels ≥ 0.5 IU/mL by D14. A direct comparison of the immunogenicity following ID compared with IM use was not made. Five years later and before the simulated PEP was received, the protective level of rabies neutralising antibodies was maintained in more than 84% of subjects who received a 4-site 1-week regimen with or without ERIG, and in 64.1% (95% CI: 55.1; 72.3) of subjects who received the new Thailand Red Cross regimen with ERIG. Eleven days after the simulated PEP with a 4-dose ID regimen performed in one visit, all the vaccinated subjects reached rabies neutralising antibody levels ≥ 0.5 IU/mL on D14 (geometric mean antibody titre [GMT] between 138 and 193 IU/mL).
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 efficacy of Verorab was assessed in 44 adult subjects bitten by animals with rabies in a phase-4 clinical trial. The subjects received the vaccine according to the 5-dose Essen regimen (D0, D3, D7, D14 and D28 by IM use) and immunoglobulin, if applicable. All subjects were alive 3 years after the post-exposure prophylaxis.

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

Data in animals, including single dose and repeated dose studies revealed no unexpected findings and no target organ toxicity. Animal developmental and reproductive toxicity studies have not been conducted with this vaccine.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder*

- Maltose.

- 20% human albumin solution.
- Basal Medium Eagle: mixture of mineral salts (including potassium), vitamins, dextrose and amino acids (including L-phenylalanine).
- Hydrochloric acid and sodium hydroxide for pH adjustment.
- Water for injections.

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

Solvent

- Sodium chloride.
- Water for injections.

6.2 Incompatibilities

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

6.3 Shelf life

3 years

After the first opening/reconstitution:
For intramuscular use: the product must be used immediately.
For intradermal use, the physical-chemical stability after reconstitution was shown to last for 6 hours at 25°C protected from light. From a microbiological perspective, the product must be used immediately. In case of non-immediate use, the duration and conditions of storage and use (see section 6.6) are the responsibility of the user.

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 (chlorobutyl or bromobutyl) and an attached needle with a needle shield. Box of 1 or 10.

Powder in vial (Type I glass) with a stopper (chlorobutyl) and a cap + 0.5 mL of solvent in prefilled syringe (Type I glass) without needle, with a plunger-stopper (chlorobutyl or bromobutyl) and a tip cap (elastomer: styrene butadiene rubber). Box of 1 or 10.
The tip caps of the prefilled syringes without attached needle contain a natural rubber latex derivative.

Not all pack size may be marketed.

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.
- For syringe without needle: Attach the reconstitution needle to the syringe
- 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.

- For syringe with attached needle
    - Remove and discard the syringe that was used for vaccine reconstitution.
    - Use a new syringe with a new needle to withdraw the reconstituted vaccine.
- For syringe without needle
    - Withdraw the suspension using a syringe.

- Replace the needle used to withdraw the vaccine with a new needle for intramuscular or intradermal injection.
- The length of the needle used for vaccine administration should be adapted to the patient.

If Verorab is administered intramuscularly, the vaccine must be used immediately after reconstitution.

If Verorab is administered intradermally, the vaccine may be used up to 6 hours after reconstitution on the condition that is stored at a temperature not exceeding 25°C and protected from light. After reconstitution, using aseptic techniques, a vaccine dose must be taken from the vial. The rest may be used for another patient. Before each withdrawal, shake the vial gently to obtain a homogenous suspension. A new sterile needle and a new sterile syringe must be used to withdraw and administer each vaccine dose to each patient to avoid cross-infection. The unused reconstituted vaccine must be thrown away after 6 hours.

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

7 MARKETING AUTHORISATION HOLDER

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14 Espace Henry Vallee
Lyon
69007
France

8 MARKETING AUTHORISATION NUMBER

PA2131/016/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 30th June 2023

10 DATE OF REVISION OF THE TEXT