Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Rabies Vaccine BP > 2.5 IU/ml, Powder and solvent for suspension for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

After reconstitution, 1 dose (1ml) contains :

Rabies virus* (inactivated, strain PM/WI 38 1503-3M).....≥2.5 IU

*produced in human diploid MRC-5 cells.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder and solvent for suspension for injection.

The powder is pinkish beige to orangey yellow.

The solvent is a clear, colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Rabies Vaccine BP is indicated for pre- exposure prophylaxis and for post-exposure prophylaxis against rabies in all age groups (see Sections 4.2 and 5.1).
The use of Rabies Vaccine BP should be based on official recommendations.

4.2 Posology and method of administration

Posology
The recommended dose is 1mL of reconstituted vaccine.

Pre-exposure prophylaxis
The primary pre-exposure immunisation course consists of 3 doses: one at D0, D7 and either D21 or D28.
Alternatively, in immunocompetent individuals, the one-week regimen with 2 doses can be used: at D0 and at D7.
Individuals should be vaccinated according to local official recommendations when available.
For individuals at continued risk, booster doses should be given in line with official recommendations.
The need for serology testing to detect the presence of rabies virus-neutralising antibodies (≥0.5 IU/ml) should be assessed and conducted, if appropriate, in accordance with official recommendations.

Post-exposure prophylaxis
Post-exposure prophylaxis should be initiated as soon as possible after suspected rabies exposure and should comprise proper wound care, vaccination, and if necessary, RIG treatment.
In all cases, proper wound care (thorough flushing and washing of all bite wounds 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 rabies vaccine or rabies immunoglobulin, when they are indicated.
The rabies vaccine administration must be performed strictly in accordance with the category of exposure, the patient immune status, and the animal status for rabies (according to local official recommendations, see Table 1 for WHO recommendations).
Post-exposure prophylaxis must be performed under medical supervision.

Table 1: WHO category of severity of exposure

Category of exposure	Type of exposure to a domestic or wild animal suspected or confirmed	Recommended post-exposure prophylaxis

	to be rabid or animal unavailable for testing	
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 vaccine immediately Stop treatment if animal remains healthy throughout an observation period of 10 days[b] or is proven to be negative for rabies by a reliable laboratory using appropriate diagnostic techniques. Treat as category III if bat exposure involved.
III	Single or multiple transdermal[c] bites or scratches, contamination of mucous membrane or broken skin with saliva from animal licks, exposures due to direct contact with bats. (severe exposure)	Administer rabies vaccine immediately, and rabies immunoglobulin, preferably as soon as possible after initiation of post-exposure prophylaxis. Rabies immunoglobulin can be injected up to 7 days after administration of first vaccine dose. Stop treatment if animal remains healthy throughout an observation period of 10 days or is proven to be negative for rabies by a reliable laboratory using appropriate diagnostic techniques.

a If an apparently healthy dog or cat in or from a low-risk area is placed under observation, treatment may be delayed.
b This observation period applies only to dogs and cats. Except for threatened or endangered species, other domestic and wild animals suspected of being rabid should be euthanized and their tissues examined for the presence of rabies antigen by appropriate laboratory techniques.
c Bites especially on the head, neck, face, hands and genitals are category III exposures because of the rich innervation of these areas.

Post-exposure prophylaxis of previously non-immunised individuals
Vaccine should be administered on D0, D3, D7, D14 and D28 (5 injections of 1mL).
For category III exposure (see Table 1), rabies immunoglobulin should be given in association with vaccine. In this case, the vaccine should be administered contra-laterally, if possible.
Vaccination should not be discontinued unless the animal is declared not rabid according to a veterinarian assessment (supervision of animal and/or laboratory analysis).

Post-exposure prophylaxis of previously immunised individuals
Previously immunised individuals should receive one dose of vaccine intramuscularly on both day 0 and day 3. Rabies immunoglobulin is not indicated in such cases.
According to WHO recommendation, previously immunised individuals are patients who can document previous complete PrEP (pre-exposure prophylaxis) or PEP (post-exposure prophylaxis) and people who discontinued a PEP series after at least two doses of a cell culture rabies vaccine.

Special population- immunocompromised individuals

- Pre-exposure prophylaxis For immunocompromised individuals, conventional 3-dose regimen should be used (see subsection "Pre-exposure prophylaxis") and serology testing of neutralizing antibodies should be performed 2 to 4 weeks after the last dose to assess the possible need for an additional dose of the vaccine.
- Post-exposure prophylaxisFor immunocompromised individuals, only a full vaccination schedule should be administered. Rabies immunoglobulin should be given in association with the vaccine for both categories II& III exposures (see Table 1).

Paediatric population
Paediatric individuals should receive the same dose as adults (1mL).

Method of Administration
The vaccine is for intramuscular administration only. The vaccine should be administered into the deltoid muscle for adults and children or the anterolateral area of the thigh muscle in infants and toddlers. For instructions on the reconstitution of the vaccine before administration, see section 6.6.

4.3 Contraindications

Pre Exposure
Known systemic hypersensitivity reaction to any component of Rabies Vaccine BP or after previous administration of the vaccine or a vaccine containing the same components as Rabies Vaccine BP.

Vaccination must be postponed in case of febrile and/or acute disease.

Post Exposure
Since declared rabies infection generally results in death, 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 the batch number of the administered product should be clearly recorded

As with any vaccine, vaccination with Rabies Vaccine BP may not protect 100% of vaccinated individuals.
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.In subjects with a history of allergy there may be an increased risk of side-effects and this possibility should be taken into account.
As with all vaccines, appropriate facilities and medication such as epinephrine (adrenaline) should be readily available for immediate use in case of anaphylaxis or hypersensitivity following injection.
The vaccine may contain traces of neomycin and betapropiolactone which are used during the manufacturing process. Caution must be exercised when the vaccine is administered to subjects with hypersensitivity to betapropiolactone, neomycin, and other antibiotics of the same class.
If Rabies Immunoglobulin is indicated in addition to Rabies Vaccine BP, then it must be administered at a different anatomical site to the vaccination site.
Rabies Vaccine BP should not be administered to patients with bleeding disorders such as haemophilia or thrombocytopenia, or to persons on anticoagulant therapy unless the potential benefit clearly outweighs the risk of administration. If the decision is taken to administer Rabies Vaccine BP in such persons, it should be given with caution with steps taken to avoid the risk of haematoma formation following injection.
The tip caps of the pre-filled syringes without attached needle contain a natural rubber latex derivative, which may cause severe allergic reactions in latex sensitive individuals.

Paediatric population
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.

4.5 Interaction with other medicinal products and other forms of interaction

Immunosuppressive treatments, including long-term systemic corticosteroid therapy, may interfere with antibody production and cause the failure of the vaccination. It is therefore advisable to perform a serological test 2 to 4 weeks after the last injection (see also Section 4.2).
There are no clinical data available on the concurrent administration of Rabies Vaccine BP with other vaccines. Official recommendations should be followed with regard to co-administration with other vaccines or drugs.
Separate injection sites and separate syringes must be used in case of concomitant administration with any other medicinal product, including rabies immunoglobulins.

As rabies immunoglobulin interferes with development of immune response to the vaccine, the recommendation of administration of rabies immunoglobulin must be strictly followed.

4.6 Fertility, pregnancy and lactation

Pregnancy

Data on limited number of exposed pregnancies do not allow a conclusion on the potential risk of Rabies HDCV for pregnancy or for the health of the foetus/newborn child. Due to the severity of disease, pregnancy is not considered a contraindication to post exposure prophylaxis. If there is substantial risk of exposure to rabies, pre-exposure prophylaxis may also be indicated during pregnancy.

Breastfeeding

Due to the severity of the disease, breast feeding is not considered a contraindication and treatment must not be discontinued. It is not known whether this vaccine is excreted in human breast milk, thus no recommendation on continuation/discontinuation of breastfeeding can be made.

Fertility

Rabies Vaccine BP has not been evaluated for impairment of male or female fertility.

4.7 Effects on ability to drive and use machines

No adverse effects reported.

4.8 Undesirable effects

Summary of the safety profile

In clinical studies, more than 1900 subjects, including approximately 800 children and adolescents, received at least one dose of Rabies Vaccine BP.

The adverse reactions were generally of mild intensity and appeared within 3 days after vaccination. Most reactions resolved spontaneously within 1 to 3 days after onset.

Most frequent adverse reactions in all age groups were injection site pain, headache, malaise and myalgia.

Tabulated list of adverse reactions

Adverse event information is derived from clinical studies and worldwide post-marketing experience. Within each system organ class the adverse events are ranked under headings of frequency, using the following CIOMS frequency rating:

- Very common ≥10%;
- Common ≥ 1 and <10%;
- Uncommon ≥0.1 and <1%;
- Rare ≥0.01 and < 0.1%;
- Very rare < 0.01%;
- Not known (cannot be estimated from available data).

Adverse Reactions	**Adults** 18 years and older	**Childrenand Adolescents** up to 17 years old
CLINICAL STUDIES		
SOC: Blood and lymphatic system disorders		
Lymphadenopathy	Uncommon	-
SOC: Gastrointestinal disorders		
Nausea	Common	-
Abdominal pain	Uncommon	-
Diarrhoea	Uncommon	-
Vomiting	Uncommon	-
SOC: General disorders and administration site condition		
Injection site pain	Very common	Very common
Malaise	Very common	Very common
Injection site erythema	Common	Common
Injection site swelling/induration	Common	Common
Fever	Common	Common
Injection site pruritus	Common	Uncommon
Injection site hematoma/ bruising	Common	Uncommon
Fatigue/ Asthenia	Common	-
Chills	Uncommon	-
SOC: Nervous system disorders		
Headache	Very common	Very common

Dizziness	Uncommon	Uncommon
Paresthesia	Uncommon	-
SOC: Musculoskeletal and connective tissue disorders		
Myalgia	Very common	Very common
Arthralgia	Uncommon	Uncommon
SOC: Immune system disorders		
Allergic reaction with skin disorders or respiratory manifestations	Uncommon	-
Angioedema	Rare	-
POST-MARKETING EXPERIENCE		
SOC: Nervous system disorders		
Encephalitis	Not Known	Not Known
Convulsion	Not Known	Not Known
Neuropathy	Not Known	Not Known
SOC: Immune system disorders		
Anaphylactic reactions	Not Known	Not Known
Serum sickness type reactions	Not Known	Not Known

Serum sickness type reactions might be associated with the presence of betapropiolactone-altered human albumin in the HDCV.

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, Earlsfort Terrace, IRL – Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517; Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

Not applicable.

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 rabies neutralizing antibodies (RNA).
Clinical studies were conducted to assess the immunogenicity of the vaccine in both pre-exposure and post-exposure situations. A rabies neutralizing antibody titer ≥ 0.5 IU/ml, is considered to confer protection.

Pre-exposure prophylaxis
In clinical trials assessing a 3-dose regimen (D0, D7, D28 (or D21))in both adults and children, almost all subjects achieved an adequate immune response with rabies neutralizing antibody titers ≥ 0.5 IU/mL by 2 weeks after the end of the primary series.
A ten-year follow-up in 17 subjects who received a 3-dose regimen (D0, D7, D28) followed by a booster dose 1 year later has shown persistence of immune response with rabies neutralizing antibody titers ≥ 0.5 IU/mL up to 10 years in 96.2% (CI95% 88.8; 100) of subjects.
The one-week pre-exposure schedule (2 doses: on D0 and D7) by IM route was assessed in one study (VAJ00001) in 228 subjects (including 101 children from 2 to 17 years). At D21, 96.7% of subjects reached a rabies neutralizing antibody titer ≥ 0.5 IU/mL.
One year later, following a simulated PEP with two doses injected 3 days apart (on D0 and D3) by IM route, a high and rapid anamnestic response was demonstrated in all subjects from D7.
In 2 other supportive studies conducted in a total of 87 subjects in the context of a conventional 3-dose regimen assessment (at D0, D7, D21 or D28) by IM route, all subjects reached a rabies neutralizing antibody titer ≥ 0.5 IU/mL after the first 2 doses, just before injection of the third dose at D21 or D28.

Post exposure prophylaxis

In clinical trials assessing the 5-dose Essen regimen (D0, D3, D7, D14, D28) in both children and adults, with or without immunoglobulin, Rabies Vaccine BP elicited adequate rabies neutralizing antibody titers (≥ 0.5 IU/mL) in almost all subjects by D14 and in all of them by D42.

In a phase 2 trial, 124 healthy seronegative adults received the 5-dose Essen regimen (D0, D3, D7, D14, D28) IM and human rabies immunoglobulin at D0. All vaccinees reached a rabies neutralizing antibody titer ≥ 0.5 IU/mL by D14 with a maximum level on D42. One year later, protective level of rabies neutralizing antibodies was maintained in 98.3% (CI95% 93.9; 99.8) of subjects.

In a clinical trial simulating post-exposure prophylaxis, 47 previously immunised adult subjects received 2 doses of Rabies Vaccine BP 3 days apart (D0 and D3), 1 year after primary immunisation. Protective rabies neutralizing antibody titer (≥ 0.5 IU/mL) was reached by D7 in all subjects.

Paediatric population

Immunogenicity of the pre-exposure schedule (3 doses: on D0, D7 and D28 by IM route) has been assessed at D42 in 112 subjects from 2 to 17 years of age included in VRV06 study, in 190 subjects from 5 to 13 years of age included in RAC03396 study and in 46 subjects from 2 to 17 years of age included in VAJ0001 study. All vaccinees reached a rabies neutralizing antibody titer ≥ 0.5 IU/mL at D35 for VAJ0001 and at D42 for the 2 other studies.

The one-week pre-exposure schedule (2 doses: on D0 and D7 by IM route) has been assessed in 101 subjects from 2 to 17 years of age included in VAJ0001 study. All vaccinees reached a rabies neutralizing antibody titer ≥ 0.5 IU/mL at D21.

One year later, following a simulated PEP with two doses injected 3 days apart (on D0 and D3) by IM route, a high and rapid anamnestic response was demonstrated in all subjects from D7.

In one other supportive study conducted in 190 children in the context of a conventional 3-dose regimen assessment (on D0, D7, D28 by IM route), all vaccinees reached a rabies neutralizing antibody titer ≥ 0.5 IU/mL, at D28, after the first 2 doses, just before injection of the third dose.

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

None stated.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Human Albumin solution

Solvent: Water for injections (1 millilitre).

6.2 Incompatibilities

In the absence of compatibility studies this vaccine must not be mixed with other medicinal products.

6.3 Shelf life

3 years.

Once reconstituted, the vaccine must be used immediately.

6.4 Special precautions for storage

Store between +2^{o}C and +8^{o}C in a refrigerator. Do not freeze.

6.5 Nature and contents of container

Powder:

Single dose (Ph Eur type 1 glass) vial with elastomeric stopper (chlorobutyl) and aluminium overcap.

Solvent:
1.0 ml disposable Needleless (Luer-lok™) prefilled syringe (type 1 glass) with rigid adapter (polycarbonate) and Plastic Rigid Tip Cap (PRTC) (polypropylene and isoprene-bromobutyl rubber), with a plunger-stopper (bromobutyl rubber). Up to two separate needles (for each syringe) may be included in the pack.
Pack of 1 vial and 1 prefilled syringe.
Not all pack presentations may be marketed.

6.6 Special precautions for disposal and other handling

Specific instructions for Luer-lok™ syringe:

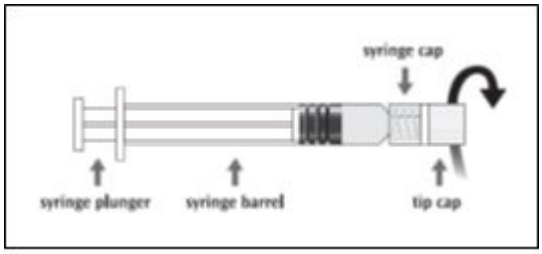
1. Holding the syringe cap in one hand (avoid holding the syringe plunger or barrel), unscrew the tip cap by twisting it counterclockwise.
2. To attach the needle to the syringe, gently twist the needle clockwise into the syringe until slight resistance is felt.

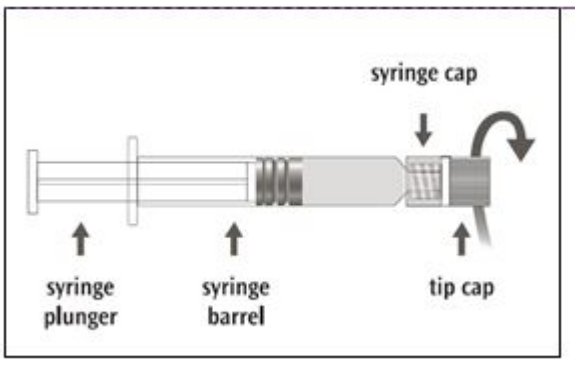
Reconstitute the freeze-dried vaccine by introducing the solvent provided in the pre-filled syringe into the vial of powder. Shake carefully until complete suspension of the powder is obtained. Following reconstitution, the suspension will be a pinkish colour and free from particles. Withdraw the suspension from the vial into the syringe prior to intramuscular injection. Remove the reconstitution needle and replace it with a needle for intramuscular injection.
Shake well immediately before use.

Use immediately after reconstitution.

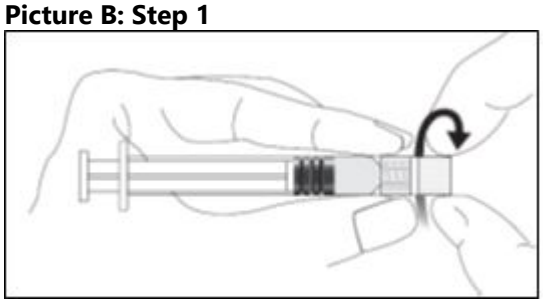
Any unused product or waste material should be disposed of, in accordance with local requirements.

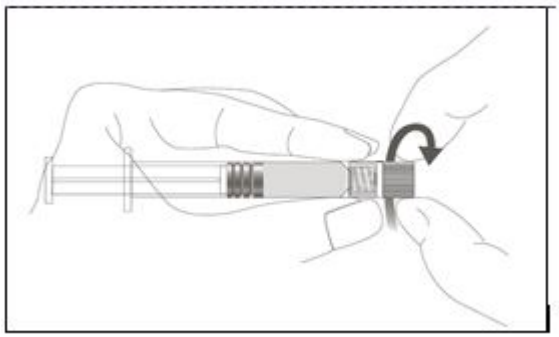
Picture A: Luer-Lok™ syringe



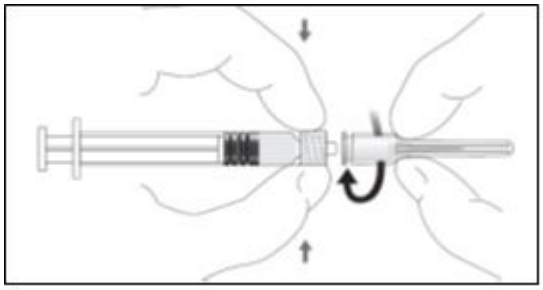


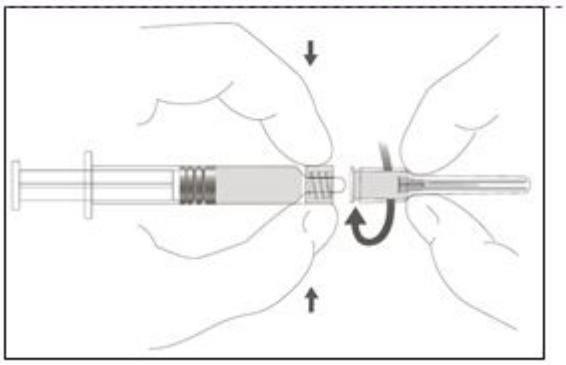
Picture B: Step 1





Picture C: Step 2





Reconstitution of the vaccine: introduce the solvent into the vial of powder and. gently swirl until complete suspension of the powder is obtained. The suspension should be clear or slightly opalescent, red to purple-red in colour. Without removing the needle from the vial, unscrew the syringe to eliminate negative pressure (as the vial is sealed under vacuum). Reattach the needle remaining in the vial to the syringe (as per step 2).
Withdraw the total contents of the vial into the syringe.
Unscrew the reconstitution needle and replace it with a sterile needle (as per step 2) of a proper length for intramuscular injection of your patient. Inject immediately.
The vaccine must be visually inspected before any administration in order to make sure there are no foreign particles in the vaccine.
Any unused medicinal product or waste material should be disposed of, in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Sanofi Pasteur
14 Espace Henry Vallée
69007
Lyons
France

8 MARKETING AUTHORISATION NUMBER

PA2131/004/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 12 December 1994

Date of last renewal: 11 November 2008

10 DATE OF REVISION OF THE TEXT

October 2022