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

For prophylactic immunisation against rabies.

Treatment of patients following suspected rabies contact.

4.2 Posology and method of administration

Administer by intramuscular injection. The vaccine should be administered into the deltoid region. For instructions on the reconstitution of the vaccine before administration, see section 6.6.

Pre-exposure prophylaxis
One injection of 1 millilitre given each day on days 0, 7 and 28.

The earliest day that the 3rd dose can be given to achieve effective immune status is day 21.

For those at regular and continuing risk, a single reinforcing dose of vaccine should be given at 1 year after the primary course has been completed. Further doses should be given at three- to five-year intervals thereafter.

For travellers at intermittent risk of exposure, booster doses may 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 treatment should begin as soon as possible after the suspected contact. Immediate wound toilet is important to reduce the risk of infection, followed by the administration of the vaccine and passive immunisation if indicated; this should be carried out in accordance with official recommendations.

(i) In persons known to have adequate prophylaxis:
In the event of contact with a suspected rabid animal, two further boosters should be given, one on day 0 and one on day 3.

(ii) In persons with no, or possibly inadequate, prophylaxis:
The first injection of rabies vaccine (day 0) should be given as soon as possible after the suspected contact and followed by four further doses on days 3, 7, 14 and 30 (the earliest that the 5th dose can be given is day 28 as per WHO recommendations). The use of Rabies Immunoglobulin should be considered in unimmunised or incompletely immunised subjects or those with uncertain immune status in accordance with official recommendations and/or expert advice. The treatment schedule may be stopped if the animal concerned is found conclusively to be free of rabies.

Subjects with incomplete prophylaxis or unknown history of immunisation should be treated as non-immune.

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

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 potential risk of apnoea and the need for respiratory monitoring for 48-72 h should be considered when administering the primary immunisation series to very premature infants (born ≤ 28 weeks of gestation) and particularly for those with a previous history of respiratory immaturity. As the benefit of vaccination is high in this group of infants, vaccination should not be withheld or delayed.

Anxiety-related reactions, including vasovagal reactions (syncope), hyperventilation or stress-related reactions can occur following, or even before, any vaccination as a psychogenic response to the needle injection. This can be accompanied by several neurological signs such as transient visual disturbance and paraesthesia. It is important that procedures are in place to avoid injury from faints.

4.5 Interaction with other medicinal products and other forms of interactions

Corticosteroids and immunosuppressive treatments may interfere with antibody production and cause the failure of the vaccination. It is therefore advisable to perform a neutralising antibody assay 2-4 weeks after the last injection.

Administration of an additional dose should be considered if the antibody titre is less than 0.5 IU/ml (*using an RFFIT analysis – Rapid Fluorescent Focus Inhibition Test*).

4.6 Fertility, pregnancy and lactation

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.

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.

4.7 Effects on ability to drive and use machines

No adverse effects reported.

4.8 Undesirable effects

Adverse reaction information is derived from clinical trials and worldwide post- marketing experience.
Two randomised controlled trials where Rabies Vaccine BP has been studied in both children (n=199) using pre-exposure schedule (3 doses, IM) and adults (n=124) using the post exposure schedule (5 doses, IM) have been selected to represent safety clinical data.
Within each system organ class the adverse reactions are ranked under headings of frequency, using the following convention:
Very common (>1/10)
Common (>1/100, <1/10)
Uncommon (>1/1000, <1/100)
Not known (cannot be estimated from the available data because only reported post marketing and not in clinical trials)
The most frequent adverse reactions are injection site pain and headache.
- Blood and lymphatic system disorders
  - *Very common*: lymphadenopathy
- Immune system disorders
  - *Common:* allergic reactions with skin disorders such as urticaria, rash and pruritus, or respiratory manifestations such as dyspnoea and wheezing. Angioedema.
  - *Not known:* anaphylactic and serum sickness type reactions, oedema

These reactions have been associated with the presence of betapropiolactone-altered human albumin (including the production of IgE antibodies in the vaccine).
Allergic reactions occurred more frequently among persons receiving booster than primary vaccination. Further information on allergic reactions see section 4.4.
- Nervous system disorders
  - *Very common:* headache
  - *Common:* dizziness
  - *Not known:* encephalitis, convulsion, Guillain-Barré Syndrome, paresis, neuropathy, paraesthesia
- Gastrointestinal disorders
  - *Very common:* nausea, diarrhoea
  - *Common:* abdominal pain, vomiting
- Musculoskeletal and connective tissue disorders
  - *Very common:* myalgia, arthralgia
- General disorders and administration site conditions
  - *Very common:* injection site reactions including pain, erythema, induration and injection site pruritus. Malaise, chills
  - *Common*: injection site bruising, pyrexia
  - *Not known:* asthenia

<u>Additional information on special populations:</u>
Apnoea in very premature infants (≤ 28 weeks of gestation) (see section 4.4).

<u>Reporting of suspected adverse reactions</u>
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

The vaccine is a lyophilised, stabilised suspension of inactivated Wistar rabies virus strain PM/WI 38-1503-3M, cultured in human diploid cells (MRC5) and inactivated by beta-propiolactone.

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:

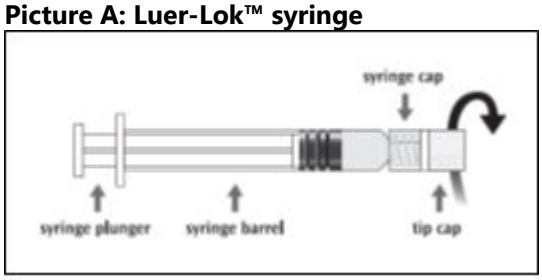
1. Holding the syringe cap in one hand (avoid holding the syringe plunger or barrel), unscrew the tip cap by twisting it counterclockwise.
2. To attach the needle to the syringe, gently twist the needle clockwise into the syringe until slight resistance is felt.

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.

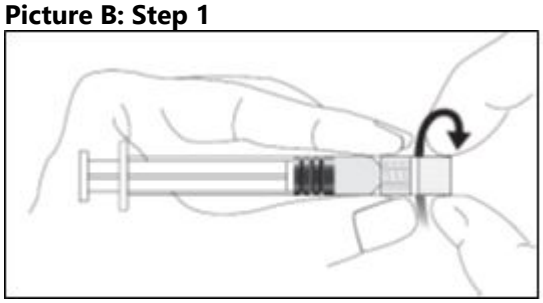
Use immediately after reconstitution.

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

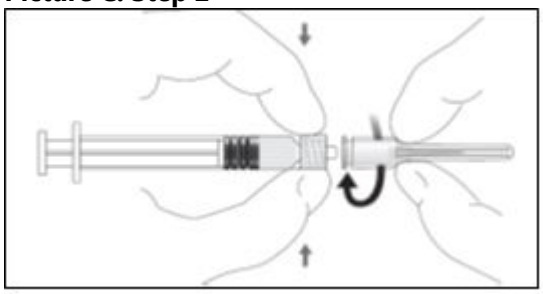
Picture A: Luer-Lok™ syringe



Picture B: Step 1



Picture C: Step 2



7 MARKETING AUTHORISATION HOLDER

Sanofi Pasteur Europe
14 Espace Henry Vallée 69007 Lyon
France.

8 MARKETING AUTHORISATION NUMBER

PA2131/004/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

February 2019